FISCAL YEARS 2009-2010

Report of the Advisory Committee on Research on Women's Health

Office of Research on Women's Health

and

NIH Support for Research on Women's Health

Report of the Advisory
Committee on Research
on Women's Health

Fiscal Years
2009–2010

Office of Research on Women's Health and NIH Support for Research on Women's Health

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Preface

The Advisory Committee on Research on Women's Health (ACRWH), in concert with the Office of Research on Women's Health (ORWH) and the National Institutes of Health (NIH) Coordinating Committee on Research on Women's Health (CCRWH), submits to the Director of NIH this biennial report for fiscal years (FY) 2009 and 2010. The report describes the comprehensive and coordinated efforts of the ORWH, NIH Institutes and Centers (ICs), and Program Offices in the Office of the Director to address women's health through increasing and enhancing research, ensuring the inclusion of women in clinical research, encouraging analyses by sex in basic research, developing programs for career advancement in the biomedical sciences for women and for both men and women as women's health researchers, and other related activities in accordance with the responsibilities defined in the NIH Revitalization Act of 1993.

The ACRWH appreciates the preparation of the comprehensive summary of activities and programs of the ORWH during the 2 years addressed in this report and the efforts of the CCRWH in summarizing the highlights of the great magnitude of women's health and sex differences research that has been conducted or funded by the ICs. The information in this biennial report summarizes significant research studies and other achievements and initiatives that have contributed to the continuing increase in scientific knowledge about women's health across the spectrum of investigative efforts. Using criteria supplied by the NIH Office of Financial Management (OFM) and the U.S. Department of Health and Human Services Office on Women's Health, and budget data provided by NIH ICs, this report also presents information on NIH budget allocations for women's health research during FY 2009 and FY 2010. In addition, the report contains information obtained from the NIH ICs and Offices documenting the inclusion of women and minorities in NIH-funded clinical research during the same time period.

The ACRWH has reviewed the information contained herein and believes that this biennial report accurately reflects the breadth and depth of research and related activities through which the NIH, in FY 2009 and FY 2010, has fulfilled its mandate from the U.S. Congress to address women's health and sex differences research and the inclusion of women in clinical research, with advances in our understanding of sex differences in health and disease resulting from analyses of results by sex and gender.

The ACRWH acknowledges the valuable contributions to this report of the CCRWH, which is composed of the directors of each of the ICs and Offices or their designated representatives. We are also grateful to the many NIH staff members who prepared and reviewed the reports of their ICs or Offices. We appreciate the work of the many members of the NIH staff who have assisted in the continued implementation and analysis of the inclusion of women and minorities in NIH-funded research, especially the Office of Extramural Research, which has assumed a central role in the analysis of inclusion data. We also recognize the work of the NIH Office of Budget in collecting and tabulating the budgetary data included in this report.

The ACRWH wishes to acknowledge the work of ORWH staff in meeting the mandates underlying the establishment of this office and for its leadership within the NIH and with the extramural research community to accomplish the many outstanding and important advances in science and in career support that are described. This biennial report reflects the achievements of the ORWH in concert with the NIH community in fulfilling the core mission of strengthening and enhancing research related to diseases and conditions that affect women; ensuring the appropriate representation of women in NIH research; supporting the advancement of women in biomedical careers; and building programs to ensure the development of a cadre of researchers, both women and men, in the field of interdisciplinary women's health research.

Finally, the members of the ACRWH collectively express their heartfelt gratitude for the opportunity to assist the Director of the ORWH, Dr. Vivian Pinn, in her dedicated and tireless mission to advance women's health research at NIH.

It has been a privilege to work with Dr. Pinn on this committee. She has been an inspiring leader. The challenges she undertook 20 years ago when she became the first full-time ORWH Director were enormous and her accomplishments have been outstanding. In Dr. Pinn's honor at this momentous time of her retirement, which coincides with the publication of the FY 2009–2010 biennial report, we renew our commitment to ORWH and NIH to work toward the goal of improving the health of all women.

While many milestones have been reached and biases overcome, the committee strongly believes that much works remains to be done to ensure the full representation and participation of women in biomedical research. As scientific discovery continues to reveal striking sex differences in health and disease, the absolute necessity of considering sex and gender as major points of study becomes apparent. Because of the tremendous skill and knowledge that Dr. Pinn has dedicated to women's health research in the last 20 years, we are well prepared to meet the challenges presented by this ever-unfolding field of inquiry. Perhaps the most fitting testament to Dr. Pinn's leadership of ORWH is the skilled workforce that has emerged as a result of the Office's programs and initiatives. To maintain this legacy, we dedicate our efforts anew to ensuring that women scientists are included in biomedical research and both men and women in biomedical careers have adequate resources, networks, and opportunities to continue making advances in women's health, vital as it is to the health of the Nation as a whole.

Advisory Committee on Research on Women's Health

(For a full listing of ACRWH members for FY 2011, please see pages v–vi.)

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Introduction

This report of the Advisory Committee on Research on Women's Health (ACRWH) for fiscal years (FY) 2009–2010 provides a summary of the accomplishments of the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) to address women's health over the past 2 years. It documents the expansive growth of women's health and sex differences research along with many other significant programs and activities across the NIH. As requested in the NIH Revitalization Act of 1993, the ACRWH, a chartered group composed of non-Federal experts, submits a report to the NIH Director every 2 years describing its findings related to the mandates for ORWH and NIH support of women's health research. This document fulfills that directive.

During FY 2009 and FY 2010, the time period addressed in this report, a number of milestones were reached. In September 2010, the ORWH celebrated the 20th anniversary of its historic establishment in 1990 as the first office within the U.S. Department of Health and Human Services to focus specifically on women's health. The anniversary celebration brought together women and men involved in women's health at the NIH as well as in the extramural community as researchers, health care providers, advocates, mentors, educators, policymakers, legislators, and other interested and dedicated individuals.

ORWH marked its first 20 years with a scientific symposium that recounted the many women's health research advances of the last two decades. At this time, ORWH also introduced a new strategic plan and research agenda for the NIH, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research* (NIH Publication No. 10-7606), which provides a plan for future women's and sex differences health research and career advancement in biomedical sciences for the coming decade. This new strategic plan, described in some detail in this report on page 9, represents the third multiyear effort by the ORWH to consult various women's health constituencies to determine the direction in which women's health research should proceed and, thus, determine priorities for new research and other funding initiatives. ORWH and other components of the NIH have used each of the previous strategic plans to move research opportunities forward and to explore the continuing gaps in knowledge about women's health and related issues.

Much progress in women's health research has been accomplished, including the following:

- A better understanding of what constitutes women's health and why
- Expanded concepts that embrace women's health across the lifespan rather than focusing exclusively on the reproductive system
- More exacting scientific endeavors using the most current diagnostic or investigative tools and skills

The new NIH strategic plan will also provide the impetus for even more advanced and redefined pathways for research initiatives in the future. ORWH has already begun to implement these new research priorities with enthusiastic trans-NIH participation. Vital to this effort is the participation and leadership of the Coordinating Committee on Research on Women's Health (CCRWH), composed of IC and Program Office directors or their representatives. Therefore, it is expected that exciting and important advances in women's health and sex differences research and career development programs can be anticipated during the years to come.

Several other milestones that should be noted with the submission of this report require personal comments. The ORWH was designed and established in 1990 by Dr. Ruth Kirschstein (at that time, the only woman director of an NIH Institute and cochair of the Public Health Service Committee on Women's Health Issues) under the leadership of Dr. William Raub, then Acting

Director of NIH. Dr. Kirschstein served as the Acting Director of ORWH until I came to the NIH in the fall of 1991 as the first full-time Director of ORWH under the leadership, support, and encouragement of Dr. Bernadine Healy, then Director of NIH, and the only woman to hold that position in the history of the NIH.

There is no doubt that the operational processes and premises for the ORWH, as established by Dr. Kirschstein, have continued to serve the ORWH and the NIH well over the past 20 years. And, there should also be no doubt that the extensive array of NIH women's health programs was possible only because of the vision that Dr. Healy had for the role that NIH should and could have in leading efforts to increase the scientific foundation for women's health care. So to both of these women leaders I, and the ORWH owe gratitude for the lasting impact their visions and their actions will have on the future of women and the science of women's health. The death of both of these trailblazers during these recent years must remind all of us to continue to build on their vision and their efforts as we move forward under the new research agenda for the coming decade and beyond.

And, finally, this report marks the end of my tenure as Director of the Office of Research on Women's Health and Associate Director of NIH for Research on Women's Health. The past nearly 20 years have, for me, been among the most personally fulfilling experiences, and I am grateful for having been given the opportunity to lead this effort for the NIH.

I have had the benefit of tremendous support and assistance from a wonderful and dedicated ORWH staff; wise and beneficial advice and collaboration from so many members of the NIH community; and exciting and stimulating encouragement from and partnerships with individuals, organizations, and legislators—especially members of the Congressional Caucus on Women's Issues, the actions of which led to the development of this Office, and whose continued interest and support have helped to sustain it. I have witnessed the growth of the ORWH, its dimensions of influence and programs, and its collaborative role in invoking science-based initiatives to augment the scientific foundation for women's health. The current state of NIH women's health research and programs constitutes this biennial report.

Organization of the FY 2009–2010 Biennial Report of the ACRWH

This FY 2009–2010 biennial report of the ACRWH bears witness to the phenomenal growth in women's health research and related programs that has occurred since the formation of the Office in 1990. It reflects major FY 2009–2010 ORWH research programs, initiatives, and activities, as well as highlights that were reported through the CCRWH from the NIH ICs and Program Offices. This report is not a comprehensive listing of all NIH research on women's health, which would necessarily be encyclopedic; the report does serve, however, to summarize, under a single cover, examples of the wealth of NIH advances in women's health research. This biennial report also provides information on and analyses of support for women's health research and related activities. The budget figures for NIH expenditures on women's health research and programs during FY 2009–2010 are included in this report, but are provided in a slightly different format because of the American Recovery and Reinvestment Act of 2009 (ARRA) funding during these years, which is accounted for separately.

This biennial report is divided into two major parts: part 1 presents ORWH programs and part 2 provides individual reports on women's health research from the NIH ICs and Program Offices. Information about ORWH programs in part 1 is organized into the following seven sections:

I. ORWH Research
II. ORWH Interdisciplinary Research and Career Development Programs
III. ORWH Biomedical Career Development Activities
IV. ORWH Research Dissemination and Outreach

V. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

VI. NIH Budget for Women's Health Research

VII. Committee Members, FY 2009–2010

Section I provides a table of ORWH-funded projects grouped by diseases and conditions, examples of special ORWH research initiatives, and highlights of scientific workshops and conferences. The voluminous research that has occurred because of ORWH support or with ORWH cofunding is well documented in this section, representing an investment in basic and clinical scientific investigations into ongoing gaps in knowledge about normal aspects of women's health; disease processes that may be unique to women, or affect both men and women with potential differences yet to be defined; and newly recognized conditions that may affect the wellness or mortality of women across their lifespan.

The previous strategic plan under which the ORWH was operating during this time period, *The Agenda for Research on Women's Health for the 21st Century*, recognized that women's health research is an inherently broad interdisciplinary endeavor, encompassing a full range of scientific activities. Since 1999, ORWH has been working to provide individual and institutional support for interdisciplinary research and career development. As the 20th anniversary of the office was celebrated, it became apparent that the ORWH-initiated interdisciplinary initiatives have evolved into the signature programs of new and exciting efforts in women's health research that are changing institutional approaches; these efforts and programs are described in detail in section II.

Section III provides information on a number of other programs through which ORWH works to promote women's biomedical career development and the development of careers in research on women's health and sex/gender factors. The ORWH-initiated, trans-NIH Reentry into Biomedical and Behavioral Careers Research Supplement Program is also described, representing an ORWH pilot initiative that now, as a trans-NIH program of the ICs, continues to be important for sustaining careers in research for those with family responsibilities that have interrupted their commitment to careers as scientists. This section also describes the activities of the NIH Director's Working Group on Women in Biomedical Careers to provide a comprehensive, action-oriented NIH response to challenges to Federal agencies posed in the 2007 National Academies report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*.

Section IV on research dissemination and outreach provides information on new ORWH Internet-based health information initiatives, including an ongoing collaborative effort with the NIH National Library of Medicine as part of its online resources for information on women's health research; a Web-based series of courses cosponsored with the Food and Drug Administration on *The Science of Sex and Gender in Human Health*; a multimedia approach to communicate advances being made from past and current women's health research; and other efforts to ensure that information generated from the NIH investment in research on women's health informs future research efforts and improves women's health and health care. Additional ORWH research dissemination and outreach activities, including the Women's Health Seminar Series, are also detailed in section IV.

Section V details NIH efforts to monitor the inclusion of women and minorities in NIH-funded clinical research, including aggregate data on the numbers of women, men, and minorities who participated as volunteers in NIH clinical research.

Section VI provides information on NIH expenditures on women's health research, including a breakdown of expenditures by disease category and other major categories of interest.

Part 2 of the biennial report is composed of individual reports from 19 NIH Institutes, 3 Centers, and 3 Program Offices located within the NIH Office of the Director. These IC and Office reports summarize their major initiatives and activities and provide highlights of the research

each has funded related to women's health and sex differences research, consistent with their specific missions. This information is presented as submitted by the ICs, most often by their CCRWH representatives, and is impressive as well as fascinating in its scope and dimensions.

You are invited to read this in-depth report to become acquainted with the tremendous advances in women's health and sex differences research that have taken place during this 2-year period and to appreciate the promise for even greater advances in the future; not just for women's health, but also for men's health through enhanced attention to sex differences research; and for careers in women's health research for both men and women.

I am encouraged, as I entrust the leadership of the NIH Office of Research on Women's Health to my successors, that women's health research and career programs including those that are interdisciplinary in nature, the inclusion of women and minorities in clinical research, and efforts to address sex differences in basic investigation are firmly secured into the fabric of the NIH. And, I have further expectations that in the future, the ideals that led to the establishment of the Office will only become strengthened and more fully appreciated for their importance to the scientific mission of the NIH and the health and health care of women and their families.

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health

August 2011

Report of the Office of Research on Women's Health

A Historical Perspective: The Development of the Office of Research on Women's Health

In 1983, the Assistant Secretary for Health, Dr. Edward N. Brandt, established the U.S. Public Health Service Task Force on Women's Health Issues in recognition of the paucity of data related to women's health. The task force produced a 1985 report, *Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume I.*[1] The report delineated a series of criteria for "differentiating a health problem, condition, or disease as a woman's issue." The criteria included the following:

- Diseases or conditions unique to women or some subgroup of women
- Diseases or conditions more prevalent in women or some subgroup of women
- Diseases or conditions more serious in women or some subgroup of women
- Diseases or conditions for which risk factors are different for women or some subgroup of women
- Diseases or conditions for which interventions are different in women or some subgroup of women

The report also recommended that "biomedical and behavioral research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women in all age groups."

Following the issuance of the task force report, the National Institutes of Health (NIH) established a policy for the inclusion of women in clinical research. This policy, which "urged" the inclusion of women, was first published in the *NIH Guide for Grants and Contracts* in 1986.[2] In the following year, minority scientists and other researchers at NIH recognized the need to address the inclusion of minority populations. As a result, a subsequent version of the *NIH Guide* published for the first time a policy "urging" the inclusion of minorities in clinical studies.[3]

In 1990, the Congressional Caucus for Women's Issues requested that the General Accounting Office (GAO), now known as the Government Accountability Office, conduct an investigation into the implementation of the guidelines for the inclusion of women by NIH. This report, included in congressional testimony, indicated that the implementation of the policy for the inclusion of women was slow and not well communicated, that gender analysis was not being performed routinely, and that the impact of this policy could not be determined.[4] GAO testimony also indicated that there were differences in the

[1] U.S. Public Health Service. (1985).Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume I. *Public Health Reports, 100*(1):74–106.

[2] National Institutes of Health. (1986, October 24). Inclusion of women in study populations. *NIH Guide for Grants and Contracts*, *15*(22):1.*Contracts*, *16*(3):2.

[3] National Institutes of Health. (1987, September 25). Inclusion of minorities in study populations. NIH Guide for Grants and Contracts, 16(32):3–4.

[4] U.S. General Accounting Office. (1990). *National Institutes of Health: Problems in Implementing Policy on Women Study Populations. Statement of Mark V. Nadel, Associate Director, National and Public Health Issues, Human Resources Division before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives* (GAO/T-HRD-90-38). Washington, DC: General Accounting Office.

implementation of the policy recommending the inclusion of minorities and that not all Institutes and Centers (ICs) factored adherence to these policies into scientific merit review. GAO findings concerning the lack of consistent implementation of policies for inclusion of women in NIH clinical trials catalyzed NIH to establish the Office of Research on Women's Health (ORWH) within the Office of the NIH Director in September 1990.

Since its establishment, ORWH has served as the focal point for women's health research at NIH. The responsibilities of the ORWH Director include the following:

(1) Advise the NIH Director and staff on matters relating to research on women's health.

(2) Strengthen and enhance research related to diseases, disorders, and conditions that affect women.

(3) Ensure that research conducted and supported by NIH adequately addresses issues regarding women's health.

(4) Ensure that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH.

(5) Develop opportunities for and supports recruitment, retention, reentry, and advancement of women in biomedical careers.

(6) Support research on women's health issues.

ORWH was established in statute in the NIH Revitalization Act of 1993.[5] An Advisory Committee on Research on Women's Health (ACRWH), composed of non-Federal members, also was statutorily mandated in the Revitalization Act as a mechanism for eliciting advice and recommendations on priority issues affecting women's health research. This committee provides leadership to ORWH by advising the ORWH Director on appropriate research activities in women's health. ACRWH members are chosen from among health practitioners, advocates, research scientists, educators, and other professionals. Committee members are actively involved in reviewing and advising on matters related to research priorities, the women's health research portfolio for NIH, career development, inclusion of women and minorities in NIH-funded clinical research, and other ORWH or NIH programs related to women's health.

ORWH also benefits from the advice of the Coordinating Committee on Research on Women's Health (CCRWH). CCRWH also was established in statute in the 1993 NIH Revitalization Act and is composed of IC Directors or their designees as a direct liaison for ORWH with NIH ICs. Both ACRWH and CCRWH provide valuable guidance, collaboration, and support for activities of ORWH in women's health research, career programs, and outreach efforts.

In 2006, the NIH Reform Act[6] called for a reorganization of the Office of the Director (OD), placing the ORWH within a new division entitled the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI). As a result of this legislation, the ORWH Director now reports to the director of DPCPSI. The ORWH continues to work in partnership with the NIH ICs and other offices within the OD to ensure that women's health research is part of the scientific framework at NIH and throughout the scientific community; that attention is given to the recruitment, retention, reentry, and advancement of women in biomedical careers; and that the policies for the inclusion of women and minorities in NIH-funded clinical research as well as the growing interest in the study of sex differences and similarities in basic science research are addressed.

ORWH does not have direct grantmaking authority. Therefore, all ORWH-funded and cofunded programs must be processed through the ICs. All research supported by the ORWH undergoes the same scrutiny and peer review as other NIH funding. This ensures that all ORWH-supported research is based on science-driven initiatives and is of the highest quality.

ORWH programs and efforts have expanded in breadth and depth. In addition to its original mission of monitoring adherence to the NIH policy on inclusion of women and minorities in clinical research and promoting women's health research, ORWH has

[5] NIH Revitalization Act of 1993, Pub. L. No. 103-43, § 141, 107 Stat. 22 (1993). Codified at 42 U.S.C. § 287d (2006).

[6] NIH Reform Act of 2006, Pub. L. No. 109-482, 120 Stat. 3675 (2007).

pioneered the development of interdisciplinary approaches to women's health research, developed and led a number of initiatives to promote women in biomedical careers, and has undertaken an active role in disseminating women's health information to both the scientific and lay communities. In addition to these efforts, ORWH continues to actively promote the development of innovative strategies based on novel paradigms and nascent science. The approach to women's health and sex differences research has now evolved to address the following areas:

- Female-specific research (primarily reproductive)
- Differences or similarities between males and females (sex differences research)
- Differences within populations of women and men (health disparities), especially those populations that traditionally have been excluded or understudied in clinical research

This approach includes the expanded concept of women's health across the lifespan, from preconception health and the intrauterine environment to the health of the frail elderly.

NIH Strategic Plan for Women's Health and Sex Differences Research

Introduction

September 2010 marked the 20th anniversary of the establishment of the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) and the release of the third NIH scientific agenda for women's health, titled *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research*[7]. This new research agenda is the culmination of a highly interactive scientific and public partnership that encompassed both looking back for historical perspectives[8] and looking forward to new research opportunities on the horizon. The resulting three volumes represent the NIH strategic plan for women's health and sex differences research for the coming decade and serve as a framework for research investigations galvanized by cutting-edge technologies and catalyzed by nascent scientific concepts to advance women's health research through interdisciplinary and multidisciplinary collaborations across the entire research spectrum from basic to clinical and translational.[9]

Following the tradition established by the ORWH from its inception, the research agenda-setting process involved members of the public and included women's health advocacy groups, public health officials, scientists, researchers, policymakers, clinicians, and individuals representing their own concerns or the perspectives of academia, government, and industry. *Federal Register* notices were issued to solicit participation of audiences not generally reached through scientific channels and resulted in unique contributions from the public at large in all aspects of the meetings. Public testimony on any aspect of women's health, sex differences research, or biomedical careers was welcomed. Using a systems-thinking approach, the intentionally informal discussion format welcomed diverse perspectives to the conversation and challenged stakeholders to broaden their vision of women's health.

The Strategic Planning Process

The five regional public hearings and scientific workshops held in 2009 and 2010 were hosted by academic and research institutions with which current or past members of the NIH Advisory Committee for Research on Women's Health (ACRWH) were affiliated. The ACRWH is the statutory non-Federal group whose function is to advise the Director of ORWH on appropriate research activities to be undertaken by the NIH with respect to research on women's health. (A diagram of the strategic planning process through a series of regional meetings is shown in figure 1). The leadership of each regional meeting was provided by extramural cochairs assisted by representatives of the NIH. The meetings were hosted by the following institutions:

- Washington University in St. Louis School of Medicine and Center for Women's Infectious Disease Research, St. Louis, MO
- University of California, San Francisco, San Francisco, CA
- The Warren Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island, Providence, RI
- Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital, Chicago, IL
- Emory University School of Medicine, Atlanta, GA

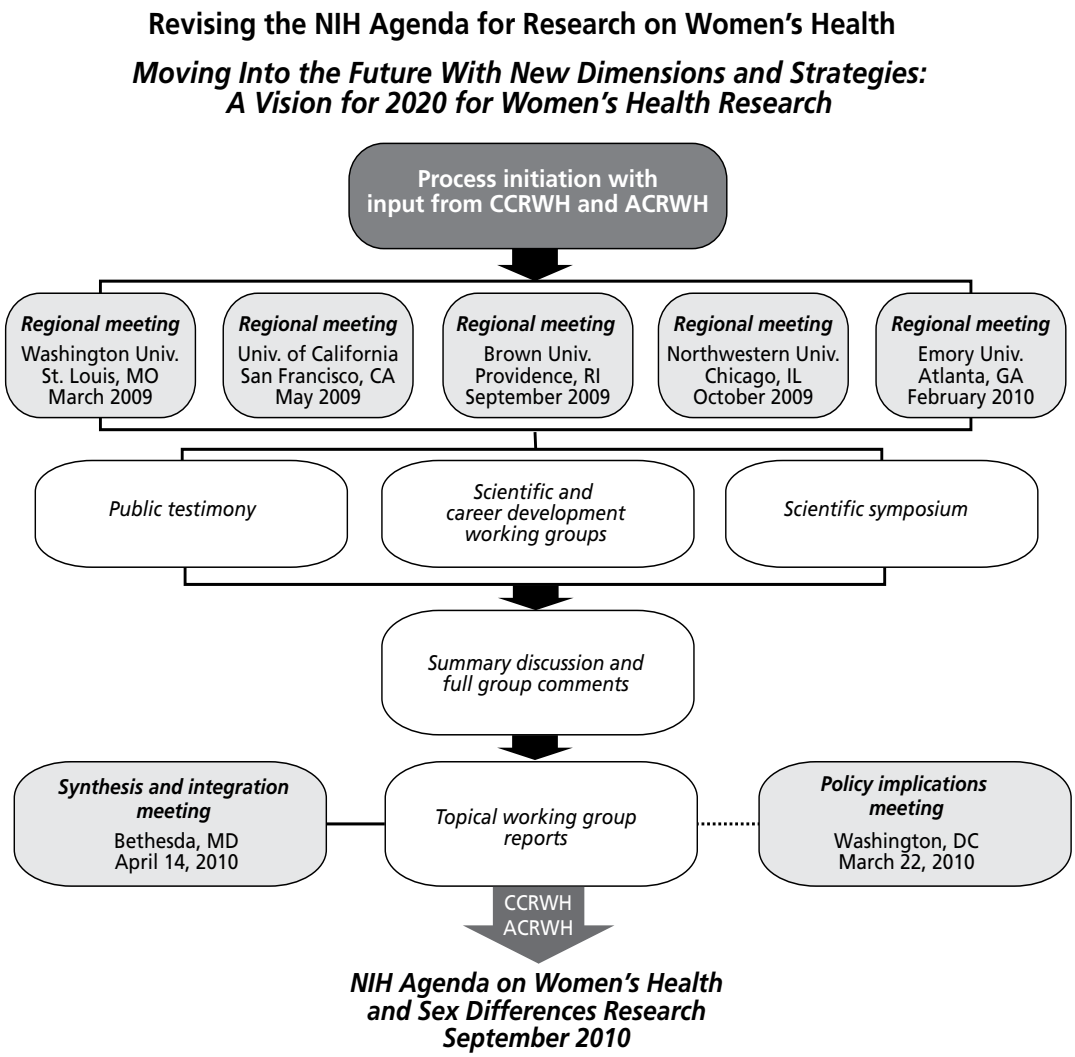
A total of 37 scientific and career development working groups were jointly cochaired by leading extramural and NIH scientists, representing 44 academic institutions, 19 NIH ICs, and the Office of the Director. The

[7] U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Strategic plan—Executive summary* (NIH Publication No. 10-7606). Bethesda, MD: National Institutes of Health.

[8] U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Highlights of NIH women's health and sex differences research 1990–2010* (NIH Publication No. 10-7606-D). Bethesda, MD: National Institutes of Health.

[9] Pinn, V. W., Clayton, J. A., Begg, L., & Sass, S. E. (2010). Public partnerships for a vision for women's health research in 2020. *Journal of Women's Health, 19*(9),1603-1607.

Figure 1. A Vision for 2020 for Women's Health Research: Strategic Planning Meetings



CCRWH = Coordinating Committee on Research on Women's Health
ACRWH = Advisory Committee on Research on Women's Health

reports of all the working groups were compiled in Volume II of the strategic plan.[10]

Public testimony has been a central and vital component of every strategic planning effort of the ORWH, and there was no exception during this process. At each meeting, self-identified members of the public, from academicians to individuals with women's health concerns, were able to provide their thoughts and recommendations in oral presentations. The comments and suggestions from the 141 public testimonies received were considered in the working group discussions and in the preparation of the final research agenda. Each written testimony was incorporated into Volume III of the strategic plan.[11] The agenda setting process is illustrated in figure 2.

Identifying the Goals for the New NIH Research Agenda for Women's Health and Sex Differences Research

Each workshop served as a dynamic forum for a mutually informative and collaborative research agenda-setting process. The resulting working group reports put forward a total of 400 recommendations, from which six cross-cutting goals were distilled. Central to the six goals is the importance of evaluating sex and gender differences across the research spectrum with an explicit emphasis on interdisciplinary approaches. The goals of the strategic plan are summarized below:

(1) Increase the study of sex differences in basic biomedical and behavioral research.

(2) Incorporate findings of sex differences in the design of new technologies, medical devices, and therapeutic drugs.

(3) Actualize personalized prevention, diagnostics, and therapeutics for women and girls.

(4) Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research.

(5) Achieve a clearer and wider understanding of women's health issues through strategic communications of research findings to diverse audiences.

(6) Employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce.

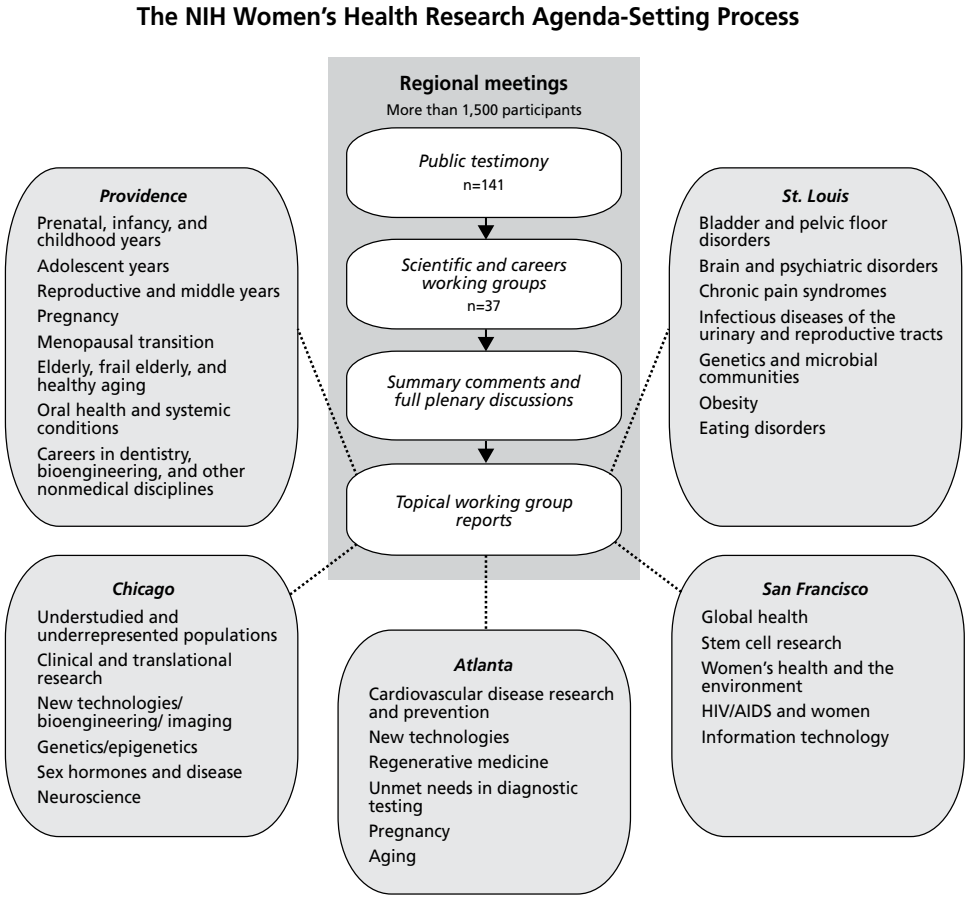
Sex Differences Research

The research agenda challenges the boundaries of women's health by calling for an increased focus on basic scientific research on sex differences at the most basic levels of research. To provide a foundation for research to improve health and accelerate advances into clinical care, the strategic plan calls for a comprehensive conceptual framework that explores variation due to sex as critical to advance many fields of study, such as genetics, immunology, endocrinology, developmental biology, cell biology, microbiology, biochemistry, and toxicology, as well as in basic and behavioral social sciences. New technologies, such as high-throughput sequencing, data acquisition, bioengineering, bioinformatics, and new modeling and data analytical techniques can contribute to innovative and effective approaches to advance emerging areas of science. The coming decade was viewed as an opportune time to expand knowledge about the effects of biological sex on normal development and the structure and function of cells, tissues, and organs. Research conducted with both female and male cells, tissues, and animal model systems is paramount for developing strategies to improve sex- and gender-appropriate medicine, including clinical diagnosis and therapy. In addition, research designed to delineate the effects of age and aging are also critical for age-appropriate health care. The study of biological, behavioral, and social variables and how they interact with environmental, age, sex, and other differences should be integral to the development of a new and expanded multidimensional scientific knowledge base.

[10] U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Regional scientific reports* (NIH Publication No. 10-7606B). Bethesda, MD: National Institutes of Health.

[11] U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research.* Public testimony (NIH Publication No. 10-7606C). Bethesda, MD: National Institutes of Health.

Figure 2. The NIH Women's Health Research Agenda-Setting Process



Since its inception, ORWH has challenged historically limited concepts of women's health and has advanced an expanded lifespan understanding of women's health and research, which provides an integrated framework that can mitigate fragmented approaches to health and health care. The increasing emphasis on sex differences research continues to broaden the perspectives and value of women's health to benefit both women and men, as well as girls and boys. In addition, ORWH continues to address the distinction between biological sex and socially derived gender and works to ensure the expansion and translation of research on both sex differences and gender identity.

Health Disparities

As long as differences exist in health status, responses to intervention, and health outcomes among different populations, research on the causes of such health disparities and how to prevent and eliminate them is vital. The research agenda illuminates knowledge gaps in women's and girls' health and calls for the biomedical and behavioral research necessary to understand how race, ethnicity, poverty, environment, gender identity, disability, immigrant status, occupation, sexual orientation, and a host of other differences intersect and influence the cause, diagnoses, progression, treatment, and outcome of disease among different populations. These concepts serve as catalysts to propel the research continuum toward the goals of prevention and individualized

treatment and the translation of such findings to promote the health and well-being of all women. Efforts to improve the health of women may also benefit the health of others; women comprise a disproportionate number of the world's caretakers and therefore often are in a position to make healthy choices for themselves, their families, and their communities, both internationally and nationally.

Moving into the Future

As ORWH moves into its third decade, it is important to reaffirm its important role within NIH. The mission of NIH is to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. In partnership with the NIH ICs and the Office of the Director, ORWH leads efforts to meet these goals, particularly as they relate to women's health and sex differences research.

ORWH continues to collaborate broadly with a wide range of partners and organizations, including groups who work specifically with minority or underrepresented or underserved populations. A shared vision of this coalition is to improve the lives of women through evidence-based knowledge derived from research encompassing an enhanced totality of women's health promoted and supported by the application of interdisciplinary research approaches.

The Jacobs Institute of Women's Health convened a workshop at the end of the strategic planning process to discuss the major policy implications of the recommendations of this new research agenda on basic science and interdisciplinary research, as well as on health professional education and training.[12] This workshop identified major opportunities to inspire current and future leadership at every level of the scientific community, health professions, Federal research agencies, and legislative policy makers to identify priorities in women's health research and to move these priorities forward in visionary and thoughtful ways.

Conclusion

In the coming decade, the exciting potential of scientific research must be realized to provide even greater progress to improve the health of women and men across the lifespan. The new research agenda can lead the way toward further innovative and promising science. A joint effort among experts in the fields of basic and clinical research sciences, practitioners interested in women's health, other governmental institutions, and representatives of advocacy groups and other organizations concerned about the health of women and girls will advance research activities identified in the new strategic plan. Such a model of collaboration, interdisciplinary approaches, and cutting-edge research in the pursuit of scientific knowledge has informed the history of ORWH and will continue to guide future efforts.

[12] Wood, S. F., Blehar, M. C., & Mauery, D. R. (2011). Policy implications of a new National Institutes of Health agenda for women's health research, 2010–2020. *Women's Health Issues, 21*(2), 99–103.

I. ORWH Research

ORWH and Research on Women's Health: Identifying Priorities

The mission of the Office of Research on Women's Health (ORWH) includes stimulating and encouraging meritorious research on women's health, including the role of sex differences in health and disease. Since its inception, ORWH has worked to strengthen and enhance research related to diseases, disorders, and conditions that affect women; ensure that research conducted and supported by NIH adequately addresses issues regarding women's health; and support research on women's health issues. ORWH works in partnership with the NIH Institutes and Centers (ICs) to ensure that women's health research is part of the scientific framework at NIH and throughout the scientific community. The new NIH/ORWH strategic plan, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research* (NIH Publication No. 10-7606), published in September 2010, will guide future research priorities. However, the *Agenda for Research on Women's Health for the 21st Century* (NIH Publication No. 99-4385) assisted in guiding programmatic priorities for research during most of the timeframe of this report.

For FY 2009 and FY 2010, the NIH research priorities for women's health are described in terms of four overarching themes, two special emphasis areas, and five areas of research interest, discussed below. These areas were selected based on opportunities to advance the science and understanding of women's health research or the study of sex and gender differences. The ad hoc Research Subcommittee of the Coordinating Committee on Research on Women's Health (CCRWH), composed of representatives from NIH Institutes and Centers (ICs), reviews the research priorities annually for gaps in knowledge and emerging scientific opportunities. (Please see appendix A for a full listing of the ad hoc Research Subcommittee.) The full CCRWH and the Advisory Committee on Research on Women's Health (ACRWH) then review and approve the subcommittee's recommendations. These priorities represent areas in which there is a need to stimulate and encourage research on women's health or sex/gender factors and the advancement of women in biomedical research careers; they are not an exclusive list of research areas important to women's health, and other innovative or significant research areas are supported.

I. Overarching Themes

The following four overarching themes are important for addressing research on women's health: (1) lifespan, (2) sex/gender determinants, (3) health disparities/differences and diversity, and (4) interdisciplinary research.

Lifespan

The health of girls and women is affected by developmental, physiologic, and psychological age. Women's lives are marked by a continuum from intrauterine life to the elderly years: infancy, childhood and adolescence, menarche, reproductive life, the menopausal transition, postmenopausal years, the elderly, and frail elderly. Many women's lives and health status also are influenced by factors such as work inside and outside the home, caregiving such as childcare and elder-care responsibilities, reproductive status, marital status, and chronic illness. Each of these factors may influence health, disease, lifestyle, treatment choices, and response to therapy.

Sex/Gender Determinants

Women are characterized by both sex and gender as highlighted in the *Agenda for Research in Women's Health for the 21st Century* and the Institute of Medicine report titled *Exploring the Biological Contributions to Human Health: Does Sex Matter*? In this context, the term "sex" refers to being male or female according to reproductive organs and functions assigned by chromosomal complement. Sex factors that contribute to biological differences include chromosomes, reproduction, and hormones. Gender refers to socially defined and derived expectations and roles rooted in biology and shaped by environment and experience. Gender and sex are important considerations in many areas of research, including basic biological, psychological, social, and behavioral studies. Consideration of these variables may be critical to the accurate interpretation and validation of

research affecting aspects of women's health. These variables determine how health or disease processes may differ among women or between men and women.

Health Disparities/Differences and Diversity

Women are disproportionately affected by some conditions and diseases in terms of incidence, diagnosis, course, and response to treatment. Some populations of women may be at higher risk for adverse disease outcomes because of factors such as biology, genes, culture, education, effects of poverty, access to care, quality of care, and access to opportunities for inclusion as research subjects in clinical trials and studies. Thus, clinical research should include, but not be limited to, population-specific characteristics such as cultural diversity, environment, race/ethnicity, immigrant status, rural or inner city (urban) residency status, effects of poverty or low socioeconomic status, sexual orientation, and physical or mental disabilities.

Interdisciplinary Research

With the increasing understanding of the interrelatedness and complexity of health and disease, the nature of scientific investigation is shifting to an interdisciplinary collaborative approach. Advances in women's health can be better achieved by promoting partnerships across disciplines, thus enhancing collaborations among researchers in academia, private industry, and Federal settings, and providing access to the latest scientific tools, technologies, and expertise for women's health and sex differences research.

II. Special Emphasis Areas

NIH is especially interested in fostering research in women's health in the high-priority areas of prevention and treatment, and the biological and behavioral basis of sex and gender differences.

Prevention and Treatment

Increased investigation into methods to prevent conditions and diseases, or to better treat them, can result in significant improvements in the quality and length of women's lives. Prevention research spans the continuum from the most basic biological studies to investigations of the basis and effects of behaviors across the lifespan and the interventions to change them, including a focus on wellness and healthy behaviors. Examples of needed prevention and treatment research studies in women's health include, but are not limited to, the following (as each applies to women):

- Research in early detection and treatment, including the development of novel tools to identify and validate biomarkers, such as genetic polymorphisms and RNA expression profiles, and functional and morphologic brain changes in relation to disease risk, pathogenesis, and progression, and to assess their clinical utility for disease prevention
- Examinations of environmental and social determinants involved in disease initiation and progression to develop prevention and treatment strategies, including the following:
  - » Studies of the impact on health of factors such as alcohol and drug use or abuse, diet and dietary supplements, eating disorders, exercise, hormones, obesity, occupations, sex practices, sleep quality, tobacco, environmental exposures, violence, or trauma
  - » Development of multimodal approaches to treating chronic diseases that contribute significantly to public health disability burden. Examples include addiction, brain injury, cancer, chronic multisystemic diseases, coronary artery disease, diabetes, neurodegenerative disorders such as Alzheimer's disease, musculoskeletal disorders, obesity, pain syndromes, stroke, and sexually transmitted diseases
  - » Studies of the effect of biological, behavioral, cultural, economic, environmental, and social factors on susceptibility to, or protection from, disease and response to treatment and, where appropriate, subset analyses that can facilitate personalized medicine

Biological and Behavioral Bases of Sex and Gender Differences

Although much research has been done to identify the cellular pathways and genes, the effects of sex as a modifier of cellular and gene function are underinvestigated. Systemic and cellular modeling of the influence of sex differences in biological pathways and systems is needed, including, but not limited to, the following:

- Mechanism of sexual dimorphism in gene expression and cellular and signaling pathways in healthy women, including the impact of puberty, the menstrual cycle, pregnancy, and menopause
- Sexual dimorphism in expression and function of genes, genetic polymorphisms, and gene defects in the risk factors, etiology, severity, and response to treatment of diseases
- Genetic, molecular, and cellular bases of action of pharmacologic agents in women, including differential effects between males and females
- Use of basic, translational, behavioral, and clinical research approaches to address sex and gender differences in the prevention, pathogenesis, course, and response to treatment

III. Areas of Research Interest

Basic, clinical, and translational research should be considered in addressing priority areas in women's health research. Some examples may include, but are not limited to, the following:

Diseases and Conditions That Affect Women

Investigate the pathogenesis and develop preventive and therapeutic interventions for acute and chronic diseases and disorders that affect women, including, but not limited to, addiction, autoimmunity, and cardiovascular, endocrine, gastrointestinal, inflammatory, metabolic, musculoskeletal, neurologic, ophthalmic, oral, psychiatric, reproductive, and urologic diseases.

Basic and Clinical Research Methodology

Develop clinical trial methodology, including novel recruitment strategies, standardized outcome measures, and statistical analyses that address ethical and study design issues. Develop new methodologies for animal model studies of the normal development of women and their health and diseases, including female animal models. Encourage methodological studies related to the conceptualization, distinction, and detection of sex and gender differences in basic and clinical biomedical research. Encourage collaborations between basic scientists and clinicians to identify and test potentially relevant therapeutic approaches.

Quality of Life

Elucidate the biologic and behavioral factors that may affect women's quality of life across the lifespan, especially in elderly women. Develop approaches to management of disease and promotion of wellness that are unique for women, their families, and their communities. This research could include examining the unique needs of different populations of women, such as women with disabilities, and their ability to seek obstetric and gynecologic care or partake in the activities of daily life or responsibilities that disproportionately fall to women, such as caretaking and homemaking.

Research Collaborations and Partnerships

Enhance trans-NIH, interagency, and public-private partnerships; public information partnerships; and community-based participatory research in women's health and career development. Promote community-based health communication and health literacy.

Career Development and Advancement of Girls and Women in Science

Identify and explore factors that affect the selection and advancement of women's careers in biomedical sciences; test the effectiveness of novel education programs directed at increasing the participation of girls and women in science, technology, engineering, and mathematics; and design and evaluate new approaches

to reduce barriers to the sustained advancement and effective mentoring of women to senior and leadership positions in science.

Summary of ORWH-Cofunded Research

ORWH partners with the NIH ICs to fund or cofund meritorious projects that advance the mission and scientific priorities of NIH and add to the growing body of evidence about women's health and sex/gender factors. The NIH research agenda on women's health and sex differences serves as a guide for prioritizing the grants and contracts supported by ORWH with the ICs.

Tables 1 and 2 on pp. 27–41 list more than 150 research grants and contracts each year that ORWH supported with the NIH ICs and Office of the Director program offices during FY 2009 and FY 2010. ORWH also collaborated with the U.S. Department of Health and Human Services (HHS) Agency for Healthcare Research and Quality (AHRQ), the Food and Drug Administration (FDA), and the Indian Health Service (IHS) to support research activities. Research summaries for these fiscal years are found in appendices B and C, respectively. The titles of the research projects are grouped by broad topical subject areas, such as aging, cancer, or cardiovascular disease.

Research support is distributed across all the major scientific areas, including a focus on health disparities. ORWH, working in partnership with the NIH ICs, supported grants and contracts in many areas, including aging; alcohol and other substance abuse; cancer; cardiovascular disease; chronic fatigue syndrome; craniofacial disorders, such as temporomandibular joint and muscle disorders (TMJD); diabetes; endocrinology; gastroenterology; genitourinary tract systems; HIV/AIDS; immunity and autoimmunity; infectious diseases; mental health; topical microbicides; musculoskeletal disorders and diseases; nutrition; obesity/overweight; ophthalmic disorders; pain; physical activity; reproductive health and developmental biology, including menopause-related topics and uterine fibroids; and violence against women.

ORWH-funded research addressed the full spectrum of a woman's lifespan, from preconception to advanced age and frailty. Attention to sex differences and health disparities was emphasized throughout most of the research portfolio funded by ORWH. The research portfolio that derives from ORWH funding in FY 2009 and FY 2010 is extensive. Because ORWH does not have direct grantmaking authority, all of its funding is with and through the NIH ICs. ORWH and the ICs use a variety of funding mechanisms to support these projects, including investigator-initiated grants, such as R01s, R03s, and R21s. However, other funding mechanisms are used as well, such as contracts and program project grants (usually P01s and P50s) and cooperative agreements (usually U01s and U10s). To stimulate research in specific areas of women's health, ORWH cosponsors several priority program announcements (PAs) and requests for applications (RFAs) with various ICs. They are listed in table 3. The Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health and the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) programs are described in detail under section II. Other activities resulting from the PAs and RFAs in table 3 are described in this section.

Examples of Long-Term ORWH-Funded Research Initiatives

Advancing Novel Science in Women's Health Research

Advancing Novel Science in Women's Health Research (ANSWHR) PAs, created by ORWH, were published in the *NIH Guide for Grants and Contracts* in 2007 and then reissued in June 2010. For FY 2009 and FY 2010, the ANSWHR program continued to be well received by the extramural scientific community and the ICs. Because of the complexity of working with up to 21 ICs on these two PAs, ORWH elected to have only an annual submission date of October 16 each year. Nearly 150 applications were submitted in October 2009, the majority of which were R21s. Due to the funding available under the American Recovery and Reinvestment Act (ARRA), 51 ANSWHR awards (42 R21s and 9 R03s) were made in FY 2009 and FY 2010.

A total of 14 ICs had 1 or more ANSWHR applications funded during these two fiscal

years, including the National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), National Institute on Aging (NIA), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institute on Drug Abuse (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Environmental Health Sciences (NIEHS), National Institute of Mental Health (NIMH), National Institute of Dental and Craniofacial Research (NIDCR), National Center for Complementary and Alternative Medicine (NCCAM), and Fogarty International Center (FIC). The areas of science covered include breast cancer, colon cancer, reproductive health, diabetes, obesity, human papillomavirus (HPV), cardiovascular disease, chronic pain, endocrine disorders, microbial exposures across the lifespan of women, mental health, and a range of neurosciences research projects.

Research Enhancement Awards Program

In 1997, ORWH created the Research Enhancement Awards Program (REAP), a trans-NIH initiative that has developed very productive partnerships across NIH. Offered annually, REAP supports meritorious research on women's health that has just missed the IC payline for funding. ORWH's policy is to fund 1 year only, so all "out year" funds are provided by the primary IC.

In FY 2009, REAP funded 12 highly meritorious investigator-initiated grant applications for a total of $2.09 million. Selected areas of science funded through the 2009 REAP included activin target genes in the ovary; regulation of ovarian follicle development; improvement of contraceptive use in high-risk women; nutritional and immunologic effects of malaria in pregnancy; sociodemographic disparities in lupus nephritis, including health care access and outcomes; function and behavior phenotype of inflammatory arthritis in the rat knee and temporomandibular joint; estrogen and psychological stress in TMJD pain; and exploratory studies on the anti-breast cancer function of bamboo extract.

In FY 2010 ORWH partnered with 7 ICs to fund 18 grants under REAP for a total of $3.17 million. The FY 2010 REAP included the following topics: mitochondria as a novel genetic modifier for breast cancer risk; refocusing therapeutics in menopause symptom clusters; cellular mechanisms of amniotic fluid volume regulation; osteocyte cell processing; genetics of polycystic ovary syndrome; mammography screening among Navajo women involving a decisionmaking framework for contralateral prophylactic mastectomy; an integrative intervention for binge eating among adolescents girls; effects of malaria on Epstein-Barr virus persistence in children; lifestyle modification to relieve fatigue in breast cancer survivors; functional networks in migraine; obesity and inflammation in breast cancer survivors; reproductive, hormonal, and genetic factors in non-Hodgkin lymphoma in women; brain imaging and neurocognitive and pubertal maturation during adolescence; biological signals of weight loss in African-American women; social determinants of outcomes in African Americans with rheumatoid arthritis; and chemical profiles of brain synapses at ages vulnerable to activity-based anorexia.

Research Dissemination Partnership with the National Library of Medicine

ORWH and the National Library of Medicine (NLM) have continued their innovative partnership that developed and implemented the Women's Health Resources Web Portal. This portal, http://www.womenshealthresources.nlm.nih.gov, uses the current NIH research priorities for women's health and sex differences to identify overarching themes, specific health topics, and research initiatives in women's health. Within each section of the Web site are topics with links to relevant and authoritative resources and research initiatives for women's health. NLM has created specific user-friendly strategies for these topics to ease searching ClinicalTrials.gov and PubMed. Other Web resources used include AIDSinfo, American Indian Health, Arctic Health, Household Products Database, MedlinePlus, and NIH SeniorHealth. Search strategies for major

studies related to women's health research also have been created. As with the topical search strategies, ClinicalTrials.gov and PubMed searches for each major report are included.

During FY 2009 and FY 2010, the Web portal was greatly expanded, both in content and with new technology, specifically incorporating Web 2.0 technologies and social media tools and news resources to engage the scientific and consumer public. Popular social media applications included Facebook, Blogger, Twitter, Delicious, RSS feeds, cloud tagging, and wikis.

In addition to adding significant new scientific content from the ICs, a major new category was created—Women and the Military—so that a one-stop Web resource could support the trans-Federal research collaboration between NIH, the Department of Defense (DoD), and the Veterans Administration (VA).

Highlights of ORWH-Cofunded Research

The following sections highlight some of the ORWH-funded research related to women's health. Although illustrative of research supported by ORWH, these examples do not cover the full spectrum of the research portfolio on women's health. ORWH continues to develop its research base in areas of programmatic importance and relevance to women. This research addresses health promotion, healthy aging, physical activity, nutrition, eating disorders, and obesity. Through successful collaboration between ORWH and the ICs, ORWH is able to provide funds for research on sex differences in health and disease in many areas, including irritable bowel syndrome, stroke, and the consequences and treatment of substance abuse. In addition, ORWH cofunds innovative grants that focus on culture and cancer disparities, end-of-life care, and caregiver research.

Breast Cancer Pharmacogenomics

ORWH is cofunding a grant with the National Institute of General Medical Sciences (NIGMS) Pharmacogenetics Research Network (PGRN) to investigate tamoxifen in breast cancer treatment. The estrogen receptor modulator tamoxifen has been used since the 1970s to treat patients with hormone-responsive breast cancer and, more recently, to help prevent the disease in those at high risk for it. Tamoxifen works by blocking estrogen's ability to promote cancer growth. Drugs that interfere with the actions of estrogen represent a cornerstone in the treatment of breast cancer and also serve as important tools with which to study the actions of estrogen in women. These drugs are increasingly effective in breast cancer, but deciding which drug is best for each woman remains unclear. Through a recent series of laboratory and clinical studies, new genetic patterns that predict the effects of tamoxifen have produced interesting data. Additional studies to build on these data will examine the influence of an extended series of candidate genes on the effects of the class of drugs known as aromatase inhibitors. These studies will refine the genetic signatures that predict tamoxifen's effects. PGRN research revealed that certain gene variations—and some medicines—can alter the effect of tamoxifen. The new information will improve treatment outcomes by helping physicians and patients choose the appropriate drug.

Human Papillomaviruses Vaccine

ORWH is providing support for NCI researchers to evaluate the safety, immunogenicity, and efficacy of the prophylactic virus-like particle HPV vaccine in a clinical trial being conducted in Costa Rica.

Results from this effort have demonstrated high efficacy in preventing new infections with HPV types contained in the vaccine formulation (HPV types 16 and 18), partial efficacy against a few additional HPV types that are genetically similar to the HPV types contained in the vaccine (HPV types 31, 33, and 45), and lack of efficacy to treat established HPV infections. These findings highlight the promise of this new vaccine and the need to vaccinate females in their adolescence for maximal benefit. Initial findings from the ORWH-supported trial in Costa Rica also suggest that fewer than the three-dose regimen currently recommended might be efficacious, a finding that has important implications for application of vaccination in poorer regions of the world where most cervical cancers occur. In recent years, support by ORWH has enabled the expansion of work by NCI in Costa Rica to include the evaluation

of vaccine efficacy at sites other than the cervix where HPV-associated cancers are known to occur (e.g., anus) and the evaluation of questions important for understanding the natural history of HPV infection at the cervix and other sites in vaccinated and unvaccinated groups. Cervical cancer is diagnosed in more than 500,000 women each year, causing approximately 250,000 deaths around the world and making it one of the most common cancers worldwide. The bulk of the impact from this disease (85 percent) is observed in poorer regions of the world where implementation of effective cervical cancer screening programs has not been possible.

A wealth of scientific evidence has shown that virtually all cases of cervical cancer are attributable to cervical infection by a subset of oncogenic HPVs and that HPV also can cause cancer at other anogenital and oral sites. About one-half of cervical cancers are attributable to cervical infection by HPV 16. The second most frequent HPV type observed in cervical cancer, HPV 18, accounts for another 10 to 20 percent of these cancers. Effectively implemented HPV vaccination programs should be able to significantly reduce the incidence of cancers attributable to HPV infection.

Uterine Leiomyomata (Uterine Fibroids)

ORWH has had a longstanding interest in fostering greater research on uterine fibroids because of the high prevalence of this condition in women of all races and ethnicities but especially in women of color. Uterine fibroids represent a health disparity that disproportionately affects African-American women. During FY 2009 and FY 2010, ORWH collaborated on a number of important projects in this area. With support from ORWH and NICHD, the Leiomyoma Tissue Bank (LTB) was maintained to support interested investigators across the United States. Research into the causes and treatment of fibroids has lagged behind other conditions, in part due to a lack of available tissues. To address the problem of tissue availability and to promote research on this condition, a tissue bank was established to provide samples to investigators funded by NIH and DoD. LTB is located in NICHD and is structured after similar tissue banks created for endometrial tissue and ovarian tissue that were established by the Specialized Cooperative Program in Reproductive Research. During this same time period, NICHD intramural investigators have partnered with colleagues across the United States to create a comprehensive clinical classification system for fibroids that is currently being evaluated as an aid to promoting more uniform research in this area.

In addition, NICHD and ORWH are cofunding several extramural research projects that address the molecular basis of uterine fibroids. ORWH and NICHD cofunded eight grants on uterine fibroids focusing on basic science and translational research. Research has confirmed that uterine fibroids are extremely prevalent, with severe morbidity seen in many women, and are an area of interest for health disparities since they are more prevalent in certain subpopulations of women. Similarly, hysterectomies, which are performed for this condition, disproportionately affect these subpopulations of women. Therefore, research is addressing the gaps in knowledge about the pathobiology of uterine fibroids and better ways to treat them.

Vulvodynia

ORWH, NICHD, other components of NIH, public advocacy groups, and other agencies in HHS are collaborating on efforts to advance research and education on vulvodynia through a variety of methods. Vulvodynia is defined as chronic discomfort or pain of the vulva. This discomfort has been referred to in a variety of ways, including "the pain down there" or "feminine pain." As a type of pelvic pain, vulvodynia can be acute or chronic. This clinical syndrome of unexplained vulvar pain may result in sexual dysfunction. The burning, stinging, or irritated feeling can be in a small area or generalized to the whole vulva. There is no apparent infection or skin disease that could cause these symptoms. No single treatment is effective for all cases, but a multifaceted approach to prevent and reduce irritation can be taken to improve quality of life. Today research continues to explore improved clinical definitions of vulvodynia, improved methods of identifying conditions that coexist with vulvodynia, and improved comprehensive clinical management tools. Three program

announcements were reissued in FY 2010, Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (PA-10-190, 191, and 192), to encourage further research that will be funded by NICHD and ORWH. Working with more than 40 partners across the spectrum of Federal agencies, professional societies, and advocacy groups, ORWH launched a vulvodynia awareness campaign (VAC). Activities associated with the VAC continue. Campaign materials include fact sheets, scientific articles, patient profiles, and Web links. (See section IV, Outreach and Community Partnerships, for the full list of VAC partners.)

Menopause-Related Research

ORWH supports an extensive research portfolio on many aspects of the menopausal transition and symptoms. ORWH has partnered with NIA, including the MsFLASH study, Menopausal Strategies: Finding Lasting Answers for Symptoms and Health. MsFLASH was created to accelerate progress in identifying effective remedies for vasomotor symptoms in women going through the menopausal transition. A network of scientists has been created for investigators who are highly knowledgeable about the menopausal transition and experienced in the conduct of women's health trials. The MsFLASH network has five clinical sites and is undertaking several randomized controlled trials testing a range of behavioral, mind-body, hormonal, and pharmacologic interventions to treat hot flashes.

ORWH also cofunded other menopause-related grants with NIA, NCCAM, and NIMH. These studies include the Study of Women across the Nation (SWAN), a landmark study of the natural history of the menopausal transition. Because this cohort represents a multiracial and multicultural group, SWAN is identifying important insights that will be informative to health care providers and women across different racial and ethnic groups.

ORWH, the Office of Dietary Supplements (ODS), and NCCAM are partnering on several grants that focus on botanical products or other complementary and alternative medicine (CAM) methods to treat symptoms associated with menopause. Additional areas of focus include the effects of botanical products on a woman's cognition and on the progression of atherosclerosis, which is a major disease outcome in postmenopausal women.

NIH Consensus and State-of-the-Science Conferences

The NIH Office of Medical Applications of Research conducted several conferences on topics relevant to women's health research during FY 2009 and FY 2010. Four state-of-the-science conferences were held on the following topics: (1) preventing Alzheimer's disease and cognitive decline, (2) diagnosing and managing ductal carcinoma of the breast, (3) family history and improving health, and (4) enhancing the use and quality of colorectal screening. Two consensus conferences were held on (1) vaginal birth after cesarean and (2) lactose intolerance and health.

Prevention Research

Although prevention has always been a component of the ORWH research portfolio, during 2009 and 2010, the Office included prevention under the special emphasis section of the NIH research priorities. Below are selected cofunded prevention projects.

Microbicides Innovation Program

The development of safe, effective, acceptable topical microbicides to prevent the sexual transmission of HIV could play a major role in worldwide reduction of new HIV infections and potentially could save millions of lives. Topical microbicides are agents that when applied vaginally, rectally, or on the penis can result in inhibition of the transmission of HIV and/or other sexually transmitted infections that may be cofactors in HIV transmission.

The Microbicides Innovation Program (MIP), a collaboration between the Office of AIDS Research (OAR), NIAID, NIMH, and ORWH, has been funded for several years and focuses on early "pipeline" investigations through innovative exploratory and developmental research. The program also facilitates technology or methodology design and development that may advance the field as a whole. The success of these tools will hinge on behavioral, cultural, and contextual factors

(e.g., product characteristics, perceived risk of infection, and partner cooperation).

Research awards have been made to advance the development of new topical microbicides approaches and additional targets through preclinical and basic research; emerging technologies or models that contribute to the development of new and/or more efficient ways of assessing microbicides safety, efficacy, and acceptability; and the design of complex prevention strategies.

A major advance in microbicides research occurred in early 2009 when an NIAID-funded clinical trial involving more than 3,000 women in the United States and southern Africa reported a finding that, for the first time, demonstrated the promise of a vaginal microbicide gel for preventing HIV infection in women. According to findings presented at the Conference on Retroviruses and Opportunistic Infections, one 0.5-percent dose of a microbicide designed to prevent HIV from attaching to cells in the genital tract was 30 percent effective. Although the results are encouraging, researchers on the study, known as HPTN 035, report that additional evidence is needed for a more definitive determination of the microbicide's effectiveness.

Other Prevention-Related Research

ORWH supports a number of research projects related to the prevention of diseases and disorders of importance to women. For example, ORWH is cofunding an NIAAA grant to reduce alcohol consumption among urban Latina and African-American adolescent girls by educating parents on the dangers associated with alcohol abuse. Three alcohol-prevention interventions are being tested, and both parents and their daughters will be monitored over several months. In addition, ORWH, in collaboration with the Fogarty International Center (FIC), has funded a number of projects that focus on HIV/AIDS prevention in international locations, including Haiti, Africa, and China. Long-term benefits of these projects will include increases in research capacity for future HIV-related research activities in these countries.

Chronic Pain Syndromes

ORWH collaborates with a number of ICs to increase research in chronic pain and pain control as important areas for women's health research. Among the chronic pain syndromes of importance to women's health are temporomandibular joint and muscle disorders (TMJD). For example, ORWH and NIDCR funded several TMJD grants, including the first research registry and repository for the evaluation of TMJ implants. Other grants focus on trigeminal pain mechanisms and control and pain management studies for TMJD. In addition, ORWH cofunded with NIDCR a number of grants addressing topics such as estrogen regulation of inflammation related to TMJD, genotype and TMJD vulnerability types, and neuronal plasticity related to TMJD and fibromyalgia.

Health Disparities Research

Despite overall improvement in the health of Americans, striking differences exist in the burden of illness, life expectancy, and mortality rates among African Americans, Hispanics, Native Americans, Alaska Natives, Pacific Islanders, and other subpopulations. These differences are thought to reflect complex interactions among biological factors, genetics, the environment, and health behaviors. Access to health care resources and socioeconomic differences also have been implicated in health disparities. ORWH and many NIH ICs and Offices have worked diligently to identify and support critical research questions that will help overcome disparities in health, especially as they pertain to women.

ORWH has also funded research on a range of conditions with male-female health disparities, such as chronic pain syndromes, autoimmune diseases, and musculoskeletal disorders, as well as projects that focus on underserved, underrepresented minorities such as Hispanics and Native Americans. However, the Office also contributes to research on diseases that differentially affect minority women, such as diabetes, which disproportionately affects African-American women.

Diabetes Prevention Program

ORWH has cofunded the Diabetes Prevention Program (DPP) since it was created in the 1990s. The original DPP demonstrated the efficacy of lifestyle modification and use of the drug metformin in decreasing the incidence of diabetes in an ethnically diverse population at high risk for diabetes. The study followed participants for an average of 2.8 years. However, many important questions remained unanswered. Specifically, it was not known whether the decrease in the development of diabetes would be sustained or whether the delayed onset or prevention of diabetes would translate into a decrease in retinopathy, nephropathy, neuropathy, and cardiovascular disease because detection of these outcomes would require more followup years than DPP afforded.

Thus, a longer term followup study of DPP—the DPP Outcomes Study (DPPOS)—was designed to evaluate the long-term effects of active DPP interventions. This study is looking at the development of diabetes over the course of 5 to 11 additional years as well as composite diabetes-related microangiopathic and cardiovascular disease outcomes. The hypotheses being tested are that both continued lifestyle intervention and metformin will continue to decrease the rate of diabetes development when compared with the placebo group and that the prevention or delay of diabetes during DPP and DPPOS will translate into reduced rates of composite outcomes and improved health status. The secondary objectives of DPPOS are to evaluate the long-term effects of DPP interventions on selected individual health outcomes, the established and putative risk factors for those outcomes, and the costs and cost-utility associated with delay or prevention of diabetes.

Based on the results of DPP, ORWH partnered with NIDDK to create a gestational diabetes mellitus (GDM) awareness campaign. GDM is a form of diabetes that occurs in some pregnant women, affecting 7 percent and possibly as many as 18 percent of U.S. pregnancies. Immediately after pregnancy, 5 to 10 percent of women with GDM are found to have diabetes, usually type 2. In addition, women with a history of GDM have a 35- to 60-percent chance of developing diabetes within the next 10 to 20 years. Based on the public health implications, ORWH and NIDDK developed materials for distribution and provided experts for interviews across the United States. The GDM campaign created a national radio interview outreach in FY 2010 that reached almost 3 million listeners.

ORWH also partners with NICHD to fund studies on a range of chronic gynecologic conditions, such as uterine fibroids and pelvic floor disorders, that affect the quality of life for many middle-aged and older women. In general, these grants focus on the etiology, prevalence, and possible treatment for these chronic conditions. In addition, ORWH participates with the HHS IHS on a youth suicide prevention project that includes capacity building within the local Native American community and research development collaborations.

Autoimmune-Related Research

ORWH continues to encourage greater attention to autoimmunity and its impact on women of all ages, races, and ethnicities. ORWH participates on the congressionally mandated Autoimmune Diseases Coordinating Committee (ADCC), a trans-NIH group that oversees and monitors research progress in this area. Led by NIAID, ADCC is charged with coordinating and monitoring progress in autoimmune research across NIH.

Since its early years, ORWH has cofunded a number of grants with NIAID to advance the understanding of the underlying causes, complications, and treatment strategies for autoimmune disorders. More recently, ORWH cofunded several Autoimmune Centers of Excellence that are studying a wide array of autoimmune disorders. These comprehensive center grants focus on common underlying mechanisms of disease etiology and include translational studies, such as randomized clinical trials for different autoimmune conditions.

Partnering with NIAID and NIAMS, ORWH cofunds autoimmune grants that focus on a number of conditions, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and multiple sclerosis.

NIDCR and ORWH cofunded the International Research Registry Network for Sjögren's

syndrome, which is contributing valuable data from several countries, including the United States.

ORWH has had a longstanding commitment to provide funding for SLE because of the complex and serious manifestations of this disorder, which is nine times more common in women than men and is particularly prevalent in women of color. ORWH and NIAMS cofunded an important SLE grant that focuses on the mechanism regulating neutrophil activation in pregnancy. This particular area had not been studied until recently and may provide important insights into ways to reduce pregnancy loss in patients with SLE. Thrombosis and pregnancy loss are common features of SLE, particularly in the presence of antiphospholipid (aPL) antibodies. The in vivo mechanisms by which aPL antibodies lead to vascular events and specifically to recurrent fetal loss are largely unknown. This research represents a first effort to translate novel research observations on the potential role of complement activation in the pathogenesis of aPL antibody-mediated pregnancy loss to a clinically relevant human study. No study has investigated whether complement is activated in patients with aPL-associated poor pregnancy outcomes (with or without SLE). Similarly, no study has compared pregnant women with SLE with disease-free women to understand whether particular patterns of complement activation characterize and distinguish SLE patients without aPL antibodies or fetal loss to non-SLE controls. Characterization of clinically applicable surrogate markers that predict poor pregnancy outcome will enable physicians to initiate an interventional trial of complement inhibition in patients at risk for aPL antibody-associated fetal loss. The identification of such surrogate markers in aPL and SLE patients also may prove generally applicable to anticipate complications during pregnancy in disease-free women.

Musculoskeletal Disorders

Musculoskeletal conditions, such as osteoarthritis and osteoporosis, contribute significant disability to women of all ages, but they are especially problematic to women who are postmenopausal. ORWH has been a long-term partner and cofunder with NIAMS, NIA, and others in a public-private partnership supporting the Osteoarthritis Initiative (OAI). OAI is a multicenter, longitudinal, prospective, observational study of knee osteoarthritis. The initiative has successfully recruited 5,000 male and female study subjects and serves as a national repository for biological materials about the natural history of osteoarthritis and the evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression. These data will eventually guide state-of-the-art treatment strategies. An ancillary study from OAI is evaluating ethnic differences in the management of this disorder, especially within African-American populations.

Osteoporosis is another important concern for women. In addition, as men are living longer, osteoporosis is increasingly important for aging men. Therefore, it is important to study osteoporosis in both men and women for sex and gender differences as well as for differences among various races and ethnic populations. ORWH supports several grants with NIAMS that focus on the genomic convergence for female osteoporosis risk genes and compares these identified genes in male samples. Additional projects evaluate the longitudinal changes in hip geometry and skeletal muscle, calcium absorption, factors affecting bone response or nonresponse, bone-sparing effects of soy phytoestrogens, and treatment effects on osteopenic bone loss.

Long-Term Scientific Collaborations

Most studies receive support from NIH for 3 to 5 years. However, some types of research, such as studies on the natural history of disease or clinical trials requiring longer followup, require sustained support for a much longer period of time.

Examples of this long-term collaboration include the aforementioned Diabetes Prevention Program (DPP) with NIDDK, as well as the weight and incontinence network, now known as the Program to Reduce Incontinence by Diet and Exercise (PRIDE). Using a cognitive behavioral intervention for 6 months, PRIDE is examining the efficacy of weight loss on incontinence in overweight women, with long-term followup of weight loss maintenance.

ORWH has collaborated with NICHD and other ICs since the initiation of the National Longitudinal Study of Adolescent Health (Add

Health). Add Health is currently funded for Wave IV data collection. At the time (the project began in 1994–1995), investigators selected a nationally representative sample of adolescents in grades 7 through 12. Participants have been followed through adolescence and the transition to adulthood with three in-home interviews. Wave IV will include additional information that encompasses social, behavioral, and biological data. In addition to data contributed in earlier surveys, these subjects, who are now between the ages of 23 and 31 years, will provide biological data to capture the prevailing health concerns as well as biological markers of future chronic health conditions.

Trans-Federal Research Collaboration

ORWH, along with a number of ICs, has established a research collaboration with the DoD Centers of Excellence in Psychological Health and Traumatic Brain Injury (DCoE) and the Veterans Administration (VA) to expand research that will benefit military service members, veterans, and their families. For the period FY 2009 and FY 2010, two major research conferences were held at NIH, coordinated by NIH research staff in cooperation with other Federal partners, including DoD, VA, and HHS agencies such as the Administration for Children and Families, Centers for Disease Control and Prevention, Health Resources and Services Administration, Substance Abuse and Mental Health Services Administration, AHRQ, and the Office of the HHS Secretary. The conferences involved research on posttraumatic stress disorder, traumatic brain injury, substance abuse, disabilities, and caregiving. The collaborations continue with annual conferences held in 2009 and 2010 and planned for December 2011.

Table 1. ORWH-Cofunded Research Initiatives, FY 2009

Subject	Title	Institute or Center	Award Amount
Adolescent Health	National Longitudinal Study of Adolescent Health (Add Health)	NICHD	$200,000
Aging	National Social Life, Health, and Aging Project	NIA	$200,000
	Teaching Resourcefulness to Women Caregivers of Elders With Dementia	NINR	$200,000
Alcohol and Other Substance Abuse	Sex Differences in Vulnerability to Cocaine Addiction	NIDA	$20,000
	Interactive Effects of Ethanol and Estrogen on Brain Vasopressin During Puberty	NIAAA	$224,250
	An Ethnographic and Economic Investigation of the Fresh Start Program (Detroit)	NIDA	$270,375
Cancer	Pharmacogenetics Research Network and Knowledge Base	NIGMS	$230,171
	Novel Ovarian Cancer Detection Agents From Phage Display	NCI	$20,000
	Exploratory Studies on the Anti-Breast Cancer Function of Bamboo Extract	NCCAM	$191,874
	Mitochondrial Catalase as a Treatment for Metastatic Breast Cancer	NCI	$171,600
	Gender Selectivity to Colon Cancer Chemoprevention by NSAIDs	NCI	$201,300
	Antagonism of the Ah Receptor in Controlling Breast Cancer Growth and Invasion	NCI	$214,500
	Costa Rica HPV-16/18 Vaccine Trial (CVT)	NCI	$400,000
	Evaluation of Vaccine Efficacy at Extracervical Sites in the Costa Rica HPV-16/18 Vaccine Trial (CVT)	NCI	$700,000
	Chemoprevention of Tamoxifen-Induced Endometrial Cancer by Black Cohosh and Red Clover	NCI	$198,211
	NIR Hypoxia Imaging of Breast Tumor Response to Neoadjuvant Chemotherapy in Vivo	NCI	$199,595
	Reactivation of Breast Cancer Micrometastases by Senescent Bone Marrow Stroma	NCI	$205,920
	Caregivers' Strengths-Skills: Managing Older Cancer Patients	NCI	$46,488

Table 1 (continued). ORWH-Cofunded Research Initiatives, FY 2009

Subject	Title	Institute or Center	Award Amount
Cancer (continued)	BRCA1, Sporadic Breast Cancer, and Aging Women	NCI	$149,600
	Targeting the Phosphoinositide Kinase Chain to Prevent Breast Cancer Metastasis	NCI	$76,750
	Development and Pilot Test of an Elective BSO Decision Support Guide	NCI	$203,940
	Spore in Endometrial Cancer	NCI	$200,000
	Immunogenicity of Quadrivalent Human Papillomavirus Vaccine (HPV Types 6, 11, 16, 18) in Recipients of Reduced Intensity Hematologic Stem Cell Transplantation (HSCT) (Bench to Bedside Program)	NCI	$100, 000
	Improving Flexible Sigmoidoscopy in Women by Optical Analysis of Microvasculature	NCI	$214,425
	Regulation of Breast Cancer Progression by FAK Expression in Tumor Macrophages	NCI	$198,087
	Role of MicroRNAs in Initiation and Progression of Breast Cancer	NCI	$79,000
Cardiovascular Disease	Cardiovascular Events in Women's Ischemia Syndrome Evaluation	NIA	$20,000
	Role of 15-Lipoxygenase in Enhanced Pulmonary Vasoconstriction in Females	NHLBI	$220,200
	Mechanisms Underlie Inverse Gender Discrepancy in Ischemic Protection	NHLBI	$222,750
	Weight, Diet, Genes, and CVD Risk Factors (Hypertension and Diabetes)	FIC	$50,000
	Sex Differences in Myocardial Ischemia Triggered by Emotional Factors After MI	NHLBI	$232,500
	Sex Differences in Myocardial Ischemia Triggered by Emotional Factors After MI	NHLBI	$291,952
Chronic Fatigue Syndrome	Autonomic Nervous System in Chronic Fatigue Syndrome (CFS)	NINDS	$383,438
	HERV-K18 as a Risk Factor for CFIDS	NIAMS	$146,500
	From Infection to Neurometabolism: A Nexus for CFS	NINDS	$10,000

Subject	Title	Institute or Center	Award Amount
Chronic Fatigue Syndrome (continued)	Cognitive Behavioral Stress Management for CFS	NINDS	$343,219
Craniofacial	Estrogen and Psychological Stress in Temporomandibular Joint Disorder (TMJD) Pain	NIDCR	$200,000
Diabetes	Post-Diabetes Prevention Program (DPP) Followup Study	NIDDK	$870,000
	Gestational Diabetes Awareness Campaign	NIDDK	$1,000,000
	Gender-Specific Complications of Diabetic Autonomic Neuropathy: A New Mouse Model	NHLBI	$238,500
	Look AHEAD: Action for Health in Diabetes	NIDDK	$100,000
	Obesity, Inflammation, and Thrombosis: Look AHEAD	NHLBI	$20,000
	Gene X Behavior Interaction in the Look AHEAD Study	NIDDK	$301,213
Dietary Supplements/CAM	Botanical Dietary Supplements for Women's Health	NCCAM	$95,158
Genitourinary	Urinary Incontinence Treatment Network: Data Coordinating Center	NIDDK	$250,000
HIV/AIDS	Gender Differences Among Women and Men Enrolled in China's National Free Antiretroviral Treatment	FIC	$56,206
	AIDS International Training and Research Program (UNC-Chapel Hill)	FIC	$20,000
	Emory AIDS International Training and Research Program (Emory)	FIC	$20,000
	AIDS International Training and Research Program (Pittsburgh)	FIC	$20,000
	Vanderbilt University-CIDRZ AIDS International Training and Research Program	FIC	$20,000
	The Microbial Ecology of Bacterial Vaginosis: A Fine Scale Resolution Metagenomic (The Human Microbiome Project)	NIAID	$125,000
	Mucus-Penetrating Nanoparticles for Sustained Microbicide Delivery	NIAID	$13,637
	Novel Mucosal Models Predictive of Microbicide Safety	NIAID	$13,637
	Novel Vaginal Microbicides Based on Stable AAV-Neutralizing Antibody Gene Transfer	NIAID	$13,637

Table 1 (continued). ORWH-Cofunded Research Initiatives, FY 2009

Subject	Title	Institute or Center	Award Amount
HIV/AIDS (continued)	HIV Integrase as a Target for Topical Microbicide Development	NIAID	$13,637
	Combinations of Entry Inhibitors as Anti-HIV-1 Microbicides	NIAID	$13,637
	Scalable Production of Recombinant Protein Microbicides	NIAID	$13,637
	Intravaginal Ring Microbicide Formulations Comprising Multiple Anti-HIV Agents	NIAID	$13,637
	HIV Sexual Transmission in Mice: Study of Microbicide Efficacy	NIAID	$13,637
	HIV Microbicides and the Vaginal Microbiome	NIAID	$13,637
	Microbicide Properties of RT Inhibitor Combinations	NIAID	$13,637
	New SHIV R5 Envs (Based on All Subtypes) for Effective Microbicide Testing	NIAID	$13,637
	Development of a Novel Semen-Activated Prodrug as an Anti-HIV Microbicide	NIAID	$37,500
	Microbicide Delivery System To Target Lymphoid Organs	NIAID	$37,500
	Small-Molecule Inhibitors of Gp41-Mediated Fusion as HIV-1 Topical Microbicides	NIAID	$37,500
	Gp340 and Syndecan Inhibition-Based Microbicide for HIV	NIAID	$37,500
	Research Support Services for the DAIDS	NIAID	$5,000
	Haiti AIDS Research Training: Models to Implementation	FIC	$20,000
Immunity/Autoimmunity	Predictors of Pregnancy Outcome in SLE and APS	NIAMS	$200,000
	Role of Sex Differences in the Expression and Function of Regulatory T Cells in SLE	NIAID	$192,500
	NARAC—The Genetics of Rheumatoid Arthritis	NIAMS	$182,442
	International Research Registry Network for Sjögren's Syndrome	NIDCR	$300,000
	OGT Overexpression in Women With Lupus	NIAMS	$20,000
	Do Estrogen Receptors in B Cells and DC Mediate Sex Bias in Murine Lupus?	NIAID	$193,750

Subject	Title	Institute or Center	Award Amount
Immunity/Autoimmunity (continued)	Sociodemographic Disparities in Lupus Nephritis: Health Care Access and Outcomes	NIAMS	$200,000
	Longitudinal Determination of Outcomes of Adolescents With Fibromyalgia	NIAMS	$200,000
	Autoimmunity Center of Excellence (ACE) at Stanford	NIAID	$30,000
	Oklahoma ACE	NIAID	$30,000
	A Systems Biology Approach for Pediatric and Adult Autoimmune Diseases—ACE	NIAID	$30,000
	Mechanisms of Beta Cell Responses in Autoimmune Disease—ACE	NIAID	$30,000
	Molecular Epidemiology of Drug Resistance and Population Genetic Structure of *Plasmodium falciparum and Plasmodium vivax*	OD	$50,000
Menopause	Menopausal Symptoms Initiative—Finding Lasting Answers for Sweats and Hot Flashes (MsFlash)	OD	$200,000
	MsFlash: An RCT of Yoga and Ultra-Low-Dose Estrogen Gel for Vasomotor Symptoms	NIA	$95,148
	SWAN: Study of Women's Health Across the Nation	NIA	$75,000
	Study of Women's Health Across the Nation III	NIA	$125,000
	Neurobiology of the Menopausal Transition	NIA	$47,579
	Biological Mechanisms of Arterial Stiffening With Age and Estrogen Deficiency	NIA	$47,579
	Impact of Endocrine Aging on Brain and Immune Responses	NIA	$47,579
	Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO	NIA	$47,579
	Estrogen: Neuroprotection in the Perimenopause	NIA	$47,579
	Menopause: Decreased Response to Increasing Inflammation	NIA	$46,199
	Genetics of Reproductive Life Period and Health Outcomes	NIA	$241,900

Table 1 (continued). ORWH-Cofunded Research Initiatives, FY 2009

Subject	Title	Institute or Center	Award Amount
Mental Health	Novel Approaches to Understanding Mental Disorder, Substance Abuse, and HIV Risk Among Homeless Women	NICHD	$145,180
	Race and HIV Risk: Contextual and Neurocognitive Influences on Sex Partnerships	NIDA	$204,426
	Antimanic Use During Pregnancy	NIMH	$200,000
	Sex Stress Emotional Disorders: Uniting Preclinical and Epidemiologic Research	NIMH	$20,000
	Sex Differences in the Entorhinal Cortex	NIMH	$20,000
	Emotions Are Emergent Events Constrained by Affective and Conceptual Processes	OD	$391,250
Musculoskeletal Systems	Function and Behavior Phenotype of Inflammatory Arthritis in the Rat Knee and TMJ	NIAMS	$74,540
	Clinical Centers for the Osteoarthritis Initiative: Rhode Island	NIAMS	$162,500
	Clinical Centers for the Osteoarthritis Initiative: Baltimore	NIAMS	$162,500
	Clinical Centers for the Osteoarthritis Initiative: Columbus	NIAMS	$162,500
	Clinical Centers for the Osteoarthritis Initiative: Pittsburgh	NIAMS	$162,500
Neurology/ Neuroscience	Identification and Validation of Human Hypothalamic Nuclei In Vivo and Ex Vivo Using 7 Tesla MRI	NIMH	$265,125
	Cellular and Molecular Basis of Hippocampal Atrophy in Depressed Female Monkeys	NIMH	$222,000
	Sex-Specific Gene Regulation of Neuronal Chloride Co-Transporter, Kcc2	NINDS	$234,000
	Respiratory Plasticity Following Spinal Cord Injury	NHLBI	$20,000
Nutrition	National Food and Nutrient Analysis Program (NFNAP)	NCI	$25,000
Obesity/Overweight	Intervening on Spontaneous Physical Activity To Prevent Weight Regain in Women	NHLBI	$205,728
	DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women (Cincinnati)	NHLBI	$234,000

Subject	Title	Institute or Center	Award Amount
Obesity/Overweight (continued)	DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women (San Antonio)	NHLBI	$169,872
Pain	Sex Differences in Acute Pain and Analgesic Responses: Psychosocial and Genetic Influences	NIDCR	$218,495
	Using fMRI To Evaluate CBT Treatment Response for Patients With Chronic Pain	NIAMS	$112,875
	Pain and Endometriosis: Effects on Ectopic Cyst Innervation and Axons	NICHD	$219,832
	N6F-Dependent Sensitization of Nocioceptors by Opiate	NIDA	$20,000
Reproductive Health/ Developmental Biology	Compromised Microcirculation in Women With Polycystic Ovary Syndrome	NHLBI	$256,203
	Advancing Research on the Sexually Transmitted Female "Nuisance" Pathogen *Trichomonas vaginalis*	NIAID	$253,688
	HPV Epidemiology and Response to Screening (HEARTS)	NIAID	$188,034
	Physiological Reactivity to Acute Stress During Pregnancy	NICHD	$181,209
	A Study of the Factors Influencing Women's Decisions About Childbirth	NICHD	$238,251
	Modulation of PAH Ovarian Toxicity by Biotransformation Enzyme Polymorphisms	NIEHS	$229,745
	Neuroactive Steroids and Seizure Control During Pregnancy in Women With Epilepsy	NINDS	$102,626
	Research To Improve Preconception Health of Adolescent Women	NICHD	$121,622
	Uterine Leiomyoma Research Center Program	NICHD	$250,000
	Role of GPR54 Signaling in Pubertal Disorders	NICHD	$20,000
	Obstetric-Fetal Pharmacology Research Units Network	NICHD	$235,025
	The History of Emergency Contraception	NLM	$75,530
	ORWH–NICHD Leiomyoma Tissue Bank	NICHD	$85,000

Table 1 (continued). ORWH-Cofunded Research Initiatives, FY 2009

Subject	Title	Institute or Center	Award Amount
Reproductive Health/ Developmental Biology (continued)	Activin Target Genes in the Ovary: Regulation of Ovarian Follicle Development	NLM	$83,333
	Improving Contraceptive Use in High-Risk Women	NICHD	$144,892
	Malaria in Pregnancy: Nutrition and Immunologic Effects	NICHD	$200,000
	Midcareer Investigator Award in Patient-Oriented Research	NICHD	$187,466
	Identification of Genes Predisposing to Pelvic Floor Disorders	NICHD	$66,667
	Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team	NICHD	$66,666
	Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and Its Association With Incidence, Progression, and Recurrence of Pelvic Floor Disorders\	NICHD	$66,667
	Pregnancy and Drug Metabolizing Enzymes and Transporters	NICHD	$285,225
	UW Obstetric-Fetal Pharmacology Research Unit	NICHD	$235,000
Pelvic Floor Disorders Network	Cleveland Clinic Clinical Site	NICHD	$25,000
	Pelvic Floor Disorders Network (Loyola)	NICHD	$25,000
	Pelvic Floor Disorders Network (UCSD)	NICHD	$25,000
	Utah Pelvic Floor Disorders Network	NICHD	$25,000
	Perioperative Pelvic Floor Rehab: A Randomized Trial	NICHD	$25,000
	Pelvic Floor Disorders Network (UTSW)	NICHD	$25,000
	Pelvic Floor Disorders Network—Data Coordinating Center (UMich)	NICHD	$25,000
	Pelvic Floor Disorders Network (Duke)	NICHD	$25,000

Table 2. ORWH-Cofunded Research Initiatives, FY 2010

Subject	Title	Institute or Center	Award Amount
Adolescent Health	National Longitudinal Study of Adolescent Health (Add Health)	NICHD	$200,000
	An Integrative Intervention for Binge Eating Among Adolescent Girls	NIMH	$200,000
	NHANES Project for Adolescents and Girls	NCI	$300,000
Aging	National Social Life, Health, and Aging Project	NIA	$200,000
Alcohol and Substance Abuse	An Ethnographic and Economic Investigation of the Fresh Start Program (Detroit)	NIDA	$154,500
	Interactive Effects of Ethanol and Estrogen on Brain Vasopressin During Puberty	NIAAA	$186,875
Cancer	A Decisionmaking Framework for Contralateral Prophylactic Mastectomy	NCI	$191,327
	Can Lifestyle Modify Fatigue in Breast Cancer Survivors?	NCI	$89,000
	Microbial Exposures Across the Lifespan and Cancer Risk in Women	NCI	$220,500
	Costa Rica HPV-16/18 Vaccine Trial (CVT)	NCI	$550,000
	Nuclear Pore Complex Architecture and Drug Resistance in Ovarian Carcinomas	NCI	$84,750
	Estrogen and Skin Cancer	NCI	$228,750
	Family Cancer Literacy To Promote Mammography Screening Among Navajo Women	NCI	$132,301
	Pharmacogenetics of Phase II Drug Metabolizing Enzymes	NIGMS	$250,000
	Mitochondria: A Novel Genetic Modifier for Breast Cancer Risk	NCI	$180,248
	BRCA1, Sporadic Breast Cancer, and Aging Women	NCI	$149,600
	Improving Flexible Sigmoidoscopy in Women by Optical Analysis of Microvasculature	NCI	$167,750
	Regulation of Breast Cancer Progression by FAK Expression in Tumor Macrophages	NCI	$164,700

Table 2 (continued). ORWH-Cofunded Research Initiatives, FY 2010

Subject	Title	Institute or Center	Award Amount
Cancer (continued)	Chemoprevention of Tamoxifen-Induced Endometrial Cancer by Black Cohosh and Red Clover	NCI	$172,698
	NIR Hypoxia Imaging of Breast Tumor Response to Neoadjuvant Chemotherapy In Vivo	NCI	$173,800
	Targeting the Phosphoinositide Kinase Chain To Prevent Breast Cancer Metastasis	NCI	$76,750
	Mitochondrial Catalase as a Treatment for Metastatic Breast Cancer	NCI	$205,823
	Gender Selectivity to Colon Cancer Chemoprevention by NSAIDS	NCI	$167,750
	Antagonism of the Ah Receptor in Controlling Breast Cancer Growth and Invasion	NCI	$178,823
	Role of MicroRNAs in Initiation and Progression of Breast Cancer	NCI	$79,000
	Reactivation of Breast Cancer Micrometastases by Senescent Bone Marrow Stroma	NCI	$171,600
	HPV Epidemiology and Response to Screening (HEARTS)	NCI	$156,969
Cardiovascular Disease	Compromised Microcirculation in Women With Polycystic Ovary Syndrome	NHLBI	$223,143
	Sex Differences in Myocardial Ischemia Triggered by Emotional Factors After MI	NHLBI	$193,750
	Weight, Diet, Genes, and CVD Risk Factors (Hypertension and Diabetes)	FIC	$50,000
	Mechanisms Underlie Inverse Gender Discrepancy in Ischemic Protection	NHLBI	$185,625
	Role of 15-Lipoxygenase in Enhanced Pulmonary Vasoconstriction in Females	NHLBI	$220,200
Chronic Fatigue Syndrome	HERV-K18 as a Risk Factor for CFIDS	NIAMS	$164,058
Craniofacial	Risk Factors for Onset and Persistence of TMD	NIDCR	$150,000
Diabetes	Gender-Specific Complications of Diabetic Autonomic Neuropathy: A New Mouse Model	NHLBI	$198,750
	Look AHEAD: Action for Health in Diabetes	NIDDK	$100,000
	Post-Diabetes Prevention Program (DPP) Followup Study	NIDDK	$650,000

Subject	Title	Institute or Center	Award Amount
Diabetes (continued)	Sex Hormones and Sex Hormone-Binding Globulin Effects on Diabetes Risk in Women in DPP	NIDDK	$350,000
Dietary Supplements/CAM	Identification of Novel Phytoprogestins From Hops and Red Clover	NCCAM	$235,500
Genetics	Genetics 2010: Model Organisms to Human Biology	NHGRI	$5,000
Genitourinary	Translating Unique Learning for Incontinence Prevention: The TULIP Project	NINR	$300,000
	Urinary Incontinence Treatment Network: DCC	NIDDK	$100,000
HIV/AIDS	AIDS International Training and Research Program (Chapel Hill)	FIC	$20,000
	Emory AIDS International Training and Research Program	FIC	$20,000
	AIDS International Training and Research Program (Pittsburgh)	NIAID	$20,000
	Vanderbilt University-CIDRZ AIDS International Training and Research Program	FIC	$20,000
	Women's Interagency HIV Study (WIHS)	NIAID	$220,869
	Development of Antimicrobial Peptides as Topical Microbicides	NIAID	$21,428
	Development of a Novel Semen-Activated Prodrug as an Anti-HIV Microbicide	NIAID	$37,500
	Targeted siRNA Delivery as an Anti-HIV Microbicide	NIAID	$21,428
	Development of a Novel Nanoparticle Pyrimidinedione Vaginal Polymeric Film as an anti-HIV microbicide	NIAID	$21,428
	Phosphorothioate Oligonucleotides as Microbicides Against HIV Transmission	NIAID	$21,428
	Microbicide Delivery System To Target Lymphoid Organs	NIAID	$37,500
	Small-Molecule Inhibitors of gp41-Mediated Fusion as HIV-1 Topical Microbicides	NIAID	$37,500
	Plant-Produced Actinohivin as a Candidate HIV Microbicide	NIAID	$21,428
	Microbial Ecology of Bacterial Vaginosis: A Fine Scale Resolution Metagenomic (The Human Microbiome Project)	NIAID	$125,000

Table 2 (continued). ORWH-Cofunded Research Initiatives, FY 2010

Subject	Title	Institute or Center	Award Amount
HIV/AIDS (continued)	Engineering Antiviral Innate Immunity for Safe and Effective Microbicides	NIAID	$21,428
	Exploring the Role of Vif Antagonists in Preventing Sexual HIV Transmission	NIAID	$21,428
	Gp-340 and Syndecan Inhibition-Based Microbicide for HIV	NIAID	$37,500
	Washington Metropolitan Women's Interagency HIV Study	NIAID	$100,000
Immunity/Autoimmunity	Role of Sex Differences in the Expression and Function of Regulatory T Cells in SLE	NIAID	$231,000
	Molecular Epidemiology of Drug Resistance and Population Genetic Structure of *Plasmodium falciparum and Plasmodium vivax*	FIC	$50,000
	Mechanisms of IL-35 Protection Against Arthritis	NIAMS	$200,000
	Effects of Malaria on EBV Persistence in Children	NCI	$167,750
	Exploring Factors Influencing Gender Disparities in Access to Transplantation	NIA	$246,000
	Sex Differences in Protective Immunity Against Influenza A Viruses	NIAID	$205,000
Menopause	Estrogen: Neuroprotection in the Perimenopause	NIA	$50,000
	SWAN: Study of Women's Health Across the Nation	NIA	$75,000
	Ovarian Hormone-Independent Sex Chromosome Effects in Menopause	NIA	$153,500
	Effects of Estrogen on Brain Morphology and Neuronal Integrity in Early Menopause	NINDS	$213,812
	Ultra-Low-Dose Estrogen Gel for Vasomotor Symptoms in Women Failing Placebo or a Behavioral Intervention: A Randomized Trial	NIA	$132,000
	Menopause: Decreased Response to Increasing Inflammation	NIA	$50,000
	Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO	NIA	$50,000

Subject	Title	Institute or Center	Award Amount
Menopause (continued)	Biological Mechanisms of Arterial Stiffening With Age and Estrogen Deficiency	NIA	$47,579
	SWAN Repository III	NIA	$100,000
	Study of Women's Health Across the Nation III	NIA	$125,000
	Menopause Symptom Clusters: Refocusing Therapeutics	NINR	$200,000
Mental Health	Novel Approaches to Understanding Mental Disorder, Substance Abuse, and HIV Risk Among Homeless Women	NICHD	$255,535
	Race and HIV Risk: Contextual and Neurocognitive Influences on Sex Partnerships	NIDA	$246,574
	Emotions Are Emergent Events Constrained by Affective and Conceptual Processes	OD	$391,250
Musculoskeletal Systems	A Link Between Parity, Trunk Muscle Function, and Degenerative Spondylolisthesis	NIAMS	$199,929
	The Osteoarthritis Initiative	NIAMS	$650,000
	Sexual Dimorphism of Skeletal Muscle	NIAMS	$209,109
	Structural, Molecular, and Functional Specialization in Osteocyte Mechanosensing	NIAMS	$200,000
	Delayed Pubertal Development on the Mechanism of Bone Loss at Maturity	NIAMS	$75,000
Neurology/Neurosciences	Identification and Validation of Human Hypothalamic Nuclei in Vivo and ex Vivo Using 7 Tesla MRI	NIMH	$221,250
	Cellular and Molecular Basis of Hippocampal Atrophy in Depressed Female Monkeys	NIMH	$185,000
	Sex-Specific Gene Regulation of Neuronal Chloride Co-Transporter, Kcc2	NINDS	$195,000
	Sex Differences in the CNS During Disease	NINDS	$231,000
Nutrition	National Food and Nutrient Analysis Program	NCI	$50,000
Obesity/Overweight	Intervening on Spontaneous Physical Activity To Prevent Weight Regain in Women	NHLBI	$156,894

Table 2 (continued). ORWH-Cofunded Research Initiatives, FY 2010

Subject	Title	Institute or Center	Award Amount
Pain	Sex Differences in Acute Pain and Analgesic Responses: Psychosocial and Genetic Influences	NIDCR	$181,294
	Epidemiology of Patellofemoral Pain Syndrome: Identifying Gender-Specific Risk Factors	NIAMS	$72,866
	Pain and Endometriosis: Effects on Ectopic Cyst Innervation and Axons	NICHD	$171,069
	Functional Networks in Migraine	NINDS	$163,523
Reproductive Health/ Developmental Biology	Advancing Research on the Sexually Transmitted Female "Nuisance" Pathogen *Trichomonas vaginalis*	NIAID	$211,250
	Role of GPR54 Signaling in Pubertal Disorders	NICHD	$65,912
	Physiological Reactivity to Acute Stress During Pregnancy	NICHD	$221,012
	Upstream Regulation of KISS1 Cells	NICHD	$78,000
	A Study of the Factors Influencing Women's Decisions About Childbirth	NICHD	$187,063
	Modulation of PAH Ovarian Toxicity by Biotransformation Enzyme Polymorphisms	NIEHS	$189,823
	Neuroactive Steroids and Seizure Control During Pregnancy in Women With Epilepsy	NINDS	$101,800
	Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women	NICHD	$83,333
	Midcareer Investigator Award in Patient-Oriented Research	NICHD	$187,466
	Uterine Leiomyoma Research Center	NICHD	$250,000
	Identification of Genes Predisposing to Pelvic Floor Disorders	NICHD	$66,667
	Cellular Mechanisms of Amniotic Fluid Volume Regulation	NICHD	$200,000
	Oklahoma Native American Research Centers for Health (ONARCH VI)	NIGMS	$100,000
	Research To Improve Preconception Health of Adolescent Women	NIGMS	$128,436

Subject	Title	Institute or Center	Award Amount
Reproductive Health/ Developmental Biology (continued)	Xenograft Study on Growth-Control of Human Uterine Leiomyomata	NICHD	$83,333
	Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team	NICHD	$66,667
	Genetic Studies of Uterine Leiomyomata	NICHD	$83,333
	Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and its Association with Incidence, Progression, and Recurrence of Pelvic Floor Disorders	NICHD	$66,667
	Racial Disparity in Adverse Pregnancy Outcomes: Ancillary Study to Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (NuMoM2b)	NICHD	$100,000
	The Role of Maternal Nutrition in Adverse Pregnancy Outcomes: Ancillary Study to Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (NuMoM2b)	NICHD	$100,000
	ORWH-NICHD Leiomyoma Tissue Bank	NICHD	$50,000
	Adrenal Hyperplasia Among Adolescent Patients With Polycystic Ovarian Syndrome (Bench to Bedside Program)	NICHD	$200,000
	Genetics of Polycystic Ovary Syndrome	NICHD	$200,000
Pelvic Floor Disorders Network	Cleveland Clinic Clinical Site	NICHD	$25,000
	Pelvic Floor Disorders Network (Loyola)	NICHD	$25,000
	Pelvic Floor Disorders Network (UCSD)	NICHD	$25,000
	Utah Pelvic Floor Disorders Network (UTSW)	NICHD	$25,000
	Perioperative Pelvic Floor Rehab: A Randomized Trial	NICHD	$25,000
	NICHD Pelvic Floor Disorders Network (UTSW)	NICHD	$25,000
	Pelvic Floor Disorders Network Data Coordinating Center (UMich)	NICHD	$25,000
	Pelvic Floor Disorders Network (Duke)	NICHD	$25,000

Table 3. RFAs and PAs Related to ORWH, FY 2009 and FY 2010

RFAs and PAs Developed and Implemented by ORWH

Title	Announcement Number	NIH Lead
Advancing Novel Science in Women's Health Research (ANSWHR) (R21)	PAS-10-226	ORWH
Chronic Fatigue Syndrome: Pathophysiology and Treatment (R21)	PA-08-247	ORWH
Chronic Fatigue Syndrome: Pathophysiology and Treatment (R01)	PA-08-246	ORWH

RFAs and PAs Cosponsored by ORWH

Title	Announcement Number	NIH Lead
Basic Research on Self-Regulation (R21)	RFA-AG-11-010	NIA [OppNet]
Bioenergetics, Fatigability, and Activity Limitations in Aging (R01)	PA-09-190	NIA
Bioenergetics, Fatigability, and Activity Limitations in Aging (R21)	PA-09-191	NIA
Effects of the Social Environment on Health: Measurement, Methods, and Mechanisms (R01)	RFA-DA-11-003	NIDA [OppNet]
Fogarty International Research Collaboration Behavioral and Social Sciences (FIRCA-BSS) Research Award (R03)	PAR-08-223	FIC
Limited Competition for the Global Research Initiative Program, Behavioral/Social Sciences (R01)	PAR-10-280	FIC
Neurobiology of Migraine (R21)	PA-10-259	NINDS
NIH Basic Behavioral and Social Science Opportunity Network (OppNet) Short-Term Interdisciplinary Research Education Program for New Investigators (R25)	RFA-NR-11-002	NINR [OppNet]
Research on Teen Dating Violence (R01)	PA-09-169	NICHD
Research on Teen Dating Violence (R21)	PA-09-170	NICHD
Scientific Meetings for Creating Interdisciplinary Research Teams in Basic Behavioral and Social Science Research (R13)	RFA-CA-10-017	NCI [OppNet]
Transdisciplinary Research on Fatigue and Fatigability in Aging (R01)	PA-08-161	NIA
Transdisciplinary Research on Fatigue and Fatigability in Aging (R21)	PA-08-162	NIA
Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (R01)	PAR-10-190	NICHD
Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (R03)	PAR-10-191	NICHD
Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (R21)	PAR-10-192	NICHD

Highlights of ORWH-Cofunded Research Conferences and Workshops

In addition to providing funding for research projects, ORWH also provides funding for research dissemination through conferences and workshops held at the NIH and around the country. Through partnerships with NIH ICs and Offices, other Federal agencies, and extramural organizations, ORWH seeks to bring together researchers working on women's health and sex differences topics to exchange ideas, foster collaborations, and explore emerging concepts and technologies. This section provides a few brief examples of such conferences held during this reporting period to demonstrate the breadth of topics and partnerships in ORWH-cofunded research conferences and workshops. A full listing of conferences and workshops cofunded by ORWH in FY 2009 and FY 2010, including greater detail, can be found in appendix D. Research conference topics included the following:

- Trauma spectrum disorders in women (posttraumatic stress disorder and caregiving) especially as these disorders are found in women in the military who have been in theatre deployment in Iraq and Afghanistan.
- The growing burden of musculoskeletal disorders on society and how to promote and advance collaborative research on bone and joint health that will lead to improvements in prevention, diagnosis, and treatment.
- Optimizing breast health care delivery in limited resource countries and promoting collaboration among national and international organizations.

Summary: ORWH Research Programs Support Implementation of the NIH Strategic Plan

For the period FY 2009 and FY 2010, numerous research planning activities were successfully undertaken, including the five regional meetings that were held to complete the new ORWH/NIH strategic plan for women's health and sex differences research. The strategic plan, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research* (NIH Publication No. 10-7606) was published in September 2010. The early-phase trans-NIH implementation has begun by inclusion of the key strategic planning goals into the FY 2011 NIH priorities for women's health and sex differences research and developing partnerships across NIH. In terms of funding opportunities, ORWH reissued the ANSWHR program announcement (PA) titled Advancing Novel Science in Women's Health Research, which can be found at http://grants.nih.gov/grants/guide/pa-files/PAS-10-226.html. This program was begun in 2007 and received widespread support through ARRA funding during FY 2009 and FY 2010. With the reissuance in FY 2010, 23 NIH ICs now cosponsor this PA, along with the Office of Behavioral and Social Science Research, ODS, and ORWH. More than 100 other research grants were funded or cofunded by ORWH each year during FY 2009 and FY 2010, in partnership with 19 NIH ICs. Many of these awards represent long-term collaborations across NIH to advance women's health and sex differences research.

II. ORWH Interdisciplinary Research and Career Development Programs

The Office of Research on Women's Health (ORWH) recognizes that the study of women's health across the lifespan can be enhanced by an interdisciplinary approach to research, bridging basic and clinical science and incorporating new models of collaboration, institutional support, and ways of evaluating those who conduct it. Interdisciplinary research can provide an opportunity for not just medical specialists but also for researchers in dentistry, pharmacy, nursing, biotechnology, social sciences, anthropology, genetics, and other disciplines, representing different perspectives and areas of expertise, to work together in a mutually beneficial collaboration to advance women's health. Women's health provides rich opportunities for collaboration and synergy of effort among clinical, basic, and applied scientists. To encourage collaborative interdisciplinary research, the ORWH has developed, implemented, and funded innovative interdisciplinary career development and research programs. The Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program and the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health program (to be renamed Specialized Centers of Research on Sex Differences) are examples of ORWH's commitment to interdisciplinary research and career development. An additional interdisciplinary research program, Advancing Novel Science in Women's Health Research (ANSWHR) is described in section I, ORWH Research, of this report.

This section on ORWH Interdisciplinary Research and Career Development Programs also includes an activities summary of the Myalgic Encephalomyelitis/trans-NIH ME/Chronic Fatigue Syndrome (ME/CFS) Research Working Group, which is chaired and coordinated by ORWH. Multiple NIH Institutes and Centers (ICs) work with ORWH in an interdisciplinary approach to support research on this complex biomedical condition that disproportionately affects women.

Building Interdisciplinary Research Careers in Women's Health

The BIRCWH program is an innovative, mentored scientist career development program implemented in 1999 to increase the number of women's health researchers using the concept of interdisciplinary research. A major component of the program is ensuring that mentors represent the diverse disciplines needed to carry out interdisciplinary projects and support the career development that will bridge the transition to research independence for BIRCWH scholars. BIRCWH is built on three pillars: interdisciplinary research, career development, and a supportive mentoring relationship. The program supports training junior faculty, called BIRCWH scholars, who have recently completed clinical training or postdoctoral fellowships and who are beginning basic, translational, clinical, and/or health services research related to women's health by pairing junior researchers with senior investigators in women's health. ORWH is now responsible for the programmatic aspects of the BIRCWH program. The grants management aspects, however, are still carried out through the ICs, primarily through the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). ORWH prepares the requests for applications (RFAs), organizes the review cycles, and serves as the primary NIH contact for each BIRCWH program.

Since the beginning of this program, ORWH has issued four additional RFAs and has made a total of 63 awards to 41 institutions. In total, the BIRCWH programs have sponsored more than 400 women and men as BIRCWH scholars. ORWH has been joined in its funding support by the Agency for Healthcare Research and Quality (AHRQ) and many NIH ICs, including the National Cancer Institute (NCI), NICHD, the National Institute on Environmental Health Sciences (NIEHS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), National Institute of Neurological Disorders and Stroke (NINDS), and the NIH Office of Dietary Supplements (ODS). ORWH provided

approximately $10 million per year in funding to the program in FY 2009 and FY 2010.

BIRCWH IV Program Sites and Principal Investigators 2007 Awards

The 15 BIRCWH programs awarded in 2007 are still active and will continue through 2011. Program sites and principal investigators are listed below in table 4a and detailed program descriptions follow.

Institution: Boston University Medical Center

Principal Investigator: Karen Freund, M.D., M.P.H.

The Boston University (BU) BIRCWH has demonstrated the ability to expand women's health research and the number of excellent investigators in women's health. The BU BIRCWH will build upon the strengths of our existing program to recruit, select, and train junior faculty in conducting clinical and health services research on women's health issues. The focus of research training and research will be addressing the needs of underserved, minority, and elderly women. The long-term goals of the BU BIRCWH are to mentor an identified cadre of outstanding scholars and to provide them with the support and training needed for them to develop independent research careers in women's health. The BU BIRCWH will train selected clinician investigators in health services research, clinical research, and clinical epidemiology to address a focus of important questions in the care of women.

Institution: Duke University

Principal Investigator: Eugene Z. Oddone, M.D.

The Duke/North Carolina Central University (NCCU) BIRCWH program is designed to develop highly skilled researchers investigating women's health issues, with a strong emphasis on interdisciplinary scholarship. The overarching theme for the Duke/NCCU program will be women's health across the lifespan, with areas of research interest that include maternal consequences of childbearing conditions that affect women, and health care use and disparities. A group of experienced

Table 4a. BIRCWH IV Program Sites and Principal Investigators

Institution	Principal Investigator
Boston University Medical Center	Karen Freund, M.D., M.P.H.
Duke University	Eugene Z. Oddone, M.D.
Medical University of South Carolina	Kathleen Brady, M.D., Ph.D.
Northwestern University	Andrea Dunaif, M.D.
Oregon Health & Science University	Jeanne-Marie Guise, M.D., M.P.H.
Pennsylvania State University	Carol Weisman, Ph.D.
Tulane University	Jeannette Magnus, M.D., Ph.D.
University of Colorado at Denver and Health Sciences Center	Judy Regensteiner, Ph.D.
University of Illinois at Chicago	Stacie Geller, Ph.D.
University of Maryland, Baltimore	Patricia Langenberg, Ph.D.
University of Minnesota, Twin Cities	Nancy Raymond, M.D.
Magee-Women's Hospital of the University of Pittsburgh Medical Center	James Roberts, M.D.
University of Wisconsin-Madison	Gloria Sarto, M.D., Ph.D.
Vanderbilt University	Nancy Brown, M.D.
Virginia Commonwealth University	Jerome Strauss, M.D., Ph.D.

core mentors will support the scholars, and a distinguished advisory committee will provide oversight as well as regular evaluations of the program and scholar progress. The collaboration between Duke and NCCU, a Historically Black University, will strengthen our goal of training minority scholars. The Duke/NCCU BIRCWH program is relevant to public health because it trains researchers whose work will lead to improved treatments for a wide range of conditions affecting women.

Institution: Medical University of South Carolina

Principal Investigator: Kathleen Brady, M.D., Ph.D.

The overall objective of the Medical University of South Carolina (MUSC) BIRCWH program is to promote the performance of research in women's health by bridging advanced training with research independence. The Interdisciplinary Women's Health Research program at MUSC will encourage interdisciplinary study of differences between women and men that impact the prevention, diagnosis, and treatment of disease in two major focus areas—aging and mental health. The convergence at MUSC of substantial expertise in these two critical areas assures our ability to mentor junior faculty to study women's health issues across the lifespan. Our faculty mentors have a broad skills basis in both aging and mental health, especially pertaining to dementia, substance use disorders, posttraumatic stress disorder (PTSD), and depression. In addition, we have specific expertise in the study of gender differences in pharmacokinetics, pharmacodynamics, and pharmacogenomics.

Institution: Northwestern University

Principal Investigator: Andrea Dunaif, M.D.

The BIRCWH program at Northwestern University will be used to develop a group of independent, tenure-track scientists with backgrounds in clinical medicine or basic science disciplines whose research will address high-priority areas relevant to women's health. We have identified six focus areas that have been historically strong within Northwestern and that are fundamental to the understanding and treatment of women's health and disease: (1) differences in cardiovascular disease risk, (2) ovarian biology, (3) obstetrical and gynecological disorders, (4) sex differences in sleep, (5) rheumatology, and (6) osteoporosis. In order to develop expertise outside the Ob/Gyn specialty, faculty members who have interdisciplinary training in basic reproductive science and gender-specific disease research must be cultivated. Northwestern has a longstanding and rich tradition of interdisciplinary excellence in the reproductive sciences and in disorders that affect women.

Institution: Oregon Health & Science University

Principal Investigator: Jeanne-Marie Guise, M.D., M.P. H.

The goal of the Oregon BIRCWH program is to create a stimulating and nurturing environment for junior faculty to develop into leading physician-scientists in women's health. Our program recognizes that research can modify the course of disease at one point in a woman's lifespan, which will affect the rest of lifelong development and aging. The program pairs basic and clinical junior faculty scientists with established mentors from different backgrounds who have expertise in women's health issues in order to enhance the scholar's research capabilities. The mix of career paths and backgrounds is integral to increasing collaboration and invigorating research in women's health across the lifespan. The extensive intellectual and research resources at the Oregon Health & Science University are available and committed to developing BIRCWH scholars. Integration is interdepartmental and is center driven to enhance collaborations between scientists and trainees in the Center for Women's Health, the Heart Research Center, the Primate Research Center, the Cancer Institute, and the Center for Gender Biology and Medicine. Sophisticated research core laboratories specializing in molecular biology, cell culture, DNA analysis, imaging, statistics, assisted reproductive techniques, endocrine assays, laboratory animals, transgenic and molecular genetics cores, among others, are established and available to the BIRCWH scholars. Advanced training in designing clinical studies and statistical evaluation for clinician scientists will be coordinated through the highly successful Human

Investigations Program. Writing skills are enhanced through structured workshops.

Institution: Pennsylvania State University

Principal Investigator: Carol Weisman, Ph.D.

The goal of the BIRCWH program at Pennsylvania State University is to increase the number and skills of investigators in women's health through a mentored research and career development experience leading to an independent interdisciplinary scientific career that will benefit the health of women. The expanding research agenda in women's health is informed by multiple scientific disciplines, including the biological, physical, and social sciences. Research integrating knowledge from multiple perspectives is needed to advance the field of women's health and to improve women's health and health services. The interdisciplinary research conducted by BIRCWH scholars may be basic, translational, behavioral, clinical, and/or health services research relevant to women's health or to sex/gender factors related to health. At Penn State, 21 senior faculty mentors have been identified in four core research areas: (1) precursors and consequences of obesity; (2) reproductive health; (3) sex and gender issues in health and disease; and (4) cancer prevention, screening, and treatment.

Institution: Tulane University

Principal Investigator: Jeanette H. Magnus, M.D., Ph.D.

The Tulane BIRCWH program is dedicated to promoting research and the transfer of findings to promote women's health by promoting research independence among junior researchers. To improve the quality and increase the quantity of women's health research, Tulane BIRCWH proposes to bridge the period between advanced training and research independence, as well as link professions, scientific disciplines, and areas of interest for selected scholars. The common theme running throughout the various research areas is interdisciplinary research on cardiovascular disease, hypertension, and renal disease. The long-term objectives of the Tulane BIRCWH program are to increase the number of skilled, independent interdisciplinary investigators with a focus on sex, gender, and women's health research; promote, through the BIRCWH program's illustration, the awareness of the need to ensure a strong pipeline when fostering independent researchers and taking advantage of interdisciplinary and multidisciplinary clinical and translational research efforts; promote collaborations with traditionally non-research-focused entities; establish institutional and individual renown both nationally and internationally for the BIRCWH program's findings on cardiovascular disease (CVD) and women's health; and improve the cardiovascular health of Louisiana women across the lifespan, particularly African-American women, by effectively training the next generation of conscientious, culturally competent, and independent academic women's health researchers.

Institution: University of Colorado at Denver and Health Sciences Center

Principal Investigator: Judy Regensteiner, Ph.D.

The broad objective of the BIRCWH program at the University of Colorado at Denver and Health Sciences Center (UCDHSC) is to develop and increase the pool of highly qualified young scientists and clinician–investigators pursuing independent interdisciplinary scientific careers in women's health. The BIRCWH grant at UCDHSC focuses on three interrelated areas affecting women's health across the lifespan, from preconception to aging. These areas are (1) pregnancy, fetal programming, and lactation; (2) aging, cardiovascular disease, diabetes, and obesity; and (3) women's cancers. These are fields in which the UCDHSC has strong interdisciplinary research programs, extending from molecular research into the basic mechanisms of disease through clinical studies to epidemiological analyses of etiology and outcomes.

Institution: University of Illinois at Chicago

Principal Investigator: Stacie Geller, Ph.D.

The University of Illinois at Chicago (UIC) BIRCWH program is a collaborative effort between the UIC's National Center of Excellence in Women's Health (CoE) and its six health colleges, including the Colleges of Medicine, Nursing, Pharmacy, Dentistry, and Applied Health Sciences; and the School

of Public Health. The overall purpose of this BIRCWH program is to institutionalize a generative scholar training program that will optimize the success of junior faculty in developing a substantive and sustained research program in women's health science. The program will contribute substantially to the development of a diverse multidisciplinary basic science, clinical, and community research work force through the interdisciplinary training, mentorship, and career development of junior investigators. These investigators will accelerate the translation of research findings into evidence-based policies and practices that improve the health of women and girls in the United States. A diverse group of scholars is selected who focus on research in one of five areas in which UIC has particular strengths: (1) reproductive health, (2) midlife and aging, (3) cancer in women, (4) heart disease in women, and (5) underserved populations. These areas encompass health and illness issues that are unique to women, more prevalent in women, or different in women than in men. Health disparities are an underlying theme in much of the research on women's health, regardless of level of analysis, reflecting the diverse urban environment in which UIC is situated. UIC's conceptual approach to women's health and to research about women's health is to view women's health in terms of life stages and on a continuum. Work in women's health ranges from the molecular and cellular level to the community level; these levels are interrelated.

Institution: University of Maryland, Baltimore
Principal Investigator: Patricia Langenberg, Ph.D.

The BIRCWH program at the University of Maryland, Baltimore (UMB) is designed to foster interdisciplinary research in women's health among junior faculty. Scholars work together with a team of senior faculty mentors to bridge the gap between specialized training and independent research careers. To achieve this goal, we have refined and adapted our current program to provide scholars with in-depth career development training in three focused and interactive research theme areas: (1) women's health and the brain; (2) the aging woman; and (3) conditions specific to women. These theme areas build on existing strengths in research at UMB and are fertile ground for interdisciplinary basic science, translational, behavioral, clinical, epidemiological, and/or health services research. They are an extension of the theme areas offered in our current program, allowing many of those mentors from the current program to participate, and allowing former scholars the opportunities to serve on mentor teams as coaches, providing a support network for new scholars. An important strength of our BIRCWH program is that scholars are able to draw from a multidisciplinary pool of senior faculty mentors for their mentor teams, but are also able to engage in research that is truly interdisciplinary. For example, a scholar could access expertise in genetics, epidemiology, and neurology to conduct clinical research on central nervous system contributions to the menopausal transition. Our former and current scholars all have benefited immensely from our rich research environment and frequently cite the interdisciplinary nature of their training experience as an extraordinary advantage to their research.

Institution: University of Minnesota,Twin Cities
Principal Investigator: Nancy Raymond, M.D.

Three aspects of the University of Minnesota make it a unique environment for a BIRCWH program: (1) Based on substantial empirical research by one of our faculty members, we have developed a comprehensive model of mentoring that systematizes the vagaries of the interdisciplinary mentoring process. (2) Across our six health science schools and other health-related departments, we have an extremely diverse institution. This diversity of disciplines reveals itself in our mentors, our course offerings, and the scholars themselves. Few universities can offer such a wide range of career development opportunities. (3) The University of Minnesota is a leader in women's health. Based on the work of the Deborah E. Powell Center of Excellence in Women's Health, we have a strategic plan related to women's health research, the goals of which are to (1) build academic capacity; (2) increase interdisciplinary collaboration; (3) increase funding opportunities; and (4) increase the visibility of women's health research.

Institution: Magee-Women's Hospital of the University of Pittsburgh Medical Center

Principal Investigator: James M. Roberts, M.D.

The BIRCWH program at the University of Pittsburgh seeks to improve women's health research at the University of Pittsburgh with several strategies. The first has been to provide excellent interdisciplinary research training in women's health to as many beginning investigators as possible. Scholars funded by the program are encouraged to obtain alternative K funding and, when successful, to continue to participate in the BIRCWH career development program. The program has publicized the availability of components of the BIRCWH program to other beginning investigators. In addition, we have recruited many of the research leaders of the University of Pittsburgh to become actively involved in the program through membership in the Advisory Committee. The training program emphasizes interdisciplinary research, and exposure to this strategy is provided through projects and also by selecting a group of scholars with diverse research interests and approaches, and encouraging their interaction.

Institution: University of Wisconsin–Madison

Principal Investigator: Gloria Sarto, M.D., Ph.D.

The goals of the BIRCWH Program at the University of Wisconsin (UW) are (1) to increase the diversity of academic leaders in the field of women's health and (2) to promote interdisciplinary research that addresses disparities in health status and health outcomes among diverse populations of women. We will accomplish these goals by selecting diverse and talented applicants and providing them with dual scientific mentorship with established investigators in both biomedical and behavioral/social sciences; a rigorous 2- to 3-year didactic curriculum (biostatistics and study design, ethics, leadership/management, presentation and teaching, and scientific writing); and individual guidance in a safe environment that values cultural diversity. We believe that the integration of biomedical sciences, public health sciences, and sociocultural and behavioral sciences is prerequisite to addressing the linkages of macro-societal levels of being with pathogenesis of disease, so important in addressing health disparities. Thus, the UW BIRCWH provides interdisciplinary and multifaceted opportunities for research that include not only biomedical and behavioral sciences, but also investigation into quality of care, cost, access, and satisfaction with services; causes of and barriers to reducing health disparities; social context; and identification of assessment measures for outcomes. To address not only the broad array of research areas outlined above, but also the interdisciplinary nature of the possible candidates, the faculty is interdisciplinary and consists of physician-scientists, perinatal researchers, sociologists, nurse-scientists, nutritional scientists, epidemiologists, and economists. The outstanding research mentors selected for the BIRCWH are enthusiastic about the opportunity to mentor more advanced scholars through the BIRCWH.

Institution: Vanderbilt University

Principal Investigator: Nancy Brown, M.D.

The Vanderbilt BIRCWH program has supported the career development of scholars engaged in basic, translational, and epidemiological women's health research in collaboration with investigators from among 15 departments or centers within Vanderbilt, Meharry Medical College, and other institutions. At the same time, the BIRCWH has served as a catalyst for recruitment and growth in the area of women's health research at Vanderbilt and for collaboration between Vanderbilt and Meharry Medical College. During the next 5 years, the BIRCWH program will focus on developing outstanding investigators in six major areas of women's health research: cardiovascular risk and gender, clinical pharmacology and vaccine development, disparities and health outcomes, endometrial biology and reproductive toxicology, neoplasia and cancer, and neuroscience and behavioral health. We strive to create a new generation of creative, successful leaders in scientific areas that will improve the health of women.

Institution: Virginia Commonwealth University

Principal Investigator: Jerome Strauss, M.D., Ph.D.

The Virginia Commonwealth University (VCU) BIRCWH program enjoys superb leadership from its PI (School of Medicine dean) and its program codirectors, both highly successful female faculty (one basic scientist, one physician-scientist). The BIRCWH program intersects with several interdisciplinary matrix organizations, such as the Institute for Women's Health National Center of Excellence, Center for Health Disparities, and Center for Translational and Clinical Science. VCU BIRCWH scholars will have the opportunity to investigate the pathogenesis and develop preventive and therapeutic interventions for preeclampsia, polycystic ovarian syndrome (PCOS), perinatal depression, preterm birth, low birthweight, vaginal bacteriosis, breast and ovarian cancer, and substance abuse. Scholars will learn innovative methods of conducting community-based health research, statistical analyses focused on distinguishing sex and gender differences in data, and culturally competent research methodology. Scholars will be required to integrate training experiences in clinical and laboratory settings and community outreach. All scholars will attend monthly group lunch brainstorming sessions at which they will make informal presentations on their research and solicit advice and assistance.

BIRCWH V Program Sites and Principal Investigators 2010 Awards

In FY 2009, ORWH reissued the BIRCWH RFA (RFA-OD-09-006). This fifth round of awards was made in July 2010. Over $6 million was awarded to 13 new and continuing BIRCWH programs through funding from ORWH, 7 ICs, and ODS. Nine of these programs were competitively renewed and 4 were new centers providing for a total of 29 active awards during this time period. These programs will continue to be funded through FY 2014. The BIRCWH V programs sites and principal investigators funded in FY 2010 are listed in table 4b and detailed program descriptions follow.

Table 4b. BIRCWH V Program Sites and Principal Investigators

Institution	Principal Investigator
Brigham and Women's Hospital/Harvard University	Jill Goldstein, Ph.D.
The Mayo Clinic	Rebecca Bahn, M.D.
Michigan State University	Mary Nettleman, M.D., M.P.H.
University of California, Davis	Claire Pomeroy, M.D., M.B.A.
University of California, San Francisco	Mary Anne Koda-Kimble, Pharm.D.
University of Cincinnati	Joel Tsevat, M.D., M.P.H
University of Kansas Medical Center	Patricia Thomas, M.D.
University of Michigan, Ann Arbor	Timothy Johnson, M.D.
University of North Carolina at Chapel Hill	Eugene Orringer, M.D.
University of Rochester Medical Center	Shanna Swan, Ph.D
University of Texas Medical Branch	Abbey Berenson, M.D.
Washington University in St. Louis	Clay Semenkovich, M.D.
Yale University	Carolyn Mazure, Ph.D.

Institution: Brigham and Women's Hospital
Principal Investigator: Jill Goldstein, Ph.D.

Women and men are at different risks for the onset, expression, and treatment response in a number of disorders that occur at different stages of development and throughout aging. The mechanisms that explain these sex differences or disorders specific to women are still unclear. The mission of the Brigham and Women's Hospital (BWH)/Harvard University BIRCWH is to develop the next generation of scientist-clinicians as leaders in the field of women's health who will contribute to understanding sex-specific vulnerabilities to clinical disorders and those disorders specific to women. This integrated interdisciplinary training program is based on a translational approach to understanding differential incidences of specific disorders important for women's health. The program is modeled in the context of a lifespan perspective to identify etiologic mechanisms during fetal development, puberty, adulthood, and aging, with some focus on female-specific periods such as child-bearing years and menopause. Further, an underlying assumption of our BIRCWH program is that an understanding of the role of hormones and genes will provide the basis for understanding sex-specific vulnerabilities to clinical disorders. The Connors Center for Women's Health & Gender Biology at BWH is and will continue to be the home site for this endeavor, in the broader context of a Harvard-wide training program. Each scholar is assigned a team of mentors in order to operationalize the concept of training scholars to think in a translational manner. The BWH/Harvard BIRCWH program focuses on the following disorders, given either the known higher incidence in women than men and/or differential expression in women, or the strengths of the Harvard community in women's health: cardiovascular disorders; reproductive endocrine and neuroendocrine disorders; neuropsychiatricdisorders; autoimmune disorders; and female cancers (e.g., breast, ovarian, and uterine). Their research programs will provide scholars with the basis for the development of sex-specific treatment approaches and public awareness as to the importance of these sex-specific health issues for families and society.

Institution: The Mayo Clinic
Principal Investigator: Rebecca Bahn, M.D.

Embedded in the design of the Mayo Clinic Interdisciplinary Women's Health Research (IWHR) Program are each of the overarching themes of the BIRCWH program, including interdisciplinary research in women's health; genetic, hormonal and environmental determinants of sex/gender differences; and health conditions disproportionately affecting women across their lifespan. A special strength of the Mayo Clinic is the collaborative and interdisciplinary nature of our clinical, educational and research activities that form the core of our patient-centered institution. Thus, the theme of our IWHR program is interdisciplinary research. This theme is exemplified by the diversity of research topics and mentors, many of whom have established collaborations with other IWHR faculty and across disciplines and departments. The scope of our program includes research training in basic and clinical sciences centered on the prevention and treatment of conditions or diseases (1) unique to women; (2) disproportionately impacting women; or (3) expressed differently in women compared to men. Within this scope lie our specific areas of research focus: autoimmunity, cardiovascular diseases, endocrine/metabolic, gastrointestinal, neuro/musculoskeletal, reproductive/gynecologic disorders, and pain management/quality of life/outcomes. Members of the IWHR program faculty were selected for their existing collaborative research programs both within and outside of Mayo, the excellence and significance of their programs to advancing women's health, and their interest and success record as a mentor/educator in interdisciplinary research.

Institution: Michigan State University
Principal Investigator: Mary Nettleman, M.D., M.P.H.

The ultimate goal of the BIRCWH program at Michigan State University (MSU) is to increase the number and diversity of researchers in women's health by providing an inspiring and supportive environment for accomplishment and advancement. The University and the College of Human Medicine (lead college) have pledged matching funds to

allow recruitment of additional scholars and to encourage participation of physician-scientists. The MSU BIRCWH program is founded on key strengths of the institution, including the Center for Breast Health and the Environment and the Center for Women's Health and Reproduction, both of which will provide mentorship and a supportive environment for scholars. BIRCWH mentors are internationally recognized senior researchers, who are experienced and skilled mentors. The mentors have been chosen to reflect the overarching theme of health across the lifespan and the dimensions that influence health: biology, environment, and behavior. The MSU Office of Inclusion has agreed to partner directly with the administrative team to ensure that the program is attractive to women and minority researchers. Each scholar will work with a primary research mentor and a secondary mentor. Each of the mentors has a defined role to ensure an organized, interdisciplinary research experience. The mentored research training and the curriculum are designed to give scholars the skills to compete for external grant funding. The MSU BIRCWH program will support scholars at a time in their careers when they are at highest risk to leave research.

Institution: University of California, Davis

Principal Investigator: Claire Pomeroy, M.D., M.B.A.

Over the past 4 years, the University of California, Davis (UC Davis) BIRCWH program has trained a cadre of diverse interdisciplinary researchers in women's health and raised the stature of women's health research at our university. We now propose to build on this strong foundation to create a next-generation BIRCWH program that will further increase the innovation and impact of this initiative. The goal of the UC Davis BIRCWH program is to create an academically stimulating and nurturing environment for women's health researchers that facilitates career development and encourages paradigm-shifting interdisciplinary collaboration and research approaches. We will build on the best practices of our well-received curriculum, which combines: (1) mentored research and career development support, (2) core didactic courses, (3) supplemental didactic training tailored to the individual scholar's needs, and (4) special interdisciplinary BIRCWH experiences. The innovative aspects of our BIRCWH program include journal clubs and work-in-progress meetings that are integrated with other training programs, monthly breakfast meetings with the VC/Dean for BIRCWH mentors and scholars to review progress, and a biannual symposium of Northern California BIRCWH programs. New advances in this renewal include our proposed BIRCWH Mentoring Academy to optimize the mentoring experience for both mentors and scholars, and expansion of our faculty mentors to additional campus disciplines. Scholars will be supported to develop a unique research experience using our new matrix approach to women's health research, with four research focus areas (neurosciences/behavioral; musculoskeletal/aging; nutrition and metabolic/inflammatory syndromes; and cancer), intersecting with cross-cutting themes (continuum across the lifespan, sex/gender determinants, health disparities/differences and diversity, and interdisciplinary research), and embracing foundational approaches of prevention and treatment as well as the biological and behavioral bases of sex and gender differences.Our scholars and mentors will define transformative interdisciplinary approaches to women's health research, allowing new insights into the lifelong continuum of sex and gender determinants of illness and wellness and reduction of health disparities.

Institution: University of California, San Francisco

Principal Investigator: Mary Anne Koda-Kimble, Pharm.D.

BIRCWH scholars and alumni in academic process and leadership. The University of California, San Francisco (UCSF) BIRCWH program is multidisciplinary, including scholars and faculty mentors from each of the UCSF schools and Kaiser DOR. It emphasizes novel interdisciplinary approaches to a wide range of women's health issues. The program will continue its strong initiatives in women's cancer, bone disease, and menopause. New foci draw upon the unique strengths of UCSF and Kaiser DOR and include occupational and environmental health; addiction, violence and traumatic stress; aging and dementia; autoimmunity; metabolism and obesity; maternal

health and child outcomes, and muscular and skeletal health. A multidisciplinary advisory committee oversees the program in partnership with leadership, including selection of new BIRCWH scholars. The program emphasizes multidisciplinary mentoring teams that cross disciplines and research methodologies. The diversity of scholars, in terms of fields of interest, background, training, ethnicity and gender is a priority. A special emphasis for this renewal is placed on the cultural and ethnic diversity of scholars and affiliated faculty. BIRCWH scholars participate in program-specific seminars, assessments of progress and mentoring activities. In addition, the program integrates in UCSF Clinical and Translational Science Institute career development and training programs. This renewal features a new emphasis on leadership development that will assess the academic progress of BIRCWH alumni and facilitate leadership training for those who qualify. The UCSF-Kaiser DOR BIRCWH program provides career development mentoring and training of scholars as an independent women's health scientists, broadens the range of women's health research, and supports the development of academic leaders in women's health.

Institution: University of Cincinnati
Principal Investigator: Joel Tsevat, M.D., M.P.H.

The mission of this program is to identify and train junior faculty members within the University of Cincinnati (UC) College of Medicine and the Cincinnati Children's Hospital Medical Center (CCHMC). The two institutions are located across the street from each other and share faculty, with all CCHMC faculty having appointments at UC. The two institutions also share a common NIH Institutional Clinical and Translational Science Award (CTSA), funded in April 2009. The academic home for the CTSA is the Center for Clinical and Translational Science and Training (CCTST). Our first BIRCWH award was based in the department of obstetrics and gynecology, but we trained scholars from many departments, including internal medicine, psychiatry, surgery, cell biology, and pediatrics. Thus, for the renewal, we will house the BIRCWH K12 program in the CCTST, through which BIRCWH K12 scholars will have access to administrative support and a vast array of research resources, including study design, database management, data analysis, pilot funding, research education, and regulatory support; the CCTST also runs the CTSA KL2 Research Scholars program and has a very successful K23 preparation process. We have assembled a cadre of mentors who have a track record of mentoring in women's health, and their own protected time for mentorship. We also plan to institute a mentor-in-training program for midcareer faculty who are beginning to mentor others.

Nationally, there is a major unmet need for training clinical and basic science trainees and faculty to conduct research in women's health. Through mentored research and coursework, the Cincinnati BIRCWH K12 program will continue to train leaders in women's health research.

Institution: University of Kansas Medical Center
Principal Investigator: Patricia Thomas, M.D.

Among the faculty at the University of Kansas are a group of very talented scientists pursuing women's health research in the schools of Allied Health, Medicine, Nursing, Pharmacy and Engineering. The existence of this talented research base in women's health ignited the interest of our leadership and resulted in the University of Kansas Medical Center (KUMC) BIRCWH Faculty Development Program (2005–2010) to formally establish and strengthen the women's health research enterprise at the University of Kansas. All four schools and others on the main campus are partners in this proposed renewal. Interdisciplinary research among schools is strongly emphasized. The KUMC Schools of Allied Health and Nursing are strong partners with Medicine and Pharmacy, ranking 12th and 31st, respectively, in the Nation for NIH funding. Mentors are in five thematic areas related to women's health: (1) women's reproductive health; (2) maternal health; (3) pathogenesis of diseases prevalent in women; (4) drug design, drug delivery, and pharmacogenomics; and (5) prevention, intervention, and health disparities. Our long-term objective is to foster career development of junior faculty pursuing basic, translational, behavioral, clinical, and health services

research relevant to women's health at the University of Kansas. In addition, interactions of mentors from multiple disciplines occurring during training of IWHR scholars has fostered new research collaborations related to women's health among established faculty and heightened awareness of the need for women's health research at our institution.

Institution: University of Michigan, Ann Arbor

Principal Investigator: Timothy Johnson, M.D.

The goal of the Michigan BIRCWH is to develop a cadre of new junior faculty scholars through a mentored scholarly research experience leading to independent scientific careers addressing interdisciplinary women's health concerns. The University of Michigan has a broad interest and significant expertise in women's health evidenced in the Institute for Research on Women and Gender (IRWG). We propose to train a total of four scholars with a minimum of two clinician scientists and one or two nonclinical postdoctoral scientists per year for a minimum of 2 years each. Recruitment and selection will focus on identifying scholars with superior academic potential and scientific skills with special attention to achieving a diversity of scholars and scholarship. Each scholar will have an assigned research mentor: an established, independent investigator with a proven track record who has been selected for his/her commitment and support of junior colleagues in their development to independence. We will target scholars' four areas of special interest: (1) pelvic floor/urogynecology research; (2) health services research; (3) reproductive science and women's medicine; and (4) biobehavioral and aging research. An individualized career development plan will be developed with each scholar and their primary research mentor along with a departmental/disciplinary mentor, and a third senior interdisciplinary mentor. All scholars participate in the monthly "First Tuesday Women's Health" interdisciplinary research seminar series at the IRWG. Access to faculty career development programs, advanced courses in biomedical research, biostatistics, epidemiology, and research methodology assistance will be available as appropriate for individual scholar needs.

Institution: University of North Carolina at Chapel Hill

Principal Investigator: Eugene Orringer, M.D.

This program seeks to identify, train, and mentor exceptional junior faculty members with the potential to conduct innovative women's health research. The goals of our BIRWCH program are to: (1) facilitate the mentored career development of junior investigators pursing research of women's health or sex/gender factors; (2) promote interdisciplinary team science that will enhance all types of women's health research; and (3) facilitate the translation of these research findings to improve community health. All scholars participate in selected didactic programs including: the BIRCWH/KL2 Seminar; the BIRCWH Women's Health Seminar; and training in the responsible conduct of research. Other components of the curriculum are tailored to the background and training of the individual Scholar, each of whom also takes part in our Women's Health Research Day and the national BIRCWH meeting. Finally, each scholar has an intensive research experience with mentors drawn from multiple disciplines. Our program focuses on eight research themes: (1) cancers affecting women; (2) nutrition, obesity, and eating disorders; (3) bone and joint health; (4) cardiovascular disease/vascular biology; (5) HIV/sexually transmitted diseases; (6) alcohol and substance abuse; (7) mental health; and (8) pain. These themes were selected because they are all highly relevant to women's health, well suited to interdisciplinary collaboration, and major strengths and areas of research emphasis at the University of North Carolina at Chapel Hill (UNC-CH). In addition, each has theme has numerous, nationally recognized mentors who are willing and available to work with selected BIRCWH scholars. The goal of the UNC-CH BIRCWH program is to create a training program that will prepare promising junior investigators to conduct innovative research in women's health. Through their mentored, interdisciplinary training, these scholars will be ideally positioned to make important new observations and then translate them into advancements that will improve the health of women throughout the community.

Institution: University of Rochester Medical Center

Principal Investigator: Shanna Swan, Ph.D.

Concerns about the potential impacts of environmental chemicals on human and environmental health have increased greatly in the past 10 years. Through their effects on hormonal pathways, environmental chemicals can differentially affect females, particularly at critical and sensitive periods across the lifespan. These critical periods include stages of particular vulnerability (such as fetal development and among the elderly), major life transitions (such as during midlife and into late life), and stages of rapid cell proliferation and growth (such as during fetal development, puberty, and lactation). The Women's Health and Environment across the Entire Lifespan (WHEEL) program at the University of Rochester Medical Center (URMC) has as its focus interdisciplinary research specific to the intersection of women's health, environment, and health issues specific to life stages. It will build on graduate training programs already in place at URMC and complement these with educational training and research experiences designed to meet the needs of scholars within the program. This program will train interdisciplinary women's health research scholars from a spectrum of disciplines and ultimately promote research and translation of findings that will benefit the health of women, particularity in the area of women's environmental health across the lifespan. Our long term objectives are to (1) "graduate" scholars who go on to successful careers in interdisciplinary research in women's environmental health; (2) establish a successful and sustainable training program in women's health research; (3) create an environment at URMC conducive to interdisciplinary research in women's health; (4) develop researchers who provide positive feedback to the research environment and the fields of women's health research; and (5) build in continuing mechanisms to effectively translate results of women's health research to health professionals and the broader community.

Results of this research will provide a strong foundation for risk assessment and regulation, when appropriate, thus decreasing risks to public health.

Institution: University of Texas Medical Branch

Principal Investigator: Abbey Berenson, M.D.

The University of Texas Medical Branch (UTMB) program includes 17 experienced senior investigators as mentors from the Schools of Medicine, Nursing, Health Professions, and Biomedical Sciences. Research focus areas reflect the strong interdisciplinary infrastructure at UTMB and include: health disparities, adolescent health, infectious disease, reproduction, and aging, especially as related to the health needs of underserved women. The Center for Interdisciplinary Research in Women's Health provides forums for interdisciplinary endeavors and administers the program. Multiple formal and informal venues provide ample opportunities for developing skills and collaborative interdisciplinary networks. Scholars may also obtain an M.S. or Ph.D. in clinical science. The UTMB BIRCWH program recruits, trains, and retains early career investigators from diverse racial/ethnic backgrounds in a variety of disciplines related to women's health. The program provides interdisciplinary mentored research experiences to promote the BIRCWH scholars' involvement in investigations aimed at improving health care and health of women across the lifespan.

Institution: Washington University in St. Louis

Principal Investigator: Clay Semenkovich, M.D.

The mechanisms underlying the unique course of several diseases affecting women remain unclear in part because of longstanding impediments to research efforts involving different disciplines. The long-term objective of the BIRCWH program at Washington University is to produce independent investigators conducting interdisciplinary research in women's health. The program has a single specific aim: to identify outstanding young scientists committed to women's health who have completed fellowship training, match them with mentors working in an environment that promotes interdisciplinary research, and provide them with career development experiences leading to their independence. The renewal proposes to extend the foundation of success by refining the didactic portion of the experience to make it even more relevant

for scholars by coordinating the coursework with that offered by the CTSA at Washington University, reshaping our mentor pool in order to enhance the interdisciplinary character of the program, integrating the program with the newly created Center for Women's Infection Disease Research at Washington University, and adding a peer-to-peer mentoring component. Our program has the potential to help fulfill the mission of NIH and ORWH by continuing to train outstanding scholars and serving as a focal point for paradigm-shifting research in women's health.

By bridging fellowship training and independent faculty status, the BIRCWH program has the potential to significantly impact women's health by increasing the number of outstanding scientists utilizing novel and cooperative approaches to address problems that include depression, osteoporosis, lupus, type 2 diabetes, urinary tract infections, heart attacks, certain cancers, and infertility.

Institution: Yale University

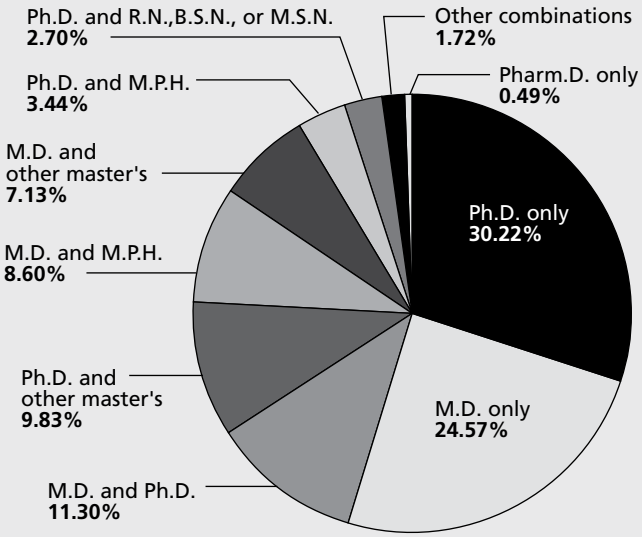
Principal Investigator: Carolyn Mazure, Ph.D.

Addictive behaviors are linked to nearly half of all causes of mortality, and disorders involving these behaviors represent the top three causes of preventable disease in the United States. Addictive behaviors in women (particularly involving tobacco, alcohol, overeating, and illicit drugs) currently rank among our most prevalent public health concerns. Emerging data suggest that sex and gender differences in these addictive behaviors and their biological substrates have important implications for the development of effective prevention and treatment strategies. We propose an innovative research career development program that will train junior faculty scholars to respond to the need for interdisciplinary research on women's health and addictive behaviors. An outstanding team of 25 experienced, productive, and dedicated mentors have been assembled with multiple ongoing interdisciplinary projects focused on addictive behaviors using basic, translational, and clinical research approaches. Our leadership team and advisory committee will direct a program that emphasizes four core career development components that will be individualized to meet the needs of each BIRCWH scholar. These components include: (1) interdisciplinary research mentoring on study planning, implementation, completion, and dissemination of results; (2) coordinated professional coaching focused on the preparation of grant applications, manuscript writing, and faculty career planning; (3) structured experiences in interdisciplinary team science, and its development and evaluation; and (4) a didactic curriculum on women's health, addictive behaviors, and academic mentoring. Our long-term goal is to generate independent investigators with the skills necessary to sustain academic productivity, grant support, collaborations across disciplines, and effective mentoring of their own future trainees. Annual medical, social, and productivity costs of addictive behaviors linked to tobacco, alcohol, overeating, and illicit drugs in the United States alone exceed $600 billion. Sex and gender differences in the etiology, course, and prognosis of these addictive behaviors have clear implications for prevention and treatment. We propose an innovative research career development program that will train junior faculty scholars in interdisciplinary research designed to make enduring contributions to the field of women's health and addictive behaviors.

BIRCWH Accomplishments, FY 2009-2010

As of November 1, 2010, a total of 407 individuals had participated in the BIRCWH program as scholars since its inception, of which 80 percent were women and 20 percent are men. Of these, 124 (30.5 percent) were currently BIRCWH scholars, 252 scholars (61.9 percent) had completed their BIRCWH program, and during the past 2 years only one scholar withdrew from the program. The distribution of academic degrees held by all BIRCWH scholars who have participated in the program is shown in the figure below.

BIRCWH Scholar Academic Degrees



A primary goal of the ORWH BIRCWH program is to support scholars in achieving research independence as determined by having been successful in obtaining their own grants. This report focuses on accomplishments by scholars who completed the BIRCWH program. The following information is based on BIRCWH scholar data maintained by ORWH and the NICHD Office of Science Policy, Analysis and Communication:

- BIRCWH scholars submitted more than 1,400 competitive NIH research* applications
- Success rates for scholar applications range from 30 to 40 percent:
  - » About 40 percent of research applications submitted by BIRCWH scholars were funded.
  - » About 30 percent of R-series applications submitted by BIRCWH scholars were funded.
  - » About 31 percent of R01 applications submitted by BIRCWH scholars were funded.
- Awards from the NIH were primarily from NHLBI, NIAID, NICHD, NIDDK, NIDA, and NINDS.

In addition, scholars have received Federal funding from AHRQ, the Centers for Disease Control and Prevention, the U.S. Department of Defense, and the U.S. Department of Energy, as well as numerous academic, foundation, and industry grants. In addition to success securing funding, scholars are also progressing up the academic pipeline.

Another measure of scholar success is the number and quality of publications that result from the program. In FY 2009–2010, BIRCWH scholars published more than 400 publications, bringing the total

number of publications to more than 4,800 since the inception of the program. These publications address the spectrum of women's health including cardiovascular disease, diabetes, breast cancer, HIV/AIDS, fibroids, substance abuse, intimate partner violence, depression, lupus, osteoporosis, and health disparities, to name a few; but also examine how sex and gender factors affect health and disease. And, scholars from different institutions are collaborating and publishing manuscripts together. For example, Emily Harville of Tulane University collaborated with Renée Boynton-Jarrett of Boston University Medical Center and other authors to study the impact of childhood hardships on future pregnancy outcomes.† A list of select BIRCWH scholar publications can be found in appendix E.

Highlights of ORWH-Supported BIRCWH Activities

In 2006, to coincide with the annual Interdisciplinary Women's Health Research Symposium (see appendix D for a detailed description) held at the NIH and attended by BIRCWH scholars, ORWH initiated the Scholars' Day on the Hill Training Program in Health Policy, in collaboration with The George Washington University, to enhance BIRCWH scholars' understanding of the legislative process. The Scholars' Day on the Hill program provides the ORWH BIRCWH scholars with a solid understanding of the health policy legislative process in Congress and its relationship to the development of health, health care, and medical research policy. The BIRCWH scholars participate in a daylong program on Capitol Hill conducted by faculty of The George Washington University Department of Health Policy led by Sara Rosenbaum, J.D., and Susan Wood, M.D., Associate Professor and Director, Jacobs Institute of Women's Health.

In 2009, the program included presentations on the Federal budget process by Timothy Westmoreland from Georgetown University Law Center. In addition, Dr. Susan Wood presented a "History of Women's Health Research and Policy" and a panel discussion on health care reform and the impact on women included representatives from Senator Barbara Mikulski's office and Representative Jan Schakowsky's office, Judy Waxman from the National Law Center, and Jessica Arons from the Center for American Progress. In 2010, the program included presentations by Dr. Lara Cartwright Smith on "Health Care Reform 101" and the panel discussion "Implementation of Health Care Reform and the Impact on Women," in addition to presentations on the Federal budget process, the appropriations process, and NIH funding and research in health care reform. As many as 50 BIRCWH scholars attend the Scholars' Day on the Hill annually.

In response to the request from BIRCWH scholars for networking opportunities, in FY 2010 ORWH developed the first edition of the *Directory of BIRCWH Scholars*, which includes scholars'/program participants' affiliations, professional titles, research areas, and a brief summary of how the BIRCWH program has influenced their research careers.

* Research applications include the R, P, and U series.

† Harville, E. W., Boynton-Jarrett, R., Power, C., & Hyppönen, E. (2010). Childhood hardship, maternal smoking, and birth outcomes: A Prospective cohort study. *Archives of Pediatric and Adolescent Medicine, 164* (6), 533–539.

Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health

The Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCOR) program represents an innovative interdisciplinary research program focusing on sex differences and major medical conditions affecting women. The SCOR program supports accomplished scientists who conduct research that integrates basic, clinical, and translational research at P50 centers. The research scope for the SCOR program is derived from three sources: (1) the Institute of Medicine report *Exploring the Biological Contributions to Human Health: Does Sex Matter?*[13] (2) the ORWH 2000 *Agenda for Research on Women's Health for the 21st Century*,[14] and (3) the NIH research priorities for women's health. The first SCOR RFA, which was issued by the ORWH and participating ICs in 2002, funded 11 SCORs through FY 2006 (SCOR I). A second RFA, issued in 2006, funded 11 SCORs through FY 2011 (SCOR II); seven of the SCOR I sites were renewed as part of SCOR II and remain active.

The day-to-day programmatic management of the SCORs resides in the participating ICs, and ORWH serves as the coordinator, overseeing the progress in advancing sex differences research across the centers. While ORWH is the major funder of the SCORs, funding is also provided by five NIH ICs (NIAMS, NICHD, NIDA, NIDDK, and NIMH) and the Food and Drug Administration (FDA).

The currently funded SCORs (see table 5) continue to thrive and are conducting interdisciplinary research on sex and gender factors in depression, pain, substance abuse, osteoporosis, urinary tract, and reproductive health. In FY 2009 and FY 2010, ORWH provided approximately $9.2 million per year in funding to the program. The SCOR represents excellent models for stimulating interdisciplinary research and for human translational research, with significant applications to gender-specific human health.

[13] Institute of Medicine. (2001). *Exploring the biological contributions to human health: Does sex matter?* Washington, DC: The National Academies Press.

[14] U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (1999). *Agenda for research on women's health for the 21st century* (NIH Publication No. 99-4385). Bethesda, MD: National Institutes of Health.

Table 5. SCOR Centers 2007–2011

Institution and Investigator	SCOR Theme
Brigham and Women's Hospital **Jill Goldstein, Ph.D.** Project 1: Genes and Hormonal Fetal Antecedents to Sex Differences in the Brain: Depression Project 2: Animal Models of Sex-Specific HPA Axis Development Project 3: Sex-Specific Programming of the HPA Axis by Glucocorticoids Administrative Core	Fetal antecedents to sex differences in depression: A translational approach
Medical University of South Carolina **Kathleen Brady, M.D., Ph.D.** Project 1: Sex and Estrous Cycle-Dependent Differences in Cocaine-Seeking Behavior Project 2: Stress-Induced Craving: The Impact of Sex and Ovarian Hormones Project 3: Gender, Menstrual Cycle, and Smoking Cue Reactivity Administrative Core	Role of sex and gender differences in substance abuse relapse
Northwestern University **Andrea Dunaif, M.D.** Project 1: Androgens, Genotype, and Insulin Resistance in PCOS Project 2: Genetic Analysis of PCOS/Diabetes Susceptibility Genes Project 3: Role of Androgen Excess in Provoking Oxidative Stress in Females Project 4: Fetal Androgen Induces Ovarian, LH, and B-Cell Defects Administrative Core	Excess male hormones (androgens) as the key to explaining polycystic ovarian syndrome (PCOS)
University of California, Los Angeles **Emeran Mayer, M.D.** Project 1: Differences in Central Stress Circuit Responsiveness Between Women With and Without Chronic Pelvic Visceral Symptoms (IBS, IC) and in an Animal Model of Chronic Stress Project 2: Sex Differences in Mucosal Neuroendocrine-Immune Interactions in IBS Patients Project 3: CRF Signaling Pathways in Stress-Related Visceral Manifestations Project 4: Role of the Peripheral CRF Signaling System Administrative Core Core B: Neuroendocrine Assay Core C: Neuroimaging Core	A coordinated study of stress, pain, emotion, and sexual factors underlying the pelvic visceral disorders of irritable bowel disorder and interstitial cystitis
University of California, San Francisco **Jeanette Brown, M.D.** Project 1: RRISK Prospective Cohort Project 2: Diabetic Voiding Dysfunction and Stem Cell Therapy for Stress Urinary Incontinence Project 3: Diabetes RRISK Prospective Cohort: Urinary Incontinence and Diabetic Voiding Dysfunction Biostatistics and Data Management Core Administrative Core	Lower urinary tract function in women

Table 5 (continued). SCOR Centers 2007–2011

Institution and Investigator	SCOR Theme
University of Chicago **David Ehrmann, M.D.** Project 1: Sleep and Metabolism in Obesity: Impact of Gender Project 2: PCOS, Sleep Apnea, and Metabolic Risk in Women Project 3: Sex Steroids, Sleep, Body Fat, and Plasma Triglycerides in Women Project 4: Assessment of Adipocyte Function in Women With PCOS Administrative Core	Sex steroids, sleep, and metabolic dysfunction in women
University of Miami **Emmalee Bandstra, M.D.** Project 1: Sex and Stress Mechanisms of Vulnerability to Addiction Project 2: Sex Differences in Drug Effects: The Adolescent Trajectory Project 3: Sex and Gender Influences on Adolescent Drug Involvement Administrative Core	Sex and gender influences on addiction and health: A developmental perspective
University of Michigan, Ann Arbor **John DeLancey, M.D.** Project 1: Biomechanics of Birth-Related Injuries Project 2: Maternal Birth-Related Neuromuscular Injury and Recovery: Phase II Project 3: Mechanisms of Posterior Vaginal Prolapse Administrative, Human Subjects, Biostatistics Core Core B: Measurement and Imaging Core	Birth, muscle injury, and pelvic floor dysfunction
University of Missouri, Kansas City **Hong-Wen Deng, Ph.D.** Project 1: Genomewide Scans for Female Osteoporosis Genes Project 2: Genomewide and Specific Gene Expression Study of Esteogenic Cells Project 3: Proteomewide Expression Study of Osteogenic Cells Administrative Core Core B: Clinical Core Core C: Biostatistics and Bioinformatics Core	Identifying the genes that put women at risk for osteoporosis
Washington University in St. Louis **Scott Hultgren, Ph.D.** Project 1: Host-Pathogen Interaction in Acute and Chronic Urinary Tract Infections Project 2: Host-Response to Recurrent Urinary Tract Infections in Women Project 3: Pangenome of *E. coli* in Bladder and Gut of Women With Recurrent Urinary Tract Infection Administrative Core	Molecular and epidemiologic basis of acute and recurrent urinary tract infections (UTIs) in women
Yale University **Rajita Sinha, Ph.D.** Project 1: Sex and Stress Mechanisms of Vulnerability to Addiction Project 2: Sex Differences in Stress Arousal in Cocaine-Exposed Youth at Risk for Addiction Project 3: Sex Differences in fMRI of Stress in Cocaine-Exposed Youth at Risk for Addiction Project 4: Sex Differences in Progesterone Effects on Responses to Stress and Drug Cues Administrative Core	Sex, stress, and substance use disorders

SCOR Publications

Overall, in FY 2010, the 11 SCORs report publishing 150 journal articles, 214 abstracts and presentations, and 44 other publications (including book chapters) during the fourth year of this cycle. Seven of the 11 SCORs were programs that competed successfully for renewal and are in their ninth year of work; 4 SCORs are completing their fourth year of work.

Greater attention to performing sex/gender analyses of scientific results is needed. Each year, SCOR investigators are asked to list publications that include a sex/gender analysis in their annual progress report. (The papers submitted by the PIs in response to this request can be found in appendix F.) It is encouraging to see that SCOR investigators are serving as a model for ensuring that scientific knowledge continues to advance and take into account variations due to sex as an integral part of the research enterprise.

Select SCOR Scientific Advances

Brigham and Women's Hospital

In project 1,500 cases of major depressive disorder (MDD) and 700 healthy controls were selected for genotyping and analyses of prenatal sera for proinflammatory cytokines and hormonal abnormalities, all of which are currently being analyzed. With regard to mapping out sex differences in brain activity deficits in MDD in response to stressful stimuli, sex differences in stress response circuitry in the brain in healthy adults were first further characterized and demonstrated to be significantly associated with gonadal hormone changes in women across the menstrual cycle. Second, the pilot functional magnetic resonance imaging (fMRI) study in MDD women demonstrated that gonadal hormone deficits in MDD were significantly associated with brain activity deficits in the stress response circuitry and dysregulation of the parasympathetic activity of the heart. In brief, the fMRI studies of 12 healthy women and 13 healthy men using our previously published fMRI paradigm of stress response circuitry, demonstrated few significant differences in activation of the stress response in men compared with women during their early follicular menstrual cycle phase, except ventromedial nucleus (VMN) and lateral hypothalamic area (LHA) of the hypothalamus, amygdala, and anterior cingulate gyrus (ACG). In contrast, men exhibited significantly greater blood oxygenation level dependent (BOLD) signal changes compared with women during mid-cycle on anterior hypothalamus, hippocampus, periacqueductal gray in the brainstem, ACG, orbitofrontal cortex (OFC), and medial and ventromedial prefrontal cortices, with the largest sex effect sizes in the cortex.[15] Findings suggested that sex differences in stress response circuitry are hormonally regulated via the impact of subcortical brain activity on the cortical control of arousal and demonstrate that females have a natural hormonal capacity to regulate the stress response that differs from males. The same paradigm was used in the pilot fMRI study of 10 women with MDD compared with 10 healthy controls scanned again (as in the previous studies) at two time points in the menstrual cycle (early follicular and ovulation). In the pilot study, fasting blood was collected to assess hormonal status in relation to brain activity during the stress response. Lower serum estradiol and higher progesterone was found in women with MDD compared with healthy controls during the mid-cycle phase of the menstrual cycle, suggesting dysregulation of the HPG-axis in MDD. fMRI analyses showed greater activation in healthy controls compared with MDD women in the anterior hypothalamus, amygdala, hippocampus, OFC, ACG, and subgenual ACC, findings that were unrelated to medication status in the MDD women. Furthermore, the relationship between hypoactivation of the stress response circuitry in the brain in MDD with heart rate variability (HRV) was investigated, hypothesizing a disruption of the parasympathetic control of the heart.

Results demonstrated that the lower high-frequency component of HRV (i.e., parasympathetic activity) was associated with hypoactivation of stress response circuitry in the regions where associations with estradiol and progesterone dysregulation were shown. These findings suggest that the neural control of the

[15] Goldstein, J. M., Jerram, M., Abbs, B., Whitfield-Gabrieli, S., & Makris, N. (2010). Sex differences in stress response circuitry activation dependent on female hormonal cycle. *The Journal of Neuroscience, 30*(2), 431–438.

autonomic nervous system also is regulated in part by hormones, affecting mood and heart regulation. Project 1 has been actively scanning the New England cohort of 40 women and men with MDD and 40 matched healthy controls to fully test the hypotheses with regard to hormonal dysregulation, brain activity deficits in response to stress, and prenatal factors and genes associated with these deficits.

The SCOR at Brigham and Women's Hospital published a manuscript showing that GABA-B receptor signaling helps determine the spread of ER-alpha immunoreactive (ir) neurons at the lateral border of the paraventricular nucleus (PVN) and a different role for GABA-A receptors, on the number of ER-alpha-ir cells in and around the PVN.[16] Closer examination followed of the potential function of PVN neurons in GABA-B receptor-deficient mice. Corticotropin-releasing hormone (CRH) peptide levels in PVN neurons were selectively upregulated in knockout female mice at birth.[17]

Progress is ongoing in the aim to characterize the cell movements in and around the PVN. Using live-cell, fluorescent video microscopy with organotypic brain slices, the movement characteristics of neurons expressing yellow fluorescent protein (YFP) driven by the Thy-1 promoter were examined. Cells in slices from embryonic day 13 (E13) are providing movement data in vitro. Exposure to 10μM saclofen increased the percentage of cells moving by 50 percent within minutes of exposure. Also, during the third year, Sim1/Cre mice and floxed BDNF mice were used to create a hybrid line that, unfortunately, does not provide a PVN selective knockout of BDNF. In addition, finding that the floxed BDNF mice have a body weight phenotype was a surprise. (This had not been reported previously.) Therefore, global BDNF KO mice will be ordered and used to examine early PVN development.

In project 3, studies to determine whether perinatal glucocorticoid treatment induces apoptosis and proapoptotic gene expression in the developing PVN and associated areas (bed nucleus of the stria terminalis, VMN, amygdala, and hippocampus) of male and female neonates have begun. Investigators found that prenatal exposure to glucocorticoids increases the number of neurons undergoing programmed cell death in the PVN of female offspring but not in males. On postnated day (PND)4, in the VMH and medial amygdala, a significant main effect of sex (female>male, $p<0.05$) were found, whereas in the VMH there was also a significant main effect of treatment (DEX>veh; $p<0.05$). Investigators also have examined activated Caspase-3 positive cells in the amygdala on PND 0 and found increases in the basomedial and medial amygdala but not the central nucleus and basolateral amydgala. Such data suggest that exposure to high levels of glucocorticoids can cause permanent changes in brain function through the loss of neurons in specific brain areas.

Medical University of South Carolina

Over the past 8 years, the MUSC SCOR has functioned as a productive interdisciplinary research center focused on treatment and relapse in substance use disorders in women.

A major goal of the center was to work to coalesce a group of investigators across different disciplines to work together exploring gender differences in relapse and treatments for substance use disorders. Three closely related core projects (one basic science and two clinical projects) were undertaken. All studies have made significant progress.

Project 1 is designed to examine sex differences and hormonal regulation in an animal model of relapse to cocaine- and nicotine-seeking behavior. Investigators have finalized a publication on the ability of exogenous progesterone to block reinstatement in female rats during the estrus phase of the cycle. A study on chronic aripiprazole effects on reinstatement and a study on the interactive effects of stress and cues on reinstatement were also completed and published. In addition, the MUSC SCOR has completed and submitted for publication a large study on yohimbine-induced stress effects on reinstatement of cocaine-seeking in females and the role of

[16] McClellan, K. M., Stratton, M. S., & Tobet, S. A. (2010). Roles for gamma-aminobutyric acid in the development of the paraventricular nucleus of the hypothalamus. *Journal of Comparative Neurology, 518*(14), 2710–2728.

[17] Stratton, M. S., Searcy, B. T., & Tobet, S. A. (2011). GABA regulates corticotropin releasing hormone levels in the paraventricular nucleus of the hypothalamus in newborn mice. *Physiology and Behavior, 104*(2), 327–333.

progesterone. Investigators found that stress potentiated cue reactivity in females more than males. Studies on sex differences in the ability of centrally administered CRH and footshock-induced stress to induce reinstatement of cocaine-seeking are being finalized. The results of these studies show several interesting patterns, including greater responding and higher heterogeneity in females. Investigators also have collected the initial data for experiments on anxiety behavior that emerges during early withdrawal from cocaine self-administration as measured by the elevated plus maze and the defensive burying paradigm.

Finally, stable nicotine self-administration in male and female rats and the initial series of reinstatement test trials have been established. The results show that males and females have fairly equivalent nicotine intake but show different patterns of responding across the various forms of reinstatement of nicotine-seeking behavior. These studies provide an integrated approach to understanding sex differences and ovarian hormonal regulation in relapse to drug-seeking behavior. Information gathered from this project will provide direction for other components and help direct the future development of gender-specific treatments for craving and relapse.

Project 2 is designed to investigate the interaction of a pharmacologic stressor with exposure to cocaine-related cues and the impact of ovarian hormones on this response in women. This project also explores the relationship between impulsivity, stress, and cocaine craving. The 2008 year of the project was focused on study recruitment for the current project and continued analysis and publication of data from our previous SCOR project. Since study initiation, approximately 1,200 telephone screens and 216 face-to-face interviews of potential study participants have been conducted. Ninety-two subjects have met inclusion criteria, and to date 55 subjects have completed study procedures. Since the previous progress report from MUSC SCOR, 22 participants have completed study procedures. At this rate of recruitment (two to three participants per month), difficulty completing the project in the proposed timeframe is not anticipated.

This study builds on the previous MUSC SCOR project, which investigated differences between cocaine-dependent men and women in reactivity to different forms of laboratory stress (psychological and pharmacologic) and cocaine-related cues, as well as gender differences in a matched control group. Investigators have been actively analyzing the data from our previous project and publishing our results. To date, investigators have four published manuscripts, one manuscript in press, one manuscript under review, and an additional three manuscripts in preparation. Furthermore, study team members have presented data at conferences and symposia, including the College on Problems of Drug Dependence and the American Psychological Association.

This project extends an animal model of pharmacologically induced stress (project 1) to a test of craving/relapse in cocaine-dependent humans. It also explores the impact of hormonal status on stress and craving response. Sex differences in response to stress may be important in the relationship between stress, cocaine cues, and craving.

Findings from the previous project may have important implications for gender-specific treatment development. In secondary analyses, investigators analyzed the influence of early childhood stress on the hypothalamic pituitary adrenal (HPA) axis hormonal response to pharmacologic and social stressors. Investigators found gender-specific differences in the HPA hormonal response to CRH as a function of the type of trauma experienced (i.e., sexual, physical, emotional, or general). Specifically, general trauma was a significant predictor of a blunted cortisol response to CRH in women but not in men. In a separate manuscript, investigators found that subjects with a history of childhood stress exhibited a significantly greater corticotropin response to CRH than subjects without a history of stress. A similar trend was found in the adrenocorticotropic hormone (ACTH) response to the social stressor. Investigators also examined the effects of childhood stress on proinflammatory cytokine levels and found a positive correlation between the number of self-reported childhood stressful experiences and basal cytokine levels. These data support previous findings demonstrating plasticity within the HPA axis and acute immune response system (IRS)

as a consequence of exposure to early childhood stress. These data demonstrate significant alterations within the HPA axis and IRS in adult subjects free of current psychiatric diagnoses. Finally, investigators examined the impact of progesterone and estrogen on subjective stress and craving in cocaine-dependent women and found a positive correlation between progesterone and craving. Furthermore, progesterone was positively correlated with the subjective stress response to CRH. These data suggest that hormonal changes across the menstrual cycle may have a significant impact on drug craving and potential relapse.

The primary specific aims of project 3 are to (1) examine the impact of the timing of quit date within the menstrual cycle on smoking cessation treatment success and (2) examine the relationship between subjective (e.g., craving) and physiologic (e.g., heart rate, skin conductance) responses to smoking cues in a human laboratory paradigm and smoking cessation treatment outcome in nicotine-dependent women. Investigators also are exploring differential treatment outcomes in women treated with varenicline versus transdermal nicotine patch.

Participants in the ongoing component study continue to be actively recruited. To date, 90 women have enrolled, and investigators are on pace to enroll the target number of participants (based on power analysis) before the conclusion of funding. Concurrent with active enrollment, investigators are keeping up to date with data collection and entry, including the complex process of cue reactivity physiologic data reduction.

Although analysis targeting the major specific aims must await completion of recruitment, the volume of data obtained to date allows for preliminary exploration of several secondary lines of investigation. Two such preliminary analyses have been completed and accepted for presentation at scientific meetings. The first was an exploration of pretreatment craving and cue reactivity as predictors of smoking behavior, measured using topographic equipment. The second was an exploration of changes in metabolic/body composition indices, measured using plethysmography, over the course of a quit attempt in women smokers. Investigators plan to pursue publication of these findings, and will continue exploring other secondary lines of investigation while recruiting and enrolling participants.

Nicotine dependence is a major public health concern, with more than 25 percent of the adult population being current smokers. Among individuals with nicotine dependence, craving is an important component of the symptoms experienced during smoking cessation and is considered to be an important factor in relapse to smoking. The present proposal builds directly on the results of the SCOR's previous study and explores the effects of ovarian hormone levels at the time of quit attempt on treatment success. By tying together a human laboratory cue-reactivity paradigm (developed during the initial funding period) with a treatment outcome study, investigators will be able to assess whether pretreatment responses to smoking cues predict measures of treatment outcome. The results of the current study may yield important practical information that will aid women in setting a quit date in the ovarian hormonal milieu most associated with successful quitting, thereby enhancing treatment outcome.

Northwestern University

Investigators report exciting results from the past year of support. Project 1 has directly tested the hypothesis that intrauterine androgen excess is present in PCOS for the first time. At term, there is no evidence for fetal androgen excess. However, cord blood androstenedione and estradiol levels were significantly decreased in female PCOS offspring, suggesting that alterations in fetal or placental steroidogenesis were present. Although the prevalence of large-for-gestational-age infants was increased in PCOS offspring in the cohort where cord blood was obtained, investigators did not confirm this finding in a much larger cohort of PCOS women and their first-degree relatives. There was no evidence in either study for fetal growth restriction in PCOS. Investigators found an increased prevalence of metabolic syndrome in male first-degree relatives of women with PCOS; however, this finding was due to an increased prevalence of obesity in the male relatives. In contrast, the increased prevalence of metabolic syndrome

in female first-degree relatives of women with PCOS was independent of obesity.

The focus of project 2 is to examine how previously identified PCOS susceptibility genes affect other insulin-resistant states such as pregnancy. To date, investigators have demonstrated that, although the susceptibility locus D19S884 contributes to insulin resistance in PCOS families, it did not affect blood glucose levels and insulin resistance in pregnant women. However, average D19S884 allele length was correlated with total testosterone levels in pregnant women. Genetic variation in sex-hormone binding globulin (SHBG) was associated with fetal growth in Mexican-American male newborns. SHBG allele length was highly correlated with SHBG levels in newborns. The association between variation at SHBG and fetal size (or adiposity) in the presence of a correlation between SHBG allele length and SHBG levels in newborns may contribute to our understanding of the mechanism by which SHBG increases risk of developing type 2 diabetes as an adult.

During the past year, project 3 has made major progress in characterizing the function of estrogen and androgen receptors in pancreatic cells and their role in metabolic diseases such as PCOS. By using mice that lacked different types of estrogen receptors (ERs) and the newly discovered G protein-coupled ER (GPER) and cultured mouse and human islets, investigators have discovered that estrogens protect islet survival in vivo via these three types of ER and via nongenomic mechanisms. Furthermore, using a pancreas-specific ER-deficient mouse, investigators discovered a mechanism for the increase in insulin production produced by the activation of ERs. The results also indicate that activation of all three types of ER suppresses the formation of fat in islets and thereby prevents lipotoxic cell failure in a classical model of type 1 diabetes.

In other experiments, investigators found that exposure of female mice to excess androgens, a model for PCOS, produced systemic oxidative stress, which may participate in cell failure. Most important, investigators found that excess androgen also impairs cell survival via a direct action on the androgen receptors (ARs) present in ER-cells. Because the current in vitro data suggest that AR action provokes ER resistance in ER cells (a hypothesis consistent with the central hypothesis of project 4), excess AR activation is expected to impair ER action in ER-cell survival, insulin biosynthesis, and the prevention of lipotoxicity and, thereby, favor ER-cell dysfunction in women with PCOS. Investigators also studied the effects of neonatal androgen exposure on fat cell biology. Investigators found that adult female mice exposed neonatally to testosterone become obese and show increased food intake due to leptin resistance. Therefore, future experiments will study this new phenotype, which is highly relevant to PCOS.

Project 4 has demonstrated that virtually all of the effects of estradiol (E2) on energy balance are mediated by nonclassical ERα signaling. Since investigators have completed these initial studies in adult animals, additional important observations have been made: (1) ERα signaling mediates increased energy expenditure in juvenile animals before the onset of obesity, confirming that obesity in mice without any type of ERα is caused by the lack of these receptors and not just a consequence of altered body weight; (2) alterations in hypothalamic anorexigenic and orexigenic neuropeptidergic gene expression, as well as the action of the appetite hormone leptin, are secondary to E2 effects on body weight and not directly altered by ERα signaling, and (3) changes occur in neurons located in the brain area called the ventromedial nucleus following estrogen treatment via a nonclassical ERα signaling mechanism. Taken together, these findings indicate that the effects of E2 on energy expenditure, body weight, and adiposity likely occur in the ventromedial nucleus neurons via nonclassical ERα signaling.

University of California, Los Angeles

The University of California, Los Angeles (UCLA) SCOR continues to play a major role on the UCLA campus and nationally to promote the importance of women's health and of studying sex-related differences in disease. All studies and grant proposals submitted by the center have sufficient sample sizes to compare male and female subjects. The PI is a member of the interdepartmental neuroscience program and the interdepartmental ACCESS program and gives annual talks to students on ongoing

research opportunities in women's health and sex differences. Several investigators of the SCOR have been invited to organize or participate in national symposia on sex differences, irritable bowel syndrome (IBS), and painful bladder syndrome/interstitial cystitis (PBS/IC).

The success and high visibility of the UCLA SCOR have resulted in recognition of these important topics by the UCLA administration, resulting in the assignment of 6,500 square feet of new space (wet lab and office space) to house all central nervous system investigators under one roof. This new proximity is expected to greatly enhance interactions between the different groups and synergy.

The UCLA SCOR has had many recent accomplishments that relate to sex and gender differences and/or the importance of examining sex and gender factors related to women's health. These include the first demonstration in human subjects implicating an important role of CRF/CRF1 receptor signaling in modulating the activity and connectivity within a stress and arousal circuit in the brain of IBS patients.[18] Another accomplishment is the demonstration that acute lowering of brain serotonin levels with acute tryptophan depletion (ATD) in healthy women produces changes in a central stress and arousal circuit, which are identical to findings without ATD in female IBS patients with constipation.[19] Finally, we have demonstrated that early maternal separation results in depletion of Paneth and goblet cells, while inducing hyperplasia of endocrine cells through activation of CRF1 receptors (endocrine cells) and CRF2 receptors (goblet and Paneth cells) may create conditions leading to the development of an epithelial barrier defect, which may underlie the susceptibility to IBS with early life trauma.[20]

SCOR investigators have published several important studies and findings. For instance, we have published the first study to evaluate the effect of early adverse life events (EAL) and cortisol responses to a visceral stressor in IBS and controls. This study found that EAL is associated with a greater cortisol response and is more robust in men than women. A slower recovery rate to baseline levels is associated with greater symptom severity and poorer quality of life in IBS patients.[21] We have also published the first studies showing altered preattentive processing as well as sex differences in patients with IBS and IC[22, 23] and the first noninvasive method to measure visceral pain in conscious mice, which provided evidence that previous assessment of visceral hypersensitivity in response to chronic stressor also involved components of previous surgery and single housing linked with a commonly used method to record visceral pain.[24] Finally, we have published the first meta-analysis and systematic review comparing individual IBS symptoms between men and women in the general population and IBS patient population, and assessing the effect of menstrual cycle, female sex hormones, and menopausal status on IBS symptoms in women. The study

[18] Hubbard et al. (2010, June). CRF Abstract. Presented at 16th Annual Meeting of the Organization for Human Brain Mapping.

[19] Labus, J. S., Mayer, E. A., Jarcho, J., Kilpatrick, L. A., Kilkens, T. O., Evers, E. A., Backes, W. H., Brummer, R. J., & van Nieuwenhoven, M. A. (2011). Acute tryptophan depletion alters the effective connectivity of emotional arousal circuitry during visceral stimuli in healthy women. *Gut, 60*(9), 1196–1203.

[20] Estienne, M., Claustre, J., Clain-Gardechaux, G., Paquet, A., Taché, Y., Fioramonti, J., & Plaisancié, P. (2010). Maternal deprivation alters epithelial secretory cell lineages in rat duodenum: Role of CRF-related peptides. *Gut, 59*(6), 754–751.

[21] Videlock, E. J., Adeyemo, M., Licudine, A., Hirano, M., Ohning, G., Mayer, M., Mayer, E. A., & Chang, L. (2009). Childhood trauma is associated with hypothalamic-pituitary-adrenal axis responsiveness in irritable bowel syndrome. *Gastroenterology, 137*(6), 1954–1962.

[22] Kilpatrick, L. A., Ornitz, E., Ibrahimovic, H., Treanor, M., Craske, M., Nazarian, M., Labus, J. S., Mayer, E. A., & Naliboff, B. D. (2010). Sex-related differences in prepulse inhibition of startle in irritable bowel syndrome (IBS). *Biological Psychology, 84*(2), 272–278.

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[24] Larauche, M., Gourcerol, G., Million, M., Adelson, D. W., & Taché, Y. (2010). Repeated psychological stress-induced alterations of visceral sensitivity and colonic motor functions in mice: influence of surgery and postoperative single housing on visceromotor responses. *Stress, 13*(4), 343–354.

showed that women report more pain-related and constipation symptoms compared with men and IBS men report more diarrheal symptoms compared with IBS women. Bloating and loose stools are more commonly reported at the onset of menses compared with other phases of the menstrual cycle.[25]

University of California, San Francisco

The UCSF SCOR generated a number of major findings involving sex and gender factors related to women's health during FY 2009 and FY 2010. These include the findings that women with IBS are more likely to have pelvic organ prolapse and sexual dysfunction and report lower quality of life than women without such disorders and that the prevalence of stage II or greater prolapse and degree of prolapse bother was similar across all racial groups. Self-reported measures may provide more clinically relevant outcomes in studies using the pelvic organ prolapse quantification (POP-Q) system. Further, mixed incontinence has the largest overall impact on quality of life, whereas stress incontinence exhibits the weakest impact. Despite the significant overlap between urinary incontinence, fecal incontinence, and pelvic organ prolapse, these conditions are distinct from one another, with unique risk factors. Looking at levels of sexual activity, SCOR researchers have found that a substantial proportion of community-dwelling women remain interested and engaged in sexual activity into older age. Lack of a partner capable of or interested in sex may contribute more to sexual inactivity than personal health problems in this population. Racial and ethnic differences in self-reported sexual desire, activity, and satisfaction may influence discussions about sexual difficulties in middle-aged and older women.

Studies concerning diabetes showed that the risk of type 2 diabetes increases when term pregnancy is followed by less than 1 month of lactation, independent of physical activity and body mass index in later life. Mothers should be encouraged to exclusively breastfeed all of their infants for at least 1 month. Also, incontinence is highly prevalent among women with diabetes. Physicians should be alert for urinary incontinence because it is often unrecognized and thereby undertreated among women with diabetes.

In a systematic review, investigators found the mean prevalence of urinary incontinence during the first 3 months postpartum to be 33 percent for all women, 29 percent for primiparous women, and 37 percent for multiparous women. The mean prevalence was double in the vaginal delivery group compared with the cesarean section group (31 percent vs. 15 percent). Mean prevalences of weekly and daily incontinence were 12 percent and 3 percent, respectively.

Investigators have completed several experiments to identify the signaling pathways involved in stem cell differentiation. Investigators have implanted adipose tissue-derived stem cells (ADSCs) in animal models of stress urinary incontinence (SUI) and overactive bladder (OAB) with significant results. Investigators noted that the action of ADSCs is most likely through their paracrine effect rather than trans differentiation of the implanted cells. The role of some miRNA in neuronal differentiation of ADSCs in culture also was identified. Finally, the beneficial effects of phosphodiesterase inhibitors on lower urinary tract symptoms have been reported in several clinical trials. In the study, a prominent expression of PDE5 proteins in the striated portion of the external urethral sphincter and levetor muscle was noticed. This may partially explain the beneficial effect.

The UCSF SCOR Biostastistics and Data Management Core (BDMC) applies state-of-the-art science in biostatistics and data management to support the design, conduct, quality assurance, analysis, and reports of UCSF SCOR projects. The centralization of the data management and statistical components in the BDMC provides efficiencies of scale, improved quality control, and cross-fertilization among multiple studies. It fosters communication between SCOR investigators by stimulating the discussion of design, analysis, and interpretive issues and thus contributes to the interaction of basic research and clinical investigators. BDMC also maintains the SCOR Web site (http://www.ucsf.edu/scor) designed

[25] Adeyemo, M. A., Spiegel, B. M., & Chang, L. (2010). Meta-analysis: do irritable bowel syndrome symptoms vary between men and women? *Alimentary Pharmacology and Therapeutics, 32*(6), 738–755.

as a portal for junior investigators to learn about UCSF SCOR projects, review questionnaires/forms, submit analysis plans, and track publications. In addition, the UCSF SCOR Web site provides UCSF SCOR investigators secure access to SCOR documents and provides extensive public information about UCSF SCOR's research and training, as well as current updates of ongoing projects and publications.

University of Chicago

The primary focus of this SCOR is on gender differences in sleep quality in individuals who do not suffer from obstructive sleep apnea (OSA) as well as in the presentation of symptoms and polysomnographic findings in individuals who suffer from OSA. Investigators expect that this project will demonstrate gender differences in the impact of sleep quality on metabolism. The University of Chicago SCOR uses an interdisciplinary approach combining endocrine and metabolic evaluations, sleep assessments, chronobiological analyses, detailed mathematical treatment of both hormonal and electroencephalographic signals, and ambulatory monitoring. The team includes physicians who specialize in pulmonary medicine and are board certified in sleep medicine, physicians who specialize in endocrinology, and clinical investigators who are experienced in the relationship between sleep, hormones, and metabolism. The team is tightly knit and highly interactive. Scientific progress is formally communicated in face-to-face meetings organized on a regular basis. The ongoing investigations into the interrelationships between the presence/absence of OSA and insulin resistance in adipocytes obtained from human fat biopsies from patients with PCOS should generate novel insights into the development of metabolic disease in women.

Investigators continue to evaluate the regulation of plasma triglyceride metabolism by sex hormones to better understand the mechanism(s) responsible for the sex differences in the plasma lipid profile, which is a major risk factor for cardiovascular disease.

Investigators evaluate how imbalances in the sex hormone milieu affect plasma fatty acid and triglyceride metabolism (hyperandrogenemia in women).

Based on findings generated from this SCOR, a faculty member in the Section of Endocrinology at the University of Chicago initiated a series of protocols to examine sleep disturbances in pregnancy and their relationship to glucose tolerance and gestational diabetes. These collaborative studies are unique in the field and were independently funded by the ResMed Corporation. SCOR investigators Drs. Ehrmann and Van Cauter, as well as faculty from the Department of Obstetrics and Gynecology at the University of Chicago, served as collaborators. The preliminary findings were accepted for oral presentation at the 70th Scientific Sessions of the American Diabetes Association, which took place June 25–29 in Orlando, FL.

University of Miami

The center's approach is to assess sex/gender-specific differences in vulnerability to drug-taking and drug effects across development in adolescent and adult females and males with and without prenatal exposure to cocaine and other drugs.

Project 1 is a series of preclinical translational studies using an established rat model of prenatal drug exposure to examine the roles of prenatal cocaine exposure, postnatal environment, and polydrug exposure (cocaine with nicotine, THC, and alcohol) in the development of drug-taking behavior in male and female adolescent rats, emphasizing sex differences in conditioned place preference (CPP) for cocaine and elucidating the potential biologic basis for sex differences by functional imaging and neurochemical assessments. The studies of CPP for aim 1 have almost been completed.

Investigators have shown thus far that adolescent males and females whose mothers received cocaine at 30 mg/kg/day during pregnancy showed a significant CPP for cocaine across a range of doses. Males showed maximal CPP at 10 mg/kg training dose regardless of rearing environment. In females, enrichment dampened CPP to control values, whereas isolated females showed robust CPP across a range of doses. Prenatal 60 groups resembled controls for the most part. The investigator's working hypothesis is that C60 overstimulated the reward system

and tolerance developed. Although the direct antiglobulin test (DAT) results are preliminary, they do show that enrichment has different effects on DAT in females and males following exposure to high-dose cocaine, a finding that does not reflect the CPP results. Because these data are different from those generated in Dr. Izenwasser's laboratory (see below), they suggest that extensive prenatal handling (stress) has a major impact on the development of the reward circuits in the offspring. Results from nontreated groups, which are currently being tested, will help clarify this point.

Project 2 is a series of preclinical translational studies using an established rat model, the focus of which is to study the effects of nicotine, marijuana (Δ-9 THC), and cocaine in male and female adolescents and adults on behavior and neurochemistry during adolescence and adulthood. Thus far, the studies show inherent differences in the rewarding effects of nicotine in males and females across development. Investigators' prior data indicated that females were more sensitive than males to cocaine CPP, yet it appears that males are more sensitive than females to nicotine reward. Nicotine (0.4 mg/kg) increased nACh receptors in the nucleus accumbens (NA) only in the female rats, and this finding correlates with a significant CPP in response to this dose. Therefore, it appears that nicotine CPP is associated with changes in nACh receptors in NA subsequent to conditioning. Thus, it is important to understand the neurochemical changes that occur with different drugs in both sexes.

In addition, nicotine pretreatment had different effects on subsequent cocaine reward in male and female adolescents. These data will help, at least in part, in the understanding of why adolescence is the period of development when people are most likely to use and become addicted to drugs, and why females become addicted more quickly than males. Understanding the underlying bases of these behaviors will aid in our ability to develop effective age- and sex-specific treatments. Results from the preclinical assessment of CPP patterns can lend support for future findings on sex/gender differences in project 3 clinical population.

The significance of the preclinical and clinical work of this SCOR is that enhanced understanding of the differential effects of drugs of abuse in females and males across development (from prenatal to postnatal exposures during adolescence and adulthood) should lead to improved sex-, gender-, and age-specific preventions and treatments for drug addiction and related conditions.

University of Michigan, Ann Arbor

Working as part of project 1, Dr. DeJun Jing successfully defended his Ph.D. thesis on biomechanical analyses of the effects of patterns of maternal effort on the duration of the second stage of labor. His thesis not only summarized his innovative findings concerning changes in pelvic floor that occur during preparation for birth and the results of biomechanical modeling of second-stage events but also has stimulated an expanded interest in second-stage events. Most specifically, it has identified the important knowledge gap concerning maternal fatigue during the second stage of labor. Although the second stage is like an extended athletic event, such as a marathon, that requires strength and endurance to have sufficient force to spontaneously deliver the fetus, the well-developed techniques of exercise physiology and human performance have not been applied to this important area. University of Michigan SCOR investigators recently collaborated with researchers in kinesiology and have begun studying the energetics of the second stage of labor. This work overlaps with project 1 aims, and the researchers have developed a novel line of investigation. In addition, investigators have made excellent progress on evaluating the site of muscle injury through histologic examination of the enthesis attaching the levator ani muscle to the pubic bone, the site of the established birth-induced injury that results in prolapse. Investigators also have developed and are piloting a stereophotogrammetric apparatus that will allow, for the first time, to record the 3D geometric changes that occur in the pelvic floor at the time of birth.

Ruth E. Zielinsky, Ph.D., the graduate research assistant on project 2 was one of eight awardees for the Universities Distinguished Dissertation Award for her work "Private Places, Private Shame: Women's Genital Body

Image and Sexual Health," from over 800 dissertations. This pioneering work on women's body image, vaginal birth, and pelvic floor disorders has added new dimensions to the understanding of the birth-related injuries and their aftermath. Work on the ongoing aims is progressing as planned with slight modifications to the groups in response to external review. Investigators have recognized the importance of including issues concerning potential pregnancy effects on the pelvic floor separate from delivery and are now including women undergoing cesarean section to address this important issue. New and previously unrecognized trauma to the pubic bone has also been discovered through the collaboration with musculoskeletal MRI specialists and is explaining much of the reported pain many women experience after vaginal birth and has become a topic of interested in radiology.

During the past year, investigators working on project 3 have made advances in our topographic understanding of posterior compartment disorders. Investigators have developed a novel technique to assess the directions in which the supportive ligaments connect to the vagina and also have developed an improved understanding of how changes in these vectors can influence the forces they are required to carry. In addition to the ongoing mechanistic studies, work with the Michigan Bowel Control Program, an interdisciplinary team of gynecologists, gastroenterologists, colorectal surgeons, specialist nurses, and physical therapists dedicated to understanding women's problems with difficult defecation, has begun. Working together, this team has started to evaluate the relationship between the morphologic patterns of posterior compartment prolapse. Investigators also are working on quantification systems to capture and quantify the key changes in pelvic floor shape that are critical to posterior compartment support. In our anterior compartment work (R01 HD 38665), specially designed local coordinate systems are now being used to assess the location of key structure so that the positions of normal and abnormal women can be compared. This work allows investigators to quantify the degree to which any given feature is associated with prolapse. The anatomy of the pelvic floor is a complex spatial arrangement, and knowing which of the many deformations are the most important to prolapse requires techniques that allow the complex structural changes to be quantified so that their relative contributions can be assessed.

University of Missouri, Kansas City

The SCOR project is aimed at identifying genes and some of their functions that are important to risk of osteoporosis, a disease that mainly affects females. Investigators will use the state-of-the-art genomic convergence approach, which may integrate knowledge from disparate sources (e.g., genetics/genomics/functional genomics/proteomics) and research teams with multiple areas of scientific expertise (e.g., bone biologists, clinicians, molecular geneticists, genetic epidemiologists, statistical geneticists, and bioinformaticians). Therefore, the University of Missouri SCOR project is closely related to the objectives of the ORWH SCOR program.

Some of the published findings in the current fiscal year unraveled sex factors related to women's health. For example, in a genome-wide association study, investigators found that the polymorphisms of the *IL21R* and *PTH* genes contribute to variation in femoral neck bone mineral density variation in a sex-specified fashion.[26]

In another study, investigators found gender and race differences of femoral neck geometric parameters in human populations.[27]

In a powerful bivariate genomewide association analysis, investigators identified the *SOX6* gene influencing both obesity and osteoporosis phenotypes in males only.[28]

[26] Guo, Y., Zhang, L. S., Yang, T. L., Tian, Q., Xiong, D. H., Pei, Y. F., & Deng, H. W. (2010). IL21R and PTH may underlie variation of femoral neck bone mineral density as revealed by a genome-wide association study. *Journal of Bone and Mineral Research, 25*(5), 1042–1048.

[27] Zhang, F., Tan, L. J., Lei, S. F., & Deng, H. W. (2010). The differences of femoral neck geometric parameters: effects of age, gender and race. *Osteoporosis International, 21*(7), 1205–1214.

[28] Liu, Y. Z., Pei, Y. F., Liu, J. F., Yang, F., Guo, Y., Zhang L, ... Deng, H. W. (2009). Powerful bivariate genome-wide association analyses suggest the SOX6 gene influencing both obesity and osteoporosis phenotypes in males. *PLoS One, 4*(8), e6827.

Investigators found that the *ALOX12* gene is associated with the onset of natural menopause in White women.[29]

Findings from this SCOR project will improve the understanding of the pathogenesis of osteoporosis and related health problems, and will eventually help improve the women's health.

Washington University in St. Louis

The overall aims of this SCOR program are to understand the host and pathogen contributions to the range of urinary tract infection (UTI) and to investigate biomarkers that will predict the outcomes of disease. UTIs are among the most common bacterial diseases, occurring in an estimated 7 to 11 million women in the United States each year, with annual clinical and treatment costs approaching $1.6 billion. More than half of all women, including young, otherwise healthy women, report having had one or more previous UTIs in their lifetime. All humans are susceptible to UTI; however, in every age group, adult women have a higher incidence of UTI than men. In one study, by age 32, more than 50 percent of women, but only 8 percent of men, report having had at least one UTI in their lifetime. (Even at age 90, only 20 percent of men report having had a UTI in their lifetime.) In a majority of cases, the causative agent of these infections is uropathogenic *Escherichia coli* (UPEC). UPEC is thought to be introduced into the bladder, via the urethra, from the gut microbiota and/or the vaginal/periurethral flora. In females, periurethral areas provide a moist environment for bacteria to colonize and persist before and between infections. In addition, the distance from the urethral opening to the gastrointestinal tract and the length of the urethra in women are significantly shorter than in men. In addition to acute UTI, recurrence is a major problem, especially in women. More than half of women who report ever having a UTI episode also report that they had multiple (three or more) UTIs in their lifetime. A woman who has an uncomplicated acute episode has a 25- to 50-percent risk of developing a second episode within 6 months. The bacteria associated with recurrent UTI often appear to be phenotypically and/or genetically identical to the bacterial strain that caused the initial infection, suggesting that selected *E. coli* strains may become uniquely adapted for colonizing and infecting their respective host's urinary tract. The difference in women's susceptibility to UTI compared with that of men has long been thought to most likely be due to anatomical differences between the sexes; however, differences in hormonal and innate immunologic aspects of the response to uropathogens also may play an important role in the outcome of an encounter between host tissue and pathogen. This SCOR's basic and clinical science analyses highlighting host backgrounds and mechanisms that result in differential disease outcomes will provide testable hypotheses for the relative susceptibilities of men and women to UTIs and the effects of sex hormones on important immune mechanisms as well as the technical expertise to test these hypotheses.

The collaborative and interdisciplinary nature of the SCOR is evidenced by the fact that members of projects 1, 2, and 3 have made considerable progress toward the goals for this SCOR funding period. Members of the scientific teams have developed new models and experimental protocols for testing the hypotheses and analyzing clinical samples and uropathogenic bacterial strains collected from women in project 2. Although each of the project PIs has responsibility for the scientific direction and budget oversight of his or her respective project, each project PI discusses scientific progress and budgetary considerations with program director Dr. Hultgren and frequent communication between the PIs have been used to coordinate the work of project 2 at the University of Washington and Duke University and projects 1 and 3 at Washington University in St. Louis. These constant interactions continue to foster new ideas and experimental directions and lead to a synergistic approach to the overall experimental design and methods.

The specific aims of project 1 are to (1) investigate intracellular bacterial community (IBC) formation and infectious outcomes of

[29] Liu, P., Lu, Y., Recker, R. R., Deng, H. W., & Dvornyk, V. (2010). ALOX12 gene is associated with the onset of natural menopause in white women. *Menopause, 17*(1), 152–156.

UTI using a diverse panel of clinical UPEC isolates and a range of host genetic backgrounds; (2) investigate the correlations between markers of host response and disease outcome; (3) investigate genes that provide UPEC with a competitive advantage during UTI; and (4) characterize soluble disease-related factors in mouse and human UTI. In this funding period, project 1 has published five peer-reviewed papers and four reviews related to this work. In addition, it has collaborated with projects 2 and 3 for two additional peer-reviewed papers. Project 1 has made contributions to a better understanding of epithelial renewal in the urinary tract subsequent to UPEC infection, defined the roles of the large plasmid resident in the prototypical UPEC strain UTI89 and the QseB/C two-component regulatory system, and detailed mechanisms used by *Enterococcus* to facilitate protein localization and biofilm formation.

The specific aims of project 2 are to (1) assess the innate immune response to infection in patients who have a single isolated UTI versus those with recurrent infection, (2) differentiate same strain and different strain recurrence, and (3) correlate elements of the innate response with urovirulence.

Yale University

The Yale environment is benefiting from a well-established interdisciplinary SCOR investigating sex-specific factors affecting stress and substance use disorders and more recently expanding to behavioral addictions such as overeating, incorporating research from the disciplines of cellular and molecular biology, human neurobiology, behavioral pharmacology, reproductive endocrinology, functional neuroimaging, human genetics, psychology, and clinical outcomes research using state-of-the art neurobiological approaches, animal and human laboratory methods, and clinical and psychosocial methods.

Through the establishment of this collaborative, interdisciplinary SCOR on women's health that addresses the study of sex-specific factors affecting stress and substance use disorders, the center achieved its original aims. The Yale SCOR has fostered the development of more than 24 research projects led by SCOR-affiliated faculty at Yale and outside institutions. The SCOR has provided research training and/or research support for 24 fellows and junior faculty in the study of sex differences or measurement of sex-specific factors in the interaction of stress and addiction and has supported 24 translational pilot and preliminary studies conducted by fellows and junior faculty. Further, the SCOR has provided consultation on methodological and strategic issues related to sex differences and gender research to a wide range of investigators at Yale and at other institutions. Inter-SCOR collaborations have been initiated to study similarities and differences in addiction mechanisms that affect stress-related disorders commonly affecting women's health. This very productive SCOR has presented research on women and drug abuse at local, regional, and national scientific meetings and organizations to promote research on women and drug abuse. In year 8 alone, investigators generated 25 SCOR-derived and 15 SCOR-related scientific publications and a total of 53 scientific presentations from its component projects and core investigators.

In the past 8 years of ORWH SCOR funding, the Yale SCOR has identified critical aspects of cocaine addiction that are different for men and women. The center's studies provide novel and consistent evidence that females show a greater susceptibility to addictive properties of drugs like cocaine and develop dependence at a faster rate than males. However, this increased susceptibility to developing drug habits is significantly increased with exposure to chronic stress and early-life stress. In its second round of funding, the SCOR has undertaken studies in at-risk adolescents to understand the vulnerability and risk pathways that contribute to such risk in girls and women. The center's basic science findings indicate that the sex chromosome and stress interact to affect the development of habits. Sex differences in brain structure, chemistry, and function pertaining to cocaine and to stress effects also have been identified. Clinical data show that stress plays a key role in the relapse process and that a sex-based biology mediates the chronic effects of cocaine on development and maintenance of dependence and risk of relapse. These novel translational findings across basic science and human studies have uniquely identified important factors

to explain the basis of greater addiction susceptibility in women. The findings are affecting the field in two ways: (1) by generating a rapidly growing interest in conducting sex-specific research on women and substance use disorders and (2) by establishing an increased awareness of and emphasis on gender-specific prevention and treatment strategies. With this greater understanding of sex differences and gender-based factors affecting substance use disorders, investigators anticipate developing new gender-specific targeted treatment initiatives that will enhance the lives of at-risk girls and addicted women and their families.

BIRCWH and SCOR Activities at the Annual NIH Interdisciplinary Women's Health Research Symposium

Select abstracts from BIRCWH scholars and SCOR PIs highlighting findings from their women's health and sex differences research are presented at the Annual NIH Interdisciplinary Women's Health Research Symposium, an event attended by more than 200 people in the scientific community in each of the past two fiscal years. These abstracts were published in the fall issue of the *Journal of Women's Health*.[30, 31]

In conjunction with the annual symposium, the BIRCWH and SCOR directors attend an annual meeting with ORWH at which BIRCWH scholars' progress is reviewed and SCOR PIs are provided an opportunity to report results of their sex differences research. A separate program also is provided for scholars that includes workshops and presentations from senior NIH officials on grant writing, peer review, career development, and the NIH loan repayment program. The annual meeting with ORWH also provides opportunities for networking and collaboration between BIRCWH PIs, BIRCWH scholars, and senior SCOR investigators. A highlight of the meeting is a roundtable discussion between the scholars and the ORWH Director to discuss their research progress, provide feedback on the career mentoring they receive in their programs, and offer suggestions for any enhancement of the BIRCWH experience.

ORWH Activities Related to NIH Chronic Fatigue Syndrome Research

ORWH coordinates and chairs the Trans-NIH ME/CFS Working Group (ME/CFS) Research Working Group, which is composed of program officials representing 17 NIH Institutes, Centers, and Offices. Established in 2001, the working group enables NIH to have an evolving action plan. Activities include workshops, meetings, and publications that strengthen trans-NIH understanding of CFS. The working group also identifies and develops funding opportunities that foster and build cross-disciplinary partnerships that can enhance CFS research in areas such as neuroendocrinology, immunology, sleep, pain, the autonomic nervous system, and infectious diseases.

CFS Background

Chronic fatigue syndrome, also referred to as chronic fatigue and immune dysfunction syndrome (CFIDS) or myalgic encephalomyelitis, is characterized by more than 6 months of incapacitating fatigue experienced as profound exhaustion and extremely poor stamina, and problems with concentration and short-term memory. A distinctive characteristic of the illness is post-exertion malaise, a worsening of symptoms following physical or mental exertion occurring within 12–48 hours of the exertion and requiring an extended recovery period. Other symptoms of CFS are highly variable and fluctuate in severity. A consensus on case definition for CFS does not exist, and the disease does not have a confirmed etiology, diagnosis, or treatment other than symptom management. CFS affects roughly 1 to 4 million people in the United States and 17 million worldwide. CFS strikes all age, racial, ethnic, and socioeconomic groups and is diagnosed 2 to 4 times more often in women (522 cases per 100,000) than in men.

[30] Kornstein, S. G. & Klein, W. S. (Eds.). (2010). Abstracts from the NIH Office of Research on Women's Health sixth annual interdisciplinary women's health research symposium [Special section]. *Journal of Women's Health, 18*(10), 1485–1523.

[31] Kornstein, S. G. & Klein, W. S. (Eds.). (2010). Abstracts from the NIH Office of Research on Women's Health seventh annual interdisciplinary women's health research symposium [Special section]. *Journal of Women's Health, 19*(10), 1775–1804.

Chronic Fatigue Syndrome Advisory Committee

NIH is an ex officio member of the U.S. Department of Health and Human Services (HHS) Chronic Fatigue Syndrome Advisory Committee (CFSAC).[32] The chair of the working group serves as the NIH representative. CFSAC provides advice and recommendations on issues related to CFS to the Secretary of HHS via the Assistant Secretary for Health of HHS. These issues include factors affecting access and care for persons with CFS; the science and definition of CFS; and broader public health, clinical, research, and educational issues related to CFS. In FY 2009 and FY 2010, the working group chair presented updates to the CFSAC on grants funded, new and existing research funding opportunities, and upcoming NIH-supported CFS conferences.

Research Activities

NIH continues to solicit and invest in a diverse portfolio of grants covering multiple aspects of CFS research. Grants awarded in response to the RFA Neuroimmune Mechanisms and Chronic Fatigue Syndrome (RFA-OD-06-002) studied cognitive behavioral stress management of CFS, the proteomics of cerebrospinal fluid in CFS, the autonomic nervous system in CFS, and the spinal cord cytokines associated with chronic pain. A program announcement (PA) solicitation titled Chronic Fatigue Syndrome: Pathophysiology and Treatment (PA-08-246 and PA-08-247) resulted in ORWH cofunding of grants to study stress management on CFS symptoms and the neuroimmune process; the molecular profile of immune responses in CFS patients; new strategies to identify infectious agents associated with CFS, including gammaretroviruses; and the role of brain mast cells in CFS. (See table 1 and table 2, pp. 27-41, for more information.)

Working group members also participate in the HHS Blood XMRV Scientific Research Working Group project that is systematically determining the prevalence of xenotropic murine leukemia virus-related virus (XMRV) in the donor population and whether XMRV is transmissible by blood transfusion.

In October 2009, a paper published in *Science* reported the presence of XMRV, a gammaretrovirus, in the blood cells and plasma of 67 percent of CFS patients and 4 percent of normal healthy controls. Many subsequent studies have not been able to confirm this finding, although one paper did find evidence of a related retrovirus, mouse leukemia virus (MLV), in more than 80 percent of CFS patients. These findings stimulated further interest in a virologic cause of CFS, and NIH received a sharp increase in the number of applications to study XMRV/MLV retroviruses in FY 2010.

Chronic Fatigue Syndrome Workshops and Conferences

A workshop cosponsored by the ORWH and the CFIDS Association of America, From Infection to Neurometabolism: A Nexus for CFS, was held in September 2009 at the Banbury Center at Cold Spring Harbor Laboratories. One goal was to create a system whereby CFS investigators funded by NIH or CFIDS could collaborate, share, discover, and validate research data in a secure networked environment. Using findings from a literature base of more than 5,000 research papers on the infections, genetics, neuropathology, and brain metabolism of patients with CFS, investigators discussed possible early biomarkers that might define and stratify CFS and be used to expedite control and prevention of CFS. There was consensus that a CFS network was necessary to accelerate progress in discovery of biomarkers for objective diagnosis and "subtyping" of CFS as well as for target treatments and leveraging existing expertise from established network models. The CFS network would serve to bring clinical and academic investigations closer together, thereby accelerating impact on the care of patients. The network would be used to engage investigators, expand communication within the research fields, promote information sharing, help new investigators enter CFS research, and pool data to better understand natural history and identify biomarkers. Efforts to develop the CFS network continued throughout FY 2009 and FY 2010.

[32] Information about HHS CFSAC is available online at http://www.hhs.gov/advcomcfs/

Working group members participated in the First International Workshop on Xenotropic Murine Leukemia Virus-Related Retrovirus (XMRV), which was cosponsored by NCI/NIH, HHS, and Abbott Diagnostics and convened in September 2010 on the NIH campus, Bethesda, MD. Attracting an international audience of more than 200 participants, the 2-day event combined a series of plenary talks with updates on different aspects of XMRV research, addressing basic gammaretrovirus biology, host response, association of XMRV with chronic fatigue syndrome and prostate cancer, assay development, and epidemiology. The conference helped to evaluate the current status of XMRV research, address concerns among the scientific community, and provide suggestions for future research.

During FY 2010, ORWH responded to a large public campaign for more funding for CFS and XMRV research.

Summary: Advancing and Implementing the NIH Strategic Plan through ORWH Interdisciplinary Research and Career Development Programs

Interdisciplinary research has blossomed during the past decade into a major component of women's health and sex differences research and careers. The BIRCWH career development initiative is expanding the number of women's health researchers with an understanding of interdisciplinary and comprehensive approaches to health and disease. The fifth round of BIRCWH resulted in 13 new programs, bringing the total to 29 active programs across the United States in 2010. The collaborative nature of the SCOR centers fuels institutional expansion of women's health, interdisciplinary efforts, and discovery of sex and gender differences in health and behavior. The annual meetings of the two interdisciplinary programs afford opportunities for mentoring, networking, and exchange of scientific dialogue between junior and senior researchers at intra- and interinstitutional levels and across disciplines and fields.

These programs, which support and advance all six of the strategic planning goals, continue to produce innovative strategies in women's health and sex differences research and translation into clinical practice. ORWH interdisciplinary research and career development programs provide opportunities for scientists to overcome the remaining and evolving gaps in knowledge, which can that may lead to improved health for women and their families as well as the delivery of evidence-based medicine to women, girls, and their families. Interdisciplinary efforts have also proven beneficial in the pursuit of expanding scientific knowledge about CFS involving many diverse areas of investigation and multiple NIH ICs. This comprehensive approach continues to be utilized to address this complex condition.

III. ORWH Biomedical Career Development Activities

Section III of this biennial report provides information on Office of Research on Women's Health (ORWH) initiatives and support for a wide range of career development activities. A major component of the ORWH mandate is to develop opportunities and support for the recruitment, retention, reentry, and advancement of women in biomedical careers. To begin efforts to accomplish these goals, ORWH held a public hearing and major career development workshop in 1992. Based on the report from this meeting, *Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century*,[33] ORWH initiated a number of programs to nurture the participation and advancement of women in biomedical careers in order to ensure that interest and priorities in women's health remain at the forefront of our Nation's research agenda. In the years since, ORWH has developed strategies and programs to continue to implement the recommendations made at this early workshop and to address career issues, barriers, and concerns of women and minorities in science.

In addition, through efforts to increase the cadre of women's health and sex differences researchers, ORWH has expanded its activities to address career advancement in research for both women and men. These programs include support for mentored research training in areas related to women's health, including support for the reentry of biomedical scientists who have interrupted careers in research to fulfill family or other obligations to restart their research careers; the Women's Reproductive Health Research (WRHR) and Career Development program described in this section; the Building Interdisciplinary Research Centers in Women's Health (BIRCWH) program described in section II; collaboration with professional societies to encourage their support of career advancement of women scientists; and outreach to girls and women with an interest in pursuing careers in biomedical science.

Section III also provides a summary of the activities of the National Institutes of Health (NIH) Working Group on Women in Biomedical Careers, which was convened in 2007 and cochaired by then-NIH Director Elias A. Zerhouni, M.D., with ORWH designated as NIH lead and the ORWH Director as the other cochair. Vivian W. Pinn, M.D., Associate Director for Women's Health and Director of ORWH, cochaired the working group in 2009 with then-Acting NIH Director Raynard S. Kington, M.D., Ph.D., and beginning in September 2010, with current NIH Director Francis S. Collins, M.D., Ph.D. The working group's activities are varied, but all of them aim to enhance the career development of women in biomedical science, through programs and policies applicable to both women and men but addressing issues that are of main concern to women.

Also in this section is a summary of activities and accomplishments of ORWH-supported NIH intramural training and women's health research programs. Activities include seminars to highlight intramural research on women's health and sex/gender differences as well as initiatives—many developed in parallel with the working group—to facilitate a successful combination of family responsibilities with a scientific career and to promote the career development of female intramural scientists.

Office of Research on Women's Health/NIH Reentry Program

The ORWH/NIH Reentry Program provides administrative supplements to existing NIH research grants for the purpose of supporting full- or part-time research by women or men reentering the scientific workforce. The program is designed to bring the scientist's existing research skills and knowledge up-to-date so that by the completion of the supplement the scientist will be prepared to apply for a career development or research award.

The Reentry Program includes three components that contribute to the process of

[33] U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (1995). *Women in biomedical careers: Dynamics of change: Strategies for the 21st century. Full report of the workshop: Bethesda Marriott, Bethesda, Maryland, June 11–12, 1992* (NIH Publication No. 95-3565). Summary of issues available online at http://womeninscience.nih.gov/resources/dynamicsofchange.asp

reestablishing awardees as independent, competitive research scientists:

- Full participation in the research project
- An opportunity to update and enhance research capabilities
- A carefully planned mentoring program developed by the mentor and the awardee

To date, more than 135 women and men have received Supplements to Promote Reentry into Biomedical and Behavioral Research Career awards.

In parallel with efforts of the NIH Working Group on Women in Biomedical Careers, ORWH led the effort to broaden program eligibility to include postdoctoral fellows. The program announcement (PA) for Research Supplements to Promote Reentry Into Biomedical and Behavioral Research Careers (PA-08-191) was reissued in July 2008 and continues through the current time period with support from 23 Institutes and Centers (ICs). The announcement states that candidates with a postdoctoral or faculty position at the time they left active research are eligible to apply.

FY 2009 Reentry Awardees

NHLBI: Tracy Baker-Herman, Ph.D. (Year 2)

Institution: University of Wisconsin

PI: Gordon S. Mitchell, Ph.D.

Grant: 5R37HL069064-07

Title: Respiratory Plasticity Following Spinal Cord Injury

After beginning her postdoctoral research in Dr. Mitchell's laboratory, Dr. Baker-Herman left research for 2 years to care for her young children but continued her affiliation with the lab by contributing to several manuscripts and completing a meta-analytic study. Her passion and commitment to pursue her research interests led her to return to a full-time career in biomedical research. She has returned to the laboratory of Dr. Mitchell and plans to develop an independent research program and seek a tenure-track faculty position.

NHLBI: L. Maria Belalcazar, M.D. (Year 2)

Institution: Baylor College of Medicine

PI: Christie M. Ballantyne, M.D.

Grant: R01HL090514

Title: Long-Chain Omega-3 Fatty Acid Intake and the Modulation of Atherothrombotic Risk in Obese Diabetics

Dr. Belalcazar received her M.D. and completed her residency in Bogotá, Colombia, then migrated to the University of Pittsburgh where she received a fellowship. She then went to the University of Texas Medical Branch and did another residency in internal medicine. Following her second residency, she had a 3-year fellowship at Baylor College of Medicine in endocrinology, diabetes, and metabolism. At the time of Dr. Belalcazar's career hiatus, she was a full-time tenure-track assistant professor. Following her divorce, the candidate's children required increased maternal support. With her family situation stable, she was eager to return to a full-time academic career. Her position then was part-time clinical assistant professor of medicine. Under the mentorship of Dr. Ballantyne, Dr. Belalcazar planned to clarify the association between obesity, inflammation, and coagulation balance in diabetics to determine the impact of weight loss, diet, and physical activity on these parameters.

NHLBI: Shannon Christian, Ph.D. (Year 1)

Institution: National Jewish Health

PI: Mark Aloia, Ph.D.

Grant: 7R01HL067209-07

Title: Motivating Adherence to CPAP in Obstructive Sleep Apnea (BREATHE)

Dr. Christian demonstrated a commitment to biomedical research and clinical service in the field of psychology. She completed several postdoctoral fellowships and authored numerous publications on asthma management before taking a hiatus from research activities to care for her ill child. Dr. Christian planned to use the funds provided to receive formal and practical experience in the area of sleep research and to better understand strategies for improving adherence to continuous positive airway pressure (CPAP) treatment for sleep apnea. This marked a new domain for Dr. Christian, and her mentoring and training plan reflected a

thoughtful approach to navigating her reentry and mastery of a new field of research.

NIDA: Katherine Peebles, Ph.D. (Year 1)

Institution: Arizona Health Sciences Center

PI: Frank Porreca, Ph.D.

Grant: 3R01DA023513-02

Title: N6F-Dependent Sensitization of Nocioceptors by Opiate

Dr. Peebles took a hiatus from her research activities because of her husband's service in the military and the relocation of her family.

FY 2010 Reentry Awardees

NHLBI: Shannon Christian, Ph.D. (Year 2)

NIDA: Katherine Peebles, Ph.D. (Year 2)

NHLBI: Dolena Ledee, Ph.D. (Year 1)

Institution: Seattle Children's Research Institute

PI: Michael Portman, M.D.

Grant: R01HL060666

Title: Metabolism During Mechanical Circulatory Support in the Developing Heart

Dr. Ledee expressed a strong desire to reestablish her research career after taking a 2-year hiatus. In 2008 her husband's work relocated the family to Seattle where Dr. Ledee found no research opportunities and instead took care of her two young children. Before this move, Dr. Ledee focused on molecular and cell biology research, and she argued convincingly that these skills are highly transferable to the field of cardiovascular research. Dr. Ledee planned to use the funds provided to receive formal and practical experience in the area of cardiovascular metabolism research, as well as mentorship from senior researchers and an extended network of collaborators. She demonstrated a high level of enthusiasm; her hope is to become an independent investigator.

Women's Reproductive Health Research Career Development Program

The Women's Reproductive Health Research (WRHR) Career Development Program was initiated by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) in 1998, and ORWH joined NICHD in cosponsoring this initiative, which has supported more than 170 scholars to date. This institutional career development award uses the K12 mechanism to support research career development of WRHR scholars, who are obstetricians-gynecologists with recently completed postgraduate clinical training and are about to commence basic, translational, and/or clinical research relevant to women's reproductive health. The goal of this initiative is to promote research that will benefit the health of women by bridging clinical training with research independence, increasing the number and skills of obstetrician-gynecologist investigators at awardee institutions through a mentored research experience leading to an independent scientific career addressing women's reproductive health concerns.

ORWH supports 17 active WRHR centers in departments of obstetrics and gynecology throughout the Nation. Ten new and competing continuation WRHR program sites were funded in 2009. An additional seven new and competing continuation programs were funded in 2010. The active WRHR program sites, along with the principal investigators (PIs) and research directors (RDs) are listed below:

2009 WRHR Sites

WRHR at the University of Washington

Institution: University of Washington, Seattle, WA

PI: David A. Eschenbach, M.D.

RD: Susan Reed, M.D., M.P.H.

Magee-Women's Basic and Translational Reproductive Health Training Program

Institution: Magee-Women's Research Institute and Foundation, Pittsburgh, PA

PI: W. Allen Hogge, M.D.

RD: Yoel Sadovsky, M.D.

WRHR Career Development Program at Washington University in St. Louis

Institution: Washington University, St. Louis, MO

PI: George A. Macones, M.D., M.S.C.E.

RD: Kelle H. Moley, M.D.

Yale WRHR Career Development Center

Institution: Yale University, New Haven, CT

PI: Charles J. Lockwood, M.D., M.H.C.M.

RD: Richard B. Hochberg, Ph.D.

Detroit Reproductive Career Development Research Center

Institution: Wayne State University, Detroit, MI

PI: Theodore B. Jones, M.D., FACOG

RD: Michael P. Diamond, M.D.

University of California, San Francisco WRHR Career Development Program

Institution: University of California, San Francisco, (2009)

PI: Linda C. Giudice, M.D., Ph.D., M.Sc.

RDs: Synthia Mellon, Ph.D. (Co-RD), Leslee Subak, M.D. (Co-RD)

WRHR: A Mentoring Program in Women's Reproductive Health Research at the University of Vermont

Institution: University of Vermont, Burlington, VT

PI: Mark Phillippe, M.D., M.H.C.M.

RDs: George Osol, Ph.D., Elizabeth Bonney, M.D. (Associate RD)

Iowa WRHR Career Development Center

Institution: University of Iowa, Iowa City, IA

PI: Kimberly K. Leslie, M.D.

RD: Mario Ascoli, Ph.D.

University of Texas Medical Branch WRHR Career Development Center of Excellence

Institution: University of Texas Medical Branch, Galveston, TX

PI: Gary D.V. Hankins, M.D.

RD: Chandra Yallampalli, D.V.M, Ph.D.

Penn Center for Career Development in Women's Health Research

Institution: University of Pennsylvania, Philadelphia, PA

PI: Deborah A. Driscoll, M.D.

RD: Christos Coutifaris, M.D., Ph.D.

2010 WRHR Sites

Brown/Women and Infants Hospital WRHR Career Development Program

Institution: Women and Infants Hospital of Rhode Island/Brown University, Providence, RI

PI: Joanna Cain, M.D.

RD: Maureen G. Phipps, M.D., M.P.H.

University of Michigan WRHR Career Development Program

Institution: University of Michigan, Ann Arbor

PI: Timothy Johnson, M.D.

RD: Yolanda R. Smith, M.D., M.S.

Research Career Development in Obstetrics and Gynecology

Institution: Northwestern University, Chicago, IL

PI: Sherman Elias, M.D., FACOG, FACMG

RD: Serdar E. Bulun, M.D.

Colorado WRHR Career Development Center

Institution: University of Colorado, Denver

PI: Nanette Santoro, M.D.

RD: James McManaman, Ph.D.

University of Kansas Medical Center WRHR Career Development Program

Institution: University of Kansas Medical Center, Kansas City, KS

PI: Carl P. Weiner, M.D., M.B.A.

Obstetrics/Gynecology Faculty Research Career Development Program

Institution: University of Alabama at Birmingham

PI: William W. Andrews, Ph.D., M.D.

RD: Ronald D. Alvarez, M.D.

Reproductive Sciences Research Career Development Center

Institution: University of California, San Diego

PI: Thomas R. Moore, M.D.

RD: Pamela L. Mellon, Ph.D.

NIH Pioneer Award

In FY 2009 and FY 2010, ORWH continued to provide funds to support the research of Lisa Feldman Barrett, Ph.D., "Emotions Are Emergent Events Constrained by Affective and Conceptual Processes." This award is part of the NIH Director's Pioneer Award Program, a high-risk research initiative of the NIH Common Fund. Pioneer awards are designed to support individual scientists of exceptional creativity who propose pioneering—and possibly transforming—approaches to major challenges in biomedical and behavioral research. Dr. Barrett's research is described as follows:

> Emotional states are central to mental and physical health. NIH invests tremendous resources in research on emotion, much of it devoted to animal models. Ironically, this research is guided by a scientific paradigm that is grounded in human experience. People experience fear and see it in others, so scientists assume there must be a literal (modular) neural circuit for fear in the mammalian brain. Rats freeze when they hear a tone paired with a foot shock, so they are presumed to be in a state of fear (versus surprise, anger, or even a general state of alarm) and undergoing "fear learning." Scientists also presume that a map of the neural circuitry of freezing behavior will yield a neural mechanism for fear that is largely preserved in humans, and a decade of neuroimaging studies has focused on locating a homologous neural circuit in the human brain.

In the past 5 years, Dr. Barrett has traced the roots of this "natural kind" model, conducted a comprehensive review of the literature to examine its veracity, and found it wanting.[34] In response, she fashioned a new systems-level model called the Conceptual Act Model, grounded in the neuroanatomy of the human brain. Her model parsimoniously incorporates neuroscience findings from rats, primates, and humans and explains the mechanisms that produce the range and variety of behavioral and introspective instances that we call "emotion".[35, 36, 37, 38, 39] The Conceptual Act Model asks different—and perhaps better—questions about what emotions are and how they function in mental and physical health.

The NIH Director's Pioneer Award will allow Dr. Barrett the intellectual freedom and resources to continue building evidence for the Conceptual Act Model of emotion, thereby shaping a new paradigm to guide the scientific study of emotion.

Dr. Barrett has published nine scholarly papers with support from the Pioneer Award.

NIH Working Group on Women in Biomedical Careers

As part of its mission to support and advance girls and women in biomedical careers, in 2005, ORWH provided the

[34] Barrett, L. F. (2006). Are emotions natural kinds? *Perspectives on Psychological Science, 1*, 28–58.

[35] Barrett, L. F. (2006). Solving the emotion paradox: Categorization and the experience of emotion. *Personality and Social Psychology Review,10*, 20–46.

[36] Barrett, L. F. (2006). Valence as a basic building block of emotional life. *Journal of Research in Personality, 40*, 35–55.

[37] Barrett, L. F., Mesquita, B., Ochsner, K. N., & Gross, J. J. (2007). The experience of emotion. *Annual Review of Psychology, 58*, 373–403.

[38] Barrett, L. F., Ochsner, K. N., & Gross, J. J. (2007). On the automaticity of emotion. In J. Bargh, (Ed.), *Social psychology and the unconscious: The automaticity of higher mental processes* (pp. 173–218). New York, NY: Psychology Press.

[39] Duncan, S. & Barrett, L. F. (2007). Affect is a form of cognition: A neurobiological analysis. *Cognition and Emotion, 21*(6), 1184–1211.

initial funding to the Committee on Science, Engineering, and Public Policy, a joint program of the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine and the National Research Council standing Committee on Women in Science and Engineering to address issues relevant to women in academic science and engineering. Later funding was provided by Eli Lilly and Co., the National Science Foundation, Ford Foundation, and the National Academies. With this funding, the National Academies created the ad hoc Committee on Maximizing the Potential of Women in Academic Science and Engineering, chaired by Donna Shalala, Ph.D., president of the University of Miami and former Secretary of the U.S. Department of Health and Human Services, to hold a workshop and release a report titled *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*.

The National Academies report noted that women today comprise an increasing proportion of science and engineering majors; nonetheless, the representation of women in leadership positions in academic institutions, scientific and professional societies, and honorary organizations is low relative to the number of women qualified to hold these positions. The report concluded that eliminating gender bias in academia would require an immediate overarching reform including decisive action by university administrators, professional societies, Federal funding agencies, foundations, Government agencies, and Congress.

Establishment of the Working Group

In response to the National Academies report, former NIH Director Elias A. Zerhouni, M.D. created the NIH Working Group on Women in Biomedical Careers in early 2007 to examine the issues raised in the report and to respond to the challenges issued to Government funding agencies to maximize the potential of women scientists and engineers, give attention to the NIH intramural community and the concerns of intramural women scientists, consider the broader context of girls and women in science, and provide special attention to issues of barriers, minority women scientists, and mentoring.

The working group, which continues to be cochaired by the NIH and ORWH Directors, is composed of individuals from across NIH at different career levels, including both men and women, individuals from underrepresented groups, postdoctoral fellows, young investigators, a dual-career couple, directors of ICs, and NIH Deputy Directors. The activities of the working group, which are implemented in collaboration with numerous NIH offices and committees, are spearheaded by seven committees, each chaired by a working group member appointed by the NIH Director and including additional appropriate intramural and extramural staff.

In January 2010, the new NIH Director, Francis S. Collins, M.D., Ph.D., enthusiastically accepted the role of working group cochair and has encouraged the working group to consider how the programs and policies they have developed and will continue to develop can be evaluated for effectiveness.

The working group Web site,[40] which is maintained by ORWH, continues to provide a central focus for career development resources for women, both from NIH and from other organizations. For example, the Web site includes links to more than 250 news articles and reports about women in science and continues to be updated. In addition, the working group maintains a listserv for *NIH Updates on Women in Science (NUWS)*, an e-newsletter containing articles and items pertaining to women in science. In 2010, *NUWS* was expanded to include profiles of outstanding early-career women scientists and examples of best practices for recruitment, retention, and advancement of women that are being implemented in universities in the United States.

ORWH/Working Group Workshop Reports

Demand for the reports of the *National Leadership Workshop on Mentoring Women in Biomedical Careers*[41] and *Women in Biomedical*

[40] NIH Working Group on Women in Biomedical Careers. Information available online at http://womeninscience.nih.gov

[41] NIH Working Group on Women in Biomedical Careers. (2008). *National leadership workshop on mentoring women in biomedical careers. Meeting proceedings* (NIH Publication No. 09-636). Bethesda, MD: National Institutes of Health.

Research: Best Practices for Sustaining Career Success[42] workshops, which were sponsored by the working group in 2007 and 2008, respectively, has been so overwhelming that they are both now in their second printing, with more than 6,500 copies of each having been distributed. The recommendations from these meetings continue to inform the activities of the working group and NIH. Videocasts of the meetings, the proceedings, and other resources are available on the Women in Biomedical Careers Web site.[43]

Extramural Initiatives

In October 2009, NIH announced that it would fund 14 grants in response to the Request for Applications (RFA) titled Research on Causal Factors and Interventions That Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering. The RFA was developed by a subcommittee of the working group and is overseen by NIGMS. The awards are estimated to total $16.8 million over 4 years with support from 11 ICs and 4 offices within the Office of the Director (OD), with 7 ICs administering the grants. The full text of the announcement, as well as the listing of sponsoring ICs and grantees, can be found on the Women in Biomedical Careers Web site.[44]

In January 2010, the application for NIH conference grants was amended to require that applicants describe plans to identify resources for child care and other types of family care at the conference site.[45] This change recognizes the fact that attendance for some individuals will depend on the availability of resources for family care and the importance of enabling these individuals to participate in conferences and training to further their skills and increase their opportunities for collaboration, while still addressing their family responsibilities.

The Office of Extramural Research compiles and posts updated data on the participation of women in the NIH extramural program. This information can be found in the *NIH Data Book* online in the section on data by gender.[46]

In addition, to promote and reward mentoring by NIH grantees, a notice was posted in the NIH *Guide for Grants and Contracts* in 2010 to encourage grantees to apply for the Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring.

Intramural Initiatives

A number of new initiatives have been developed in conjunction with the Office of Intramural Research (OIR) and the Council of Scientific Directors (SDs) aimed at improving and expanding mentoring in the Intramural Research Program (IRP) and improving the environment to attract and advance a more diverse scientific workforce. The reports of the Trans-NIH Mentoring Committee and focus groups of tenure-track investigators, postdoctoral fellows, and staff scientists and clinicians have been presented to the SDs, and the recommendations have resulted in new policies and practices in the intramural program. In particular, the OIR Web site now features "Goals for Enhanced Mentoring in the IRP" that are being implemented; demographics on gender and race/ethnicity of IRP investigators; and a reorganized listing of responsibilities, benefits, resources, and policies for each position in IRP.

The Mid-Atlantic Higher Education Recruitment Consortium (M-A HERC), which NIH helped establish, continues to grow in membership, expanding the resources available to members of dual-career couples. M-A HERC now includes more than 50 area colleges, universities, Federal agencies, and professional societies located throughout Maryland, Virginia, and the District of Columbia, with more than 4,000 job opportunities currently listed. In addition, it now

[42] NIH Working Group on Women in Biomedical Careers. (2009). *Women in biomedical research: Best practices for sustaining career success. Meeting proceedings* (NIH Publication No. 09-7366). Bethesda, MD: National Institutes of Health.

[43] Women in biomedical careers: Workshops and events. Available online at http://womeninscience.nih.gov/workshops.asp

[44] Funding opportunity: Research on causal factors and interventions that promote and support the careers of women in biomedical and behavioral science and engineering (RFA-GM-09-012). Available online at http://womeninscience.nih.gov/funding/index.asp

[45] NIH support for conferences and scientific meetings (PA-10-071). Available online at http://grants.nih.gov/grants/guide/pa-files/PA-10-071.html

[46] NIH data book. Available online at http://report.nih.gov/nihdatabook

features a CV/resume database to make it even easier for individuals and dual-career couples to locate a position in the area. In addition to the Web site, which lists job opportunities at all member institutions, M-A HERC serves as a network for increasing collaboration between regional institutions, providing additional job placement opportunities for "trailing partners," and sharing best practices for recruiting dual-career couples, methods to improve diversity achieved by search committees, and policies that support work/life balance and workplace flexibilities. More information on M-A HERC can be found on its Web site.[47]

The NIH Leave Bank, which was launched in 2010 by the Office of Human Resources with support from the working group and ORWH, offers income protection to eligible NIH employees who are affected by a personal or family medical emergency. The Leave Bank allows members to receive paid annual leave for medical emergencies, including the birth of a child, after they have exhausted their own leave. The Leave Bank differs from the existing Voluntary Leave Transfer Program (VLTP) in that under VLTP, donations are made from individuals directly to other individuals, whereas under the Leave Bank, this process is streamlined by collecting all of the donated leave into a pool and then distributing it as needed. ORWH provided a total of $120,000 during FY 2009 and FY 2010 to launch the preliminary activities for the initiation of the Leave Bank. These efforts include modifying the NIH Integrated Time and Attendance System to include the option for the Leave Bank and supporting an independent Federal Occupational Health Medical Review Board, which includes a physician's assistant, a doctor, and a program coordinator, to ensure that requests are appropriate and medically sound. The Leave Bank was piloted in the National Cancer Institute (NCI) in 2010 with the National Human Genome Research Institute (NHGRI) and National Institute of Allergy and Infectious Diseases (NIAID) added in 2011. The goal is to open the program to all NIH employees in 2012. More information on the NIH Leave Bank can be found on the Office of Human Resources Web site.[48]

Funds for the construction of the Northwest Child Care Center on the NIH campus were included in the FY 2010 budget and transferred to the U.S. Army Corps of Engineers, which will serve as a general contractor for the project. This action is a culmination of the efforts of a variety of people and groups at NIH, including the Office of Research Services, the Office of Research Facilities Development, the NIH Child Care Board, and OD. Members of the working group in both OIR and ORWH played an active role in marshaling these efforts closer to their ultimate successful conclusion.

Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering

ORWH provided support for 2 of the 14 awards made under the RFA entitled Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering. For a detailed description of the program, see "Extramural Initiatives" on page 85.

Institution: University of New Mexico, Albuquerque, NM

PI: Deborah Lynne Helitzer, Sc.D.

Grant: 1R01HD064655-01 (FY 2009); 5R01HD6455-02 (FY 2010)

Title: Achieving a Critical Mass of Women in Biomedical Faculty

Although numerous career development programs exist for women faculty, women continue to leave academic medicine at alarmingly high rates. This study examined the impact on the retention and career success of individual women faculty who participated in three long-standing national programs, each of which targeted a separate career stage, compared with women and men at the same career stages who did not participate in these programs. This research also aimed to elucidate the patterns and processes that contribute to the experience

[47] Mid-Atlantic higher education recruitment consortium, http://www.midatlanticherc.org

[48] NIH Office of Human Resources. NIH voluntary leave bank program. http://hr.od.nih.gov/benefits/leave/vlbp/default.htm

of individuals and their institutions as a means to identify the barriers and facilitators—historic and new, individual and institutional—that women faculty face in attaining positions of leadership at academic health centers and transforming institutional culture. Informed by the guidance of an advisory board composed of highly respected female and male senior leaders in academic medicine, the goal of the research is to assess the impact of participation in intensive career development training programs on individual women faculty at early- and middle-career stages and their institutions, in terms of retention and promotion, while verifying and illuminating the ways in which participation in these programs affects career trajectories.

The researchers attempted to discover how the findings on retention, academic promotion, and administrative advancement are influenced by (1) individual dynamics and personal/professional development factors addressed in leadership development programs; (2) organizational factors in institutions that send their women faculty to such programs; (3) the way in which these factors may have led to enhancement of leadership development and gender experience for women participating in these programs; and (4) the way in which the interaction of these factors has or can lead to a change in organizational culture to ensure the ability of institutions to capitalize on the intellectual capital of women science faculty members. Along with this retrospective analysis, the researchers prospectively identified emerging challenges that affect women assistant and associate professors attending intensive career development programs and create an infrastructure for future research on retention and promotion.

In addition, this study provided a comprehensive set of findings to serve as the basis for a future design of an innovative women-focused leadership program as well as provide helpful information on the culture change needed to improve recruitment and retention of America's leading scientific minds. This research assessed the efficacy of three specific interventions that have been in place over the past 20 years to support women's career development within academic health centers. The results of this research identified the ways in which interventions such as these can address the obstacles and facilitators—historic and new, individual and institutional—that women faculty face in attaining positions of leadership and the ways in which these interventions help or hinder changes in institutional culture.

Institution: Cornell University, Ithaca, NY

PI: Yael M. Levitte, Ph.D.

Grant: 1R01NR011988-01, (FY 2009)

Title: Entry and Retention of Women in the Sciences: A Cohort Comparison

Women's underrepresentation in the science labor force has been of great concern to policymakers and researchers. Despite making impressive strides in educational attainment in science, math, engineering, and behavioral (SMEB) fields, women lag behind in entry into and retention in the labor force in these areas. These trends reflect diminished returns on the billions of dollars in public investments in educating this labor force and on women's contribution to the U.S. economy. Moreover, jobs in SMEB disciplines are linked to higher wages, prestige, favorable conditions, and upward mobility and, consequently, to women's well-being; exiting the labor force or transitioning into lower status occupations also has implications for women's quality of life. Understanding women's performance in the science labor force is therefore seen as crucial given their potential role in the U.S. economy.

Researchers have begun to explore the labor force dynamics and the challenges to the optimal participation of women in the science-based workplace. The majority of this research, however, has focused on women in academia, evaluating programs to advance women in educational institutions. Only a handful of researchers have looked at other sectors, such as industry. Moreover, most scholarly research has been retrospective, rather than following women prospectively across the life cycle.

The central goal of the proposed project was to identify the role of attitudes, personal characteristics and family circumstances, and institutional environments in women's career pathways over time. Data for the study came from the National Longitudinal Surveys of Youth of 1979 and 1997, ongoing panel surveys of nationally representative samples of 12,686 young men and women who were aged

14 to 22 in 1979, and 8,984 men and women who were between 13 and 17 in 1997. The data allowed the researchers to draw comparisons between women scientists, men scientists, and women in other disciplines over a 27-year period for the older cohort and over 9 years for the younger cohort. The aging of the older cohort provided an unprecedented opportunity to examine the long-term consequences of marriage and childbearing on career pathways, as well as compare them with opportunities and barriers facing younger women. The researchers planned to make specific policy recommendations for both entry and retention of women in the science workforce based on the results.

Fogarty International Clinical Research Training for Scholars and Fellows Program

ORWH provided support to two postdoctoral fellows in the Fogarty International Clinical Research Training for Scholars and Fellows program for the study of air pollution, fetal growth, and maternal health in China. The expected outcome of this training program is to create a network of leaders in the global health research arena.

National Institute of Diabetes and Digestive and Kidney Diseases Travel Awards—Academic Medicine Programs and Workshop at the 2010 National Medical Association Annual Convention

Since 1998, ORWH has collaborated with the National Institute of Diabetes and Digestive and Kidney Diseases and the National Medical Association (NMA) in supporting residents and fellows interested in academic medicine who participate in a special 2-day academic skills workshop conducted by NIH and held in conjunction with the annual convention and scientific assembly of the NMA. The topics of the workshop range from grantsmanship to time management skills.

The intent of this award is to enhance the potential careers of residents and fellows of all medical and surgical specialties interested in an academic career and to encourage research in disease areas that disproportionately affect the health of underserved communities. NIH anticipates that, through this scientific opportunity, a greater number of physicians from communities that are underrepresented in science will enter into and remain in academic research positions.

Women's Health Issues in the Dental School Curriculum

Background

A comprehensive study of how women's health and gender-related issues are taught in basic and clinical sciences in U.S. dental schools was reported in 1999. The report, *Women's Health in the Dental School Curriculum*,[49] followed a similar 1996 study of medical school curricula and was supported by ORWH and the Health Resources and Services Administration. The 1999 curriculum survey report identified areas of the curriculum needing specific review/revision. Recommendations 4 and 8 are as follows:

- Recommendation 4. Dental curricula should reflect a "life span" approach to women's health. This approach includes girls and women from birth through menopause and past menopause, and a redefinition of terms and treatments for women of "child bearing" age.
- Recommendation 8. Areas of the curricula needing specific review/revision are:
  - » Integrating women's health into the basic science portion of the curriculum;
  - » Improving the instruction of psychosocial and socioeconomic issues, where women are disproportionately influenced;
  - » Considering gender issues in access to care and in planning therapeutics and treatments;

[49] Silverton, S., Sinkford, J., Inglehart, M., Tedesco, L., & Valachovic, R. (1999). *Women's health in the dental school curriculum: Report of a survey and recommendations* (NIH Publication No. 99-4399). Bethesda, MD: National Institutes of Health.

» Increasing the knowledge of future oral health care providers in the social and legal responsibilities of their profession especially as their responsibilities relate to women and the promotion of health and well-being.

One of the major outcomes of the study has been the inclusion of sex and gender issues in the revised American Dental Education Association (ADEA) Competencies for the New General Dentist:[50] "6.1. Manage the oral health care of the infant, child, and adult, as well as the unique needs of women, geriatric and special needs patients."

The seminal report titled *Exploring the Biological Contributions to Human Health: Does Sex Matter?*[51] serves as a basis for the generation of new knowledge from interdisciplinary approaches to research affecting health behaviors and outcomes of women and girls across the lifespan. The dental curriculum is a mechanism through which new science enters the thought and learning processes of future dental practitioners. It is through curriculum change that new scientific discoveries and technologies can be applied to diagnostic and treatment regimes.

There is a need to update and validate the current status of women's health in the curricula of U.S. dental schools. Emerging data related to oral cancer, periodontal disease and low-birth weight infants, obesity and taste, violence, and other factors affect the health of women across the lifespan.

Project Description

In FY 2010, ORWH provided funding for a new dental curriculum study that will contribute to the understanding of newer factors affecting the oral/systemic health of women. Outcomes will affect curriculum change in the future and identify knowledge gaps that require continuous research for solutions.

This project supports goal 6 of the ORWH/NIH strategic plan, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research*[52] through support for interdisciplinary knowledge and training of dental practitioners who contribute to the general health and well-being of women:

> Goal 6: Employ innovative strategies to build a well-trained, diverse and vigorous women's health research resource.

The study will "promote recognition and understanding of women's health among future health professionals and scientists by incorporating sex differences and fundamental knowledge on women's health issues in medical, graduate and dental school curricula." The project comprises the following components:

- A survey of the 58 U.S. dental schools with regard to their curriculum content and objectives for women's health and related issues across the lifespan. The survey will expand on the previous survey with revised content that is especially relevant to the deficiencies identified in the 1999 survey. The survey will identify current knowledge gaps regarding the oral/systemic relationships that affect the health and well-being of women and girls. Outcomes of the survey will serve as the basis for curriculum modification and future research directed toward women's health.
- Production of a written report documenting the survey findings. The report will be published by ADEA for broad dissemination and will ultimately be available on the ADEA Web site in the public domain.
- Presentation of a symposium titled Women's Health in the Dental Curriculum, Implications for Future Research. The symposium will be sponsored by the ADEA Center for Equity and Diversity and the Division of Knowledge Management in tandem with the 2012 ADEA Annual Session and Exhibition (National Program) in Orlando, FL, in March 2012.

[50] American Dental Education Association competencies for the new general dentist. (2008). Available online at http://www.adea.org/about_adea/governance/Pages/Competencies-for-the-New-General-Dentist.aspx

[51] Institute of Medicine. (2001). *Exploring the biological contributions to human health: Does sex matter?* Washington, DC: The National Academies Press.

[52] Moving into the Future, Strategic Plan 2010, 21.

INTEL International Science and Engineering Fair

ORWH provided support for the 2009 Intel International Science and Engineering Fair held in Reno, NV, in May 2009. NIH was a sponsor of the Medicine and Health category. In 2009, three women high school students each won the top prize of $50,000.

National Center for Minority Health and Health Disparities Travel Scholarships

ORWH provided scholarships for 10 young investigators to attend the National Center for Minority Health and Health Disparities/NIH summit, titled The Science of Eliminating Health Disparities, which highlighted the research progress of NIH on health issues among racial/ethnic minority and medically underserved populations.

Association of Women in Science Seminar Series—Bethesda Chapter

The Association of Women in Science (AWIS) seminar series is a continuing program that includes a free yearlong seminar series covering a range of issues of general interest and of special interest to women. The seminars, which are held on the NIH campus, are well attended and include both men and women. Each year the series includes a networking event called "Have a Meal with Your Mentor." In addition, the Bethesda AWIS chapter honors one scientist every year with an award for his or her role in mentoring young women scientists.

FY 2009 seminar topics included the following:

- Motherhood: The Elephant in the Lab
- Money Shy to Money Sure: A Road Map Toward Financial Serenity in Troubled Times
- NIH Efforts To Advance Women in Biomedical Careers
- Researcher Panel—Advice for Young Women Scientists
- Perspectives from NIH 2009 Pittman Lecturer

FY 2010 seminar topics included the following:

- Are We Up To the Task? Improving the Status of NIH Intramural Women Scientists
- Falling Off the Bandwagon: Why Women Scientists Fail To Make the Transition From Postdoc to PI
- Life in Academics: A Panel Discussion Featuring Scientists From DC-Area Universities
- Panel Discussion on Policy, Program, and Review
- Stranger in a Strange Land: Musings from a Neurologist Living Among Psychiatrists—NIH 2010 Pittman Lecturer Helen S. Mayberg, M.D.

Women in the Environmental Mutagen Society

In 2009, ORWH provided funding to support the programmatic activities of the newly organized Women in the Environmental Mutagen Society (WEMS) during the 39th annual meeting of the Environmental Mutagen Society (EMS). The mission of WEMS is to (1) create opportunities for networking and mentoring for women, (2) encourage leadership and career development, and (3) encourage and support representation of women throughout society and in the broader scientific community. Together with the Education and Student Affairs and the Membership and Professional Development Committees of EMS, WEMS also held a special mentoring workshop to introduce a new mentoring program to nurture students, postdoctoral fellows, and early-career investigators in the environmental health sciences. This program was designed to connect more seasoned scientists working in academia, industry, and regulatory agencies with young female scientists to help them in establishing connections that would allow them to flourish.

American Society for Cell Biology (ASCB)—Women in Cell Biology Workshops

Women in Cell Biology (WICB) is a long-standing committee of the American Society for Cell Biology (ASCB). WICB provides year-round career support and advice. The committee responds to reports of discriminatory practices, offers a speaker referral service to help program organizers identify women speakers, and produces monthly columns for the ASCB newsletter. ORWH provided support to ASCB to produce a book in FY 2009, *Career Advice for Life Scientists Volume III: Women in Cell Biology*.[53]

In addition, WICB has a traditional presence at the ASCB annual meeting, providing networking and workshop opportunities. ORWH supported a career development roundtable and forum at the 48th annual meeting in San Francisco in FY 2009 and at the 49th annual meeting in San Diego in FY 2010, providing an opportunity for networking, mentoring discussions, advising early-career investigators on how to negotiate the system, and one-on-one discussions.

Intramural Women's Health Scientific Interest Group Seminar Series

The Intramural Women's Health Scientific Interest Group (WHSIG) Seminar Series, sponsored by ORWH and the Intramural Research Program on Women's Health (IPRWH), began in October 2002. Lectures on both basic science and clinical research topics of relevance to women's health have been presented by experts in a wide variety of scientific disciplines from within the NIH intramural program as well as the outside scientific community.

WHSIG is a forum for researchers across NIH to meet, establish collaborations, and learn about sex differences beyond the effects of sex hormones that are relevant to molecular, cellular, genetic, and developmental processes that affect organ systems, behavior, and the organism as a whole. This lecture series has provided an important avenue for scientific interchange and has resulted in the formation of new scientific collaborations between NIH intramural researchers and scientists around the world, highlighting the value of an interdisciplinary research approach to sex and gender differences in biology and disease from the molecular level to therapeutic clinical trials.

In 2009, the lecture topics included heart health for women, nutrition and age-related macular degeneration, posttraumatic stress disorder and mild traumatic brain injury, and infertility research and implications for clinical practice.

In 2010, seminar titles included Approaches to a Cure for Diabetes: Opportunities and Controversies; Defining Optimal Glucose Control; Rhythms of the Night and Day: Update on Insomnia and Sleep Disruptions; Nutrition, Fitness, and Weight Management in Women's Health; Breast Cancer Chemoprevention and Anti-inflammatories; Myofascial Pain Syndrome: Translating the Evidence To Improve Outcomes Through Physical Medicine and Rehabilitation; and Update on Reproductive Health Challenges and Approaches to Fertility.

Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH

The NIH Women Scientist Advisors Committee, with support from ORWH, continues to host a seminar series to highlight outstanding research achievements of women scientists in the Intramural Research Program. The seminar series is dedicated to the memory of Dr. Anita B. Roberts and honors her role as an exceptional mentor and scientist. In FY 2009, Jennifer Lippincott-Schwartz, Ph.D., of NICHD, spoke on "Emerging Fluorescence Technology for the Analysis of Protein Localization and Organelle Dynamics," and Kanta Subbarao, M.B., B.S., M.P.H., NIAID, spoke on "The Pandemic Threat of Avian Influenza Viruses." In FY 2010, Sharon Wahl, Ph.D., of the National Institute of Dental and Craniofacial Research (NIDCR) spoke on "Host Defense Gone Awry: From Inflammation to Cancer," and Judith Rapoport, Ph.D., of the National Institute of Mental Health (NIMH) spoke on "Brain Development in Healthy, Hyperactive, and Psychotic Children."

[53] Goodenough, U. W., & Marincola, E. (Eds.). (2009). *Career advice for life scientists III: Women in cell biology.* Bethesda, MD: American Society for Cell Biology.

Summer Internship Programs

ORWH–Foundation for Advanced Education in the Sciences–NIH High School Summer Student Program

This program exposes Washington metropolitan area high school students (more than 50 percent female) to biomedical research at a time when they are still forming their future plans and thereby enhances the possibility that they will choose science careers. Students came from both public and private schools in Maryland, Virginia, and Washington, DC. They learn how to design and carry out experiments as well as how to present their research. Funds are used for stipend support for fellows across all NIH ICs.

In summer 2009, the program hosted 26 new and 15 returning students, including 24 women and 17 men, with 22 minorities and 1 student with mild autism. In summer 2010, the program hosted 23 new and 14 returning students, including 23 women and 14 men, with 18 minority students (3 African Americans and 1 Hispanic).

Each summer starts with an informational meeting at which the students learn the history of the program; hear about the structure of NIH, the Intramural Research Program, and ORWH; and receive guidance on how to make research presentations. During each of the following 4 weeks, the students meet as a group for a lunchtime session at which six to eight of them make presentations on their research to each other. The audience includes their preceptors, some of the advisors for the program (all members of the NIH scientific staff), and Michael Gottesman, M.D., Deputy Director for Intramural Research, or one of his Assistant Directors, Joan Schwartz, Ph.D., Roland Owens, Ph.D., or Chuck Dearolf, Ph.D. The presence of these NIH senior scientific staff ensures a lively discussion of each presentation and put each research project into a broader biomedical context. The students also presented posters at the NIH summer student poster presentations day in August. They learned not only how to carry out a research project, how to ask important questions, and how to design experiments to answer those questions, but also how to communicate their results to other scientists.

One sign of the success of the program is that a student who participated in 2008 recently won one of three grand prizes in the Intel Science Competition. In addition, several students have had publications result from their work in the program.

Wellesley-in-Washington Program

Each summer during the reporting period ORWH participated in the Wellesley in Washington Program, which provides a unique experience for Wellesley College students between their junior and senior years. Summer interns at ORWH focus on women's health research and policy. In 2009, ORWH hosted Porsha Eden, who performed background research on NIH programs that support research on minority health. In 2010, ORWH hosted Samantha Sass, who worked on several projects, including serving as a co-author for a peer-reviewed journal article about the development of the ORWH strategic plan.

Women's Health Summer Research Internship (Public-Private Partnership)

The partnership with cosmetics firm Clinique Laboratories, Inc., through the Foundation for the NIH that provided support for a summer internship program for undergraduate students interested in pursuing a career in nursing or science was discontinued before summer 2009. However, because the program had been successful, the Steering Committee of the Intramural Program on Research on Women's Health (IPRWH) used existing funds to continue the program and supported two summer interns in each of 2009 and 2010. The program continued to focus on skin cancer and dermatology research, although it was expanded to increase the focus on women's health.

Candidates were selected from the pool of applicants who had applied for the NIH Summer Internship Program in Biomedical Research based on enrollment in an undergraduate program and an expressed interest in skin, skin cancer, and/or dermatology. The Women's Health Summer Research Internship Program provided an 8- to 10-week intensive biomedical research experience for the four students in NCI, the National Institute on

Aging (NIA), and NHGRI laboratories. The selection committee included IPRWH members from NCI, NIAID, the National Institute on Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIMH, the National Center for Research Resources, and ORWH, with assistance from the Office of Intramural Training and Education. At the end of the summer, the interns presented their research findings at the NIH summer poster day.

The following students were selected in 2009 for this fellowship:

Recipient: Catherine Cheng, Wellesley College
Institute: NHGRI
Mentor: Yardena Samuels, Ph.D.
Project: Mutational Analysis of the Melanoma Genome

Recipient: Annie Sullivan, Middlebury College
Institute: NCI
Mentor: Thomas Hornyak, M.D., Ph.D.
Project: Analysis of the Role of Ezh2 in Transformed Murine Melanocytes

In 2010, the following students were selected:

Recipient: Shelly Hwang, Dickinson College
Institute: NCI
Mentors: Stuart H. Yuspa, M.D. and Padmakumar Velayuthan, Ph.D.
Project: Overlapping Functions of CLIC1 and CLIC4 in Skin Keratinocytes

Recipient: Lauren Prew, Texas A&M University
Institute: NIA
Mentors: Ashani Weeraratna, Ph.D. and Michael O'Connell, Ph.D.
Project: The Relationship Between Cell Cycle Arrest, Wnt5A Expression, and Metastasis in Melanoma

Support for Intramural OIR/ Office of Intramural Training and Education Training Activities

The mission of the NIH Office of Intramural Training and Education (OITE) in OIR, OD, is to help prepare NIH trainees to become creative and productive leaders in the biomedical research community. To accomplish this goal, OITE coordinates programs, provides individual assistance, and prepares resources to enhance the scientific, professional, and career development of NIH trainees. OITE leads trans-NIH initiatives aimed at providing a comprehensive training experience for each trainee, from the trainee's arrival at NIH to his or her transition back to school or into the scientific workforce. The expectation is that NIH will lead the biomedical research community in promoting best mentoring practices and in developing outstanding and innovative training programs for all trainees, including women, underrepresented minorities, and trainees from disadvantaged backgrounds. NIH trainees come from more than 75 countries and about 50 percent are women, providing NIH with the unique opportunity to promote the career development of women scientists and future leaders in women's health research across the globe. Although postdoctoral, research, and clinical fellows are the largest trainee population in the Intramural Research Program (about 4,000), there are also approximately 450 graduate students and 700 postbaccalaureate Intramural Research Training Award recipients working on NIH campuses. In addition, OITE serves the career development needs of about 1,200 summer interns, ranging from high school to graduate and professional school students.

Skill Building Workshops and Courses at NIH

ORWH has supported the development and implementation of a number of workshops for NIH intramural trainees by OITE for many years. The topics include career planning, teaching skills, and science communication and writing. In 2009, OITE developed a series of workshops designed to help NIH trainees develop the interpersonal skills needed to succeed in a team-oriented science environment. These workshops included a focus on Myers-Briggs Type Indicator (MBTI) and personality styles, goal setting and self-assessment, conflict management, assertiveness, and the development of supervisory skills. These workshops were developed with input from experts in each of the fields, and NIH staff is now being trained to lead each of the workshops so that

large groups of trainees on all NIH campuses can be reached.

OITE sponsors career and professional skills development activities for all trainee groups. The educational programs follow a range of formats including (1) all-day symposia; (2) 1- to 3-hour workshops featuring a speaker and/or panel discussion; (3) short workshops followed by breakout and small group meetings; (4) courses on a focused topic that meet for multiple sessions; and (5) small group discussions, support groups, and brown bag lunches. OITE workshops and programs supported in whole or part by ORWH are briefly described below.

Assertiveness Training. This workshop, open to all trainees, explores strategies for communicating one's needs in a variety of situations and helps fellows learn how to be more assertive, how to speak up for themselves, and how to decide when to speak up and when not to.

Basic Science Writing. This 4-week course is for any trainee interested in improving his or her writing skills and was designed for native and non-native English speakers. The workshop focuses on English grammar, punctuation, and sentence and paragraph structure. Other topics include avoiding writer's block, scheduling the writing process, and reworking for clarity, readability, and brevity.

Career Advancement Toolkit Tracks. The Career Advancement Toolkit (CAT) consisted of three workshop series for postdoctoral fellows and graduate students: (1) Career Decisions 101, (2) The Academic Job Search, and (3) The Industry Job Search. Each series included three to four workshops presented throughout the year covering topics such as job materials, networking, interviewing, and negotiating. Substantial portions of each CAT track were videocast for viewing by NIH and non-NIH trainees. These recorded workshops are archived on the OITE Web site.

Improving Spoken English. This workshop covers scientific vocabulary, diction, voice production, tempo, and general guidelines for speaking to native English speakers and before a group. Participants also may attend small group sessions for interactive exercises and can request individual coaching from OITE staff. Exercises focus on informal conversation, an "elevator speech" suitable for introducing oneself to a colleague or supervisor, a research update such as might be presented at a lab meeting, and a brief scientific presentation.

Introduction to Grant Writing. This series is largely focused on NIH grants and consists of two parts. Session 1 covers funding opportunities, the submission and review process, and a section on demystifying study sections. Session 2 is more focused on planning and writing grants, discussion of the major sections of the grant, tips for success, reading summary statements, and responding to reviewers' comments. This series is intended to provide the background that fellows need to begin crafting a grant application. The entire OITE grant-writing program was videocast in 2010.

Leadership Development Program. This series of workshops provides trainees the opportunity to gain awareness of self and others through the MBTI instrument and interactive exercises exploring communication, conflict, influence, and teams. Elements of the program were piloted with fellows from Rocky Mountain Labs, NICHD, NHGRI, and NIDCR. After gathering feedback, the organizers developed a series of five workshops on (1) gaining self-awareness; (2) communication, learning, and influencing others; (3) conflict and feedback; (4) team skills; and (5) leading teams. Programs on cross-cultural communication and mentoring supplement the leadership series. The leadership series was substantially developed in FY 2010; the first two workshops were delivered to more than 200 NIH fellows, and a modified MBTI workshop was offered at the National Postdoctoral Association meeting to more than 175 postdoctoral fellows and postdoctoral office administrators in attendance at the meeting. Similar workshops focusing on self-awareness and workplace interactions will be presented at the Annual Biomedical Research Conference for Minority Students, Morehouse University School of Medicine, City of Hope, and St. Jude Research Center.

NIH Career Symposium. Now in its third year, the NIH Career Symposium provides an opportunity for NIH graduate students and postdoctoral trainees to learn about the

various career opportunities available to doctoral-prepared scientists. Panel sessions focus on both research-intensive careers and careers away from the bench in all sectors, with experts providing insights into their diverse career paths. This year "skill blitzes" provided fellows with 20-minute focused talks on topics such as interviewing, networking, and the job search. The NIH Career Symposium was planned by a group of 24 fellows representing 17 Institutes and was led by the Director of the OITE Office of Postdoctoral Services. One innovation in 2010 was a career resource guide that compiled Web sites, written materials, and professional associations.

Scientists Teaching Science. A 2-hour workshop introduces graduate students and postdoctoral fellows to concepts related to classroom teaching, including learning styles, cultural awareness and diversity, inquiry-based teaching, writing course objectives, creating valid assessments, alternatives to lecturing, writing a syllabus, and the history/philosophy of teaching. Workshop attendees may participate in a 9-week course that explores each topic in greater detail. Graduate students and fellows who participate in the teaching workshop teach summer intern journal clubs and participate in other OITE outreach activities that involve teaching and sharing their love of science with younger students.

Writing and Publishing a Scientific Paper. This 4-week course for postdoctoral fellows and graduate students offers trainees the opportunity to write a rough draft of a scientific paper. Students write and receive feedback on sections of their manuscript, learn how to construct figures and tables, discuss the abstract and the submission cover letter, and develop a greater understanding of the publishing process.

Attendance at OITE programs remains high, with participation by fellows at all training levels and on all campuses. OITE speakers often are invited to NIH Institute retreats and meetings to present workshops, and videocasts and podcasts produced by the speakers were downloaded 64,000 times in the past year. With the redesign of the OITE Web site, outreach has been extended to neighboring universities; with the exception of some very expensive and oversubscribed offerings (writing courses and Scientists Teaching Science), attendance by students and fellows from local colleges and universities is encouraged. The OITE regularly surveys workshop participants. As part of the survey, each participant is asked to rate the following three statements, ranking from 1 to 5 (1=strongly disagree; 3=neutral; and 5=strongly agree): (1) The workshop was helpful to me; (2) The presenter(s) was/were knowledgeable about the material being presented; and (3) I would recommend this workshop to my colleagues. In FY 2010, 97 percent of OITE workshops and courses were ranked 4.5 or higher in each of these three categories.

Skill Building Workshops and Courses Presented around the Nation

OITE and ORWH also collaborate on a number of programs focused on increasing diversity in the scientific community and on recruiting students to NIH training programs. As part of OITE's effort to be a leader in the educational community, they also present at a variety of professional and career development programs at colleges and universities across the United States and at national scientific meetings. Regardless of the topic, OITE speakers begin all career development programs with an overview of NIH training programs and welcome students to meet with them following the program. In the past year, OITE presented workshops and met with students during campus visits as listed below. (OITE staff member is noted in parentheses.)

- Alliance/Merck Ciencia Hispanic Scholars Program: Creating and Presenting Effective Science Posters (Mullen)
- American Association for Cancer Research Annual Meeting: Overview of the Industry Job Search (Conlan)
- Annual Biomedical Conference for Minority Students: Going to Graduate School; NIH Training Opportunities (Murray)
- Annual Society for Advancement of Chicanos and Native Americans in Science (SACNAS) National Conference: NIH Training Opportunities (Murray)

- Association of Immunologists Annual Meeting: Finding Postdoctoral Opportunities at NIH and Beyond (Murray)
- Beta Kappa Chi Scientific Honor Society: NIH Training Opportunities (Murray)
- Biomedical Science Careers Program: Training and Careers at NIH (four presentations) (Milgram/Murray)
- Experimental Biology Annual Meeting: Training and Careers at NIH (twice for the American Society for Biochemistry and Molecular Biology and the Association for Psychological Science) (Milgram)
- Georgia State University: NIH Training Opportunities (Murray)
- George Washington University Graduate Student Symposium: NIH Training and Career Opportunities (Mullen)
- Harvard University Faculty Diversity Program: NIH Intramural Loan Repayment (Cole)
- Howard University Biodiversity Club: NIH Training Opportunities (Mock-Hawkins)
- Johns Hopkins University, Carson Smoot Watkins Lecture: NIH Training Opportunities (Murray)
- Johns Hopkins University, School of Public Health, Center for American Indian Health: NIH Training Opportunities (Wang)
- Michigan Regional Meeting of the National Postdoctoral Association: Training and Careers at NIH (Conlan)
- Mid-Atlantic Career Symposium: "What Can You Be With a Ph.D.?"; NIH Postdoctoral Opportunities; Jobs at NIH; Networking and Job Search Skills (Milgram and Conlan)
- Morehouse College NIH visit: NIH Training Opportunities (Mock-Hawkins)
- Morehouse/Clarke Atlanta Complex: NIH Training Opportunities (Murray)
- Morgan State University: NIH Training Opportunities; Overview of the Graduate School Application Process (Sokolove)
- National Hispanic Scientist Network: NIH Training Opportunities; Keynote Address on Developing Mentoring Relationships (Milgram)
- National Postdoctoral Association National Meeting: Using the MBTI in Lab and Life (Milgram)
- SACNAS Board of Directors: NIH Training Opportunities (Milgram)
- SACNAS Community College Outreach: Academic Planning; NIH Training Opportunities (Murray)
- Society of Toxicology Annual Meeting: Networking Skills (Conlan)
- Towson University NIH Visit: NIH Training Opportunities and Laboratory Tours (Cohen)
- Undergraduate Student NIH Tour (Warren Wilson, Washington Adventist and Ohio State): NIH Training Opportunities and Laboratory Tours (Wang)
- University of Alabama Birmingham Career Symposium: Keynote Speaker on Improving Mentoring Relationships (Milgram)
- University of Maryland, Baltimore, Integrative Membrane Biology Training Program Retreat: Postdoctoral Opportunities at NIH (Sokolove)
- University of Maryland, Baltimore County, Meyerhoff Scholars Program: NIH Training Opportunities (Murray)
- University of Texas at Southwestern: Training and Careers at NIH; Making the Most of Your Graduate School Experience (Milgram)
- University of Texas El Paso, National Science Foundation/Alliances for Graduate Education and the Professoriate Meeting for Minority-Serving Institutions: Training and Careers at NIH; Keynote Address on Mentoring and Career Development (Milgram)
- Virginia Commonwealth University: Training and Careers at NIH; Networking Skills (Conlan)
- Webinar sponsored by the American Association for the Advancement of Science (AAAS): Nonbench Careers in Science (Conlan)

- Webinar sponsored by AAAS: The Academic Job Search (Milgram)
- Webinar sponsored by the New York Academy of Sciences: Postdoctoral Opportunities (Conlan)
- Western Region Centers of Biomedical Research Excellence and IDeA Networks of Biomedical Research Excellence Scientific Conference: NIH Training Opportunities (Sokolove)

Diversity-Building Initiatives

A major mission of the NIH Intramural Program is to train the current and next generation of biomedical researchers to tackle increasingly complex, multidisciplinary problems in human health and disease. To succeed in this mission, the diversity of intramural trainees must be significantly increased at all levels. In the past, ORWH has generously supported the Undergraduate Scholarship Program (UGSP), one of NIH's most successful diversity programs. In 2010, no funding for UGSP was requested from ORWH; however, ORWH did partner with OITE on new efforts aimed at increasing diversity in all NIH training programs. These new initiatives included the following programs and activities:

NIH Community College Day. The purpose of NIH Community College Day is to provide community college students and faculty an opportunity to visit the NIH campus, learn about NIH, and discuss careers and training opportunities in biomedical and health care fields. NIH hosted the first NIH Community College Day in fall 2009. The all-day event included seminars on biomedical careers and clinical research followed by a variety of panel discussions focused on research careers, biotechnology, and medical careers. The day was a great success, with more than 95 percent of the participants expressing a desire to return to NIH for more educational opportunities. Many participants expressed frustration at the lack of internship opportunities at NIH. Indeed, data from the 2009 Summer Internship Program indicate that only seven community college students were offered positions in NIH research labs. This feedback prompted the development of the Community College Summer Enrichment Program, which was successfully launched in 2010.

Community College Summer Enrichment Program. In 2010 OITE coordinated the first NIH Community College Summer Enrichment Program (CCSEP). The program was directed by a trans-NIH committee with significant leadership provided by the OITE Director and training directors/coordinators from NIAMS and NHGRI, with administrative support provided by OITE. CCSEP student stipend support was paid using American Recovery and Reinvestment Act funds, and additional financial support was provided by ORWH, the Office of AIDS Research, and OD. A total of 56 applications were reviewed and 21 students were selected from local and nationwide community colleges. The majority of the CCSEP students were members of an underserved or disadvantaged community, and 40 percent of the participants were women, including several with children. Twenty CCSEP students worked in a lab for a minimum of 8 weeks and a maximum of 12 weeks. Two students remained at NIH full-time for the fall semester. At the conclusion of the summer, CCSEP students presented their research at the NIH summer poster session. Eight postdoctoral fellows (selected by competition from the pool of fellows who completed the OITE pedagogy course) prepared and taught a series of workshops to the program participants. These workshops were provided during an extensive 3-day orientation and during weekly group meetings.

One of the CCSEP directors attended each workshop and provided feedback to the postdoctoral teacher. Topics covered included laboratory culture, how to keep a lab notebook, science writing, workplace dynamics, science ethics, giving an effective talk, lab math, creating a dynamic poster, reading a science paper, career planning, and team building and leadership.

All CCSEP participants were provided with two mentors (a CCSEP program director and a postdoctoral instructor) outside of their research environment. The purpose was to encourage them throughout their NIH experience, assist them with their research presentations and summer posters, answer any questions they had about a research career,

and discuss their career goals. This mentorship was especially important because in a presurvey of CCSEP participants, more than half responded in the negative when asked if anyone had ever discussed pursuing a research career or the importance of networking in science education/career planning. Participants completed surveys at the beginning and conclusion of the program that showed they had increased confidence in a number of areas as a result of their participation.

NIH Outreach to Minority-Serving Colleges and Universities. OITE has enhanced its efforts to visit minority-serving colleges and universities to meet with faculty regarding NIH training programs and to provide workshops and career development activities for students at all levels. The trips are a combination of recruiting on behalf of NIH and ensuring that students have access to outstanding professional development activities and help with science career planning. For example, at a visit to Morgan State University, OITE staff delivered a workshop on graduate school and met individually with students to review their resumes, graduate school essays, and applications for NIH postbaccalaureate programs. OITE also is exploring the possibility, with funding from ORWH, of establishing a Graduate Partnership Program or other collaborative programs with minority-serving colleges and universities, and discussions with institutional leaders will be an important part of each visit.

Fellows Award for Research Excellence

The Fellows Award for Research Excellence (FARE) competition is open to all graduate students and postdoctoral, research, and clinical fellows at NIH. The award recipients receive $1,000 in financial support to attend a scientific meeting, usually within the United States. To participate in the competition, applicants must submit an abstract, which is reviewed by a panel composed of three postdoctoral fellows and two principal investigators. The award is sponsored by the NIH Fellows Committee, the Scientific Directors, ORWH, and OITE, and is funded by the Scientific Directors and ORWH.

Minority Faculty Student Partnership (MFSP) and the MFSP Biotechnology Training Course (Bio-Trac)

ORWH provided support in 2009 and 2010 to the Foundation for the Advanced Education in the Sciences to conduct biotechnology training courses to train minority students and faculty members, primarily from historically Black colleges and universities, Hispanic-serving institutions, and Indian tribal colleges or universities, in the nature and application of the latest principles and techniques of biotechnology. For the MFSP biotechnology training course, 12 faculty members along with 12 second-, third-, or fourth-year biology majors were selected and trained at NIH for a 1-week period. Through the Bio-Trac program, 1-week lecture and hands-on laboratory training workshops were provided in different areas of biotechnology that are topical and in demand in the sciences.

Summary: Biomedical Career Development Program Success Supports Implementation of the ORWH Strategic Plan

The career development activities supported by ORWH and the NIH Working Group on Women in Biomedical Careers have made great strides in addressing the sixth goal of ORWH's new strategic plan, which is to employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce. With a focus on mentoring and providing unique opportunities for professional growth, these programs meet a wide range of needs for scientists at all levels, with special emphasis on students, fellows, and early-career scientists. Through these efforts, which are undertaken in collaboration with the NIH ICs and external professional societies, ORWH aims to promote the recruitment, retention, reentry, and advancement of women in biomedical careers, and men and women in women's health and sex differences research. The activities supported in FY 2009 and FY 2010 have paved the way for future endeavors that will help expand and fortify the pipeline of scientists and clinicians in these fields.

IV. ORWH Research Dissemination and Outreach

The Office of Research on Women's Health (ORWH) works in partnership with the National Institutes of Health (NIH) Institutes and Centers (ICs), other Federal agencies, and various national, state, and community organizations utilizing a variety of outreach efforts to disseminate information on research on women's health. Working together, ORWH and its partners ensure that timely and relevant information is distributed to advocacy groups, public and private institutions, and individuals interested in women's health research. ORWH also provides scientific information on women's health research to the public, health professionals, voluntary organizations, and other key stakeholders. The goal is to facilitate the translation of information derived from research on women's health to clinical care and public health policy, to improve health care for women, men, and their families.

ORWH and the National Library of Medicine Online Partnership

ORWH and the National Library of Medicine (NLM) have continued their innovative partnership that developed and implemented the Women's Health Resources Web Portal. This portal, http://www.womenshealthresources.nlm.nih.gov, serves as a vehicle for outreach to professional groups, advocates, and the public. Major scientific advances are summarized and included, along with research resources and other NIH links, such as specific health topics and initiatives in women's health and sex differences research. Within each section of the Web site are topics with links to relevant and authoritative resources. NLM has a lengthy history of creating specific user-friendly strategies for these topics to ease searching ClinicalTrials.gov and PubMed. Other NLM Web resources used include AIDSinfo, American Indian Health, Arctic Health, Household Products Database, MedlinePlus, and NIH SeniorHealth. Search strategies for major studies related to women's health research also have been created. As with the topical search strategies, ClinicalTrials.gov and PubMed searches for each major report are included.

During FY 2009 and FY 2010, the Web portal was greatly expanded, both in content and with new technology, specifically incorporating Web 2.0 technologies and social media tools and news resources to engage the scientific and consumer public. Popular social media applications included Facebook, Blogger, Twitter, Delicious, RSS feeds, cloud tagging, and wikis.

In addition to adding significant new scientific content from the ICs, a major new category was created—Women and the Military—so that a one-stop Web resource could support the trans-Federal research collaboration between NIH, the Department of Defense (DoD), the Veterans Administration (VA), and a number of other Federal agencies.

NIH Strategic Planning Process: Regional Scientific Meetings and ORWH 20th Anniversary Scientific Symposium

The planning process for the new NIH strategic plan, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research*, involved five regional public hearings and scientific workshops during FY 2009 and FY 2010. The meetings were hosted by academic and research institutions with which current or past members of the Advisory Committee for Research on Women's Health (ACRWH) were affiliated. Each regional meeting featured scientific symposia; facilitated working groups on a variety of health, technology, and career development topics; and an exhibit of ORWH publications and resources. Below is the list of the meeting locations and their host institution:

FY 2009

- Washington University in St. Louis School of Medicine, St. Louis, MO (March 2009)
- University of California, San Francisco, San Francisco, CA (May 2009)
- The Warren Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island, Providence, RI (September 2009)

FY 2010

- Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital, Chicago, IL (October 2009)
- Emory University School of Medicine, Atlanta, GA (February 2010)

On September 27, 2010, NIH held a scientific symposium in honor of the 20th anniversary of the establishment of ORWH. The new strategic plan was presented at the symposium. The event highlighted some of the scientific advances that have increased our understanding of women's health, differences between males and females, and implications for sex/gender-appropriate clinical care and personalized medicine. The daylong event, which included a reception and poster session, provided a forum to recognize some of the major contributors to the establishment and continued success of the ORWH. The symposium celebrated progress in the field of women's health research realized through the dedicated work of investigators, clinicians, and scientific colleagues from a wide range of disciplines and arenas—both women and men. The 20th anniversary celebration also acknowledged the role of the many advocates who have worked tirelessly to energize support and set the stage for the realization of a vision—ensuring NIH-wide attention to research on women's health issues across the lifespan and the role of sex/gender in health and disease. This event was open to the public and well attended.

ORWH-Cofunded Research Conferences and Workshops

ORWH provides funding for research projects and research dissemination through conferences and workshops held at the NIH and nationwide. Through partnerships with NIH ICs and Offices, other Federal agencies, and extramural organizations, ORWH seeks to bring together researchers investigating women's health and sex differences to exchange ideas, foster collaborations, and explore emerging concepts and technologies. Several examples of ORWH-cofunded conferences and workshops that took place during this reporting period are provided below. A complete, detailed description of the conferences can be found in appendix D.

FY 2010

U.S. Bone and Joint Decade Global Network Conference. ORWH cosponsored, with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the U.S. Bone and Joint Decade Global Network Conference in October 2009 in Washington, DC.

Second Annual Trauma Spectrum Disorders Conference. The second annual trauma spectrum disorders conference, titled A Scientific Conference on the Impact of Military Service on Family and Caregivers was held on the NIH campus in December 2009. The conference examined the needs of families and caregivers in support of military and veterans with trauma spectrum disorders.

Fourth Global Summit on International Breast Health. The Breast Health Global Initiative and the Latin American and Caribbean Society of Medical Oncology convened the biennial global summit in June 2010 in Chicago, bringing together collaborating national and international organizations to address the optimization of breast health care delivery in limited resource countries.

Workshop: Challenges in Infant Immunity. The objectives of the Challenges in Infant Immunity workshop held in June 2010 were to understand and assess the scientific knowledge base on infant immunity, including maternal-fetal interactions, as they relate to vaccines and responses to infections; to identify gaps and key issues in immune mechanisms in the mother and infant that would inform the design of improved vaccines; and to foster collaborations among investigators studying infectious disease pathogenesis, vaccine design and development, and immune mechanisms.

Add Health Users Conference. In July 2010, the ninth Add Health Users Conference took place in Bethesda, Maryland on the NIH campus. More than 100 researchers who are working with Add Health data assembled to share research goals, experiences and results.[54]

[54] Add Health Users Conference materials and presentations are available online at http://www.cpc.unc.edu/projects/addhealth/news/add-health-2010-users-conference-materials-and-methodology-presentations-now-available/

17th Ovarian Workshop: A Global Perspective of Ovarian Function. The ovarian workshop, held in July 2010, provides a forum for clinicians, scientists, and students to exchange ideas and current concepts on the development, regulation, and maintenance of the ovary without regard to disciplinary boundaries.

Workshop on Virtual Reality Technologies for Research and Education in Obesity and Diabetes. This workshop in July 2010 explored the research potential of virtual reality (VR) technologies as tools for behavioral and neuroscience studies in diabetes and obesity and the practical potential of VR technology in fostering more effective utilization of diabetes and obesity-related nutrition and lifestyle information.

Sixth International Symposium on Hormonal Oncogenesis. The Sixth International Symposium on Hormonal Oncogenesis in September 2010 was a joint venture with the Universities and Pharmaceutical Consortium of Japan. The format of the symposium consisted of a symposium address, state-of-the-art lectures, speaker presentations, and two poster sessions.

ORWH Women's Health Seminar Series

The ORWH Women's Health Seminar Series features nationally recognized leaders in women's health research who present the latest information on topics important to women's health. The seminar series began in 1993, and its goal is to educate the NIH community and the public at large on issues that affect the health of women and to showcase sex and gender research. In FY 2009 and FY 2010, ORWH continued its program on sex and gender research with the seminars listed below.

FY 2009

Sex and Gender Research: Metabolic Dysfunction

Metabolic syndrome refers to a group of risk factors linked to overweight and obesity that increase the chance for heart disease and other health problems such as diabetes and stroke. This seminar held in June 2009 provided four perspectives on metabolic dysfunction in women, looking at sleep apnea, type 2 diabetes, and cardiovascular disease:

- *Androgens, Insulin Resistance, and Metabolic Syndrome in Women,* Andrea Dunaif, M.D., The Feinberg School of Medicine, Northwestern University
- *Obstructive Sleep Apnea and its Metabolic Consequences,* David A. Ehrmann, M.D., The University of Chicago Medical Center
- *The Type 2 Diabetes Epidemic,* Judith Fradkin, M.D., National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK)
- *Why Can't a Woman be More Like a Man (When It Comes to Hypertension)? Is the Renin Angiotensin System to Blame or to Thank?* Kathryn Sandberg, Ph.D., Georgetown University Medical Center

Sex and Gender Research: The Interaction of Depression With Other Diseases

Depression is not only a significant public health concern that can be particularly devastating to women and families; it is also linked to many other prevalent diseases. This seminar discussed the interaction of depression with other diseases such as osteoporosis, cancer, and heart disease. The September seminar was moderated by Catharine Roca, M.D., of the National Institute of Mental Health (NIMH) and included the following presentations:

- *Fetal Antecedents to Depression*, Jill M. Goldstein, Ph.D., Harvard Medical School and Brigham and Women's Hospital
- *Osteoporosis and Other Endocrine and Metabolic Consequences of Major Depression in Premenopausal Women*, Giovanni Cizza, M.D., NIDDK
- *Depression and Cancer*, Mary Jane Massie, M.D., Memorial Sloan-Kettering Cancer Center
- *Depression and Heart Disease*, Viola Vaccarino, M.D., Ph.D., Emory University School of Medicine

FY 2010

Environmental Exposures and Women's Health

Environmental exposures as they relate to women's health is an emerging area of science, and this series of seminars addressed some of the current issues—particularly as they relate to cancer risk, endocrine disruptors, and female fertility. The seminar presented in March included videotaped remarks from Dr. Linda Birnbaum, NIEHS, and the following presentations:

- *Early Life Environmental Exposures: Lifelong Impact on Breast Development and Function*, Suzanne Fenton, Ph.D., NIEHS
- *Environmental Influences on Female Fecundity and Fertility*, Maureen Cooney, Ph.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
- *Early Exposure to Endocrine Disruptors and Its Effect on Women's Health: Evidence From Two Longitudinal Studies*, Brenda Eskenazi, Ph.D., Center for Children's Environmental Health Research, University of California, Berkeley
- *Implications of Endocrine Disruptor Exposure on Breast Cancer*, Jose Russo, M.D., Breast Cancer Research Laboratory, Fox Chase Cancer Center, Philadelphia, PA

The second seminar, in October 2010, explored these topics specific to environmental exposures and women's health and included the following presentations:

- *Risks From Environmental Exposures During Pregnancy*, Frederica P. Perera, Dr.P.H., Columbia Center for Children's Environmental Health and the DISCOVER Center, Columbia University
- *Endocrine Disruption, Developmental Epigenetic Reprogramming, and Adult Cancer Risk*, Shuk-mei Ho, Ph.D., University of Cincinnati College of Medicine
- *Environmental Aspects of Autoimmune Diseases*, Frederick Miller, M.D., Ph.D., NIEHS
- *Occupational Exposures and Cancer Risk: Women Are Not Just Small Men*, Melissa Friesen, Ph.D., NCI

Women's Health Scientific Interest Group Seminar Series

The Women's Health Scientific Interest Group (WHSIG) Seminar Series, sponsored by ORWH and organized by the NIH Intramural Program on Research on Women's Health, presents lectures by experts in women's health research from within the NIH intramural program as well as the outside scientific community. WHSIG is a forum for researchers across NIH to meet, collaborate, and learn about sex and gender differences that are relevant to molecular, cellular, genetic, and developmental processes. The seminar takes an interdisciplinary approach to sex and gender differences in biology and disease from the molecular level to therapeutic clinical trials. The seminars held in FY 2009 and FY 2010 are listed below.

FY 2009

- *Heart Health for Women: Using Old Knowledge, Generating New Knowledge*, Rose Marie Robertson, M.D., Vanderbilt University (March 2009)
- *Nutrition and Age-Related Macular Degeneration*, Emily Y. Chew, M.D., NEI (April 2009)
- *Invisible Wounds—Post-Traumatic Stress Disorder/Mild Traumatic Brain Injury: Military Perspective*, David F. Moore, M.D., Ph.D., Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury; Terri Tanielian, M.A., Rand Center for Military Health Policy Research (June 2009)
- *Update on Infertility Research and Implications for Clinical Practice*, Eric Levens, M.D., NICHD; Carmen J. Williams, M.D., Ph.D., NIEHS; James Segars, M.D., NICHD (September 2009)

FY 2010

- *Hot Topics in Diabetes Research*, Christopher Saudek, M.D., The Johns Hopkins University School of Medicine; Jill Crandall, M.D., Albert Einstein College of Medicine; Judith Fradkin, M.D., NIDDK (November 2009)
- *Rhythms of the Night and Day: Update on Insomnia and Sleep Disruptions*, William Riley, Ph.D., NHLBI; Michael Twery, Ph.D., NHLBI (December 2009)
- *Women's Health: Update on Nutrition, Fitness, and Weight Management*, Richard Kreider, Ph.D., Texas A&M University; Kathryn Y. McMurry, M.S., Office of Disease Prevention and Health Promotion, DHHS (March 2010)
- *Breast Cancer Chemoprevention and Anti-Inflammatories*, Michelle Holmes, M.D., Dr.P.H., Brigham and Women's Hospital, Harvard Medical School; Louise R. Howe, Ph.D., Weill Cornell Medical College; Jo Anne Zujewski, M.D., NCI (June 2010)
- *Update on Myofascial Pain Syndrome: Translating the Evidence to Improve Outcomes Through Physical Medicine and Rehabilitation*, Jay Shah, M.D., NIH Clinical Center; Ana T. Acevedo, M.D., NIH Clinical Center (August 2010)
- *Update on Reproductive Health-Challenges and Approaches to Fertility* (with the Intramural Research Program on Reproductive and Adult Endocrinology and the NIH Inter-Institute Endocrinology Fellowship Program) Lawrence M. Nelson, M.D., NICHD; Teresa K. Woodruff, Ph.D., Northwestern University Feinberg School of Medicine; Alan DeCherney, M.D., NICHD (September 2010)

Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH

As in previous years, the Anita B. Roberts Lecture Series, *Distinguished Women Scientists at NIH*, was jointly sponsored by ORWH and the NIH Women Scientist Advisors Committee to highlight outstanding research achievements of women scientists at NIH. The series is dedicated to the memory of Anita Roberts, chief of the Laboratory of Cell Regulation and Carcinogenesis at NCI from 1995 to 2006, and honors her role as an exceptional mentor and scientist. Each year, two senior women NIH researchers are chosen to present these lectures. The following lectures were presented in FY 2009 and FY 2010:

FY 2009

- *Emerging Fluorescence Technology for the Analysis of Protein Localization and Organelle Dynamics*, Jennifer Lippincott-Schwartz, Ph.D., NICHD (October 2008)
- *The Pandemic Threat of Avian Influenza Viruses*, Kanta Subbarao, M.B., National Institute of Allergy and Infectious Diseases (NIAID) (April 2009)

FY 2010

- *Host Defense Gone Awry: From Inflammation to Cancer* ,Sharon Wahl, Ph.D., Chief, National Institute of Dental and Craniofacial Research (NIDCR) (October 2009)
- *Brain Development in Healthy, Hyperactive, and Psychotic Children*, Dr. Judith Rapaport, National Institute of Mental Health (NIMH) (March 2010)

Association for Women in Science Seminar Series

Each year, ORWH funds a seminar series for the Bethesda chapter of the Association for Women in Science. The series includes well-attended seminars of interest to early career investigators. In addition to lectures, the chapter holds an additional annual unique event, *Have a Meal with your Mentor*, which allows young scientists to network with potential mentors in an informal environment. The FY 2009–2010 seminar series included the following presentations:

FY 2009:

- *Motherhood: the Elephant in the Lab*, Anne Douglass, Ph.D., NASA; Katherine Douglass, M.D., M.P.H., The George Washington University; Marla McIntosh, Ph.D., University of Maryland; Catherine O'Riordan, Ph.D., American Institute of Physics (October 2008)

- *Money Shy to Money Sure: A Road Map toward Financial Serenity in Troubled Times*, Olivia Mellan, Olivia Mellan & Associates, Inc. (November 2008)
- *NIH Efforts to Advance Women in Biomedical Careers*, Vivian W. Pinn, M.D., ORWH (February 2009)
- *Managing your Laboratory and your Life—Researcher Panel*, Francesca Bosetti, Ph.D., NIA; Edith Miles, Ph.D., NIDDK; Wei Yang, Ph.D., NIDDK (April 2009)
- *Perspectives from the NIH 2009 Pittman Lecturer*, Susan Lindquist, Ph.D., Whitehead Institute for Biomedical Research, Howard Hughes Medical Institute, Broad Institute of MIT and Harvard (June 2009)

FY 2010:

- *Are We Up To the Task? Improving the Status of NIH Intramural Women Scientists*, Joan P. Schwartz, Ph.D., Office of Intramural Research and *Falling off the Bandwagon: Why Women Scientists Fail to Make the Transition from Post-Doc to PI,* Orna Cohen-Fix, Ph.D., Laboratory of Molecular and Cellular Biology, NIDDK (September 2009)
- *Life in Academics—A Panel Discussion Featuring Scientists from DC-Area Universities*, Stephanie Constant, Ph.D., George Washington University; Kathleen DeCicco-Skinner, Ph.D., American University; Brenda Fredericksen, Ph.D., University of Maryland; Anne Simon, Ph.D., University of Maryland (October 2009)
- *Stranger in a Strange Land: Musings from a Neurologist Living Among Psychiatrists* (NIH 2010 Pittman Lecturer), Helen S. Mayberg, M.D., Department of Psychiatry, Emory University School of Medicine, Atlanta, GA (February 2010)
- *Panel Discussion on Policy, Program, and Review*, Francesca Macchiarini, Ph.D., Basic Immunology Branch, NIAID; Sheryl Brining, Ph.D., Office of Review, NCRR; Marina Volkow, Ph.D., Office of Science Policy, Planning & Communications, NIMH (March 2010)

Pinn Point on Women's Health: The ORWH Podcast

The *Pinn Point on Women's Health* podcasts, which feature conversations between Dr. Pinn and NIH intramural and extramural scientists on a wide variety of subjects, are posted on both the ORWH and NIH Web sites to provide easy access to the information.[55] The podcasts have brought hundreds of new visitors to the ORWH site and won the NIH Plain Language Award for 2008 in recognition of translating scientific information into plain language. The FY 2009–2010 ORWH podcast series covered the following topics:

FY 2009

Uterine Fibroids. Dr. Pinn discussed uterine fibroids with James Segars, M.D., Head, Unit on Reproductive Endocrinology and Infertility in the Reproductive Biology and Medicine Branch of NICHD. (January)

Preterm Birth and Healthy Pregnancy. Dr. Pinn spoke with Catherine Spong, M.D., of the Pregnancy and Perinatology Branch of NICHD about healthy pregnancies and how to reduce the risk of preterm births. (April)

Autoimmune Diseases and Their Impact on Women. Dr. Pinn talked about autoimmune diseases such as rheumatoid arthritis, lupus, and scleroderma with Robert Carter, M.D., Deputy Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, an expert in the field of autoimmune diseases. (August)

FY 2010

Prescription Drug Abuse in Women. Dr. Pinn interviewed Nora Volkow, M.D., Director of the National Institute on Drug Abuse (NIDA) about prescription drug abuse in women. (April)

Vaginal Birth After Cesarean. Dr. Pinn was joined by Caroline Signore, M.D., M.P.H., a board-certified obstetrician/gynecologist at

[55] Pinn Point on Women's Health podcasts are available online at http://orwh.od.nih.gov/podcast/podcast_archive.html

NICHD, to discuss the NIH consensus conference on vaginal birth after cesarean. (June)

Gestational Diabetes Prevention. Dr. Pinn hosted this podcast with Griffin P. Rodgers, M.D., Director of NIDDK to discuss the increased risk of developing type 2 diabetes for women with a history of gestational diabetes. (August)

Hormonal Therapy and Breast Cancer. Dr. Pinn spoke with Rowan T. Chlebowski, M.D., Ph.D., professor of medicine at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA). Dr. Chlebowski examined the relationship between hormonal therapy and breast cancer among postmenopausal women taking part in the Women's Health Initiative. (September)

ORWH Publications and Resources

ORWH provides evidence-based information on women's health research to the public, health professionals, voluntary organizations, and other key stakeholders. The goal is to facilitate the translation of information derived from research on women's health and, through its translation to clinical care and public health policy, improve health care for women, men, and their families. Below is a list of materials published in FY 2009 and FY 2010:

Publications on Women's Health Topics

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2009). *NIH publications on women's health issues.* Bethesda, MD: National Institutes of Health.

Pinn, V. W., Bates, A., Kravitz, J. Y., & Corry, N. (2009). *NIH research and other efforts related to the menopausal transition*. Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2009). *Science Series Fact Sheets: Lupus* (NIH Publication No. 10-7516). Bethesda, MD: National Institutes of Health.

Pinn, V. W. & Bates, A. (2010). *Monitoring adherence to the NIH policy on the inclusion of women and minorities as subjects in clinical research: Comprehensive report: Tracking of human subjects research as reported in fiscal year 2008 and fiscal year 2009*. Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010, May). The basic science and the biological basis for sex- and gender-related differences. *The science of sex and gender in human health*. Retrieved from http://sexandgendercourse.od.nih.gov

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *A Primer for women's health: Learn about your body in 52 weeks* (NIH Publication No. 10-7498). Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Women of color health information collection: Diabetes mellitus* (NIH Publication No. 10-7680). Bethesda, MD: National Institutes of Health.

Publications on Careers

Goodenough, U. W., & Marincola, E. (2009). *Career advice for life scientists. Vol. III: Women in cell biology*. Bethesda, MD: American Society for Cell Biology.

Pohlhaus, J. R., Love, M. S., Rudick, J., Clayton, J. A., & Pinn, V. W. (2009). *National leadership workshop on mentoring women in biomedical careers: Meeting proceedings* (NIH Publication No. 09-6364). Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2009). *Women in science at the National Institutes of Health, 2007–2008* (NIH Publication No. 09-6462). Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health. (2009). *Women in biomedical research: best practices for sustaining career success* (NIH Publication No. 09-7366). Bethesda, MD: National Institutes of Health.

The NIH Strategic Plan on Women's Health and Sex Differences Research and Related Publications

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Strategic plan—Executive summary* (NIH Publication No. 10-7606). Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010*). Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Regional scientific reports* (NIH Publication No. 10-7606-B). Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Public testimony* (NIH Publication No. 10-7606-C). Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Highlights of NIH women's health and sex differences research 1990–2010* (NIH Publication No. 10-7606-D). Bethesda, MD: National Institutes of Health.

ORWH Exhibit Program

ORWH exhibits nationwide at a variety of women's health and/or community-related events. Listed below are examples of exhibits during FY 2009 and FY 2010 for which ORWH provided materials and/or other support.

FY 2009

- Men's Health at FedEx Field, Landover, MD (October 2008)
- Sister to Sister: Everyone Has a Heart Foundation, National Women's Heart Day Health Fair, Verizon Center, Washington, DC (February 2009)
- Conditioning and Relaxation Week Event, Rockledge Drive, Bethesda, MD (February 2009)
- Caregivers Symposium, Washington, DC Chapter of Links, Inc., Providence Hospital, Washington, DC (April 2009)
- Radio One: Take a Loved One to the Doctor, Providence Hospital/Health Fair, Washington, DC (April 2009)
- Spring Into Wellness Health Fair, NIH Campus, Bethesda, MD (May 2009)
- Sixteenth Annual Health Expo, First Baptist Church of Glenarden, Upper Marlboro, MD (May 2009)
- From Women's Health Research to Sex- and Gender-Appropriate Medicine. University of Virginia Summer Medical and Dental Education Program, 15th Dean's Distinguished Lecturer, Charlottesville, VA (June 2009)
- Nansemond Indian Tribe Powwow, Chesapeake, VA (August 2009)
- Bureau of Engraving and Printing Health and Fitness Fair, Washington, DC (August 2009)
- Hispanic Community Health Fair, Mayor's Office, Washington, DC (August 2009)
- INTEGRIS Health, African American Women's Health Forum, Oklahoma City, OK (September 2009)
- National Indian Health Board Annual Consumer Conference, Washington, DC (September 2009)

FY 2010

- Women in Transition: Managing Change Workshop, Washington, DC Chapter of Links, Inc., Howard University, Washington, DC (April 2010)

- Health and Wellness Workshop Washington, D.C., Washington, D.C., Chapter of Links, Inc., St. Paul's A.M.E. Church, Washington, DC (April 2010)
- Teen Girl Health Fair, Fauquier Hospital, Warrenton, VA (May 2010)
- ORWH 20th Anniversary Scientific Symposium, NIH Campus, Bethesda, MD (September 2010)
- Community Health Fair for Veterans, Washington Redskins and U.S. Department of Veterans Affairs, FedEx Field, Landover, MD (November 2010)

National Women's Health Week at NIH

Each year, ORWH coordinates the National Women's Health Week activities at NIH. Publications and resources from ORWH and other NIH ICs are disseminated at a large ORWH exhibit located at the NIH Clinical Center. In addition, ORWH participates in outreach activities throughout the week. Women's Health Week exhibits, programs, and other activities are described below.

FY 2009

More than 16,000 publications were distributed at the exhibit in the Clinical Center. In addition, ORWH participated in the following activities:

- ORWH cosponsored, with the NIH Division of Police, a "safety celebration" barbecue in recognition of National Police Week and Women's Health Week on the NIH campus. Hundreds of NIH staff collected women's health materials and asked ORWH staff health questions.
- ORWH sponsored a scientific forum and panel discussion, *The Intersection of Research, Policy, and Healthcare for the Future of Women's Health.* Three leaders in women's health issued a call to action to health care providers, researchers, and women to take charge of their health. Featured speakers were Kay Dickersin, Ph.D.; Celia Maxwell, M.D.; and Susan F. Wood, Ph.D. Presentation topics included the issue of sex and gender bias in selecting editors of medical journals, HIV/AIDS and women of color, and health care policy related to women's health care needs.
- ORWH also cosponsored a wellness seminar coordinated by NHLBI and the Office of Research Services. The conditioning and relaxation seminar titled *Focus on You—Promoting Employee Health and Well-Being at NIH*, presented by Rezvan Ameli, Ph.D., from NIMH, was an interactive class that demonstrated how to incorporate mind-body relaxation and stress reduction techniques into work and home life.

FY 2010

More than 14,000 publications and materials were disseminated at the National Women's Health Week exhibit in the Clinical Center. In addition, ORWH organized several events, including the following:

- *Women.Smokefree.gov: Quit Smoking Today! We Can Help*, presented by Erik Augustson, Ph.D., M.P.H., NCI
- "A Focus on Breast Cancer," which featured the following presentations:
  - » *Mammograms: When to Get Them*, Robert Smith, Ph.D., Director of Cancer Screening, American Cancer Society
  - » *Reflections of a Women's Health Advocate and Breast Cancer Survivor*, Ngina Lythcott, Dr.P.H., M.S.W., RN, Boston University School of Public Health
  - » *Women's Health Initiative Findings and the Changing Pattern of Breast Cancer Incidence*, Rowan T. Chlebowski, M.D., Ph.D., Professor and Chief, Department of Internal Medicine, Harbor/UCLA Medical Center
- Safety celebration barbecue with the NIH Division of Police. Proceeds from the event benefited the Friends of the Clinical Center in recognition of National Police Week and Women's Health Week. The exhibit featured a variety of consumer-oriented materials on women's health.
- A conditioning and relaxation seminar presented by Rezvan Ameli, Ph.D. Similar to Dr. Ameli's popular and well-received presentation in 2009, this seminar presented relaxation and stress reduction strategies.

V. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

NIH Monitoring Efforts

Introduction

The Office of Research on Women's Health (ORWH) was established in response to concerns from members of Congress and the women's health community that women should be included in clinical research funded by the NIH. Today, after years of attention to NIH inclusion policies and extended focus on sex differences research, ORWH is expanding the foundation for the inclusion of both women and men, minorities, and other understudied populations in clinical research.advancing scientific reasoning to better facilitate understanding of its importance. Over the years of its existence, ORWH has focused on the importance of providing data that can inform both the research community and potential volunteer communities of the trends and shifts in inclusion figures and to be able to provide such figures and information to inquiries from members of Congress, the media, scientific organizations, advocacy groups, and individuals. A number of challenges related to the issue of the inclusion still exist, such as the enrollment of pregnant women in clinical research and the associated ethics issues. However, ORWH and the NIH community continue to stress the importance of inclusion of understudied populations and analyses of differences in response to interventions, based on analyses of research. Results by sex, race/ethnicity, or other factors such as age and geographic status are important to determine whether populations may benefit from the results of clinical studies. Inclusion is not just a matter of having women and minorities along with men included in clinical studies, but to cause the scientific design of research studies to be able to broaden the knowledge about differences and/or similarities between different populations.

How can monitoring of inclusion policies and implementation best be accomplished? What can be done to increase the transition of the results of research studies into clinical practice? What are the effects of a lack of consistent editorial policies requiring or publishing analyses by sex/gender or race/ethnicity? During the 2 years included in this report, ORWH has continued to call attention to all of these issues. The Task Force on the Inclusion of Women, Minorities, and Other Populations in Clinical Research that was established in 2009 by the acting Director of NIH has suggested some recommendations that are pending further discussion before implementation. In the interim, responsibility for reporting and monitoring, educating NIH staff and extramural scientists, and other related responsibilities has been assumed by the Office of Extramural Research (OER). The trans-NIH Tracking and Inclusion committee, formerly reporting to the ORWH, no longer exists. The current process entails the generation of data by OER that then is presented to the Advisory Committee on Research on Women's Health (ACRWH) for their review and approval in accordance with the NIH Revitalization Act of 1993.[56]

To demonstrate effective implementation of the Revitalization Act and implementation of NIH policies on the tracking and inclusion of women and minorities in clinical research, ORWH has, over the years, led the efforts in collaboration with OER, the Office of Intramural Research (OIR), the National Center (now Institute) on Minority Health and Health Disparities (NIMHD), and other ICs to monitor efforts for compliance, especially through the long existing trans-NIH Tracking and Inclusion Committee. Monitoring efforts included documentation of the numbers of females and males by ethnicity and race enrolled in clinical studies funded by NIH (all clinical research, phase III clinical trials with and without sex-specific studies, etc.), as well as biennial statements from each Institute and Center (IC) advisory council to confirm compliance with NIH

[56] NIH Revitalization Act of 1993, Pub. L. No. 103-43, § 141, 107 Stat. 22 (1993). Codified at 42 U.S.C. § 287d (2006).

policies. These and other efforts ensured that NIH procedures were in compliance with the NIH policy on the inclusion of women and minorities in clinical studies.

Data monitoring for the magnitude and diversity of clinical studies funded by NIH is not a simple task, and many representatives from the NIH ICs have contributed to efforts to ensure consistency of data entry and reporting and understanding of the NIH inclusion policy. There has been an extensive and dedicated effort to provide accurate and reproducible data. Modifications in this process for FY 2009 and FY 2010 data reflect the current reporting and trends of the inclusion of participants in NIH clinical research studies, as reported by OER.

Historical Context

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by NIH has its origins in the women's health movement. Following the issuance of the report of the Public Health Service Task Force on Women's Health in 1985,[57] NIH established a policy for the inclusion of women in clinical research. This policy, which "urged" the inclusion of women, was first published in the *NIH Guide for Grants and Contracts* in 1986.[58] In the following year, minority scientists and other researchers at NIH recognized the need to address the inclusion of minority populations. As a result, a subsequent version of the *NIH Guide* published for the first time a policy "urging" the inclusion of minorities in clinical studies.[59]

To ensure that the policies for inclusion were firmly implemented by NIH, Congress made what had previously been policy into public law, through a section in the NIH Revitalization Act of 1993 titled "Women and Minorities as Subjects in Clinical Research." In 1994, NIH revised its inclusion policy to be in compliance with the statutory language. The Revitalization Act essentially reinforced the existing NIH policies, but with the following four major differences:

(1) Ensure that women and minorities and their subpopulations are included in all clinical research.

(2) Include women and minorities and their subpopulations in phase III clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect.

(3) Cost is not allowed as an acceptable reason for excluding these groups.

(4) Initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as participants in clinical studies.

Revised inclusion guidelines developed in response to this law were published in the *Federal Register* in March 1994,[60] and they became effective in September 1994. The result was that NIH could not and would not fund any grant, cooperative agreement, or contract or support any intramural project to be conducted or funded in FY 1995 and thereafter that did not comply with this policy.

Strategies to ensure uniform implementation of the revised guidelines across NIH were developed through the establishment and deliberations of the NIH Tracking and Inclusion Committee made up of representatives of the Directors of each of the ICs. This trans-NIH committee, convened by ORWH and cochaired with a senior IC official, meets on a regular basis, focusing on consistent and widespread adherence to the NIH guidelines by all the ICs. Working in collaboration with OER, OIR, and other components of NIH, ORWH coordinates the activity of developing and establishing data collection and reporting methodologies to ensure uniform standards and definitions in the reporting of data on women and minority participants in NIH-funded clinical research.

[57] U.S. Public Health Service. (1985). *Women's health: Report of the Public Health Service Task Force on Women's Health Issues*, Volume I. Public Health Reports, 100(1),74–106.

[58] National Institutes of Health (NIH). (1986, October 24). Inclusion of women in study populations. *NIH Guide for Grants and Contracts, 15*(22),1.

[59] NIH. (1987, September 25). Inclusion of minorities in study populations. *NIH Guide for Grants and Contracts, 16*(32),3–4.

[60] NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. (FR Doc. No. 94-5435). (March 9, 1994).

To ensure NIH-wide adherence to the revised inclusion guidelines, in 1994 NIH conducted extensive training on the revised inclusion guidelines. In June 1994, ORWH convened a meeting of institutional review board chairs to discuss their role in implementing the revised policy. Training was especially important in light of 1990 General Accounting Office (GAO) findings[61] that an earlier policy was inconsistently applied and had not been well communicated or understood within NIH or in the research community. A variety of outreach activities were initiated to explain the revised policy to the scientific research community and to clear up common misunderstandings about the new requirements.

GAO Report, May 2000: Recommendations and Actions Taken

Following a congressional request for an assessment of NIH progress in implementing the 1994 guidelines on including women in clinical research, GAO issued another report in May 2000 titled *Women's Health—NIH Has Increased Its Efforts To Include Women in Research*. It concluded that in the past decade, NIH had made significant progress in implementing a strengthened policy on including women in clinical research.

The GAO report also included the following two specific recommendations to the Director of NIH:

(1) Ensure that the agency implements the requirement that phase III clinical trials be designed and carried out to allow for the valid analysis of differences between women and men as fully as it implements other elements of the inclusion policy. Specifically, we recommend that NIH appropriately communicate this requirement to applicants, that peer review groups explicitly determine whether each proposed phase III clinical trial is required to have such a study design, and that summary statements document the initial reviewers' decisions.

(2) Ensure that NIH staff who transmit data to the inclusion tracking data system receive ongoing training on the requirements and purpose of the system.[62]

Immediately following the release of this report, an NIH subcommittee to review inclusion issues was formed, consisting of representatives from several ICs, ORWH, OER, and OIR, to reexamine NIH's system for tracking data on the inclusion of women and minorities in clinical research, recommend any necessary changes to improve its accuracy and performance, and reiterate the NIH policy. Several actions resulted to clarify the requirement for NIH-defined phase III clinical trials to include women and minority groups, if scientifically appropriate, and for analysis of sex/gender and/or racial/ethnic differences to be planned and conducted by investigators engaged in NIH-funded research. Significant actions included the following:

- Updating the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research and posting it on the ORWH Web siste and NIH Web site.[63]
- Developing a new terms and conditions of award statement for awards made after October 1, 2000 that have NIH-defined phase III clinical trials.
- Incorporating language in NIH solicitations for grant applications and contract proposals to clarify the submission requirement for NIH-defined phase III clinical trials; a description of plans for sex/gender and/or race/ethnicity analysis including subgroups, if applicable; and reporting enrollment annually and results of analyses, as appropriate.
- Developing guidelines and instructions for reviewers and scientific review officers (SROs) to emphasize and clarify the need

[61] U.S. General Accounting Office. (1990). *National Institutes of Health: Problems in Implementing Policy on Women Study Populations. Statement of Mark V. Nadel, Associate Director, National and Public Health Issues, Human Resources Division before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives* (GAO/T-HRD-90-38). Washington, DC: General Accounting Office.

[62] U.S. General Accounting Office. (2000, May). *Women's Health: NIH Has Increased Its Efforts to Include Women in Research.* (GAO/HEHS-00-96). Retrieved from http://www.gao.gov/new.items/he00096.pdf

[63] NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research—Amended, October 2001(NOT-OD-02-001). (2001, October 9). *NIH Guide for Grants and Contracts*, October 12, 2001. Bethesda, MD: National Institutes of Health. Available on the NIH Web site at http://grants.nih.gov/grants/funding/women_min/women_min.htm

to review research proposals classified as NIH-defined phase III clinical trials for both inclusion requirements and issues related to analyses by sex/gender and/or race/ethnicity. Instructions were developed for the proper documentation to include in summary statements to address adherence to these policies.

- Providing training to NIH program and review officials, grants and contracts management staff, and current and prospective research investigators to ensure compliance with this policy. NIH committed to GAO that NIH staff who transmit data will receive ongoing training on the requirements and purpose of the inclusion tracking data system. Several initiatives were implemented for review, grants management, and program staff since 2000, including specific topics addressing revisions to the NIH inclusion policy, a grants policy update, and SRO orientation on specific issues related to review meetings and proceedings.

Format Changes for Reporting Race and Ethnicity Data as of FY 2002

Beginning in FY 2002, NIH changed how data are reported based on the 1997 Office of Management and Budget (OMB) revisions to the 1977 Directive 15 "Race and Ethnic Standards for Federal Statistics and Administrative Reporting," which provided minimum standards for maintaining, collecting, and reporting data on race and ethnicity. In October 1997, OMB published "Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity."[64] Implementation involved a number of changes, including collecting and reporting information on race and ethnicity separately, whereas the 1977 OMB standards used a combined race and ethnicity format. NIH aggregate population data tables describe data using both the 1997 and 1977 OMB standards for reporting data on race and ethnicity. Since 2002, the number of studies reporting data using the 1997 format (New Form) has steadily increased, whereas the number of studies using the 1977 format (Old Form) has steadily decreased as the studies funded prior to FY 2002 are completed. (See appendix J for a comparison of the old and new forms.) The system does not easily allow for direct comparison of ethnic and racial data because the categories and methods for collecting the data both in the 1977 and 1997 reporting formats are fundamentally different. However, trends can be approximated as demonstrated in this report.

Continuing Implementation and Monitoring Activities

In fall 2009, the Acting Director of NIH established the Task Force on the Inclusion of Women, Minorities, and Other Populations in Clinical Research to consider the strengths and weaknesses of the current NIH approach and potential alternative approaches for accomplishing the goals of NIH's current policy for including women and minorities in all NIH-funded clinical research, including phase III clinical trials, and also to examine NIH's current policy for inclusion of children in all NIH clinical research.

The task force was chaired by the Director of the NIAMS and cochaired by the Director of ORWH and the Director of NIMHD, with members drawn from senior leadership in OER, OIR, other offices within the NIH Office of the Director, and representatives from some NIH ICs with responsibility for inclusion and research data.

The task force has completed its activities. For the past 20 years, ORWH has led NIH activities to ensure compliance with the NIH inclusion policy. However, with the establishment of the task force, responsibility for monitoring compliance, data analysis, and generation of the annual and biennial comprehensive reports has resided within OER. Final consideration of these recommendations is still pending. In the interim, OER has assumed a leadership role in monitoring adherence to the NIH inclusion policy, but oversight remains with the ORWH and the ACRWH.

[64] Recommendations from the Interagency Committee for the Review of the Racial and Ethnic Standards to the Office of Management and Budget Concerning Changes to the Standards for the Classification of Federal Data on Race and Ethnicity, 62 Fed. Reg. 36,873–36,946 (1997). The full text of the 1997 revision, which includes the 1977 directive (as appendix 1), can be found online at http://www.whitehouse.gov/omb/fedreg_directive_15

Communication and Outreach Efforts to the Scientific Community

NIH staff provides outreach to the scientific community to help increase understanding of any revised inclusion policies. These training and outreach efforts improve understanding of the NIH inclusion policy and assist investigators and NIH intramural research staff on how to appropriately address these issues throughout the research grant and contract process. Investigators are instructed to address women and minority inclusion issues in the development of their applications and proposals for clinical research.

Reference documents such as the *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research*[65] and the *Frequently Asked Questions (FAQs) on the Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research*[66] have been published and distributed for investigators and NIH staff. These publications discuss the elements of recruitment and retention, the NIH inclusion policy, current OMB requirements for reporting race and ethnicity data, and information for application submission, peer review, and funding. Both the Outreach Notebook and the FAQs are posted on the ORWH Web site[67] and the NIH Web site for the inclusion of women and minorities policy implementation.[68] These publications continue to be available to the research community to further explore the NIH inclusion policy and its intent. In addition, a slide show titled "Sex/Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!" was developed to assist NIH staff when working with the extramural community and is also available electronically.[69]

Monitoring Compliance: Extramural and Intramural Population Data Analysis

As a way of monitoring compliance with the policy, aggregate data tables compiled from each NIH IC are provided. Because the data included in the tables are aggregate data from across NIH, the data tables provide documentation of the monitoring of inclusion with some degree of analysis of data. Caution should be used in interpreting these figures. Conclusions that can be reasonably drawn from the data are provided.

When assessing inclusion data, enrollment figures should not be compared directly with the national census figures. The goal of the NIH policy is not to satisfy any quotas for proportional representation based on census data but rather to conduct biomedical and behavioral research in such a manner that the scientific knowledge acquired will be generalizable to the entire population of the United States. The number of women, men, and/or representatives of racial/ethnic subpopulations included in a particular study depends on the scientific question addressed in the study and the prevalence among women, men, and/or racial/ethnic subpopulations of the disease, disorder, or condition under investigation.

Scientific review groups (SRGs) are instructed to focus on scientific considerations when assessing the planned enrollment for a particular study. The SRG determines whether the implementation plan for an application is unacceptable if it (1) fails to provide sufficient information about target enrollment, (2) does not adequately justify limited or lack of inclusion of women or minorities, or (3) does not realistically address recruitment and retention. For NIH-defined phase III clinical trials, the SRG also evaluates the description of plans to conduct analyses, as appropriate, to address differences in the intervention effect by sex/gender and/or racial/ethnic group.

[65] NIH, Office of the Director. (2002). *Outreach notebook for the inclusion, recruitment and retention of women and minority subjects in clinical research: principal investigators' notebook* (NIH Publication No. 03-7036). Retrieved from http://orwh.od.nih.gov/inclusion/outreach.pdf

[66] NIH, Office of the Director. (2002). *Outreach notebook: Frequently asked questions concerning the NIH guidelines on the inclusion of women and minorities in clinical research.* Retrieved from http://orwh.od.nih.gov/inclusion/outreach-FAQ.pdf

[67] Office of Research on Women's Health, http://orwh.od.nih.gov

[68] Inclusion of Women and Minorities as Participants in Research Involving Human Subjects—Policy Implementation Page, http://grants1.nih.gov/grants/funding/women_min/women_min.htm

[69] NIH. *Sex/gender and minority inclusion in NIH clinical research: What investigators need to know!* Retrieved from the NIH Office of Extramural Research Inclusion of Women and Minorities Policy Implementation Web site, http://grants.nih.gov/grants/funding/women_min/women_min.htm

Applications with unacceptable inclusion plans cannot be funded until NIH staff is assured that revised inclusion plans from the investigators meet the inclusion policy requirements. Research awards covered by this policy require the grantee to report annually on the enrollment of research participants by sex/gender and race/ethnicity in order to monitor compliance with the NIH inclusion policy.

NIH has monitored aggregate demographic data for study populations through the evolving NIH computerized tracking system since FY 1994, and monitoring compliance with the NIH inclusion policy is well established in all ICs. In May 2002, NIH successfully deployed a population tracking system for monitoring inclusion data that was designed to provide easier data entry and project monitoring of investigator data reporting for NIH staff.

Definitions

Clinical Research

The term "clinical research" as defined by the 1997 Report of the NIH Director's Panel on Clinical Research[70] refers to

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. This area of research includes:
   a. Mechanisms of human disease
   b. Therapeutic interventions
   c. Clinical trials
   d. Development of new technologies

(2) Epidemiologic and behavioral studies

(3) Outcomes research and health services research

The report's definition of clinical research further notes: "Excluded from this definition are in vitro studies that utilize human tissues but do not deal directly with patients," i.e., the tissues cannot be linked to a living individual.

NIH-Defined Phase III Clinical Study

For the purpose of these guidelines, an NIH-defined clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, nonpharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials also are included.

Valid Analysis

The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are as follows:

- Allocation of study participants of both sexes/genders (males and females) and different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization
- Unbiased evaluation of the outcome(s) of study participants
- Use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups

Significant Difference

For purposes of this policy, a significant difference is a difference that is of clinical or public health importance based on substantial

[70] NIH Director's Panel on Clinical Research. (1997). *Report to the advisory committee to the NIH Director*. Bethesda, MD: National Institutes of Health.

scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends on the amount of information in the data set. With a very large amount of information, one could find a statistically significant but clinically small difference that is of very little clinical importance. Conversely, with less information, one could find a large difference of potential importance that is not statistically significant.

Domestic Organization

The term "domestic organization" refers to a public (including a State or other governmental agency) or private nonprofit or for-profit organization that is located in the United States or its territories, is subject to U.S. laws, and assumes legal and financial accountability for awarded funds and for the performance of the grant-supported activities.

Foreign Institution

The term "foreign institution" refers to an organization located in a country other than the United States and its territories that is subject to the laws of that country, regardless of the citizenship of the proposed principal investigator (PI).

Other Activities Related to the NIH Inclusion Policy

The inclusion and enrollment of pregnant women as participants in clinical research has taken on a renewed interest in the scientific community. Pregnant women are often excluded from clinical studies and few studies are designed to address health concerns and questions relevant to pregnant women. This has resulted in a lack of evidence, on this clinical issue, to inform health care and treatment decisions by clinicians. In October, 2010, ORWH convened a scientific forum to address the ethical/Institutional Review Board (IRB) and recruitment issues that investigators face in the conceptualization, initiation, and conduct of clinical research studies enrolling pregnant women with the intention of providing general guidance to enhance the formulation of recruitment plans, development of new protocols, enrich interactions with local IRBs, and facilitate the conduct of clinical studies enrolling pregnant women. More than 100 medical ethicists, clinical investigators, academic researchers, and others with an interest in clinical research in women shared information related to risk perception, risk reasoning, and the ethics of balancing risks and benefits for pregnant women in the clinical arena. Examples of challenges and strategies for overcoming barriers to clinical research in treating pregnant women with chronic or infectious diseases, and the evaluation of preventive measures such as vaccines in pregnancy were discussed and presented.

In 2008, Congress directed HHS to ask the Institute of Medicine (IOM) of the National Academies to examine what has been learned from research on women's health and how well it has been put into practice and communicated to both providers and women. In the resulting publication, *Women's Health Research: Progress, Pitfalls, and Promise* (September 2010)[71], the IOM found that while progress has been made over the last 20 years, gaps remain in research areas and in the application of results of research to benefit women in general and across multiple population groups. Based on recommendations from this report, as well as a second IOM report, *Sex Differences and Implications for Translational Neuroscience Research*,[72] ORWH is funding the IOM to convene a committee to address the need to increase publication of sex differences results in scientific literature and to facilitate establishment of guidelines to encourage authors to include sex-related subject information.

Conclusion and Current Status

NIH staff continue to monitor, document, and work with grantees and contractors to ensure compliance with the inclusion policy. Program officers/staff provide technical assistance to investigators as they develop their

[71] Institute of Medicine (IOM). (2010). *Women's health research: Progress, pitfalls, and promise*. Washington, DC: The National Academies Press.

[72] IOM. (2011). *Sex differences and implications for translational neuroscience research: Workshop summary.* Washington, DC: The National Academies Press.

applications and proposals throughout the application process. Review officers introduce and discuss with reviewers the guidelines/instructions for reviewing the inclusion of women and minorities in clinical research as well as the instructions and requirements for designing NIH-defined phase III clinical trials so that valid analyses can be conducted for sex/gender and ethnic/racial differences. At the time of award and submission of progress reports, program officials monitor and verify that inclusion policy requirements are met. When new and competing continuation applications selected for payment are deficient in meeting policy requirements, grants management staff and program officials are required to withhold funding until the investigator has satisfactorily addressed the policy requirements.

Summary Report of NIH Inclusion Data

NIH Aggregate Population Data Reported in FY 2009 and FY 2010

Because new clinical research studies begin each year while other studies may be ending, the inclusion data will vary from year to year due to the scientific topics under study and the prevalence of those conditions within each individual study. These data help to establish trends on the inclusion of women and minorities as subjects in clinical research. Data on inclusion are tabulated from human subject populations in NIH-defined phase III clinical trials and other human subject research studies and are based on self-identification by the participants. NIH clinical research studies are determined in accordance with the NIH definition of clinical research to include, for example, nonintervention clinical research, non-phase III clinical trials, epidemiologic studies, behavioral studies, and database studies.

Analysis of aggregate NIH data on inclusion for FY 2009 and FY 2010 documents that substantial numbers of women and men, including minorities, have been included as research subjects in NIH clinical trials and other human subject research studies during these fiscal years. However, caution should be used to avoid overinterpreting the figures that are provided.

Previous inclusion reports and aggregate enrollment figures for women, men, and minority groups from FY 1994 to the present can be found on the ORWH Web site at http://orwh.od.nih.gov/inclusion.html.

NIH Clinical Research: FY 2009 and FY 2010

In FY 2009, there were 16,689 extramural and intramural clinical research protocols, including phase III and other clinical studies, of which 11,171 protocols reported human subject participation as noted in this report's trend summary tables (table 6A). Of these, 91.9 percent were domestic protocols and 8.1 percent were foreign protocols (table 6A). Approximately 19.1 million participants were enrolled in extramural and intramural research protocols, of which 93.3 percent were domestic participants and 6.7 percent were foreign participants (table 6B). Of the 19.1 million participants, 59.8 percent were women, 39.6 percent were men, and 0.7 percent did not provide sex identification (table 6B). Furthermore, 30.2 percent of the total participants and 27.4 percent of the domestic-only participants were reported as minorities following the 1977 and 1997 OMB categories for reporting race and ethnicity (table 6C).

Correspondingly, in FY 2010, there were 17,251 extramural and intramural clinical research protocols, including phase III and other clinical studies, of which 12,079 protocols reported human subject participation (table 7A). Of these, 92.6 percent were domestic protocols and 7.4 percent were foreign protocols (table 7A). Approximately 23.4 million participants were enrolled in extramural and intramural research protocols, of which 92.1 percent were domestic participants and 7.9 percent were foreign participants (table 7B). Of the 23.4 million participants, 56.1 percent were women, 43 percent were men, and 0.9 percent did not provide sex identification (table 7B). Furthermore, 32.1 percent of the total participants and 28.1 percent of the domestic-only participants were reported as minorities following the 1977 and 1997 OMB categories for reporting race and ethnicity (table 7C).

While the number of participants in all extramural and intramural clinical research increased from 19.1 million in FY 2009 (table 6B) to 23.4 million in FY 2010 (table 7B), the proportion of women and men shifted slightly, from 59.8 percent women and 39.6 percent men in FY 2009 (table 6B) to 56.1 percent women and 43 percent men in FY 2010 (table 7B).

NIH-Defined Phase III Clinical Research: FY 2009 and FY 2010

In FY 2009, there were 662 extramural and intramural phase III clinical research protocols, of which 630 protocols reported human subject participation (table 8A). Of these, 71.6 percent were domestic protocols and 28.4 percent were foreign protocols (table 8A). Clinical trials not included in this analysis are those studies that have just begun and have not reported enrollment data or have not begun recruiting patients. A total of 652,300 participants were enrolled in extramural and intramural phase III research protocols, of which 66.5 percent were domestic participants and 33.5 percent were foreign participants (table 8B). Of the 652,300 participants, 53 percent were women, 42.3 percent were men, and 4.7 percent did not provide sex identification (table 8B). Furthermore, 44.8 percent of the total participants and 22.4 percent of domestic-protocol participants in phase III clinical research studies were reported as minorities following the 1977 and 1997 OMB categories for reporting race and ethnicity (table 8C).

Moreover, in FY 2009, there were 434 extramural and intramural phase III research protocols reporting data following the 1997 OMB standards for reporting by both race and ethnicity (table 9B). Accordingly, minority representation by race was highest for Blacks at 23.9 percent and lowest for Hawaiian/Pacific Islanders at 0.2 percent. American Indian/Alaska Natives represented 3.6 percent, Asians 19.1 percent, and Whites 39 percent of participants (table 9B.I). Participants identifying as *More Than One Race* were 1 percent of the total number of participants (table 9B.I). In addition, 13.3 percent did not identify a race category (table 9B.I). Of the 486,563 participants enrolled in extramural and intramural phase III research protocols in FY 2009 and reported following the current OMB standards, 80.6 percent identified as Not Hispanic, 10.7 percent identified as Hispanic or Latino, and 8.7 percent did not identify an ethnicity category (table 9B.II). The racial distribution of the Hispanic or Latino participants is provided separately (table 9B.III).

In FY 2009, 196 extramural and intramural phase III research protocols reported data following the 1977 OMB standards; minority representation was highest for Blacks at 9 percent and lowest for American Indian/Alaska Natives at 0.4 percent (table 9C). Asians/Pacific Islanders represented 2 percent, Hispanics were approximately 3.9 percent, and Whites were 82.1 percent of the participants (table 9C). The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations following the 1977 OMB standards.

Correspondingly, in FY 2010, there were 743 extramural and intramural phase III clinical research protocols, of which 696 protocols reported human subject participation (table 10A). Of these, 77.6 percent were domestic protocols and 22.4 percent were foreign protocols (table 10A). Clinical trials not included in this analysis are those studies that have just begun and have not reported enrollment data or have not begun recruiting patients. A total of 769,885 participants were enrolled in extramural and intramural phase III research protocols, of which 51 percent were domestic participants and 49 percent were foreign participants (table 10B). Of the 769,885 participants, 53 percent were women, 43 percent were men, and 4 percent did not provide sex identification (table 10B). Furthermore, 58.1 percent of the total participants and 23.5 percent of domestic-only participants in phase III clinical research were reported as minorities following the 1977 and 1997 OMB categories for reporting race and ethnicity (table 10C).

Moreover, in FY 2010, there were 634 extramural and intramural phase III research protocols reporting data following the 1997 OMB standards for reporting by both race and ethnicity (table 11B). Accordingly, minority representation by race was highest for Blacks at 36.8 percent and lowest for Hawaiian/Pacific Islanders at 0.1 percent (table 11B.I). American Indian/Alaska Natives represented 2.3 percent, Asians 16.4 percent, and Whites 33.2 percent of participants (table 11B.I). Participants

identifying as *More Than One Race* were 1.2 percent of the total number of participants (table 11B.I). In addition, 10 percent did not identify a race category (table 11B.I). Of the 691,450 participants enrolled in extramural and intramural phase III research protocols in FY 2010 and reported following the 1997 OMB standards, 84.2 percent identified as Not Hispanic, 8.8 percent identified as Hispanic or Latino, and 7 percent did not identify an ethnicity category (table 11B.II). The racial distribution of the Hispanic or Latino participants is provided separately (table 11B.III).

Sixty-two extramural and intramural phase III research protocols reported in FY 2009 following the 1977 OMB standards; minority representation was highest for Blacks at 8.8 percent and lowest for American Indian/Alaska Natives at 0.4 percent. Asian/Pacific Islanders represented approximately 1.5 percent, Hispanics were 4.1 percent, and Whites were 84.2 percent of the participants (table 11C). The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations following the 1977 OMB standards.

The number of participants in phase III extramural and intramural clinical research in FY 2010 (769,885) remained within the ranges reported since FY 1995. Similarly, the proportion of males and females, 53 female and 43 male in FY 2010, is similar to previous years (table 12A).

The following sections provide data on extramural research and intramural research separately.

Extramural Clinical Research: FY 2009 and FY 2010

In FY 2009, there were 14,725 extramural clinical research protocols, including phase III and other clinical studies (table 13A.I), of which 9,444 protocols reported human subject participation (table 13A.I). Of these, 91.4 percent were domestic protocols and 8.6 percent were foreign protocols (table 13A.I). Approximately 16.2 million participants were enrolled in extramural research protocols (table 13B.I), of which 95.3 percent of the total enrollment were domestic participants and 4.7 percent of the total enrollment were foreign participants (table 13B.I). Of the approximately 16.2 million participants, 62.9 percent were women, 36.5 percent were men, and 0.52 percent did not provide sex identification (table 14A). Furthermore, 30.4 percent of the total participants were reported as minorities (table 14A).

Correspondingly, in FY 2010, there were 15,201 extramural clinical research protocols (table 15A.I), including phase III and other clinical studies, of which 10,309 protocols reported human subject participation (table 15A.I). Of these, 92.4 percent were domestic protocols and 7.6 percent were foreign protocols (table 15A.I). Approximately 20.3 million participants were enrolled in extramural research protocols (Table 15B.I), of which 93.7 percent of the total enrollment were domestic participants and 6.3 percent of the total enrollment were foreign participants (table 15B.I). Of the approximately 20.3 million participants, 58.1 percent were women, 41.2 percent were men, and 0.74 percent did not provide sex identification (table 16A). Furthermore, 32.5 percent of the total extramural participants were reported as minorities (table 16A).

While the number of participants in extramural clinical research protocols increased from16.2 million in FY 2009 (table 13B.I) to 20.3 million in FY 2010 (table 15B.I), the proportions of women and men shifted slightly from 62.9 percent women and 36.5 percent men in FY 2009 (table 14A) to 58.1 percent women and 41.2 percent men in FY 2010 (table 16A). When sex-specific studies were excluded, the proportions of women and men in extramural clinical research reported in FY 2009 were 50.2 percent for women and 49 percent for men (table 17A), and in FY 2010, 51.7 percent for women and 47.3 percent for men (table 18A).

NIH-Defined Phase III Extramural Clinical Research: FY 2009 and FY 2010

In FY 2009, there were 619 extramural phase III clinical research protocols (table 19A.I), of which 592 protocols reported human subject participation (table 19A.I). A total of 635,825 participants were enrolled in extramural phase III research protocols, of which 52.6 percent were women, 42.6 percent

were men, and 4.8 percent did not provide sex identification (table 20A).

In FY 2009, there were 407 extramural phase III research protocols reporting data following the 1997 OMB standards for reporting race and ethnicity (table 20B). Minority representation by race was highest for Blacks at 24.4 percent and lowest for Hawaiian/Pacific Islanders at 0.18 percent (table 20B.I). American Indian/Alaska Natives represented 3.7 percent, Asians 19.6 percent, and Whites 39.9 percent of participants (table 20B.I). Participants identifying as *More Than One* Race were 0.99 percent of the total number of participants (table 20B.I). In addition, 11.3 percent did not identify a race category (table 20B.I). Of the 473,128 participants enrolled in extramural phase III research protocols in FY 2009 and reported following the 1997 OMB standards, 82.3 percent identified as Not Hispanic, 9.4 percent identified as Hispanic or Latino, and 8.3 percent did not identify an ethnicity category (table 20B.II). The racial distribution of the Hispanic or Latino participants is provided separately (table 20B.III).

In FY 2010, there were 696 extramural phase III clinical research protocols (table 21A.I), of which 650 protocols reported human subject participation (table 21A.I). A total of 749,518 participants were enrolled in extramural phase III research protocols, of which 52.3 percent were women, 43.6 percent were men, and 4.1 percent did not provide sex identification (table 22A).

Correspondingly, in FY 2010, there were 599 extramural phase III research protocols reporting data following the 1997 OMB standards for reporting race and ethnicity (table 22B). Minority representation by race was highest for Blacks at 37.4 percent and lowest for Hawaiian/Pacific Islanders at 0.14 percent. American Indian/Alaska Natives represented 2.3 percent, Asians 16.7 percent, and Whites 33.5 percent of participants (table 22B.I). Participants identifying as *More Than One Race* were 1.2 percent of the total number of participants (table 22B.I). In addition, 8.7 percent did not identify a race category (table 22B.I). Of the 674,142 participants enrolled in extramural phase III research protocols in FY 2010 and reported following the 1997 OMB standards, 85.4 percent identified as Not Hispanic, 7.8 percent identified as Hispanic or Latino, and 6.8 percent did not identify an ethnicity category (table 22B.II). The racial distribution of the Hispanic or Latino participants is provided separately (table 22B.III).

The number of extramural phase III clinical research protocols and participants increased from 619 protocols (table 19A.I) and 635,825 participants (table 19B.I) in FY 2009 to 696 protocols (table 21A.I) and 749,815 participants (table 21B.I) in FY 2010, but the proportion of women remained relatively stable at 52.6 percent women and 42.6 percent men in FY 2009 (table 20A) and 52.3 percent women and 43.6 percent men in FY 2010 (table 22A), as did the proportion not providing sex identification—4.8 percent in FY 2009 (table 20A) and 4.1 percent in FY 2010 (table 22A). There was a sharp increase in the reported enrollment of Blacks in FY 2010 to 252,174 participants (table 22B.I) compared with 115,252 participants in FY 2009 (table 20B.I), resulting primarily from expanded enrollment in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Global Network for Women's and Children's Health Research, a large foreign phase III clinical trial (U01HD040636).

Intramural Clinical Research: FY 2009 and FY 2010

In FY 2009, there were 1,964 intramural clinical research protocols (table 13A.I), including phase III and other clinical studies, of which 1,727 protocols reported human subject participation (table 13A.I). Approximately 3 million participants were enrolled in intramural research protocols, of which 42.4 percent were women, 56.1 percent were men, and 1.5 percent did not provide sex identification (table 23A).

For the 1,335 intramural clinical research studies that reported data following the current OMB standards in FY 2009, the largest racial minority group was Asians at 10 percent and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.05 percent (table 23B.I). American Indian/Alaska Natives represented 0.75 percent, Blacks 9.8 percent, and Whites 63.5 percent of participants in all intramural clinical research (table 23B.I).

Approximately 5.5 percent of participants reported *More Than One Race* as their racial category. In addition, 10.5 percent did not identify a race category (table 23B.I). Of the 2,790,196 participants enrolled in intramural clinical research protocols in FY 2009 and reported following the 1997 OMB standards, 81.2 percent identified as Not Hispanic, 4 percent identified as Hispanic or Latino, and 14.8 percent did not identify an ethnicity category (table 23B.II). The racial distribution of the Hispanic or Latino participants is provided separately (table 23B.III).

Among the 392 intramural research protocols that reported data following the 1977 OMB standards, minority representation was highest for Blacks at 13.6 percent and lowest for American Indian/Alaska Natives at 0.17 percent (table 23C). Asian/Pacific Islanders represented 4.2 percent, Hispanics 5.6 percent, and Whites 74.9 percent of the intramural research study population (table 23C). The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations following the 1977 OMB standards.

Correspondingly, in FY 2010, there were 2,050 intramural clinical research protocols (table 15A.I), including phase III and other clinical studies, of which 1,770 protocols reported human subject participation (table 15A.I). Approximately 3.1 million participants were enrolled in intramural research protocols, of which 43.2 percent were women, 54.7 percent were men, and 2.2 percent did not provide sex identification (table 24A).

For the 1,408 intramural clinical research studies that reported data following the 1997 OMB standards in FY 2010, the largest racial minority group was Black or African Americans at 10.3 percent, and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.13 percent (table 24B.I). American Indian/Alaska Natives represented 0.79 percent, Asians 9.8 percent, and Whites 62 percent of participants in all intramural clinical research (table 24B.I). Approximately 5.4 percent of participants reported *More Than One Race* as their racial category (table 24B.I). In addition, 11.6 percent did not identify a race category (table 24B.I). Of the 2,947,158 participants enrolled in intramural clinical research protocols in FY 2010 and reported following the 1997 OMB standards, 80 percent identified as Not Hispanic, 4.2 percent identified as Hispanic or Latino, and 15.9 percent did not identify an ethnicity category (table 24B. II). The racial distribution of the Hispanic or Latino participants is provided separately (table 24B.III).

Among the 362 intramural research protocols that report data following the 1977 OMB standards, minority representation was highest for Blacks at 13.7 percent and lowest for American Indian/Alaska Natives at 0.19 percent (table 24C). Asian/Pacific Islanders represented 4.3 percent, Hispanics 5.3 percent, and Whites (not Hispanic) 74.9 percent of the intramural research study population (table 24C). The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations following the 1977 OMB standards.

Although the number of participants in intramural clinical research protocols increased slightly from 3 million in FY 2009 (table 13B.I) to 3.1 million in FY 2010 (table 15B.I), there was no substantive change in the proportions of women and men—42.4 percent women and 56.1 percent men in FY 2009 (table 23A) and 43.2 percent women and 54.7 percent men in FY 2010 (table 24A).

NIH-Defined Phase III Intramural Clinical Research: FY 2009 and FY 2010

In FY 2009, there were 43 intramural phase III clinical research protocols (table 19A.I), of which 38 protocols reported human subject participation (table 19A.I). Of these, 89.5 percent were domestic and 10.5 percent were foreign (table 19A.I). A total of 16,475 participants was enrolled in intramural phase III research protocols (table 19B.I), of which 36.4 percent were domestic participants and 63.6 percent were foreign participants (table 19B.I). Of the 16,475 participants, 68.7 percent were women, 31.2 percent were men, and 0.08 percent did not provide sex identification (table 25A). Furthermore, 56.1 percent of total participants in phase III intramural clinical research protocols were reported as minorities (table 25A).

Correspondingly, in FY 2010, there were 47 intramural phase III clinical research protocols (table 21A.I), of which 46 protocols reported

human subject participation (table 21A.I). Of these, 91.3 percent were domestic and 8.7 percent were foreign (table 21A.I). A total of 20,367 participants was enrolled in intramural phase III research protocols (table 21B.I), of which 48.5 percent were domestic participants and 51.5 percent were foreign participants (table 21B.I). Of the 20,367 participants, 79.2 percent were women, 20.8 percent were men, and 0.06 percent did not provide sex identification (table 26A). Furthermore, 55 percent of total participants in intramural phase III clinical research protocols were reported as minorities following the 1977 and 1997 OMB categories for race and ethnicity (table 26A).

The number of participants enrolled in phase III intramural clinical research protocols increased, from 16,475 in FY 2009 (table 19B.I) to 20,367 in FY 2010 (Table 21B.I), as did the proportions of women—from 68.7 percent women and 31.2 percent men in FY 2009 (table 25A) to 79.2 percent women and 20.8 percent men in FY 2010 (table 26A).

Trend Report on NIH Aggregate Population Data: FY 1995–FY 2010

Trend data vary over time because the data for each year represent the net total of data resulting from (1) studies continuing from the prior year, (2) the addition of new studies reported, and (3) the subtraction of studies that are no longer reported.

Number of Protocols, Enrollment, and Domestic and Foreign Protocols

Table 27 includes a 16-year summary report showing a steady increase in the number of protocols and enrollment. Overall, the number of protocols with enrollment increased from 3,188 in FY 1995 to 12,079 in FY 2010—a 3.8-fold increase (table 27A.I). Reported enrollment increased from approximately 1 million (FY 1995) to 23.4 million (FY 2010)—a 22.9-fold increase; minority enrollment increased from approximately 0.4 million (FY 1995) to 7.5 million (FY 2010)—a 20.1-fold increase in the number of minority participants in NIH clinical research (table 27A.I). The total number of protocols reported with enrollment data has increased such that since FY 2003 the number is in excess of 10,000 protocols per year.

Table 27 also includes a 9-year summary report of domestic and foreign protocols. With the deployment of an updated population tracking system in 2002 and the OMB requirement to report data using the current format, NIH was able to report domestic and foreign data in a better way. Thus, trend data are available for domestic and foreign protocols and participation beginning in FY 2002. Domestic enrollment increased from 10.2 million (FY 2002) to 21.5 million (FY 2010)—a 2.1-fold increase (table 27A.II). Foreign enrollment increased from 0.9 million (FY 2002) to 1.8 million (FY 2010)—a 1.9-fold increase (table 27A.II). Overall, the total enrollment has increased, with domestic participation ranging between 75.9 and 93.3 percent and foreign participation ranging between 6.7 and 24.1 percent. In FY 2010, domestic and foreign enrollment was 92.1 percent and 7.9 percent, respectively (table 27C).

Minority Participation in All Extramural and Intramural Clinical Research

Table 28 is a summary report of all extramural and intramural clinical research by sex/gender and minority representation following the 1977 and 1997 data formats for domestic and foreign studies. The report demonstrates that female participation in all extramural and intramural research generally ranged between 51.7 and 64.2 percent, and male participation in all extramural and intramural research ranged between 34 and 45 percent (table 28A). Overall minority participation in all extramural and intramural clinical research ranged between 28.6 and 43.1 percent (table 28A).

Table 28E provides a comparison of domestic and foreign participation between FY 2002 and FY 2010. The vast majority of the total clinical research protocols was domestic (91.9 to 96.4 percent, table 28E). Although the number of foreign protocols has increased, they comprise only about 3.6 to 8.1 percent of the total clinical research protocols with enrollment (table 28E). Table 28F shows domestic and foreign minority enrollment for the 9-year period (FY 2002 to FY 2010). Minority enrollment varied between 24.1 and 28.9 percent of total domestic participation, whereas minority enrollment varied between 67.7 and 90.9 percent of total foreign participation (table 28F).

Minority Participation in Phase III Extramural and Intramural Clinical Research

Table 12 is a summary of NIH-funded phase III extramural and intramural clinical research by sex/gender and minority enrollment following the old and new data reporting formats for domestic and foreign studies. This table demonstrates that female participation in NIH-funded phase III extramural and intramural clinical research generally ranged between 53 and 74.8 percent and male participation in NIH-funded phase III extramural and intramural clinical research ranged between 24.3 and 44.6 percent (table 12A). Overall minority participation in NIH-funded phase III extramural and intramural clinical research ranged from 22.5 to 58.1 percent (table 12A). Table 12E provides a comparison of domestic and foreign participation between FY 2002 and FY 2010. The majority of protocols are domestic, ranging from 71.6 and 95.8 percent of the total phase III clinical research protocols. The number of foreign protocols ranged from 4.2 to 28.4 percent of total phase III protocols during this time. Table 12F shows minority domestic and foreign enrollment for the same 9-year period. Minority enrollment varied between 20.2 and 25.4 percent of total domestic participation, whereas minority enrollment in NIH-funded phase III clinical research varied between 48.4 and 96.2 percent of total foreign participation (table 12F).

Table 6. Summary of NIH Clinical Research Reported In FY 2009: Total Number of Protocols and Enrollment by Sex and Domestic Versus Foreign Protocols

Table 6A. Protocols Reported

Protocols	Total all clinical studies*	Domestic	Domestic (%)	Foreign	Foreign (%)
Protocols with enrollment	11,171	10,263	91.9%	908	8.1%
Protocols with enrollment (%)	66.9%	65.9%		81.3%	
Protocols with zero enrollment**	5,518	5,309	96.2%	209	3.8%
Protocols with zero enrollment (%)	33.1%	34.1%		18.7%	
Total protocols	**16,689**	**15,572**	93.3%	**1,117**	6.7%
Total % of protocols	100.0%	100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** "Protocols with zero enrollment" may indicate that enrollment data have not yet been submitted.

Table 6B. Enrollment Reported

Sex/Gender	Total all clinical studies*	Domestic	Domestic (%)	Foreign	Foreign (%)
Females enrolled	11,439,143	10,694,225	93.5%	744,918	6.5%
Females enrolled (%)	59.8%	59.9%		57.7%	
Males enrolled	7,570,646	7,033,607	92.9%	537,039	7.1%
Males enrolled (%)	39.6%	39.4%		41.6%	
Unknown sex/gender	128,949	120,242	93.2%	8,707	6.8%
Unknown sex/gender (%)	0.7%	0.7%		0.7%	
Total subjects enrolled	**19,138,738**	**17,848,074**	93.3%	**1,290,664**	6.7%
Total subjects enrolled (%)	100.0%	100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

Table 6C. Minority Enrollment Reported

Minority enrollment	Total all clinical studies*	Domestic	Domestic (%)	Foreign	Foreign (%)
Minority enrollment**	**5,783,543**	**4,883,794**	84.4%	**899,749**	15.6%
Minority enrollment (%)	30.2%	27.4%		69.7%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** See appendix J of this report for the race and ethnicity categories included in minority enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Table 7. Summary of NIH Clinical Research Reported In FY 2010: Total Number of Protocols and Enrollment by Sex and Domestic Versus Foreign Protocols

Table 7A. Protocols Reported

Protocols	Total all clinical studies*	Domestic	Domestic (%)	Foreign	Foreign (%)
Protocols with enrollment	12,079	11,189	92.6%	890	7.4%
Protocols with enrollment (%)	70.0%	69.7%		74.2%	
Protocols with zero enrollment**	5,172	4,862	94.0%	310	6.0%
Protocols with zero enrollment (%)	30.0%	30.3%		25.8%	
Total protocols	**17,251**	**16,051**	93.0%	**1,200**	7.0%
Total % of protocols	100.0%	100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** "Protocols with zero enrollment" may indicate that enrollment data have not yet been submitted.

Table 7B. Enrollment Reported

Sex/Gender	Total all clinical studies*	Domestic	Domestic (%)	Foreign	Foreign (%)
Females enrolled	13,102,832	12,018,942	91.7%	1,083,890	8.3%
Females enrolled (%)	56.1%	55.8%		58.9%	
Males enrolled	10,044,444	9,301,128	92.6%	743,316	7.4%
Males enrolled (%)	43.0%	43.2%		40.4%	
Unknown sex/gender	216,359	203,006	93.8%	13,353	6.2%
Unknown sex/gender (%)	0.9%	0.9%		0.7%	
Total subjects enrolled	**23,363,635**	**21,523,076**	92.1%	**1,840,559**	7.9%
Total subjects enrolled (%)	100.0%	100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

Table 7C. Minority Enrollment Reported

Minority enrollment	Total all clinical studies*	Domestic	Domestic (%)	Foreign	Foreign (%)
Minority enrollment**	**7,510,763**	**6,041,531**	80.4%	**1,469,232**	19.6%
Minority enrollment (%)	32.1%	28.1%		79.8%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** See appendix J of this report for the race and ethnicity categories included in minority enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Table 8. Summary of NIH Phase III Clinical Research Reported In FY 2009: Total Number of Protocols, Enrollment by Sex, and Minority Enrollment in Domestic Versus Foreign Protocols

Table 8A. Protocols Reported

Protocols	Total of Phase III Clinical Trials*	Domestic	Domestic (%)	Foreign	Foreign (%)
Protocols with enrollment	630	451	71.6%	179	28.4%
Protocols with enrollment (%)	95.2%	94.2%		97.8%	
Protocols with zero enrollment**	32	28	87.5%	4	12.5%
Protocols with zero enrollment (%)	4.8%	5.8%		2.2%	
Total protocols	**662**	**479**	72.4%	**183**	27.6%
Total % of protocols	100.0%	100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** "Protocols with zero enrollment" may indicate that enrollment data have not yet been submitted.

Table 8B. Enrollment Reported

Sex/Gender	Total of Phase III Clinical Trials*	Domestic	Domestic (%)	Foreign	Foreign (%)
Females enrolled	345,748	232,936	67.4%	112,812	32.6%
Females enrolled (%)	53.0%	53.7%		51.7%	
Males enrolled	276,159	171,078	61.9%	105,081	38.1%
Males enrolled (%)	42.3%	39.4%		48.1%	
Unknown sex/gender	30,393	29,881	98.3%	512	0.0%
Unknown sex/gender (%)	4.7%	6.9%		0.2%	
Total subjects enrolled	**652,300**	**433,895**	66.5%	**218,405**	33.5%
Total subjects enrolled (%)	100.0%	100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

Table 8C. Minority Enrollment Reported

Minority enrollment	Total of Phase III Clinical Trials*	Domestic	Domestic (%)	Foreign	Foreign (%)
Minority enrollment**	**291,949**	**97,079**	33.3%	**194,870**	66.7%
Minority enrollment (%)	44.8%	22.4%		89.2%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** See appendix J of this report for the race and ethnicity categories included in minority enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Table 9. Aggregate Enrollment Data for Extramural and Intramural Phase III Research Funded in FY 2008 and Reported in FY 2009: Percent Analysis

Table 9A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 630

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**345,748**	**157,952**		**45.68%**
Females (% of total)	**53.00%**	**54.10%**		
Males	**276,159**	**133,282**		**48.26%**
Males (% of total)	**42.34%**	**45.65%**		
Unknown	**30,393**	**715**		**2.35%**
Unknown (% of total)	**4.66%**	**0.24%**		
Total	**652,300**	**291,949**	**44.76%**	
Total (%)	100.00%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 11B (new form) and table 11C (old form).

Table 9B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 434

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	9,875	47,848	61,823	438	107,105	2,283	23,530	252,902
% of total enrollment	**2.03%**	**9.83%**	**12.71%**	**0.09%**	**22.01%**	**0.47%**	**4.84%**	**51.98%**
% of all females	*3.90%*	*18.92%*	*24.45%*	*0.17%*	*42.35%*	*0.90%*	*9.30%*	*100.00%*
% of race are female	56.40%	51.52%	53.19%	50.99%	56.51%	48.82%	36.26%	51.98%
Male (number)	7,575	44,912	54,229	417	81,253	2,334	12,585	203,305
% of total enrollment	**1.56%**	**9.23%**	**11.15%**	**0.09%**	**16.70%**	**0.48%**	**2.59%**	**41.78%**
% of all males	*3.73%*	*22.09%*	*26.67%*	*0.21%*	*39.97%*	*1.15%*	6.19%	*100.00%*
% of race are male	43.26%	48.36%	46.66%	48.54%	42.87%	49.91%	19.39%	41.78%
Unknown (number)	59	108	181	4	1,169	59	28,776	30,356
% of total enrollment	**0.01%**	**0.02%**	**0.04%**	**0.00%**	**0.24%**	**0.01%**	***5.91%***	**6.24%**
% of all unknown	*0.19%*	*0.36%*	*0.60%*	0.01%	*3.85%*	*0.19%*	*94.80%*	*100.00%*
% of race are unknown	0.34%	0.12%	0.16%	0.47%	0.62%	1.26%	44.35%	6.24%
Total (number)	17,509	92,868	116,233	859	189,527	4,676	64,891	486,563
% of total enrollment	**3.60%**	**19.09%**	**23.89%**	**0.18%**	**38.95%**	**0.96%**	**13.34%**	**100.00%**
% of sex/gender	*3.60%*	*19.09%*	*23.89%*	*0.18%*	*38.95%*	*0.96%*	*13.34%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 9B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/ Not reported	Total
Female (number)	210,945	34,357	7,600	252,902
% of total enrollment	**43.35%**	**7.06%**	**1.56%**	**51.98%**
% of all females	*83.41%*	*13.59%*	*3.01%*	*100.00%*
% of race are female	53.81%	65.79%	17.95%	51.98%
Male (number)	179,583	17,487	6,235	203,305
% of total enrollment	**36.91%**	**3.59%**	**1.28%**	**41.78%**
% of all males	*88.33%*	*8.60%*	*3.07%*	*100.00%*
% of race are male	45.81%	33.49%	14.72%	41.78%
Unknown (number)	1,462	379	28,515	30,356
% of total enrollment	**0.30%**	**0.08%**	**5.86%**	**6.24%**
% of all unknown	*4.82%*	*1.25%*	*93.94%*	*100.00%*
% of race are unknown	0.37%	0.73%	67.33%	6.24%
Total (number)	391,990	52,223	42,350	486,563
% of total enrollment	**80.56%**	**10.73%**	**8.70%**	**100.00%**
% of sex/gender	*80.56%*	*10.73%*	*8.70%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 9B.I–9B.III
Female (number)	8,729	138	488	99	7,265	431	17,207	34,357	146,739
% of total enrollment	**16.71%**	**0.26%**	**0.93%**	**0.19%**	**13.91%**	**0.83%**	**32.95%**	**65.79%**	**30.16%**
% of all females	*25.41%*	*0.40%*	*1.42%*	*0.29%*	*21.15%*	*1.25%*	*50.08%*	*100.00%*	*58.02%*
% of race are female	57.00%	39.32%	52.08%	50.00%	63.25%	44.71%	74.90%	65.79%	55.04%
Male (number)	6,543	203	439	95	4,160	521	5,526	17,487	119,153
% of total enrollment	**12.53%**	**0.39%**	**0.84%**	**0.18%**	**7.97%**	**1.00%**	**10.58%**	**33.49%**	**24.49%**
% of all males	*37.42%*	*1.16%*	*2.51%*	*0.54%*	*23.79%*	*2.98%*	*31.60%*	*100.00%*	*58.61%*
% of race are male	42.73%	57.83%	46.85%	47.98%	36.21%	54.05%	24.05%	33.49%	44.69%
Unknown (number)	41	10	10	4	62	12	240	379	713
% of total enrollment	**0.08%**	**0.02%**	**0.02%**	**0.01%**	**0.12%**	**0.02%**	**0.46%**	**0.73%**	**0.15%**
% of all unknown	*10.82%*	*2.64%*	*2.64%*	*1.06%*	*16.36%*	*3.17%*	*63.32%*	*100.00%*	*2.35%*
% of race are unknown	0.27%	2.85%	1.07%	2.02%	0.54%	1.24%	1.04%	0.73%	0.27%
Total (number)	15,313	351	937	198	11,487	964	22,973	52,223	266,605
% of total enrollment	**29.32%**	**0.67%**	**1.79%**	**0.38%**	**22.00%**	**1.85%**	**43.99%**	**100.00%**	**54.79%**
% of sex/gender	*29.32%*	*0.67%*	*1.79%*	*0.38%*	*22.00%*	*1.85%*	*43.99%*	*100.00%*	*54.79%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 9C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 196

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	352	2,114	6,122	2,625	79,752	1,881	92,846	11,213
% of total enrollment	**0.21%**	**1.28%**	**3.69%**	**1.58%**	**48.12%**	**1.13%**	**56.02%**	**6.77%**
% of all females	*0.38%*	*2.28%*	*6.59%*	*2.83%*	*85.90%*	*2.03%*	*100.00%*	*12.08%*
% of race are female	57.42%	64.24%	40.93%	40.48%	58.61%	43.63%	56.02%	44.24%
Male (number)	261	1,176	8,833	3,859	56,319	2,406	72,854	14,129
% of total enrollment	**0.16%**	**0.71%**	**5.33%**	**2.33%**	**33.98%**	**1.45%**	**43.96%**	**8.52%**
% of all males	*0.36%*	*1.61%*	*12.12%*	*5.30%*	*77.30%*	*3.30%*	*100.00%*	*19.39%*
% of race are male	42.58%	35.73%	59.06%	59.52%	41.39%	55.81%	43.96%	55.75%
Unknown (number)	0	1	1	0	11	24	37	2
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.01%**	**0.02%**	**0.00%**
% of all unknown	*0.00%*	*2.70%*	*2.70%*	*0.00%*	*29.73%*	*64.86%*	*100.00%*	*5.41%*
% of race are unknown	0.00%	0.03%	0.01%	0.00%	0.01%	0.56%	0.02%	0.01%
Total (number)	613	3,291	14,956	6,484	136,082	4,311	165,737	25,344
% of total enrollment	**0.37%**	**1.99%**	**9.02%**	**3.91%**	**82.11%**	**2.60%**	**100.00%**	**15.29%**
% of sex/gender	*0.37%*	*1.99%*	*9.02%*	*3.91%*	*82.11%*	*2.60%*	*100.00%*	*15.29%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 9B and 9C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 10. Summary of NIH Phase III Clinical Research Reported In FY 2010: Total Number of Protocols, Enrollment by Sex, and Minority Enrollment in Domestic Versus Foreign Protocols

Table 10A. Protocols Reported

Protocols	Total of Phase III Clinical Trials*	Domestic	Domestic (%)	Foreign	Foreign (%)
Protocols with enrollment	696	540	77.6%	156	22.4%
Protocols with enrollment (%)	93.7%	93.1%		95.7%	
Protocols with zero enrollment**	47	40	85.1%	7	14.9%
Protocols with zero enrollment (%)	6.3%	6.9%		4.3%	
Total protocols	**743**	**580**	78.1%	**163**	21.9%
Total % of protocols	100.0%	100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** "Protocols with zero enrollment" may indicate that enrollment data have not yet been submitted.

Table 10B. Enrollment Reported

Sex/Gender	Total of Phase III Clinical Trials*	Domestic	Domestic (%)	Foreign	Foreign (%)
Females enrolled	408,181	197,608	48.4%	210,573	51.6%
Females enrolled (%)	53.0%	50.3%		55.9%	
Males enrolled	330,808	165,205	49.9%	165,603	50.1%
Males enrolled (%)	43.0%	42.1%		43.9%	
Unknown sex/gender	30,896	30,054	97.3%	842	0.0%
Unknown sex/gender (%)	4.0%	7.6%		0.2%	
Total subjects enrolled	**769,885**	**392,867**	51.0%	**377,018**	49.0%
Total subjects enrolled (%)	100.0%	100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

Table 10C. Minority Enrollment Reported

Minority enrollment	Total of Phase III Clinical Trials*	Domestic	Domestic (%)	Foreign	Foreign (%)
Minority enrollment**	**447,187**	**92,509**	20.7%	**354,678**	79.3%
Minority enrollment (%)	58.1%	23.5%		94.1%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

** See appendix J of this report for the race and ethnicity categories included in minority enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Table 11. Aggregate Enrollment Data for Extramural and Intramural Phase III Research Funded in FY 2009 and Reported in FY 2010: Percent Analysis

Table 11A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 696

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**408,181**	**250,716**		**61.42%**
Females (% of total)	**53.02%**	**56.07%**		
Males	**330,808**	**195,249**		**59.02%**
Males (% of total)	**42.97%**	**43.66%**		
Unknown	**30,896**	**1,222**		**3.96%**
Unknown (% of total)	**4.01%**	**0.27%**		
Total	**769,885**	**447,187**	**58.08%**	
Total (%)	100.00%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 9B (new form) and table 9C (old form).

Table 11B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 634

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	7,972	62,284	143,931	482	129,143	3,125	27,173	374,110
% of total enrollment	**1.15%**	**9.01%**	**20.82%**	**0.07%**	**18.68%**	**0.45%**	**3.93%**	**54.11%**
% of all females	*2.13%*	*16.65%*	*38.47%*	*0.13%*	*34.52%*	*0.84%*	*7.26%*	*100.00%*
% of race are female	50.31%	55.10%	56.50%	51.50%	56.29%	37.84%	39.26%	54.11%
Male (number)	7,817	50,663	110,032	450	99,645	5,073	12,768	286,448
% of total enrollment	**1.13%**	**7.33%**	**15.91%**	**0.07%**	**14.41%**	**0.73%**	**1.85%**	**41.43%**
% of all males	*2.73%*	*17.69%*	*38.41%*	*0.16%*	*34.79%*	*1.77%*	4.46%	*100.00%*
% of race are male	49.33%	44.82%	43.19%	48.08%	43.44%	61.43%	18.45%	41.43%
Unknown (number)	57	95	775	4	622	60	29,279	30,892
% of total enrollment	**0.01%**	**0.01%**	**0.11%**	**0.00%**	**0.09%**	**0.01%**	***4.23%***	**4.47%**
% of all unknown	*0.18%*	*0.31%*	*2.51%*	0.01%	*2.01%*	*0.19%*	*94.78%*	*100.00%*
% of race are unknown	0.36%	0.08%	0.30%	0.43%	0.27%	0.73%	42.30%	4.47%
Total (number)	15,846	113,042	254,738	936	229,410	8,258	69,220	691,450
% of total enrollment	**2.29%**	**16.35%**	**36.84%**	**0.14%**	**33.18%**	**1.19%**	**10.01%**	**100.00%**
% of sex/gender	*2.29%*	*16.35%*	*36.84%*	*0.14%*	*33.18%*	*1.19%*	*10.01%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 11B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/ Not reported	Total
Female (number)	325,083	38,153	10,874	374,110
% of total enrollment	**47.01%**	**5.52%**	**1.57%**	**54.11%**
% of all females	*86.90%*	*10.20%*	*2.91%*	*100.00%*
% of race are female	55.83%	62.94%	22.39%	54.11%
Male (number)	255,655	22,154	8,639	286,448
% of total enrollment	**36.97%**	**3.20%**	**1.25%**	**41.43%**
% of all males	*89.25%*	*7.73%*	*3.02%*	*100.00%*
% of race are male	43.91%	36.55%	17.79%	41.43%
Unknown (number)	1,529	311	29,052	30,892
% of total enrollment	**0.22%**	**0.04%**	**4.20%**	**4.47%**
% of all unknown	*4.95%*	*1.01%*	*94.04%*	*100.00%*
% of race are unknown	0.26%	0.51%	59.82%	4.47%
Total (number)	582,267	60,618	48,565	691,450
% of total enrollment	**84.21%**	**8.77%**	**7.02%**	**100.00%**
% of sex/gender	*84.21%*	*8.77%*	*7.02%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 9B.I–9B.III
Female (number)	6,517	144	565	104	9,687	642	20,494	38,153	247,975
% of total enrollment	**10.75%**	**0.24%**	**0.93%**	**0.17%**	**15.98%**	**1.06%**	**33.81%**	**62.94%**	**35.86%**
% of all females	*17.08%*	*0.38%*	*1.48%*	*0.27%*	*25.39%*	*1.68%*	*53.72%*	*100.00%*	*66.28%*
% of race are female	49.71%	40.00%	52.51%	50.98%	62.99%	20.70%	74.83%	62.94%	56.93%
Male (number)	6,553	206	501	96	5,645	2,444	6,709	22,154	186,389
% of total enrollment	**10.81%**	**0.34%**	**0.83%**	**0.16%**	**9.31%**	**4.03%**	**11.07%**	**36.55%**	**26.96%**
% of all males	*29.58%*	*0.93%*	*2.26%*	*0.43%*	*25.48%*	*11.03%*	*30.28%*	*100.00%*	*65.07%*
% of race are male	49.98%	57.22%	46.56%	47.06%	36.71%	78.81%	24.50%	36.55%	42.79%
Unknown (number)	41	10	10	4	46	15	185	311	1,222
% of total enrollment	**0.07%**	**0.02%**	**0.02%**	**0.01%**	**0.08%**	**0.02%**	**0.31%**	**0.51%**	**0.18%**
% of all unknown	*13.18%*	*3.22%*	*3.22%*	*1.29%*	*14.79%*	*4.82%*	*59.49%*	*100.00%*	*3.96%*
% of race are unknown	0.31%	2.78%	0.93%	1.96%	0.30%	0.48%	0.68%	0.51%	0.28%
Total (number)	13,111	360	1,076	204	15,378	3,101	27,388	60,618	435,586
% of total enrollment	**21.63%**	**0.59%**	**1.78%**	**0.34%**	**25.37%**	**5.12%**	**45.18%**	**100.00%**	**63.00%**
% of sex/gender	*21.63%*	*0.59%*	*1.78%*	*0.34%*	*25.37%*	*5.12%*	*45.18%*	*100.00%*	*63.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 11C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 62

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	142	565	1,304	730	30,962	368	34,071	2,741
% of total enrollment	**0.18%**	**0.72%**	**1.66%**	**0.93%**	**39.47%**	**0.47%**	**43.44%**	**3.49%**
% of all females	*0.42%*	*1.66%*	*3.83%*	*2.14%*	*90.87%*	*1.08%*	*100.00%*	*8.04%*
% of race are female	47.97%	47.40%	18.93%	22.64%	46.85%	49.13%	43.44%	23.63%
Male (number)	154	627	5,584	2,495	35,120	380	44,360	8,860
% of total enrollment	**0.20%**	**0.80%**	**7.12%**	**3.18%**	**44.78%**	**0.48%**	**56.56%**	**11.30%**
% of all males	*0.35%*	*1.41%*	*12.59%*	*5.62%*	*79.17%*	*0.86%*	*100.00%*	*19.97%*
% of race are male	52.03%	52.60%	81.07%	77.36%	53.14%	50.73%	56.56%	76.37%
Unknown (number)	0	0	0	0	3	1	4	0
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**
% of all unknown	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*75.00%*	*25.00%*	*100.00%*	*0.00%*
% of race are unknown	0.00%	0.00%	0.00%	0.00%	0.00%	0.13%	0.01%	0.00%
Total (number)	296	1,192	6,888	3,225	66,085	749	78,435	11,601
% of total enrollment	**0.38%**	**1.52%**	**8.78%**	**4.11%**	**84.25%**	**0.95%**	**100.00%**	**14.79%**
% of sex/gender	*0.38%*	*1.52%*	*8.78%*	*4.11%*	*84.25%*	*0.95%*	*100.00%*	*14.79%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 11B and 11C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 12. Sixteen-Year Trend Summary of NIH Extramural and Intramural Phase III Clinical Research Reported for FY 1995–2010

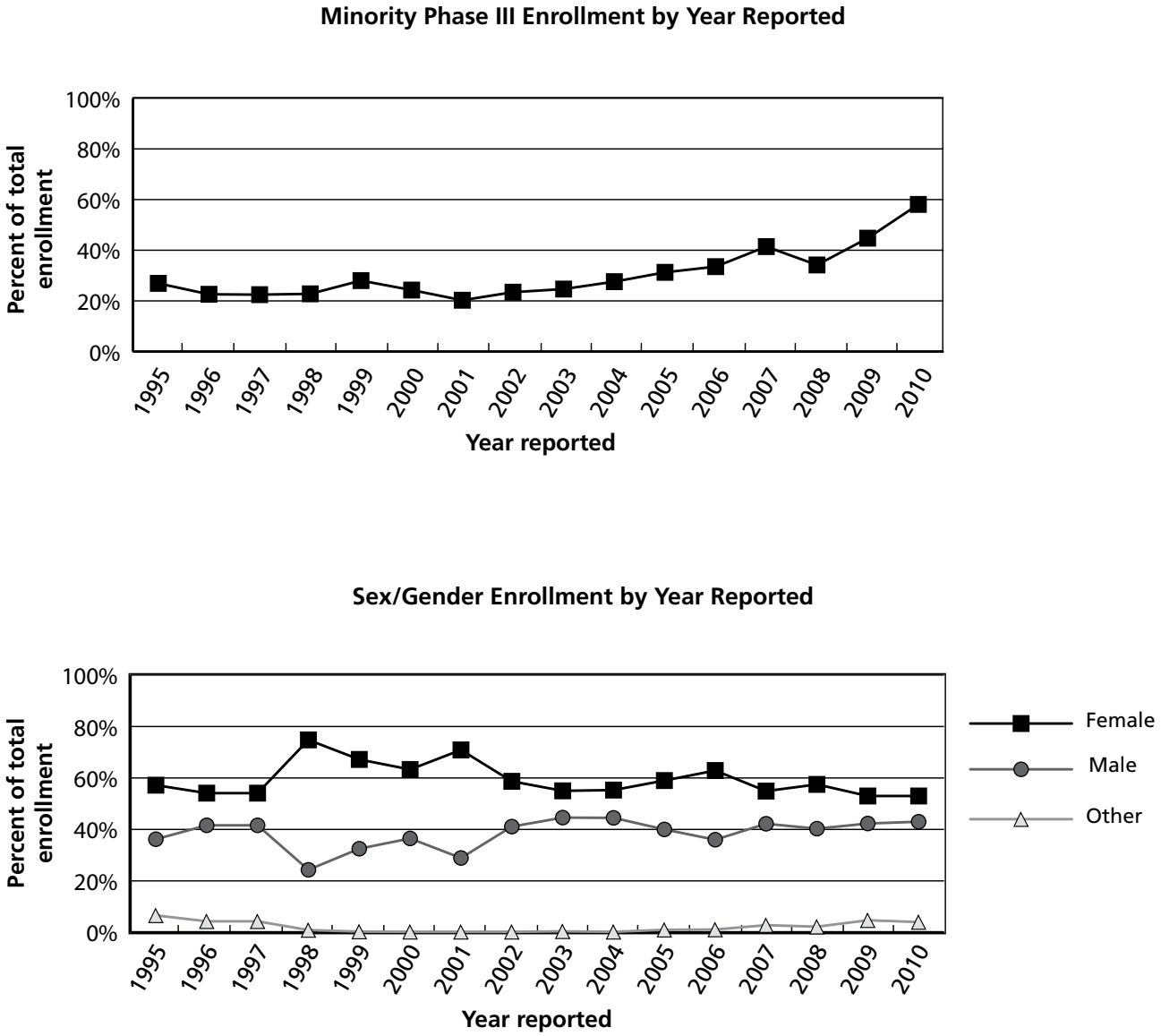
Table 12A. Phase III Sixteen-Year Summary Totals: Enrollment by Sex/Gender in All Phase III Protocols (Old and New Forms)

FY reported	FY funded	Form(s) used	Females	Males	Unknown sex/gender	Total all subjects	Subtotal of minority subjects enrolled*	Protocols with enrollment data
1995	**1994**	**Old**	**171,181**	**108,324**	**19,818**	**299,323**	**80,562**	**560**
1995	1994	Old	57.2%	36.2%	6.6%	100.0%	26.9%	—
1996	**1995**	**Old**	**264,755**	**203,698**	**21,210**	**489,663**	**110,669**	**608**
1996	1995	Old	54.1%	41.6%	4.3%	100.0%	22.6%	—
1997	**1996**	**Old**	**264,755**	**203,698**	**21,210**	**489,663**	**110,000**	**608**
1997	1996	Old	54.1%	41.6%	4.3%	100.0%	22.5%	—
1998	**1997**	**Old**	**228,417**	**74,389**	**2,705**	**305,511**	**69,599**	**320**
1998	1997	Old	74.8%	24.3%	0.9%	100.0%	22.8%	—
1999	**1998**	**Old**	**339,533**	**163,950**	**1,446**	**504,929**	**141,449**	**578**
1999	1998	Old	67.2%	32.5%	0.3%	100.0%	28.0%	—
2000	**1999**	**Old**	**313,952**	**180,705**	**1,086**	**495,743**	**120,339**	**589**
2000	1999	Old	63.3%	36.5%	0.2%	100.0%	24.3%	—
2001	**2000**	**Old**	**412,379**	**168,085**	**1,273**	**581,737**	**117,873**	**645**
2001	2000	Old	70.9%	28.9%	0.2%	100.0%	20.3%	—
2002	**2001**	**Old & new**	**278,876**	**195,090**	**781**	**474,747**	**111,269**	**754**
2002	2001	Old & new	58.7%	41.1%	0.2%	100.0%	23.4%	—
2003	**2002**	**Old & new**	**294,950**	**239,403**	**1,914**	**536,267**	**132,302**	**852**
2003	2002	Old & new	55.0%	44.6%	0.4%	100.0%	24.7%	—
2004	**2003**	**Old & new**	**301,353**	**242,913**	**1,101**	**545,367**	**150,456**	**573**
2004	2003	Old & new	55.3%	44.5%	0.2%	100.0%	27.6%	—
2005	**2004**	**Old & new**	**290,977**	**197,300**	**4,723**	**493,000**	**154,191**	**547**
2005	2004	Old & new	59.0%	40.0%	1.0%	100.0%	31.3%	—
2006	**2005**	**Old & new**	**314,066**	**179,975**	**5,389**	**499,430**	**167,446**	**624**
2006	2005	Old & new	62.9%	36.0%	1.1%	100.0%	33.5%	—
2007	**2006**	**Old & new**	**324,694**	**249,633**	**16,832**	**591,159**	**244,932**	**621**
2007	2006	Old & new	54.9%	42.2%	2.8%	100.0%	41.4%	—
2008	**2007**	**Old & new**	**455,612**	**319,732**	**17,234**	**792,578**	**270,899**	**639**
2008	2007	Old & new	57.5%	40.3%	2.2%	100.0%	34.2%	—
2009	**2008**	**Old & new**	**345,748**	**276,159**	**30,393**	**652,300**	**291,949**	**630**
2009	2008	Old & new	53.0%	42.3%	4.7%	100.0%	44.8%	—
2010	**2009**	**Old & new**	**408,181**	**330,808**	30,896	769,885	447,187	**696**
2010	2009	Old & new	53.0%	43.0%	4.0%	100.0%	58.1%	—

Note 1: Table 12A summarizes enrollment by sex/gender and minority race/ethnicity categories for the 16-year reporting period (1995–2010). The data are compiled from tables 12B, 12C and 12D, below, which provide the detailed distributions by sex/gender and race/ethnicity using the *old* enrollment form (table 12B) and the *new* enrollment form (tables 12C and 12D).

Note 2: Individual race and ethnicity categories in the old form and the new form cannot be combined because the categories reflect different OMB standards used in 1977 (old form) and 1997 (new form).

Figure 12A. Sixteen-Year Trend Summary of Enrollment in NIH Extramural and Intramural Phase III Clinical Research



Note: Trend data vary over time because the data for each year represent the net total resulting from (1) studies continuing from the prior year; (2) addition of new studies reported; and (3) subtraction of studies that are no longer reported.

Table 12B. Phase III Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Note 1: The shaded portions of tables 12B, 12C, and 12D, below, show the race/ethnicity categories that are identified as minority categories. The data reported in FY 2002 and later are from the population tracking system that was deployed with data reported in FY 2002 and later that allows separate reporting using the old form and the new form, and separate reporting for foreign and domestic data.

Note 2: Data from tables 12B, 12C, and 12D are combined to provide the summary data in table 12A.

FY reported	FY funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Minority subtotal	Protocols with enrollment data
1995	**1994**	5,358	2,740	52,433	20,031	172,773	45,988	299,323	80,562	560
1995	1994	1.8%	0.9%	17.5%	6.7%	57.7%	15.4%	100.0%	26.9%	—
1996	**1995**	4,235	40,126	46,838	19,470	321,445	57,549	489,663	110,669	608
1996	1995	0.9%	8.2%	9.6%	4.0%	65.6%	11.8%	100.0%	22.6%	—
1997	**1996**	4,235	40,126	46,838	19,470	321,445	57,549	489,663	110,669	608
1997	1996	0.9%	8.2%	9.6%	4.0%	65.6%	11.8%	100.0%	22.6%	—
1998	**1997**	5,030	5,324	42,805	16,440	229,534	6,378	305,511	69,599	320
1998	1997	1.6%	1.7%	14.0%	5.4%	75.1%	2.1%	100.0%	22.8%	—
1999	**1998**	3,685	20,276	76,921	40,567	336,703	26,777	504,929	141,449	578
1999	1998	0.7%	4.0%	15.2%	8.0%	66.7%	5.3%	100.0%	28.0%	—
2000	**1999**	3,726	24,017	62,512	30,084	335,824	39,580	495,743	120,339	589
2000	1999	0.8%	4.8%	12.6%	6.1%	67.7%	8.0%	100.0%	24.3%	—
2001	**2000**	4,079	11,132	70,110	32,552	422,802	41,062	581,737	117,873	645
2001	2000	0.7%	1.9%	12.1%	5.6%	72.7%	7.1%	100.0%	20.3%	—
2002	**2001**	1,645	20,560	51,991	29,636	315,543	12,228	431,603	103,832	**660**
2002	2001	0.38%	4.8%	12.0%	6.9%	73.1%	2.8%	100.00%	24.1%	—
2003	**2002**	1,689	20,038	49,255	29,066	337,654	16,615	454,317	100,048	**656**
2003	2002	0.4%	4.4%	10.8%	6.4%	74.3%	3.7%	100.0%	22.0%	—
2004	**2003**	1,505	18,807	45,285	32,974	265,764	14,050	378,385	98,571	**296**
2004	2003	0.4%	5.0%	12.0%	8.7%	70.2%	3.7%	100.0%	26.1%	—
2005	**2004**	1,319	17,740	39,402	21,829	231,492	4,507	316,289	80,290	**210**
2005	2004	0.4%	5.6%	12.5%	6.9%	73.2%	1.4%	100.0%	25.4%	—
2006	**2005**	1,012	16,800	20,355	9,524	175,724	6,348	229,763	47,691	**215**
2006	2005	0.4%	7.3%	8.9%	4.1%	76.5%	2.8%	100.0%	20.8%	—
2007	**2006**	751	3,943	21,582	9,333	169,789	4,259	209,657	35,609	**197**
2007	2006	0.4%	1.9%	10.3%	4.5%	81.0%	2.0%	100.0%	17.0%	—
2008	**2007**	900	4,542	22,445	9,642	190,753	4,262	232,544	37,529	**164**
2008	2007	0.4%	2.0%	9.7%	4.1%	82.0%	1.8%	100.0%	16.1%	—
2009	**2008**	613	3,291	14,956	6,484	136,082	4,311	165,737	25,344	**196**
2009	2008	0.4%	2.0%	9.0%	3.9%	82.1%	2.6%	100.0%	15.3%	—
2010	**2009**	**296**	**1,192**	**6,888**	**3,225**	**66,085**	**749**	**78,435**	**11,601**	**62**
2010	2009	0.4%	1.5%	8.8%	4.1%	84.3%	1.0%	100.0%	14.8%	—

Table 12C. Phase III New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Note 1: The new form consists of parts A and B (tables 12C and 12D) for reporting years 2002–2010. This form is provided as part of the annual progress report.

Note 2: Table 12C displays the new form part A for reporting separate race and ethnicity data.

Note 3: Table 12D displays the new form part B, which is the distribution of Hispanics reported by race, using the totals from the "Hispanic or Latino" column in part A.

Note 4: In FY 2009, the NICHD Global Network for Women's and Children's Health Research, a large, foreign phase III clinical trial (U01HD040636) expanded enrollment, causing a sharp increase in the reported enrollment of Blacks or African Americans reported in FY 2010.

I. All Subjects by Race

FY reported	FY funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian or Pacific Islander	White	More than one race	Unknown/ Other	Total
2002	**2001**	**159**	**799**	**4,647**	**52**	**34,654**	**560**	**2,273**	**43,144**
2002	2001	0.37%	1.85%	10.77%	0.12%	80.32%	1.30%	5.27%	100.00%
2003	**2002**	**484**	**2,609**	**21,641**	**220**	**47,869**	**989**	**8,138**	**81,950**
2003	2002	0.6%	3.2%	26.4%	0.3%	58.4%	1.2%	9.9%	100.0%
2004	**2003**	**1,396**	**4,385**	**43,721**	**611**	**106,793**	**4,419**	**5,657**	**166,982**
2004	2003	0.8%	2.6%	26.2%	0.4%	64.0%	2.6%	3.4%	100.0%
2005	**2004**	**2,164**	**9,192**	**50,338**	**462**	**101,238**	**3,063**	**10,254**	**176,711**
2005	2004	1.2%	5.2%	28.5%	0.3%	57.3%	1.7%	5.8%	100.0%
2006	**2005**	**4,630**	**32,360**	**50,780**	**535**	**126,670**	**4,246**	**50,446**	**269,667**
2006	2005	1.7%	12.0%	18.8%	0.2%	47.0%	1.6%	18.7%	100.0%
2007	**2006**	**9,351**	**47,364**	**84,468**	**555**	**133,002**	**4,145**	**102,617**	**381,502**
2007	2006	2.5%	12.4%	22.1%	0.1%	34.9%	1.1%	26.9%	100.0%
2008	**2007**	**15,006**	**95,296**	**103,166**	**716**	**281,344**	**12,136**	**52,370**	**560,034**
2008	2007	2.7%	17.0%	18.4%	0.1%	50.2%	2.2%	9.4%	100.0%
2009	**2008**	**17,509**	**92,868**	**116,233**	**859**	**189,527**	**4,676**	**64,891**	**486,563**
2009	2008	3.6%	19.1%	23.9%	0.2%	39.0%	1.0%	13.3%	100.0%
2010	**2009**	**15,846**	**113,042**	**254,738**	**936**	**229,410**	**8,258**	**69,220**	**691,450**
2010	2009	2.3%	16.3%	36.8%	0.1%	33.2%	1.2%	10.0%	100.0%

II. Subjects by Ethnicity

FY reported	FY funded	Not Hispanic	Hispanic or Latino**	Unknown/Not reported	Total*
2002	**2001**	**36,224**	**1,629**	**5,291**	**43,144**
2002	2001	83.96%	3.78%	12.26%	100.00%
2003	**2002**	**64,295**	**7,831**	**9,824**	**81,950**
2003	2002	78.5%	9.6%	12.0%	100.0%
2004	**2003**	**145,742**	**13,435**	**7,805**	**166,982**
2004	2003	87.3%	8.0%	4.7%	100.0%
2005	**2004**	**156,650**	**10,397**	**9,664**	**176,711**
2005	2004	88.6%	5.9%	5.5%	100.0%
2006	**2005**	**202,358**	**31,034**	**36,275**	**269,667**
2006	2005	75.0%	11.5%	13.5%	100.0%
2007	**2006**	**254,692**	**71,622**	**55,188**	**381,502**
2007	2006	66.8%	18.8%	14.5%	100.0%
2008	**2007**	**460,862**	**64,351**	**34,821**	**560,034**
2008	2007	82.3%	11.5%	6.2%	100.0%
2009	**2008**	**391,990**	**52,223**	**42,350**	**486,563**
2009	2008	80.6%	10.7%	8.7%	100.0%
2010	**2009**	**582,267**	**60,618**	**48,565**	**691,450**
2010	2009	84.2%	8.8%	7.0%	100.0%

* The "Total" columns of tables 12C.I and 12C.II must agree.

** The "Hispanic or Latino" column of table 12C.II must agree with the "Total" column of table 12D.

Table 12D. Nine-Year Phase III Hispanic Enrollment Report: Hispanics or Latinos Enrolled Sorted by Race

FY reported	FY funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian or Pacific Islander	White	More than one race	Unknown/ Other	Total*	Minority subtotal	Protocols with enrollment data
2002	**2001**	**49**	**22**	**31**	**4**	**660**	**304**	**560**	**1,630**	**7,437**	**94**
2002	2001	3.0%	1.3%	1.9%	0.2%	40.5%	18.7%	34.4%	100.0%	17.2%	—
2003	**2002**	**37**	**70**	**186**	**23**	**2,115**	**203**	**5,197**	**7,831**	**32,254**	**196**
2003	2002	0.5%	0.9%	2.4%	0.3%	27.0%	2.6%	66.4%	100.0%	39.4%	—
2004	**2003**	**269**	**59**	**193**	**26**	**7,264**	**3,052**	**2,572**	**13,435**	**54,405**	**277**
2004	2003	2.0%	0.4%	1.4%	0.2%	54.1%	22.7%	19.1%	100.0%	32.6%	—
2005	**2004**	**759**	**42**	**446**	**45**	**3,667**	**423**	**5,015**	**10,397**	**73,901**	**337**
2005	2004	7.3%	0.4%	4.3%	0.4%	35.3%	4.1%	48.2%	100.0%	41.8%	—
2006	**2005**	**2,307**	**50**	**720**	**40**	**6,872**	**713**	**20,332**	**31,034**	**119,755**	**409**
2006	2005	7.4%	0.2%	2.3%	0.1%	22.1%	2.3%	65.5%	100.0%	44.4%	—
2007	**2006**	**7,333**	**45**	**458**	**24**	**7,430**	**322**	**56,010**	**71,622**	**209,323**	**424**
2007	2006	10.2%	0.1%	0.6%	0.0%	10.4%	0.4%	78.2%	100.0%	54.9%	—
2008	**2007**	**13,060**	**229**	**717**	**122**	**22,293**	**5,654**	**22,276**	**64,351**	**270,889**	**475**
2008	2007	7.3%	0.4%	4.3%	0.4%	35.3%	4.1%	48.2%	100.0%	48.4%	—
2009	**2008**	**15,313**	**351**	**937**	**198**	**11,487**	**964**	**22,973**	**52,223**	**266,605**	**434**
2009	2008	29.3%	0.7%	1.8%	0.4%	22.0%	1.8%	44.0%	100.0%	54.8%	—
2010	**2009**	**13,111**	**360**	**1,076**	**204**	**15,378**	**3,101**	**27,388**	**60,618**	**435,586**	**634**
2010	2009	21.6%	0.6%	1.8%	0.3%	25.4%	5.1%	45.2%	100.0%	0.0%	—

*The "Total" column in table 12D must agree with the "Hispanic or Latino" column in table 12C.II.

Table 12E. Comparison of Domestic and Foreign Phase III Enrollment and Protocols With Enrollment for FY 2002–2010

Note 1: The total enrollment, total domestic enrollment, and total foreign enrollment increased overall from FY 2002 to FY 2010.

Note 2: The percent domestic enrollment decreased from more than 90% reported in FY 2002 to less than 80% reported in FY 2010. Percent foreign enrollment correspondingly increased during the same period.

FY reported	FY funded	Total enrollment*	Total domestic enrollment	Percent domestic enrollment	Total foreign enrollment	Percent foreign enrollment	Total number of protocols with enrollment data*	Number domestic protocols	Percent domestic protocols	Number foreign protocols	Percent foreign protocols
2002	**2001**	**474,747**	444,436	93.6%	30,311	6.4%	**754**	582	77.2%	172	22.8%
2003	**2002**	**536,267**	486,857	90.8%	49,410	9.2%	**852**	643	75.5%	209	24.5%
2004	**2003**	**545,367**	496,241	91.0%	49,126	9.0%	**573**	549	95.8%	24	4.2%
2005	**2004**	**493,000**	437,902	88.8%	55,098	11.2%	**547**	517	94.5%	30	5.5%
2006	**2005**	**499,430**	400,297	80.2%	99,133	19.8%	**624**	564	90.4%	60	9.6%
2007	**2006**	**591,159**	428,440	72.5%	162,719	27.5%	**653**	609	93.3%	44	6.7%
2008	**2007**	**792,578**	591,105	74.6%	201,473	25.4%	**639**	585	91.5%	54	8.5%
2009	**2008**	**652,300**	433,895	66.5%	218,405	33.5%	**630**	451	71.6%	179	28.4%
2010	**2009**	**769,885**	392,867	51.0%	377,018	49.0%	**696**	540	77.6%	156	22.4%

*Total enrollment data and total number of protocols reported using the old and new forms.

Figure 12B. Nine-Year Trend Summary of Domestic and Foreign NIH Extramural and Intramural Phase III Clinical Research

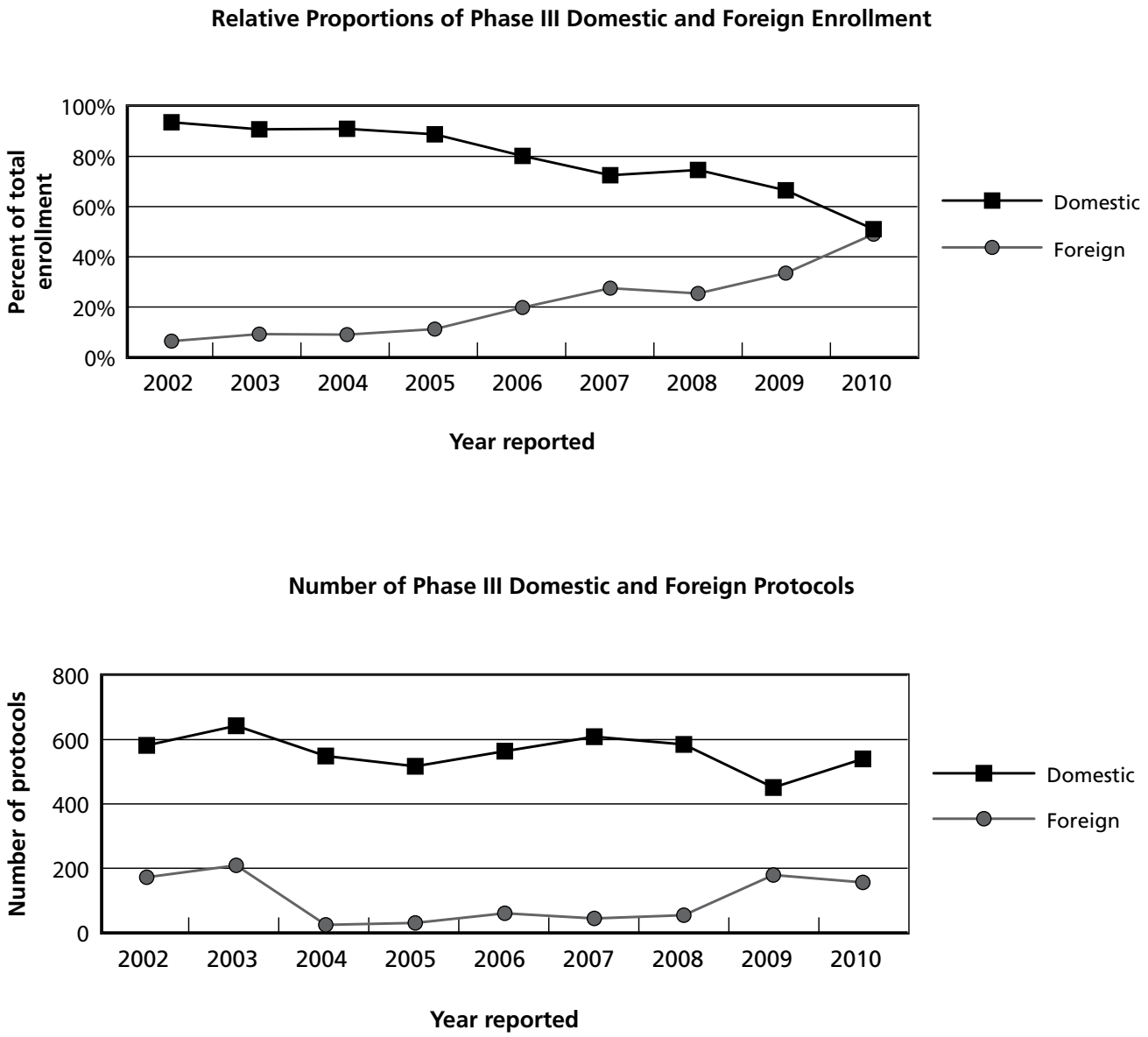


Table 12F. Phase III Foreign and Domestic Minority Comparison for FY 2002–2010

FY reported	FY funded	Minority enrollment in foreign protocols*	Total enrollment in foreign protocols	Minority enrollment in domestic protocols	Total enrollment in domestic protocols
2002	**2001**	**18,308**	**30,311**	**92,961**	**444,436**
2002	2001	60.4%	100.0%	20.9%	100.0%
2003	**2002**	**23,927**	**49,410**	**109,376**	**486,857**
2003	2002	48.4%	100.0%	22.5%	100.0%
2004	**2003**	**37,126**	**49,126**	**125,813**	**496,241**
2004	2003	75.6%	100.0%	25.4%	100.0%
2005	**2004**	**44,281**	**55,098**	**109,910**	**437,902**
2005	2004	80.4%	100.0%	25.1%	100.0%
2006	**2005**	**84,412**	**99,133**	**83,034**	**400,297**
2006	2005	85.2%	100.0%	20.7%	100.0%
2007	**2006**	**156,533**	**162,713**	**79,769**	**383,050**
2007	2006	96.2%	100.0%	20.8%	100.0%
2008	**2007**	**188,851**	**201,473**	**119,582**	**591,105**
2008	2007	93.7%	100.0%	20.2%	100.0%
2009	**2008**	**194,870**	**218,405**	**97,079**	**433,895**
2009	2008	89.2%	100.0%	22.4%	100.0%
2010	**2009**	**354,678**	**377,018**	**92,509**	**392,867**
2010	2010	94.1%	100.0%	23.5%	100.0%

*In FY 2009, the NICHD Global Network for Women's and Children's Health Research, a large, foreign phase III clinical trial (U01HD040636) expanded enrollment, causing a sharp increase in the reported enrollment of Blacks or African Americans reported in FY 2010.

Figure 12C. Phase III Foreign and Domestic Minority Enrollment Comparison for FY 2002–2010

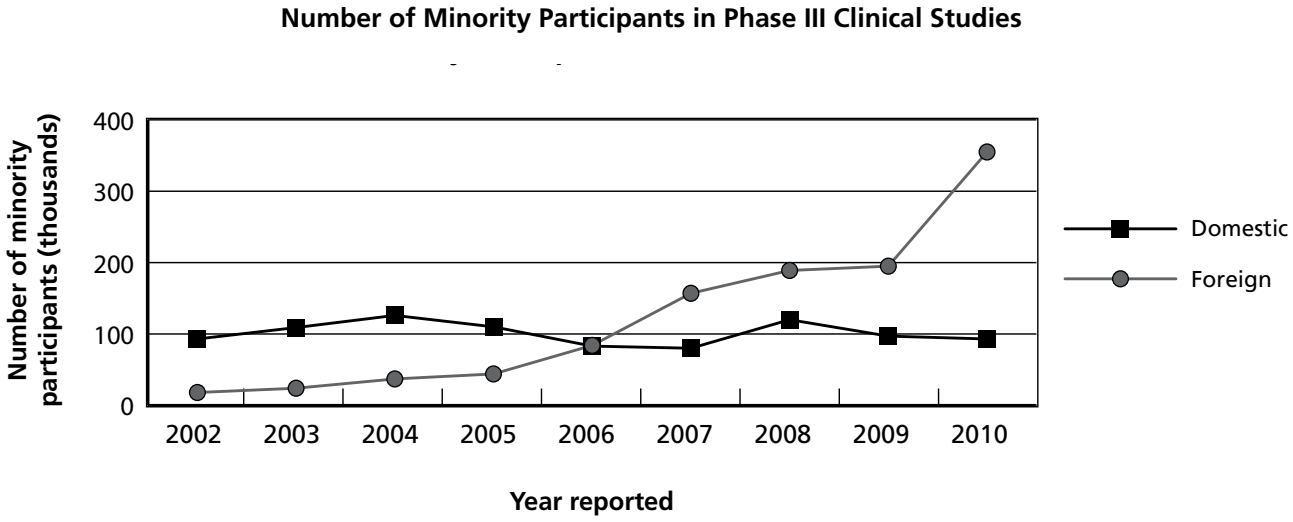


Table 13. Overview of NIH Extramural and Intramural Clinical Research Reported in FY 2009: Number of Sex-Specific Protocols and Domestic vs. Foreign Protocols

Table 13A. Protocols Reported

I. Summary of Domestic and Foreign Extramural and Intramural Protocols

Protocols	Total protocols	Protocols reporting enrollment	Domestic with enrollment	Domestic with enrollment (%)	Foreign with enrollment	Foreign with enrollment (%)
Extramural protocols	14,725	9,444	8,631	91.4%	813	8.6%
Intramural protocols	1,964	1,727	1,632	94.5%	95	5.5%
Total protocols	**16,689**	**11,171**	**10,263**	**91.9%**	**908**	**8.1%**

II. Domestic and Foreign Extramural and Intramural Protocols by Sex/Gender

Protocols	Total all clinical studies*	Domestic extramural (number)	Domestic extramural (%)	Domestic intramural (number)	Domestic intramural (%)	Foreign extramural (number)	Foreign extramural (%)	Foreign intramural (number)	Foreign intramural (%)
Protocols reporting females only	1,356	1,069	78.8%	131	9.7%	149	11.0%	7	0.5%
Protocols reporting females only (%)	8.1%	7.8%	—	7.0%	—	14.7%	—	6.7%	—
Protocols reporting males only	624	434	69.6%	102	16.3%	85	13.6%	3	0.5%
Protocols reporting males only (%)	3.7%	3.2%	—	5.5%	—	8.4%	—	2.9%	—
Protocols with both female and male enrollment **	9,191	7,128	77.6%	1,399	15.2%	579	6.3%	85	0.9%
Protocols with both female and male enrollment (%)	55.1%	52.0%	—	75.3%	—	57.2%	—	81.0%	—
Total protocols with enrollment	**11,171**	**8,631**	77.3%	**1,632**	14.6%	**813**	7.3%	**95**	0.9%
Total protocols with enrollment (%)	66.9%	63%	—	87.8%	—	80.3%	—	90.5%	—
Protocols with zero enrollment†	5,518	5,082	92.1%	227	4.1%	199	3.6%	10	0.2%
Protocols with zero enrollment (%)	33.1%	37.1%	—	12.2%	—	19.7%	—	9.5%	—
Total protocols	**16,689**	**13,713**	82.2%	**1,859**	11.1%	**1,012**	6.1%	**105**	0.6%
Total % of protocols	100.0%	100.0%	—	100.0%	—	100.0%	—	100.0%	—

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** "Protocols with both female and male enrollment" excludes sex-specific protocols.

† "Protocols with zero enrollment" may indicate that enrollment data have not yet been submitted.

Table 13B. Enrollment Reported

I. Summary of Enrollment in Domestic and Foreign Extramural and Intramural Protocols

Enrollment	Total enrollment	Total domestic	Total domestic (%)	Total foreign	Total foreign (%)
Extramural	16,187,065	15,431,545	95.3%	755,520	4.7%
Intramural	2,951,673	2,416,529	81.9%	535,144	18.1%
Total enrollment	**19,138,738**	**17,848,074**	**93.3%**	**1,290,664**	**6.7%**

II. Enrollment in Domestic and Foreign Extramural and Intramural Protocols by Sex/Gender

Enrollment	Total all clinical studies*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
In protocols reporting females only	4,830,093	4,460,062	92.3%	159,063	3.3%	39,730	0.8%	171,238	3.5%
In protocols reporting females only (%)	25.2%	28.9%	—	6.6%	—	5.3%	—	32.0%	—
In protocols reporting males only	396,076	338,422	85.4%	9,472	2.4%	22,741	5.7%	25,441	6.4%
In protocols reporting males only (%)	2.1%	2.2%	—	0.4%	—	3.0%	—	4.8%	—
In protocols with both female and male enrollment **	13,912,569	10,633,061	76.4%	2,247,994	16.2%	693,049	5.0%	338,465	2.4%
In protocols with both female and male enrollment (%)	72.7%	68.9%	—	93.0%	—	91.7%	—	63.2%	—
Total enrollment	**19,138,738**	**15,431,545**	80.6%	**2,416,529**	12.6%	**755,520**	3.9%	**535,144**	2.8%
Total enrollment (%)	100.0%	100.0%	—	100.0%	—	100.0%	—	100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** "Protocols with both female and male enrollment" excludes sex-specific protocols.

Table 13C. Minority Enrollment Reported

Minority enrollment	Total all clinical studies*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
Minority enrollment**	**5,783,543**	**4,304,509**	74.4%	**579,285**	10.0%	**614,724**	10.6%	**285,025**	4.9%
Minority enrollment (%)	30.2%	27.9%	—	24.0%	—	81.4%	—	53.3%	—

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** See appendix J of this report for the race and ethnicity categories included in minority enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Table 14. Aggregate Enrollment Data for Extramural Research Protocols Funded in FY 2008 and Reported in FY 2009: Percent Analysis

Table 14A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 9,444

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**10,188,246**	**3,022,938**		**29.67%**
Females (% of total)	**62.94%**	**61.45%**		
Males	**5,914,676**	**1,881,416**		**31.81%**
Males (% of total)	**36.54%**	**38.25%**		
Unknown	**84,143**	**14,879**		**17.68%**
Unknown (% of total)	**0.52%**	**0.30%**		
Total	**16,187,065**	**4,919,233**	**30.39%**	
Total (%)	100.00%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 14B (new form) and table 14C (old form).

Table 14B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 8,993

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	91,643	1,090,555	1,073,690	29,381	6,939,461	108,399	728,852	10,061,981
% of total enrollment	**0.57%**	**6.83%**	**6.73%**	**0.18%**	**43.48%**	**0.68%**	**4.57%**	**63.05%**
% of all females	*0.91%*	*10.84%*	*10.67%*	*0.29%*	*68.97%*	*1.08%*	*7.24%*	*100.00%*
% of race are female	68.59%	69.82%	53.28%	60.09%	62.98%	63.37%	72.24%	63.05%
Male (number)	41,411	469,956	933,867	19,392	4,072,005	61,291	215,172	5,813,094
% of total enrollment	**0.26%**	**2.94%**	**5.85%**	**0.12%**	**25.52%**	**0.38%**	**1.35%**	**36.43%**
% of all males	*0.71%*	*8.08%*	*16.06%*	*0.33%*	*70.05%*	*1.05%*	3.70%	*100.00%*
% of race are male	30.99%	30.09%	46.34%	39.66%	36.95%	35.83%	21.33%	36.43%
Unknown (number)	553	1,387	7,798	123	7,831	1,358	64,951	84,001
% of total enrollment	**0.00%**	**0.01%**	**0.05%**	**0.00%**	**0.05%**	**0.01%**	***0.41%***	**0.53%**
% of all unknown	*0.66%*	*1.65%*	*9.28%*	0.15%	*9.32%*	*1.62%*	*77.32%*	*100.00%*
% of race are unknown	0.41%	0.09%	0.39%	0.25%	0.07%	0.79%	6.44%	0.53%
Total (number)	133,607	1,561,898	2,015,355	48,896	11,019,297	171,048	1,008,975	15,959,076
% of total enrollment	**0.84%**	**9.79%**	**12.63%**	**0.31%**	**69.05%**	**1.07%**	**6.32%**	**100.00%**
% of sex/gender	*0.84%*	*9.79%*	*12.63%*	*0.31%*	*69.05%*	*1.07%*	*6.32%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 14B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	8,658,138	728,314	675,529	10,061,981
% of total enrollment	**54.25%**	**4.56%**	**4.23%**	**63.05%**
% of all females	*86.05%*	*7.24%*	*6.71%*	*100.00%*
% of race are female	62.89%	61.08%	67.56%	63.05%
Male (number)	5,093,038	459,455	260,601	5,813,094
% of total enrollment	**31.91%**	**2.88%**	**1.63%**	**36.43%**
% of all males	*87.61%*	*7.90%*	*4.48%*	*100.00%*
% of race are male	36.99%	38.53%	26.06%	36.43%
Unknown (number)	15,669	4,596	63,736	84,001
% of total enrollment	**0.10%**	**0.03%**	**0.40%**	**0.53%**
% of all unknown	*18.65%*	*5.47%*	*75.88%*	*100.00%*
% of race are unknown	0.11%	0.39%	6.37%	0.53%
Total (number)	13,766,845	1,192,365	999,866	15,959,076
% of total enrollment	**86.26%**	**7.47%**	**6.27%**	**100.00%**
% of sex/gender	*86.26%*	*7.47%*	*6.27%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 14B.I–14B. III
Female (number)	22,861	28,987	29,538	1,701	427,774	33,373	184,098	728,332	3,005,540
% of total enrollment	**1.92%**	**2.43%**	**2.48%**	**0.14%**	**35.87%**	**2.80%**	**15.44%**	**61.07%**	**18.83%**
% of all females	*3.14%*	*3.98%*	*4.06%*	*0.23%*	*58.73%*	*4.58%*	*25.28%*	*100.00%*	*29.87%*
% of race are female	58.60%	54.22%	33.76%	56.53%	63.93%	57.90%	65.09%	61.07%	61.55%
Male (number)	15,986	24,346	57,394	1270	240,495	24,228	95,902	459,621	1,862,314
% of total enrollment	**1.34%**	**2.04%**	**4.81%**	**0.11%**	**20.17%**	**2.03%**	**8.04%**	**38.54%**	**11.67%**
% of all males	*3.48%*	*5.30%*	*12.49%*	*0.28%*	*52.32%*	*5.27%*	*20.87%*	*100.00%*	*32.04%*
% of race are male	40.97%	45.54%	65.59%	42.21%	35.94%	42.03%	33.91%	38.54%	38.14%
Unknown (number)	168	129	566	38	820	39	2,836	4,596	14,875
% of total enrollment	**0.01%**	**0.01%**	**0.05%**	**0.00%**	**0.07%**	**0.00%**	**0.24%**	**0.39%**	**0.09%**
% of all unknown	*3.66%*	*2.81%*	*12.32%*	*0.83%*	*17.84%*	*0.85%*	*61.71%*	*100.00%*	*17.71%*
% of race are unknown	0.43%	0.24%	0.65%	1.26%	0.12%	0.07%	1.00%	0.39%	0.30%
Total (number)	39,015	53,462	87,498	3,009	669,089	57,640	282,836	1,192,549	4,882,729
% of total enrollment	**3.27%**	**4.48%**	**7.34%**	**0.25%**	**56.11%**	**4.83%**	**23.72%**	**100.00%**	**30.60%**
% of sex/gender	*3.27%*	*4.48%*	*7.34%*	*0.25%*	*56.11%*	*4.83%*	*23.72%*	*100.00%*	*30.60%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 14C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 451

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	585	2,908	8,926	4,979	102,183	6,684	126,265	17,398
% of total enrollment	**0.26%**	**1.28%**	**3.92%**	**2.18%**	**44.82%**	**2.93%**	**55.38%**	**7.63%**
% of all females	*0.46%*	*2.30%*	*7.07%*	*3.94%*	*80.93%*	*5.29%*	*100.00%*	*13.78%*
% of race are female	62.77%	59.30%	43.65%	48.72%	57.37%	49.95%	55.38%	47.66%
Male (number)	347	1,994	11,522	5,239	75,906	6,574	101,582	19,102
% of total enrollment	**0.15%**	**0.87%**	**5.05%**	**2.30%**	**33.29%**	**2.88%**	**44.56%**	**8.38%**
% of all males	*0.34%*	*1.96%*	*11.34%*	*5.16%*	*74.72%*	*6.47%*	*100.00%*	*18.80%*
% of race are male	37.23%	40.66%	56.35%	51.27%	42.62%	49.13%	44.56%	52.33%
Unknown (number)	0	2	1	1	15	123	142	4
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.05%**	**0.06%**	**0.00%**
% of all unknown	*0.00%*	*1.41%*	*0.70%*	*0.70%*	*10.56%*	*86.62%*	*100.00%*	*2.82%*
% of race are unknown	0.00%	0.04%	0.00%	0.01%	0.01%	0.92%	0.06%	0.01%
Total (number)	932	4,904	20,449	10,219	178,104	13,381	227,989	36,504
% of total enrollment	**0.41%**	**2.15%**	**8.97%**	**4.48%**	**78.12%**	**5.87%**	**100.00%**	**16.01%**
% of sex/gender	*0.41%*	*2.15%*	*8.97%*	*4.48%*	*78.12%*	*5.87%*	*100.00%*	*16.01%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 14B and 14C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 15. Overview of NIH Extramural and Intramural Clinical Research Reported in FY 2010: Number of Sex-Specific Protocols and Domestic vs. Foreign Protocols

Table 15A. Protocols Reported

I. Summary of Domestic and Foreign Extramural and Intramural Protocols

Protocols	Total protocols	Protocols reporting enrollment	Domestic with enrollment	Domestic with enrollment (%)	Foreign with enrollment	Foreign with enrollment (%)
Extramural protocols	15,201	10,309	9,525	92.4%	784	7.6%
Intramural protocols	2,050	1,770	1,664	94.0%	106	6.0%
Total protocols	**17,251**	**12,079**	**11,189**	**92.6%**	**890**	**7.4%**

II. Domestic and Foreign Extramural and Intramural Protocols by Sex/Gender

Protocols	Total all clinical studies*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
Protocols reporting females only	1,373	1,089	79.3%	146	10.6%	128	9.3%	10	0.7%
Protocols reporting females only (%)	8.0%	7.7%		7.6%		11.8%		8.5%	
Protocols reporting males only	691	491	71.1%	111	16.1%	85	12.3%	4	0.6%
Protocols reporting males only (%)	4.0%	3.5%		5.7%		7.8%		3.4%	
Protocols with both female and male enrollment**	10,015	7,945	79.3%	1,407	14.0%	571	5.7%	92	0.9%
Protocols with both female and male enrollment (%)	58.1%	56.3%		72.8%		52.7%		78.6%	
Total protocols with enrollment	**12,079**	**9,525**	78.9%	**1,664**	13.8%	**784**	6.5%	**106**	0.9%
Total protocols with enrollment (%)	70.0%	67%		86.1%		72.4%		90.6%	
Protocols with zero enrollment†	5,172	4,593	88.8%	269	5.2%	299	5.8%	11	0.2%
Protocols with zero enrollment (%)	30.0%	32.5%		13.9%		27.6%		9.4%	
Total protocols	**17,251**	**14,118**	81.8%	**1,933**	11.2%	**1,083**	6.3%	**117**	0.7%
Total % of protocols	100.0%	100.0%		100.0%		100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** "Protocols with both female and male enrollment" excludes sex-specific protocols.

† "Protocols with zero enrollment" may indicate that enrollment data have not yet been submitted.

Table 15B. Enrollment Reported

I. Summary of Enrollment in Domestic and Foreign Extramural and Intramural Protocols

Enrollment	Total enrollment	Total domestic	Total domestic (%)	Total foreign	Total foreign (%)
Extramural	20,252,793	18,974,363	93.7%	1,278,430	6.3%
Intramural	3,110,842	2,548,713	81.9%	562,129	18.1%
Total enrollment	**23,363,635**	**21,523,076**	**92.1%**	**1,840,559**	**7.9%**

II. Enrollment in Domestic and Foreign Extramural and Intramural Protocols by Sex/Gender

Enrollment	Total all clinical studies*	Domestic extramural (number)	Domestic extramural (%)	Domestic intramural (number)	Domestic intramural (%)	Foreign extramural (number)	Foreign extramural (%)	Foreign intramural (number)	Foreign intramural (%)
In protocols reporting females only	4,440,402	4,004,391	90.2%	198,571	4.5%	52,143	1.2%	185,297	4.2%
In protocols reporting females only (%)	19.0%	21.1%		7.8%		4.1%		33.0%	
In protocols reporting males only	1,328,551	1,274,647	95.9%	11,609	0.9%	15,928	1.2%	26,367	2.0%
In protocols reporting males only (%)	5.7%	6.7%		0.5%		1.2%		4.7%	
In protocols with both female and male enrollment**	17,594,682	13,695,325	77.8%	2,338,533	13.3%	1,210,359	6.9%	350,465	2.0%
In protocols with both female and male enrollment (%)	75.3%	72.2%		91.8%		94.7%		62.3%	
Total enrollment	**23,363,635**	**18,974,363**	81.2%	**2,548,713**	10.9%	**1,278,430**	5.5%	**562,129**	2.4%
Total enrollment (%)	100.0%	100.0%		100.0%		100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** "Protocols with both female and male enrollment" excludes sex-specific protocols.

Table 15C. Minority Enrollment Reported

Minority enrollment	Total all clinical studies*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
Minority enrollment**	**7,510,763**	**5,423,294**	72.2%	**618,237**	8.2%	**1,165,228**	15.5%	**304,004**	4.0%
Minority enrollment (%)	32.1%	28.6%		24.3%		91.1%		54.1%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total all clinical studies" includes NIH-defined phase III clinical trials.

** See appendix J of this report for the race and ethnicity categories included in minority enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Table 16. Aggregate Enrollment Data for Extramural Research Protocols Funded in FY 2009 and Reported in FY 2010: Percent Analysis

Table 16A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 10,309

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**11,758,980**	**3,970,845**		**33.77%**
Females (% of total)	**58.06%**	**60.27%**		
Males	**8,344,426**	**2,577,783**		**30.89%**
Males (% of total)	**41.20%**	**39.13%**		
Unknown	**149,387**	**39,894**		**26.71%**
Unknown (% of total)	**0.74%**	**0.61%**		
Total	**20,252,793**	**6,588,522**	**32.53%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 16B (new form) and table 16C (old form).

Table 16B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 10,139

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	200,172	1,280,862	1,443,812	85,453	7,609,654	116,266	975,655	11,711,874
% of total enrollment	**0.99%**	**6.36%**	**7.17%**	**0.42%**	**37.77%**	**0.58%**	**4.84%**	**58.12%**
% of all females	*1.71%*	*10.94%*	*12.33%*	*0.73%*	*64.97%*	*0.99%*	*8.33%*	*100.00%*
% of race are female	59.21%	69.40%	54.56%	58.11%	56.58%	58.26%	64.08%	58.12%
Male (number)	137,288	561,819	1,192,524	61,491	5,817,603	82,192	436,197	8,289,114
% of total enrollment	**0.68%**	**2.79%**	**5.92%**	**0.31%**	**28.87%**	**0.41%**	**2.16%**	**41.14%**
% of all males	*1.66%*	*6.78%*	*14.39%*	*0.74%*	*70.18%*	*0.99%*	5.26%	*100.00%*
% of race are male	40.61%	30.44%	45.06%	41.82%	43.25%	41.19%	28.65%	41.14%
Unknown (number)	612	2,983	10,087	106	23,225	1,099	110,620	148,732
% of total enrollment	**0.00%**	**0.01%**	**0.05%**	**0.00%**	**0.12%**	**0.01%**	***0.55%***	**0.74%**
% of all unknown	*0.41%*	*2.01%*	*6.78%*	0.07%	*15.62%*	*0.74%*	*74.38%*	*100.00%*
% of race are unknown	0.18%	0.16%	0.38%	0.07%	0.17%	0.55%	7.27%	0.74%
Total (number)	338,072	1,845,664	2,646,423	147,050	13,450,482	199,557	1,522,472	20,149,720
% of total enrollment	**1.68%**	**9.16%**	**13.13%**	**0.73%**	**66.75%**	**0.99%**	**7.56%**	**100.00%**
% of sex/gender	*1.68%*	*9.16%*	*13.13%*	*0.73%*	*66.75%*	*0.99%*	*7.56%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 16B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	9,649,854	1,055,739	1,006,281	11,711,874
% of total enrollment	**47.89%**	**5.24%**	**4.99%**	**58.12%**
% of all females	*82.39%*	*9.01%*	*8.59%*	*100.00%*
% of race are female	58.11%	57.52%	58.91%	58.12%
Male (number)	6,936,676	752,923	599,515	8,289,114
% of total enrollment	**34.43%**	**3.74%**	**2.98%**	**41.14%**
% of all males	*83.68%*	*9.08%*	*7.23%*	*100.00%*
% of race are male	41.77%	41.02%	35.10%	41.14%
Unknown (number)	19,792	26,675	102,265	148,732
% of total enrollment	**0.10%**	**0.13%**	**0.51%**	**0.74%**
% of all unknown	*13.31%*	*17.93%*	*68.76%*	*100.00%*
% of race are unknown	0.12%	1.45%	5.99%	0.74%
Total (number)	16,606,322	1,835,337	1,708,061	20,149,720
% of total enrollment	**82.41%**	**9.11%**	**8.48%**	**100.00%**
% of sex/gender	*82.41%*	*9.11%*	*8.48%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 16B.I–16B. III
Female (number)	109,588	6,372	68,868	1,526	564,744	31,912	272,729	1,055,739	3,964,038
% of total enrollment	**5.97%**	**0.35%**	**3.75%**	**0.08%**	**30.77%**	**1.74%**	**14.86%**	**57.52%**	**19.67%**
% of all females	*10.38%*	*0.60%*	*6.52%*	*0.14%*	*53.49%*	*3.02%*	*25.83%*	*100.00%*	*33.85%*
% of race are female	54.01%	65.41%	41.37%	56.06%	59.36%	52.20%	61.85%	57.52%	60.34%
Male (number)	93,129	3,170	96,463	1147	372,988	28,968	157,058	752,923	2,565,360
% of total enrollment	**5.07%**	**0.17%**	**5.26%**	**0.06%**	**20.32%**	**1.58%**	**8.56%**	**41.02%**	**12.73%**
% of all males	*12.37%*	*0.42%*	*12.81%*	*0.15%*	*49.54%*	*3.85%*	*20.86%*	*100.00%*	*30.95%*
% of race are male	45.90%	32.54%	57.95%	42.14%	39.20%	47.39%	35.62%	41.02%	39.05%
Unknown (number)	175	199	1134	49	13733	250	11,135	26,675	39,755
% of total enrollment	**0.01%**	**0.01%**	**0.06%**	**0.00%**	**0.75%**	**0.01%**	**0.61%**	**1.45%**	**0.20%**
% of all unknown	*0.66%*	*0.75%*	*4.25%*	*0.18%*	*51.48%*	*0.94%*	*41.74%*	*100.00%*	*26.73%*
% of race are unknown	0.09%	2.04%	0.68%	1.80%	1.44%	0.41%	2.53%	1.45%	0.61%
Total (number)	202,892	9,741	166,465	2,722	951,465	61,130	440,922	1,835,337	6,569,153
% of total enrollment	**11.05%**	**0.53%**	**9.07%**	**0.15%**	**51.84%**	**3.33%**	**24.02%**	**100.00%**	**32.60%**
% of sex/gender	*11.05%*	*0.53%*	*9.07%*	*0.15%*	*51.84%*	*3.33%*	*24.02%*	*100.00%*	*32.60%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 16C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 170

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	185	978	2,745	2,899	38,859	1,440	47,106	6,807
% of total enrollment	**0.18%**	**0.95%**	**2.66%**	**2.81%**	**37.70%**	**1.40%**	**45.70%**	**6.60%**
% of all females	*0.39%*	*2.08%*	*5.83%*	*6.15%*	*82.49%*	*3.06%*	*100.00%*	*14.45%*
% of race are female	49.47%	46.02%	27.26%	42.64%	48.19%	47.06%	45.70%	35.14%
Male (number)	189	1,075	7,284	3,875	41,381	1,508	55,312	12,423
% of total enrollment	**0.18%**	**1.04%**	**7.07%**	**3.76%**	**40.15%**	**1.46%**	**53.66%**	**12.05%**
% of all males	*0.34%*	*1.94%*	*13.17%*	*7.01%*	*74.81%*	*2.73%*	*100.00%*	*22.46%*
% of race are male	50.53%	50.59%	72.33%	56.99%	51.31%	49.28%	53.66%	64.14%
Unknown (number)	0	72	42	25	404	112	655	139
% of total enrollment	**0.00%**	**0.07%**	**0.04%**	**0.02%**	**0.39%**	**0.11%**	**0.64%**	**0.13%**
% of all unknown	*0.00%*	*10.99%*	*6.41%*	*3.82%*	*61.68%*	*17.10%*	*100.00%*	*21.22%*
% of race are unknown	0.00%	3.39%	0.42%	0.37%	0.50%	3.66%	0.64%	0.72%
Total (number)	374	2,125	10,071	6,799	80,644	3,060	103,073	19,369
% of total enrollment	**0.36%**	**2.06%**	**9.77%**	**6.60%**	**78.24%**	**2.97%**	**100.00%**	**18.79%**
% of sex/gender	*0.36%*	*2.06%*	*9.77%*	*6.60%*	*78.24%*	*2.97%*	*100.00%*	*18.79%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 16B and 16C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 17. Aggregate Enrollment Data for Extramural Research Protocols Excluding Male-Only and Female-Only Protocols Funded in FY 2008 and Reported in FY 2009: Percent Analysis

Table 17A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 7,707

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**5,688,454**	**1,759,483**		**30.93%**
Females (% of total)	**50.22%**	**49.89%**		
Males	**5,553,513**	**1,752,572**		**31.56%**
Males (% of total)	**49.03%**	**49.69%**		
Unknown	**84,143**	**14,879**		**17.68%**
Unknown (% of total)	**0.74%**	**0.42%**		
Total	**11,326,110**	**3,526,934**	**31.14%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 17B (new form) and table 17C (old form).

Table 17B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 7,404

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	44,382	433,527	816,068	26,622	4,011,827	75,247	226,437	5,634,110
% of total enrollment	**0.40%**	**3.87%**	**7.28%**	**0.24%**	**35.77%**	**0.67%**	**2.02%**	**50.23%**
% of all females	*0.79%*	*7.69%*	*14.48%*	*0.47%*	*71.21%*	*1.34%*	*4.02%*	*100.00%*
% of race are female	51.75%	52.20%	47.38%	57.97%	50.82%	55.27%	45.23%	50.23%
Male (number)	40,828	395,569	898,353	19,179	3,875,190	59,547	209,270	5,497,936
% of total enrollment	**0.36%**	**3.53%**	**8.01%**	**0.17%**	**34.55%**	**0.53%**	**1.87%**	**49.02%**
% of all males	*0.74%*	*7.19%*	*16.34%*	*0.35%*	*70.48%*	*1.08%*	3.81%	*100.00%*
% of race are male	47.61%	47.63%	52.16%	41.76%	49.09%	43.74%	41.80%	49.02%
Unknown (number)	553	1,387	7,798	123	7,831	1,358	64,951	84,001
% of total enrollment	**0.00%**	**0.01%**	**0.07%**	**0.00%**	**0.07%**	**0.01%**	***0.58%***	**0.75%**
% of all unknown	*0.66%*	*1.65%*	*9.28%*	0.15%	*9.32%*	*1.62%*	*77.32%*	*100.00%*
% of race are unknown	0.64%	0.17%	0.45%	0.27%	0.10%	1.00%	12.97%	0.75%
Total (number)	85,763	830,483	1,722,219	45,924	7,894,848	136,152	500,658	11,216,047
% of total enrollment	**0.76%**	**7.40%**	**15.35%**	**0.41%**	**70.39%**	**1.21%**	**4.46%**	**100.00%**
% of sex/gender	*0.76%*	*7.40%*	*15.35%*	*0.41%*	*70.39%*	*1.21%*	*4.46%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	4,980,970	449,485	203,655	5,634,110
% of total enrollment	**44.41%**	**4.01%**	**1.82%**	**50.23%**
% of all females	*88.41%*	*7.98%*	*3.61%*	*100.00%*
% of race are female	50.55%	49.79%	44.38%	50.23%
Male (number)	4,857,833	448,637	191,466	5,497,936
% of total enrollment	**43.31%**	**4.00%**	**1.71%**	**49.02%**
% of all males	*88.36%*	*8.16%*	*3.48%*	*100.00%*
% of race are male	49.30%	49.70%	41.73%	49.02%
Unknown (number)	15,669	4,596	63,736	84,001
% of total enrollment	**0.14%**	**0.04%**	**0.57%**	**0.75%**
% of all unknown	*18.65%*	*5.47%*	*75.88%*	*100.00%*
% of race are unknown	0.16%	0.51%	13.89%	0.75%
Total (number)	9,854,472	902,718	458,857	11,216,047
% of total enrollment	**87.86%**	**8.05%**	**4.09%**	**100.00%**
% of sex/gender	*87.86%*	*8.05%*	*4.09%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 17B.I–17B.III
Female (number)	16,377	25,246	25,141	1,408	259,664	25,744	95,923	449,503	1,751,433
% of total enrollment	**1.81%**	**2.80%**	**2.78%**	**0.16%**	**28.76%**	**2.85%**	**10.62%**	**49.78%**	**15.62%**
% of all females	*3.64%*	*5.62%*	*5.59%*	*0.31%*	*57.77%*	*5.73%*	*21.34%*	*100.00%*	*31.09%*
% of race are female	50.72%	50.80%	30.49%	52.13%	52.10%	54.81%	50.37%	49.78%	49.91%
Male (number)	15,741	24,322	56,761	1255	237,869	21,183	91,672	448,803	1,743,017
% of total enrollment	**1.74%**	**2.69%**	**6.29%**	**0.14%**	**26.34%**	**2.35%**	**10.15%**	**49.71%**	**15.54%**
% of all males	*3.51%*	*5.42%*	*12.65%*	*0.28%*	*53.00%*	*4.72%*	*20.43%*	*100.00%*	*31.70%*
% of race are male	48.75%	48.94%	68.83%	46.46%	47.73%	45.10%	48.14%	49.71%	49.67%
Unknown (number)	168	129	566	38	820	39	2,836	4,596	14,875
% of total enrollment	**0.02%**	**0.01%**	**0.06%**	**0.00%**	**0.09%**	**0.00%**	**0.31%**	**0.51%**	**0.13%**
% of all unknown	*3.66%*	*2.81%*	*12.32%*	*0.83%*	*17.84%*	*0.85%*	*61.71%*	*100.00%*	*17.71%*
% of race are unknown	0.52%	0.26%	0.69%	1.41%	0.16%	0.08%	1.49%	0.51%	0.42%
Total (number)	32,286	49,697	82,468	2,701	498,353	46,966	190,431	902,902	3,509,325
% of total enrollment	**3.58%**	**5.50%**	**9.13%**	**0.30%**	**55.19%**	**5.20%**	**21.09%**	**100.00%**	**31.29%**
% of sex/gender	*3.58%*	*5.50%*	*9.13%*	*0.30%*	*55.19%*	*5.20%*	*21.09%*	*100.00%*	*31.29%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 17C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 303

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	303	1,343	4,259	2,145	40,823	5,471	54,344	8,050
% of total enrollment	**0.28%**	**1.22%**	**3.87%**	**1.95%**	**37.09%**	**4.97%**	**49.38%**	**7.31%**
% of all females	*0.56%*	*2.47%*	*7.84%*	*3.95%*	*75.12%*	*10.07%*	*100.00%*	*14.81%*
% of race are female	60.97%	48.66%	44.95%	43.99%	49.91%	51.36%	49.38%	45.72%
Male (number)	194	1,415	5,216	2,730	40,963	5,059	55,577	9,555
% of total enrollment	**0.18%**	**1.29%**	**4.74%**	**2.48%**	**37.22%**	**4.60%**	**50.50%**	**8.68%**
% of all males	*0.35%*	*2.55%*	*9.39%*	*4.91%*	*73.70%*	*9.10%*	*100.00%*	*17.19%*
% of race are male	39.03%	51.27%	55.04%	55.99%	50.08%	47.49%	50.50%	54.26%
Unknown (number)	0	2	1	1	15	123	142	4
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.11%**	**0.13%**	**0.00%**
% of all unknown	*0.00%*	*1.41%*	*0.70%*	*0.70%*	*10.56%*	*86.62%*	*100.00%*	*2.82%*
% of race are unknown	0.00%	0.07%	0.01%	0.02%	0.02%	1.15%	0.13%	0.02%
Total (number)	497	2,760	9,476	4,876	81,801	10,653	110,063	17,609
% of total enrollment	**0.45%**	**2.51%**	**8.61%**	**4.43%**	**74.32%**	**9.68%**	**100.00%**	**16.00%**
% of sex/gender	*0.45%*	*2.51%*	*8.61%*	*4.43%*	*74.32%*	*9.68%*	*100.00%*	*16.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 17B and 17C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 18. Aggregate Enrollment Data for Extramural Research Protocols Excluding Male-Only and Female-Only Protocols Funded in FY 2009 and Reported in FY 2010: Percent Analysis

Table 18A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 8,516

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**7,702,446**	**2,677,903**		**34.77%**
Females (% of total)	**51.67%**	**52.65%**		
Males	**7,053,851**	**2,368,203**		**33.57%**
Males (% of total)	**47.32%**	**46.56%**		
Unknown	**149,387**	**39,894**		**26.71%**
Unknown (% of total)	**1.00%**	**0.78%**		
Total	**14,905,684**	**5,086,000**	**34.12%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 18B (new form) and table 18C (old form).

Table 18B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 8,397

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	155,136	622,191	1,146,324	83,175	5,110,922	89,055	481,207	7,688,010
% of total enrollment	**1.04%**	**4.18%**	**7.71%**	**0.56%**	**34.37%**	**0.60%**	**3.24%**	**51.69%**
% of all females	*2.02%*	*8.09%*	*14.91%*	*1.08%*	*66.48%*	*1.16%*	*6.26%*	*100.00%*
% of race are female	53.69%	55.94%	50.81%	57.55%	51.63%	54.40%	47.81%	51.69%
Male (number)	133,215	487,148	1,099,558	61,237	4,765,892	73,550	414,770	7,035,370
% of total enrollment	**0.90%**	**3.28%**	**7.39%**	**0.41%**	**32.05%**	**0.49%**	**2.79%**	**47.31%**
% of all males	*1.89%*	*6.92%*	*15.63%*	*0.87%*	*67.74%*	*1.05%*	5.90%	*100.00%*
% of race are male	46.10%	43.80%	48.74%	42.37%	48.14%	44.93%	41.21%	47.31%
Unknown (number)	612	2,983	10,087	106	23,225	1,099	110,620	148,732
% of total enrollment	**0.00%**	**0.02%**	**0.07%**	**0.00%**	**0.16%**	**0.01%**	***0.74%***	**1.00%**
% of all unknown	*0.41%*	*2.01%*	*6.78%*	0.07%	*15.62%*	*0.74%*	*74.38%*	*100.00%*
% of race are unknown	0.21%	0.27%	0.45%	0.07%	0.23%	0.67%	10.99%	1.00%
Total (number)	288,963	1,112,322	2,255,969	144,518	9,900,039	163,704	1,006,597	14,872,112
% of total enrollment	**1.94%**	**7.48%**	**15.17%**	**0.97%**	**66.57%**	**1.10%**	**6.77%**	**100.00%**
% of sex/gender	*1.94%*	*7.48%*	*15.17%*	*0.97%*	*66.57%*	*1.10%*	*6.77%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 18B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	6,499,513	779,245	409,252	7,688,010
% of total enrollment	**43.70%**	**5.24%**	**2.75%**	**51.69%**
% of all females	*84.54%*	*10.14%*	*5.32%*	*100.00%*
% of race are female	52.49%	50.97%	42.57%	51.69%
Male (number)	5,862,747	722,809	449,814	7,035,370
% of total enrollment	**39.42%**	**4.86%**	**3.02%**	**47.31%**
% of all males	*83.33%*	*10.27%*	*6.39%*	*100.00%*
% of race are male	47.35%	47.28%	46.79%	47.31%
Unknown (number)	19,792	26,675	102,265	148,732
% of total enrollment	**0.13%**	**0.18%**	**0.69%**	**1.00%**
% of all unknown	*13.31%*	*17.93%*	*68.76%*	*100.00%*
% of race are unknown	0.16%	1.74%	10.64%	1.00%
Total (number)	12,382,052	1,528,729	961,331	14,872,112
% of total enrollment	**83.26%**	**10.28%**	**6.46%**	**100.00%**
% of sex/gender	*83.26%*	*10.28%*	*6.46%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 18B.I–18B. III
Female (number)	105,387	3,469	64,946	1,238	396,565	25,411	182,229	779,245	2,674,675
% of total enrollment	**6.89%**	**0.23%**	**4.25%**	**0.08%**	**25.94%**	**1.66%**	**11.92%**	**50.97%**	**17.98%**
% of all females	*13.52%*	*0.45%*	*8.33%*	*0.16%*	*50.89%*	*3.26%*	*23.39%*	*100.00%*	*34.79%*
% of race are female	53.27%	50.97%	40.39%	51.20%	51.75%	52.84%	52.61%	50.97%	52.67%
Male (number)	92,284	3,138	94,730	1131	356,065	22,429	153,032	722,809	2,363,805
% of total enrollment	**6.04%**	**0.21%**	**6.20%**	**0.07%**	**23.29%**	**1.47%**	**10.01%**	**47.28%**	**15.89%**
% of all males	*12.77%*	*0.43%*	*13.11%*	*0.16%*	*49.26%*	*3.10%*	*21.17%*	*100.00%*	*33.60%*
% of race are male	46.64%	46.11%	58.91%	46.77%	46.46%	46.64%	44.18%	47.28%	46.55%
Unknown (number)	175	199	1134	49	13733	250	11,135	26,675	39,755
% of total enrollment	**0.01%**	**0.01%**	**0.07%**	**0.00%**	**0.90%**	**0.02%**	**0.73%**	**1.74%**	**0.27%**
% of all unknown	*0.66%*	*0.75%*	*4.25%*	*0.18%*	*51.48%*	*0.94%*	*41.74%*	*100.00%*	*26.73%*
% of race are unknown	0.09%	2.92%	0.71%	2.03%	1.79%	0.52%	3.21%	1.74%	0.78%
Total (number)	197,846	6,806	160,810	2,418	766,363	48,090	346,396	1,528,729	5,078,235
% of total enrollment	**12.94%**	**0.45%**	**10.52%**	**0.16%**	**50.13%**	**3.15%**	**22.66%**	**100.00%**	**34.15%**
% of sex/gender	*12.94%*	*0.45%*	*10.52%*	*0.16%*	*50.13%*	*3.15%*	*22.66%*	*100.00%*	*34.15%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 18C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 119

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	51	485	1,457	1,235	10,067	1,141	14,436	3,228
% of total enrollment	**0.15%**	**1.44%**	**4.34%**	**3.68%**	**29.99%**	**3.40%**	**43.00%**	**9.62%**
% of all females	*0.35%*	*3.36%*	*10.09%*	*8.56%*	*69.74%*	*7.90%*	*100.00%*	*22.36%*
% of race are female	42.86%	42.36%	39.73%	43.58%	43.31%	44.48%	43.00%	41.57%
Male (number)	68	588	2,168	1,574	12,771	1,312	18,481	4,398
% of total enrollment	**0.20%**	**1.75%**	**6.46%**	**4.69%**	**38.04%**	**3.91%**	**55.05%**	**13.10%**
% of all males	*0.37%*	*3.18%*	*11.73%*	*8.52%*	*69.10%*	*7.10%*	*100.00%*	*23.80%*
% of race are male	57.14%	51.35%	59.12%	55.54%	54.95%	51.15%	55.05%	56.64%
Unknown (number)	0	72	42	25	404	112	655	139
% of total enrollment	**0.00%**	**0.21%**	**0.13%**	**0.07%**	**1.20%**	**0.33%**	**1.95%**	**0.41%**
% of all unknown	*0.00%*	*10.99%*	*6.41%*	*3.82%*	*61.68%*	*17.10%*	*100.00%*	*21.22%*
% of race are unknown	0.00%	6.29%	1.15%	0.88%	1.74%	4.37%	1.95%	1.79%
Total (number)	119	1,145	3,667	2,834	23,242	2,565	33,572	7,765
% of total enrollment	**0.35%**	**3.41%**	**10.92%**	**8.44%**	**69.23%**	**7.64%**	**100.00%**	**23.13%**
% of sex/gender	*0.35%*	*3.41%*	*10.92%*	*8.44%*	*69.23%*	*7.64%*	*100.00%*	*23.13%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 18B and 18C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 19. Overview of NIH Phase III Extramural and Intramural Clinical Research Reported In FY 2009: Number of Sex-Specific Protocols, Enrollment, and Domestic vs. Foreign Protocols

Table 19A. Protocols Reported

I. Summary of Domestic and Foreign Phase III Extramural and Intramural Protocols

Protocols	Total protocols	Protocols reporting enrollment	Domestic with enrollment	Domestic with enrollment (%)	Foreign with enrollment	Foreign with enrollment (%)
Extramural	619	592	417	70.4%	175	29.6%
Intramural	43	38	34	89.5%	4	10.5%
Total protocols	**662**	**630**	**451**	**71.6%**	**179**	**28.4%**

II. Domestic and Foreign Phase III Extramural and Intramural Protocols by Sex/Gender

Protocols	Total all phase III clinical trials*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
Protocols reporting females only	151	94	62.3%	2	1.3%	54	35.8%	1	0.8%
Protocols reporting females only (%)	22.8%	21.4%		5.1%		30.2%		25.0%	
Protocols reporting males only	48	25	52.1%	2	4.2%	21	43.8%	0	0.0%
Protocols reporting males only (%)	7.3%	5.7%		5.1%		11.7%		0.0%	
Protocols with both female and male enrollment**	431	298	69.1%	30	7.0%	100	23.2%	3	0.7%
Protocols with both female and male enrollment (%)	65.1%	67.7%		76.9%		55.9%		75.0%	
Total protocols with enrollment	**630**	**417**	66.2%	**34**	5.4%	**175**	27.8%	**4**	0.6%
Total protocols with enrollment (%)	95.2%	95%		87.2%		97.8%		100.0%	
Protocols with zero enrollment†	32	23	71.9%	5	15.6%	4	12.5%	0	0.0%
Protocols with zero enrollment (%)	4.8%	5.2%		12.8%		2.2%		0.0%	
Total protocols	**662**	**440**	66.5%	**39**	5.9%	**179**	27.0%	**4**	0.6%
Total % of protocols	100.0%	100.0%		100.0%		100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** "Protocols with both female and male enrollment" excludes sex-specific protocols.

† "Protocols with zero enrollment" may indicate that enrollment data have not yet been submitted.

Table 19B. Enrollment Reported

I. Summary of Enrollment in Domestic and Foreign Phase III Extramural and Intramural Protocols

Enrollment	Total enrollment	Total domestic	Total domestic (%)	Total foreign	Total foreign (%)
Extramural	635,825	427,895	67.3%	207,930	32.7%
Intramural	16,475	6,000	36.4%	10,475	63.6%
Total enrollment	**652,300**	**433,895**	**66.5%**	**218,405**	**33.5%**

II. Enrollment in Domestic and Foreign Phase III Extramural and Intramural Protocols by Sex/Gender

Enrollment	Total all phase III clinical trials*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
In protocols reporting females only	141,892	123,187	86.8%	5	0.0%	11,234	7.9%	7,466	5.3%
In protocols reporting females only (%)	21.8%	28.8%		0.1%		5.4%		71.3%	
In protocols reporting males only	65,516	59,488	90.8%	155	0.2%	5,873	9.0%	0	0.0%
In protocols reporting males only (%)	10.0%	13.9%		2.6%		2.8%		0.0%	
In protocols with both female and male enrollment**	444,892	245,220	55.1%	5,840	1.3%	190,823	42.9%	3,009	0.7%
In protocols with both female and male enrollment (%)	68.2%	57.3%		97.3%		91.8%		28.7%	
Total enrollment	**652,300**	**427,895**	65.6%	**6,000**	0.92%	**207,930**	31.88%	**10,475**	1.6%
Total enrollment (%)	100.0%	100.0%		100.0%		100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** "Protocols with both female and male enrollment" excludes sex-specific protocols.

Table 19C. Minority Enrollment Reported

Minority enrollment	Total all phase III clinical trials*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
Minority enrollment**	**291,949**	**95,512**	32.7%	**1,567**	0.5%	**187,194**	64.1%	**7,676**	2.6%
Minority enrollment (%)	44.8%	22.3%		26.1%		90.0%		73.3%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** See appendix J of this report for the race and ethnicity categories included in minority enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Table 20. Aggregate Enrollment Data for Extramural Phase III Research Funded in FY 2008 and Reported in FY 2009: Percent Analysis

Table 20A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 592

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**334,429**	**149,550**		**44.72%**
Females (% of total)	**52.60%**	**52.90%**		
Males	**271,016**	**132,454**		**48.87%**
Males (% of total)	**42.62%**	**46.85%**		
Unknown	**30,380**	**702**		**2.31%**
Unknown (% of total)	**4.78%**	**0.25%**		
Total	**635,825**	**282,706**	**44.46%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 20B (new form) and table 20C (old form).

Table 20B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 407

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	9,746	47,842	61,229	438	106,737	2,281	14,361	242,634
% of total enrollment	**2.06%**	**10.11%**	**12.94%**	**0.09%**	**22.56%**	**0.48%**	**3.04%**	**51.28%**
% of all females	*4.02%*	*19.72%*	*25.24%*	*0.18%*	*43.99%*	*0.94%*	*5.92%*	*100.00%*
% of race are female	56.23%	51.53%	53.13%	51.05%	56.50%	48.82%	26.96%	51.28%
Male (number)	7,528	44,893	53,855	416	80,993	2,332	10,134	200,151
% of total enrollment	**1.59%**	**9.49%**	**11.38%**	**0.09%**	**17.12%**	**0.49%**	**2.14%**	**42.30%**
% of all males	*3.76%*	*22.43%*	*26.91%*	*0.21%*	*40.47%*	*1.17%*	5.06%	*100.00%*
% of race are male	43.43%	48.35%	46.73%	48.48%	42.88%	49.91%	19.02%	42.30%
Unknown (number)	59	108	168	4	1,169	59	28,776	30,343
% of total enrollment	**0.01%**	**0.02%**	**0.04%**	**0.00%**	**0.25%**	**0.01%**	***6.08%***	**6.41%**
% of all unknown	*0.19%*	*0.36%*	*0.55%*	0.01%	*3.85%*	*0.19%*	*94.84%*	*100.00%*
% of race are unknown	0.34%	0.12%	0.15%	0.47%	0.62%	1.26%	54.02%	6.41%
Total (number)	17,333	92,843	115,252	858	188,899	4,672	53,271	473,128
% of total enrollment	**3.66%**	**19.62%**	**24.36%**	**0.18%**	**39.93%**	**0.99%**	**11.26%**	**100.00%**
% of sex/gender	*3.66%*	*19.62%*	*24.36%*	*0.18%*	*39.93%*	*0.99%*	*11.26%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 20B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	209,663	26,804	6,167	242,634
% of total enrollment	**44.31%**	**5.67%**	**1.30%**	**51.28%**
% of all females	*86.41%*	*11.05%*	*2.54%*	*100.00%*
% of race are female	53.85%	60.18%	15.72%	51.28%
Male (number)	178,242	17,354	4,555	200,151
% of total enrollment	**37.67%**	**3.67%**	**0.96%**	**42.30%**
% of all males	*89.05%*	*8.67%*	*2.28%*	*100.00%*
% of race are male	45.78%	38.97%	11.61%	42.30%
Unknown (number)	1,449	379	28,515	30,343
% of total enrollment	**0.31%**	**0.08%**	**6.03%**	**6.41%**
% of all unknown	*4.78%*	*1.25%*	*93.98%*	*100.00%*
% of race are unknown	0.37%	0.85%	72.67%	6.41%
Total (number)	389,354	44,537	39,237	473,128
% of total enrollment	**82.29%**	**9.41%**	**8.29%**	**100.00%**
% of sex/gender	*82.29%*	*9.41%*	*8.29%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 20B.I–20B.III
Female (number)	8,728	138	488	99	7,263	431	9,657	26,804	138,456
% of total enrollment	**19.60%**	**0.31%**	**1.10%**	**0.22%**	**16.31%**	**0.97%**	**21.68%**	**60.18%**	**29.26%**
% of all females	*32.56%*	*0.51%*	*1.82%*	*0.37%*	*27.10%*	*1.61%*	*36.03%*	*100.00%*	*57.06%*
% of race are female	57.00%	39.32%	52.08%	50.00%	63.24%	44.71%	63.15%	60.18%	53.72%
Male (number)	6,543	203	439	95	4,159	521	5,394	17,354	118,577
% of total enrollment	**14.69%**	**0.46%**	**0.99%**	**0.21%**	**9.34%**	**1.17%**	**12.11%**	**38.97%**	**25.06%**
% of all males	*37.70%*	*1.17%*	*2.53%*	*0.55%*	*23.97%*	*3.00%*	*31.08%*	*100.00%*	*59.24%*
% of race are male	42.73%	57.83%	46.85%	47.98%	36.22%	54.05%	35.28%	38.97%	46.01%
Unknown (number)	41	10	10	4	62	12	240	379	700
% of total enrollment	**0.09%**	**0.02%**	**0.02%**	**0.01%**	**0.14%**	**0.03%**	**0.54%**	**0.85%**	**0.15%**
% of all unknown	*10.82%*	*2.64%*	*2.64%*	*1.06%*	*16.36%*	*3.17%*	*63.32%*	*100.00%*	*2.31%*
% of race are unknown	0.27%	2.85%	1.07%	2.02%	0.54%	1.24%	1.57%	0.85%	0.27%
Total (number)	15,312	351	937	198	11,484	964	15,291	44,537	257,733
% of total enrollment	**34.38%**	**0.79%**	**2.10%**	**0.44%**	**25.79%**	**2.16%**	**34.33%**	**100.00%**	**54.47%**
% of sex/gender	*34.38%*	*0.79%*	*2.10%*	*0.44%*	*25.79%*	*2.16%*	*34.33%*	*100.00%*	*54.47%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 20C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 185

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	351	2,094	6,053	2,596	78,830	1,871	91,795	11,094
% of total enrollment	**0.22%**	**1.29%**	**3.72%**	**1.60%**	**48.45%**	**1.15%**	**56.42%**	**6.82%**
% of all females	*0.38%*	*2.28%*	*6.59%*	*2.83%*	*85.88%*	*2.04%*	*100.00%*	*12.09%*
% of race are female	57.64%	64.85%	41.09%	40.53%	59.08%	43.64%	56.42%	44.42%
Male (number)	258	1,134	8,676	3,809	54,596	2,392	70,865	13,877
% of total enrollment	**0.16%**	**0.70%**	**5.33%**	**2.34%**	**33.56%**	**1.47%**	**43.56%**	**8.53%**
% of all males	*0.36%*	*1.60%*	*12.24%*	*5.38%*	*77.04%*	*3.38%*	*100.00%*	*19.58%*
% of race are male	42.36%	35.12%	58.90%	59.47%	40.92%	55.80%	43.56%	55.57%
Unknown (number)	0	1	1	0	11	24	37	2
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.01%**	**0.02%**	**0.00%**
% of all unknown	*0.00%*	*2.70%*	*2.70%*	*0.00%*	*29.73%*	*64.86%*	*100.00%*	*5.41%*
% of race are unknown	0.00%	0.03%	0.01%	0.00%	0.01%	0.56%	0.02%	0.01%
Total (number)	609	3,229	14,730	6,405	133,437	4,287	162,697	24,973
% of total enrollment	**0.37%**	**1.98%**	**9.05%**	**3.94%**	**82.02%**	**2.63%**	**100.00%**	**15.35%**
% of sex/gender	*0.37%*	*1.98%*	*9.05%*	*3.94%*	*82.02%*	*2.63%*	*100.00%*	*15.35%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 21. Overview of NIH Phase III Extramural and Intramural Clinical Research Reported In FY 2010: Number of Sex-Specific Protocols, Enrollment, and Domestic vs. Foreign Protocols

Table 21A. Protocols Reported

I. Summary of Domestic and Foreign Phase III Extramural and Intramural Protocols

Protocols	Total protocols	Protocols reporting enrollment	Domestic with enrollment	Domestic with enrollment (%)	Foreign with enrollment	Foreign with enrollment (%)
Extramural	696	650	498	76.6%	152	23.4%
Intramural	47	46	42	91.3%	4	8.7%
Total protocols	**743**	**696**	**540**	**77.6%**	**156**	**22.4%**

II. Domestic and Foreign Phase III Extramural and Intramural Protocols by Sex/Gender

Protocols	Total of phase III clinical studies*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
Protocols reporting females only	140	93	66.4%	6	4.3%	40	28.6%	1	0.8%
Protocols reporting females only (%)	18.8%	17.3%		14.0%		25.2%		25.0%	
Protocols reporting males only	61	32	52.5%	5	8.2%	24	39.3%	0	0.0%
Protocols reporting males only (%)	8.2%	6.0%		11.6%		15.1%		0.0%	
Protocols with both female and male enrollment**	495	373	75.4%	31	6.3%	88	17.8%	3	0.6%
Protocols with both female and male enrollment (%)	66.6%	69.5%		72.1%		55.3%		75.0%	
Total protocols with enrollment	**696**	**498**	71.6%	**42**	6.0%	**152**	21.8%	**4**	0.6%
Total protocols with enrollment (%)	93.7%	93%		97.7%		95.6%		100.0%	
Protocols with zero enrollment†	47	39	83.0%	1	2.1%	7	14.9%	0	0.0%
Protocols with zero enrollment (%)	6.3%	7.3%		2.3%		4.4%		0.0%	
Total protocols	**743**	**537**	72.3%	**43**	5.8%	**159**	21.4%	**4**	0.5%
Total % of protocols	100.0%	100.0%		100.0%		100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** "Protocols with both female and male enrollment" excludes sex-specific protocols.

† "Protocols with zero enrollment" may indicate that enrollment data have not yet been submitted.

Table 21B. Enrollment Reported

I. Summary of Enrollment in Domestic and Foreign Phase III Extramural and Intramural Protocols

Enrollment	Total enrollment	Total domestic	Total domestic (%)	Total foreign	Total foreign (%)
Extramural	749,518	382,998	51.1%	366,520	48.9%
Intramural	20,367	9,869	48.5%	10,498	51.5%
Total enrollment	**769,885**	**392,867**	**51.0%**	**377,018**	**49.0%**

II. Enrollment in Domestic and Foreign Phase III Extramural and Intramural Protocols by Sex/Gender

Enrollment	Total all phase III clinical trials*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
In protocols reporting females only	119,103	84,405	70.9%	5,095	4.3%	22,137	18.6%	7,466	6.3%
In protocols reporting females only (%)	15.5%	22.0%		51.6%		6.0%		71.1%	
In protocols reporting males only	62,315	56,117	90.1%	164	0.3%	6,034	9.7%	0	0.0%
In protocols reporting males only (%)	8.1%	14.7%		1.7%		1.6%		0.0%	
In protocols with both female and male enrollment**	588,467	242,476	41.2%	4,610	0.8%	338,349	57.5%	3,032	0.5%
In protocols with both female and male enrollment (%)	76.4%	63.3%		46.7%		92.3%		28.9%	
Total enrollment	**769,885**	**382,998**	49.7%	**9,869**	1.28%	**366,520**	47.61%	**10,498**	1.4%
Total enrollment (%)	100.0%	100.0%		100.0%		100.0%		100.0%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** "Protocols with female and male enrollment" excludes sex-specific protocols.

Table 21C. Minority Enrollment Reported

Minority enrollment	Total all phase III clinical trials*	Domestic extramural	Domestic extramural (%)	Domestic intramural	Domestic intramural (%)	Foreign extramural	Foreign extramural (%)	Foreign intramural	Foreign intramural (%)
Minority enrollment**	**447,187**	**89,006**	19.9%	**3,503**	0.8%	**346,979**	77.6%	**7,699**	1.7%
Minority enrollment (%)	58.1%	23.2%		35.5%		94.7%		73.3%	

Note: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

* An NIH-defined phase III clinical trial is a broadly based prospective phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

** See appendix J of this report for the race and ethnicity categories included in minority enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Table 22. Aggregate Enrollment Data for Extramural Phase III Research Protocols Funded in FY 2009 and Reported in FY 2010: Percent Analysis

Table 22A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 650

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**392,053**	**240,290**		**61.29%**
Females (% of total)	**52.31%**	**55.11%**		
Males	**326,582**	**194,486**		**59.55%**
Males (% of total)	**43.57%**	**44.61%**		
Unknown	**30,883**	**1,209**		**3.91%**
Unknown (% of total)	**4.12%**	**0.28%**		
Total	**749,518**	**435,985**	**58.17%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 22B (new form) and table 22C (old form).

Table 22B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 599

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	7,735	62,107	141,753	482	125,544	3,122	18,294	359,037
% of total enrollment	**1.15%**	**9.21%**	**21.03%**	**0.07%**	**18.62%**	**0.46%**	**2.71%**	**53.26%**
% of all females	*2.15%*	*17.30%*	*39.48%*	*0.13%*	*34.97%*	*0.87%*	*5.10%*	*100.00%*
% of race are female	49.70%	55.04%	56.21%	51.55%	55.66%	37.83%	31.10%	53.26%
Male (number)	7,770	50,641	109,659	449	99,388	5,071	11,248	284,226
% of total enrollment	**1.15%**	**7.51%**	**16.27%**	**0.07%**	**14.74%**	**0.75%**	**1.67%**	**42.16%**
% of all males	*2.73%*	*17.82%*	*38.58%*	*0.16%*	*34.97%*	*1.78%*	3.96%	*100.00%*
% of race are male	49.93%	44.88%	43.49%	48.02%	44.06%	61.44%	19.12%	42.16%
Unknown (number)	57	95	762	4	622	60	29,279	30,879
% of total enrollment	**0.01%**	**0.01%**	**0.11%**	**0.00%**	**0.09%**	**0.01%**	***4.34%***	**4.58%**
% of all unknown	*0.18%*	*0.31%*	*2.47%*	0.01%	*2.01%*	*0.19%*	*94.82%*	*100.00%*
% of race are unknown	0.37%	0.08%	0.30%	0.43%	0.28%	0.73%	49.78%	4.58%
Total (number)	15,562	112,843	252,174	935	225,554	8,253	58,821	674,142
% of total enrollment	**2.31%**	**16.74%**	**37.41%**	**0.14%**	**33.46%**	**1.22%**	**8.73%**	**100.00%**
% of sex/gender	*2.31%*	*16.74%*	*37.41%*	*0.14%*	*33.46%*	*1.22%*	*8.73%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 22B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	319,083	30,441	9,513	359,037
% of total enrollment	**47.33%**	**4.52%**	**1.41%**	**53.26%**
% of all females	*88.87%*	*8.48%*	*2.65%*	*100.00%*
% of race are female	55.44%	57.61%	20.80%	53.26%
Male (number)	254,960	22,090	7,176	284,226
% of total enrollment	**37.82%**	**3.28%**	**1.06%**	**42.16%**
% of all males	*89.70%*	*7.77%*	*2.52%*	*100.00%*
% of race are male	44.30%	41.80%	15.69%	42.16%
Unknown (number)	1,516	311	29,052	30,879
% of total enrollment	**0.22%**	**0.05%**	**4.31%**	**4.58%**
% of all unknown	*4.91%*	*1.01%*	*94.08%*	*100.00%*
% of race are unknown	0.26%	0.59%	63.51%	4.58%
Total (number)	575,559	52,842	45,741	674,142
% of total enrollment	**85.38%**	**7.84%**	**6.79%**	**100.00%**
% of sex/gender	*85.38%*	*7.84%*	*6.79%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 22B.I–22B.III
Female (number)	6,516	144	565	104	9,497	642	12,973	30,441	237,669
% of total enrollment	**12.33%**	**0.27%**	**1.07%**	**0.20%**	**17.97%**	**1.21%**	**24.55%**	**57.61%**	**35.26%**
% of all females	*21.41%*	*0.47%*	*1.86%*	*0.34%*	*31.20%*	*2.11%*	*42.62%*	*100.00%*	*66.20%*
% of race are female	49.70%	40.00%	52.51%	50.98%	62.53%	20.70%	65.51%	57.61%	55.95%
Male (number)	6,553	206	501	96	5,644	2,444	6,646	22,090	185,880
% of total enrollment	**12.40%**	**0.39%**	**0.95%**	**0.18%**	**10.68%**	**4.63%**	**12.58%**	**41.80%**	**27.57%**
% of all males	*29.67%*	*0.93%*	*2.27%*	*0.43%*	*25.55%*	*11.06%*	*30.09%*	*100.00%*	*65.40%*
% of race are male	49.98%	57.22%	46.56%	47.06%	37.16%	78.81%	33.56%	41.80%	43.76%
Unknown (number)	41	10	10	4	46	15	185	311	1,209
% of total enrollment	**0.08%**	**0.02%**	**0.02%**	**0.01%**	**0.09%**	**0.03%**	**0.35%**	**0.59%**	**0.18%**
% of all unknown	*13.18%*	*3.22%*	*3.22%*	*1.29%*	*14.79%*	*4.82%*	*59.49%*	*100.00%*	*3.92%*
% of race are unknown	0.31%	2.78%	0.93%	1.96%	0.30%	0.48%	0.93%	0.59%	0.28%
Total (number)	13,110	360	1,076	204	15,187	3,101	19,804	52,842	424,758
% of total enrollment	**24.81%**	**0.68%**	**2.04%**	**0.39%**	**28.74%**	**5.87%**	**37.48%**	**100.00%**	**63.01%**
% of sex/gender	*24.81%*	*0.68%*	*2.04%*	*0.39%*	*28.74%*	*5.87%*	*37.48%*	*100.00%*	*63.01%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 22C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 51

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	141	544	1,234	702	30,036	359	33,016	2,621
% of total enrollment	**0.19%**	**0.72%**	**1.64%**	**0.93%**	**39.85%**	**0.48%**	**43.80%**	**3.48%**
% of all females	*0.43%*	*1.65%*	*3.74%*	*2.13%*	*90.97%*	*1.09%*	*100.00%*	*7.94%*
% of race are female	48.45%	48.18%	18.53%	22.29%	47.36%	49.45%	43.80%	23.35%
Male (number)	150	585	5,424	2,447	33,384	366	42,356	8,606
% of total enrollment	**0.20%**	**0.78%**	**7.20%**	**3.25%**	**44.29%**	**0.49%**	**56.19%**	**11.42%**
% of all males	*0.35%*	*1.38%*	*12.81%*	*5.78%*	*78.82%*	*0.86%*	*100.00%*	*20.32%*
% of race are male	51.55%	51.82%	81.47%	77.71%	52.64%	50.41%	56.19%	76.65%
Unknown (number)	0	0	0	0	3	1	4	0
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**
% of all unknown	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*75.00%*	*25.00%*	*100.00%*	*0.00%*
% of race are unknown	0.00%	0.00%	0.00%	0.00%	0.00%	0.14%	0.01%	0.00%
Total (number)	291	1,129	6,658	3,149	63,423	726	75,376	11,227
% of total enrollment	**0.39%**	**1.50%**	**8.83%**	**4.18%**	**84.14%**	**0.96%**	**100.00%**	**14.89%**
% of sex/gender	*0.39%*	*1.50%*	*8.83%*	*4.18%*	*84.14%*	*0.96%*	*100.00%*	*14.89%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 22B and 22C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 23. Aggregate Enrollment Data for Intramural Research Protocols Funded in FY 2008 and Reported in FY 2009: Percent Analysis

Table 23A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 1,727

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**1,250,897**	**416,054**		**33.26%**
Females (% of total)	**42.38%**	**48.14%**		
Males	**1,655,970**	**443,986**		**26.81%**
Males (% of total)	**56.10%**	**51.37%**		
Unknown	**44,806**	**4,270**		**9.53%**
Unknown (% of total)	**1.52%**	**0.49%**		
Total	**2,951,673**	**864,310**	**29.28%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 23B (new form) and table 23C (old form).

Table 23B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 1,335

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	9,820	176,141	72,500	654	740,001	78,852	90,893	1,168,861
% of total enrollment	**0.35%**	**6.31%**	**2.60%**	**0.02%**	**26.52%**	**2.83%**	**3.26%**	**41.89%**
% of all females	*0.84%*	*15.07%*	*6.20%*	*0.06%*	*63.31%*	*6.75%*	*7.78%*	*100.00%*
% of race are female	46.97%	63.21%	26.63%	45.32%	41.77%	51.61%	31.07%	41.89%
Male (number)	11,064	102,131	195,873	789	1,020,111	73,920	172,687	1,576,575
% of total enrollment	**0.40%**	**3.66%**	**7.02%**	**0.03%**	**36.56%**	**2.65%**	**6.19%**	**56.50%**
% of all males	*0.70%*	*6.48%*	*12.42%*	*0.05%*	*64.70%*	*4.69%*	10.95%	*100.00%*
% of race are male	52.92%	36.65%	71.95%	54.68%	57.58%	48.38%	59.03%	56.50%
Unknown (number)	24	369	3,849	0	11,536	19	28,963	44,760
% of total enrollment	**0.00%**	**0.01%**	**0.14%**	**0.00%**	**0.41%**	**0.00%**	***1.04%***	**1.60%**
% of all unknown	*0.05%*	*0.82%*	*8.60%*	0.00%	*25.77%*	*0.04%*	*64.71%*	*100.00%*
% of race are unknown	0.11%	0.13%	1.41%	0.00%	0.65%	0.01%	9.90%	1.60%
Total (number)	20,908	278,641	272,222	1,443	1,771,648	152,791	292,543	2,790,196
% of total enrollment	**0.75%**	**9.99%**	**9.76%**	**0.05%**	**63.50%**	**5.48%**	**10.48%**	**100.00%**
% of sex/gender	*0.75%*	*9.99%*	*9.76%*	*0.05%*	*63.50%*	*5.48%*	*10.48%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 23B (continued). Aggregate Enrollment Data for Intramural Research Protocols Funded in FY 2008 and Reported in FY 2009: Percent Analysis

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	967,503	61,626	139,732	1,168,861
% of total enrollment	**34.68%**	**2.21%**	**5.01%**	**41.89%**
% of all females	*82.77%*	*5.27%*	*11.95%*	*100.00%*
% of race are female	42.68%	55.73%	33.84%	41.89%
Male (number)	1,283,484	48,930	244,161	1,576,575
% of total enrollment	**46.00%**	**1.75%**	**8.75%**	**56.50%**
% of all males	*81.41%*	*3.10%*	*15.49%*	*100.00%*
% of race are male	56.62%	44.25%	59.13%	56.50%
Unknown (number)	15,715	23	29,022	44,760
% of total enrollment	**0.56%**	**0.00%**	**1.04%**	**1.60%**
% of all unknown	*35.11%*	*0.05%*	*64.84%*	*100.00%*
% of race are unknown	0.69%	0.02%	7.03%	1.60%
Total (number)	2,266,702	110,579	412,915	2,790,196
% of total enrollment	**81.24%**	**3.96%**	**14.80%**	**100.00%**
% of sex/gender	*81.24%*	*3.96%*	*14.80%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 23B.I–23B.III
Female (number)	118	43	806	59	28,524	3,224	28,852	61,626	395,343
% of total enrollment	**0.11%**	**0.04%**	**0.73%**	**0.05%**	**25.80%**	**2.92%**	**26.09%**	**55.73%**	**14.17%**
% of all females	*0.19%*	*0.07%*	*1.31%*	*0.10%*	*46.29%*	*5.23%*	*46.82%*	*100.00%*	*33.82%*
% of race are female	64.48%	51.19%	21.87%	62.77%	47.33%	51.22%	72.18%	55.73%	47.85%
Male (number)	64	41	2,880	35	31,742	3,054	11,114	48,930	426,633
% of total enrollment	**0.06%**	**0.04%**	**2.60%**	**0.03%**	**28.71%**	**2.76%**	**10.05%**	**44.25%**	**15.29%**
% of all males	*0.13%*	*0.08%*	*5.89%*	*0.07%*	*64.87%*	*6.24%*	*22.71%*	*100.00%*	*27.06%*
% of race are male	34.97%	48.81%	78.13%	37.23%	52.67%	48.52%	27.80%	44.25%	51.64%
Unknown (number)	1	0	0	0	0	16	6	23	4,267
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.01%**	**0.02%**	**0.15%**
% of all unknown	*4.35%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*69.57%*	*26.09%*	*100.00%*	*9.53%*
% of race are unknown	0.55%	0.00%	0.00%	0.00%	0.00%	0.25%	0.02%	0.02%	0.52%
Total (number)	183	84	3,686	94	60,266	6,294	39,972	110,579	826,243
% of total enrollment	**0.17%**	**0.08%**	**3.33%**	**0.09%**	**54.50%**	**5.69%**	**36.15%**	**100.00%**	**29.61%**
% of sex/gender	*0.17%*	*0.08%*	*3.33%*	*0.09%*	*54.50%*	*5.69%*	*36.15%*	*100.00%*	*29.61%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 23C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 392

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	135	3,548	12,179	4,849	60,009	1,316	82,036	20,711
% of total enrollment	**0.08%**	**2.20%**	**7.54%**	**3.00%**	**37.16%**	**0.81%**	**50.80%**	**12.83%**
% of all females	*0.16%*	*4.32%*	*14.85%*	*5.91%*	*73.15%*	*1.60%*	*100.00%*	*25.25%*
% of race are female	48.04%	52.58%	55.47%	53.39%	49.59%	54.86%	50.80%	54.41%
Male (number)	146	3,200	9,775	4,232	60,987	1,055	79,395	17,353
% of total enrollment	**0.09%**	**1.98%**	**6.05%**	**2.62%**	**37.77%**	**0.65%**	**49.17%**	**10.75%**
% of all males	*0.18%*	*4.03%*	*12.31%*	*5.33%*	*76.81%*	*1.33%*	*100.00%*	*21.86%*
% of race are male	51.96%	47.42%	44.52%	46.60%	50.40%	43.98%	49.17%	45.59%
Unknown (number)	0	0	2	1	15	28	46	3
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.02%**	**0.03%**	**0.00%**
% of all unknown	*0.00%*	*0.00%*	*4.35%*	*2.17%*	*32.61%*	*60.87%*	*100.00%*	*6.52%*
% of race are unknown	0.00%	0.00%	0.01%	0.01%	0.01%	1.17%	0.03%	0.01%
Total (number)	281	6,748	21,956	9,082	121,011	2,399	161,477	38,067
% of total enrollment	**0.17%**	**4.18%**	**13.60%**	**5.62%**	**74.94%**	**1.49%**	**100.00%**	**23.57%**
% of sex/gender	*0.17%*	*4.18%*	*13.60%*	*5.62%*	*74.94%*	*1.49%*	*100.00%*	*23.57%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 23B and 23C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 24. Aggregate Enrollment Data for Intramural Research Protocols Funded in FY 2009 and Reported in FY 2010: Percent Analysis

Table 24A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 1,770

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**1,343,852**	**452,629**		**33.68%**
Females (% of total)	**43.20%**	**49.08%**		
Males	**1,700,018**	**463,613**		**27.27%**
Males (% of total)	**54.65%**	**50.27%**		
Unknown	**66,972**	**5,999**		**8.96%**
Unknown (% of total)	**2.15%**	**0.65%**		
Total	**3,110,842**	**922,241**	**29.65%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 24B (new form) and table 24C (old form).

Table 24B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 1,408

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	11,067	181,870	91,854	2,038	780,240	82,887	110,830	1,260,786
% of total enrollment	**0.38%**	**6.17%**	**3.12%**	**0.07%**	**26.47%**	**2.81%**	**3.76%**	**42.78%**
% of all females	*0.88%*	*14.43%*	*7.29%*	*0.16%*	*61.89%*	*6.57%*	*8.79%*	*100.00%*
% of race are female	47.79%	63.16%	30.30%	53.55%	42.69%	52.00%	32.40%	42.78%
Male (number)	12,060	105,762	205,788	1,767	1,040,096	76,408	177,574	1,619,455
% of total enrollment	**0.41%**	**3.59%**	**6.98%**	**0.06%**	**35.29%**	**2.59%**	**6.03%**	**54.95%**
% of all males	*0.74%*	*6.53%*	*12.71%*	*0.11%*	*64.23%*	*4.72%*	10.97%	*100.00%*
% of race are male	52.08%	36.73%	67.87%	46.43%	56.91%	47.94%	51.91%	54.95%
Unknown (number)	30	300	5,549	1	7,299	94	53,644	66,917
% of total enrollment	**0.00%**	**0.01%**	**0.19%**	**0.00%**	**0.25%**	**0.00%**	***1.82%***	**2.27%**
% of all unknown	*0.04%*	*0.45%*	*8.29%*	0.00%	*10.91%*	*0.14%*	*80.16%*	*100.00%*
% of race are unknown	0.13%	0.10%	1.83%	0.03%	0.40%	0.06%	15.68%	2.27%
Total (number)	23,157	287,932	303,191	3,806	1,827,635	159,389	342,048	2,947,158
% of total enrollment	**0.79%**	**9.77%**	**10.29%**	**0.13%**	**62.01%**	**5.41%**	**11.61%**	**100.00%**
% of sex/gender	*0.79%*	*9.77%*	*10.29%*	*0.13%*	*62.01%*	*5.41%*	*11.61%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 24B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	1,028,074	70,601	162,111	1,260,786
% of total enrollment	**34.88%**	**2.40%**	**5.50%**	**42.78%**
% of all females	*81.54%*	*5.60%*	*12.86%*	*100.00%*
% of race are female	43.63%	57.53%	34.64%	42.78%
Male (number)	1,314,404	52,052	252,999	1,619,455
% of total enrollment	**44.60%**	**1.77%**	**8.58%**	**54.95%**
% of all males	*81.16%*	*3.21%*	*15.62%*	*100.00%*
% of race are male	55.78%	42.41%	54.07%	54.95%
Unknown (number)	14,036	70	52,811	66,917
% of total enrollment	**0.48%**	**0.00%**	**1.79%**	**2.27%**
% of all unknown	*20.98%*	*0.10%*	*78.92%*	*100.00%*
% of race are unknown	0.60%	0.06%	11.29%	2.27%
Total (number)	2,356,514	122,723	467,921	2,947,158
% of total enrollment	**79.96%**	**4.16%**	**15.88%**	**100.00%**
% of sex/gender	*79.96%*	*4.16%*	*15.88%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 24B.I–24B.III
Female (number)	139	48	1,043	66	31,969	7,315	30,021	70,601	431,706
% of total enrollment	**0.11%**	**0.04%**	**0.85%**	**0.05%**	**26.05%**	**5.96%**	**24.46%**	**57.53%**	**14.65%**
% of all females	*0.20%*	*0.07%*	*1.48%*	*0.09%*	*45.28%*	*10.36%*	*42.52%*	*100.00%*	*34.24%*
% of race are female	64.95%	50.53%	25.51%	64.71%	49.65%	61.76%	71.50%	57.53%	48.84%
Male (number)	74	47	3,042	36	32,408	4,484	11,961	52,052	446,154
% of total enrollment	**0.06%**	**0.04%**	**2.48%**	**0.03%**	**26.41%**	**3.65%**	**9.75%**	**42.41%**	**15.14%**
% of all males	*0.14%*	*0.09%*	*5.84%*	*0.07%*	*62.26%*	*8.61%*	*22.98%*	*100.00%*	*27.55%*
% of race are male	34.58%	49.47%	74.41%	35.29%	50.33%	37.86%	28.49%	42.41%	50.48%
Unknown (number)	1	0	3	0	17	45	4	70	5,995
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.04%**	**0.00%**	**0.06%**	**0.20%**
% of all unknown	*1.43%*	*0.00%*	*4.29%*	*0.00%*	*24.29%*	*64.29%*	*5.71%*	*100.00%*	*8.96%*
% of race are unknown	0.47%	0.00%	0.07%	0.00%	0.03%	0.38%	0.01%	0.06%	0.68%
Total (number)	214	95	4,088	102	64,394	11,844	41,986	122,723	883,855
% of total enrollment	**0.17%**	**0.08%**	**3.33%**	**0.08%**	**52.47%**	**9.65%**	**34.21%**	**100.00%**	**29.99%**
% of sex/gender	*0.17%*	*0.08%*	*3.33%*	*0.08%*	*52.47%*	*9.65%*	*34.21%*	*100.00%*	*29.99%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 24C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 362

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	144	3,708	12,443	4,628	60,708	1,435	83,066	20,923
% of total enrollment	**0.09%**	**2.27%**	**7.60%**	**2.83%**	**37.09%**	**0.88%**	**50.75%**	**12.78%**
% of all females	*0.17%*	*4.46%*	*14.98%*	*5.57%*	*73.08%*	*1.73%*	*100.00%*	*25.19%*
% of race are female	46.75%	53.31%	55.35%	53.55%	49.49%	54.38%	50.75%	54.51%
Male (number)	164	3,247	10,036	4,012	61,935	1,169	80,563	17,459
% of total enrollment	**0.10%**	**1.98%**	**6.13%**	**2.45%**	**37.84%**	**0.71%**	**49.22%**	**10.67%**
% of all males	*0.20%*	*4.03%*	*12.46%*	*4.98%*	*76.88%*	*1.45%*	*100.00%*	*21.67%*
% of race are male	53.25%	46.68%	44.64%	46.42%	50.49%	44.30%	49.22%	45.48%
Unknown (number)	0	1	1	2	16	35	55	4
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.02%**	**0.03%**	**0.00%**
% of all unknown	*0.00%*	*1.82%*	*1.82%*	*3.64%*	*29.09%*	*63.64%*	*100.00%*	*7.27%*
% of race are unknown	0.00%	0.01%	0.00%	0.02%	0.01%	1.33%	0.03%	0.01%
Total (number)	308	6,956	22,480	8,642	122,659	2,639	163,684	38,386
% of total enrollment	**0.19%**	**4.25%**	**13.73%**	**5.28%**	**74.94%**	**1.61%**	**100.00%**	**23.45%**
% of sex/gender	*0.19%*	*4.25%*	*13.73%*	*5.28%*	*74.94%*	*1.61%*	*100.00%*	*23.45%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 24B and 24C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 25. Aggregate Enrollment Data for Intramural Phase III Research Protocols Funded in FY 2008 and Reported in FY 2009: Percent Analysis

Table 25A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 38

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**11,319**	**8,402**		**74.23%**
Females (% of total)	**68.70%**	**90.90%**		
Males	**5,143**	**828**		**16.10%**
Males (% of total)	**31.22%**	**8.96%**		
Unknown	**13**	**13**		**100.00%**
Unknown (% of total)	**0.08%**	**0.14%**		
Total	**16,475**	**9,243**	**56.10%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 25B (new form) and table 25C (old form).

Table 25B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 27

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	129	6	594	0	368	2	9,169	10,268
% of total enrollment	**0.96%**	**0.04%**	**4.42%**	**0.00%**	**2.74%**	**0.01%**	**68.25%**	**76.43%**
% of all females	*1.26%*	*0.06%*	*5.78%*	*0.00%*	*3.58%*	*0.02%*	*89.30%*	*100.00%*
% of race are female	73.30%	24.00%	60.55%	0.00%	58.60%	50.00%	78.91%	76.43%
Male (number)	47	19	374	1	260	2	2,451	3,154
% of total enrollment	**0.35%**	**0.14%**	**2.78%**	**0.01%**	**1.94%**	**0.01%**	**18.24%**	**23.48%**
% of all males	*1.49%*	*0.60%*	*11.86%*	*0.03%*	*8.24%*	*0.06%*	77.71%	*100.00%*
% of race are male	26.70%	76.00%	38.12%	100.00%	41.40%	50.00%	21.09%	23.48%
Unknown (number)	0	0	13	0	0	0	0	13
% of total enrollment	**0.00%**	**0.00%**	**0.10%**	**0.00%**	**0.00%**	**0.00%**	***0.00%***	**0.10%**
% of all unknown	*0.00%*	*0.00%*	*100.00%*	0.00%	*0.00%*	*0.00%*	*0.00%*	*100.00%*
% of race are unknown	0.00%	0.00%	1.33%	0.00%	0.00%	0.00%	0.00%	0.10%
Total (number)	176	25	981	1	628	4	11,620	13,435
% of total enrollment	**1.31%**	**0.19%**	**7.30%**	**0.01%**	**4.67%**	**0.03%**	**86.49%**	**100.00%**
% of sex/gender	*1.31%*	*0.19%*	*7.30%*	*0.01%*	*4.67%*	*0.03%*	*86.49%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 25B (continued). Aggregate Enrollment Data for Intramural Phase III Research Protocols Funded in FY 2008 and Reported in FY 2009: Percent Analysis

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	1,282	7,553	1,433	10,268
% of total enrollment	**9.54%**	**56.22%**	**10.67%**	**76.43%**
% of all females	*12.49%*	*73.56%*	*13.96%*	*100.00%*
% of race are female	48.63%	98.27%	46.03%	76.43%
Male (number)	1,341	133	1,680	3,154
% of total enrollment	**9.98%**	**0.99%**	**12.50%**	**23.48%**
% of all males	*42.52%*	*4.22%*	*53.27%*	*100.00%*
% of race are male	50.87%	1.73%	53.97%	23.48%
Unknown (number)	13	0	0	13
% of total enrollment	**0.10%**	**0.00%**	**0.00%**	**0.10%**
% of all unknown	*100.00%*	*0.00%*	*0.00%*	*100.00%*
% of race are unknown	0.49%	0.00%	0.00%	0.10%
Total (number)	2,636	7,686	3,113	13,435
% of total enrollment	**19.62%**	**57.21%**	**23.17%**	**100.00%**
% of sex/gender	*19.62%*	*57.21%*	*23.17%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 25B.I–25B.III
Female (number)	1	0	0	0	2	0	7,550	7,553	8,283
% of total enrollment	**0.01%**	**0.00%**	**0.00%**	**0.00%**	**0.03%**	**0.00%**	**98.23%**	**98.27%**	**61.65%**
% of all females	*0.01%*	*0.00%*	*0.00%*	*0.00%*	*0.03%*	*0.00%*	*99.96%*	*100.00%*	*80.67%*
% of race are female	100.00%	0.00%	0.00%	0.00%	66.67%	0.00%	98.28%	98.27%	93.36%
Male (number)	0	0	0	0	1	0	132	133	576
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**	**1.72%**	**1.73%**	**4.29%**
% of all males	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.75%*	*0.00%*	*99.25%*	*100.00%*	*18.26%*
% of race are male	0.00%	0.00%	0.00%	0.00%	33.33%	0.00%	1.72%	1.73%	6.49%
Unknown (number)	0	0	0	0	0	0	0	0	13
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.10%**
% of all unknown	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*
% of race are unknown	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.15%
Total (number)	1	0	0	0	3	0	7,682	7,686	8,872
% of total enrollment	**0.01%**	**0.00%**	**0.00%**	**0.00%**	**0.04%**	**0.00%**	**99.95%**	**100.00%**	**66.04%**
% of sex/gender	*0.01%*	*0.00%*	*0.00%*	*0.00%*	*0.04%*	*0.00%*	*99.95%*	*100.00%*	*66.04%*
Total (%)	100.00%	0.00%	0.00%	0.00%	100.00%	0.00%	100.00%	100.00%	100.00%

Table 25C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 11

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	1	20	69	29	922	10	1,051	119
% of total enrollment	**0.03%**	**0.66%**	**2.27%**	**0.95%**	**30.33%**	**0.33%**	**34.57%**	**3.91%**
% of all females	*0.10%*	*1.90%*	*6.57%*	*2.76%*	*87.73%*	*0.95%*	*100.00%*	*11.32%*
% of race are female	25.00%	32.26%	30.53%	36.71%	34.86%	41.67%	34.57%	32.08%
Male (number)	3	42	157	50	1,723	14	1,989	252
% of total enrollment	**0.10%**	**1.38%**	**5.16%**	**1.64%**	**56.68%**	**0.46%**	**65.43%**	**8.29%**
% of all males	*0.15%*	*2.11%*	*7.89%*	*2.51%*	*86.63%*	*0.70%*	*100.00%*	*12.67%*
% of race are male	75.00%	67.74%	69.47%	63.29%	65.14%	58.33%	65.43%	67.92%
Unknown (number)	0	0	0	0	0	0	0	0
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
% of all unknown	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*0.00%*
% of race are unknown	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Total (number)	4	62	226	79	2,645	24	3,040	371
% of total enrollment	**0.13%**	**2.04%**	**7.43%**	**2.60%**	**87.01%**	**0.79%**	**100.00%**	**12.20%**
% of sex/gender	*0.13%*	*2.04%*	*7.43%*	*2.60%*	*87.01%*	*0.79%*	*100.00%*	*12.20%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 25B and 25C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 26. Aggregate Enrollment Data for Intramural Phase III Research Protocols Funded in FY 2009 and Reported in FY 2010: Percent Analysis

Table 26A. Summary Totals: Old Form + New Form

Total number of protocols with enrollment data: 46

Sex/Gender	Total enrollment	Minority enrollment	Minority % of total	% Minority by sex
Females	**16,128**	**10,426**		**64.65%**
Females (% of total)	**79.19%**	**93.07%**		
Males	**4,226**	**763**		**18.05%**
Males (% of total)	**20.75%**	**6.81%**		
Unknown	**13**	**13**		**100.00%**
Unknown (% of total)	**0.06%**	**0.12%**		
Total	**20,367**	**11,202**	**55.00%**	
Total (%)	100%	100.00%		

Note: Total minority enrollment is the sum of the total number for each shaded column in table 26B (new form) and table 26C (old form).

Table 26B. New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

Number of protocols with enrollment data reported on new form: 35

I. Total Enrollment Report: All Subjects by Race (New Form, Part A)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total
Female (number)	237	177	2,178	0	3,599	3	8,879	15,073
% of total enrollment	**1.37%**	**1.02%**	**12.58%**	**0.00%**	**20.79%**	**0.02%**	**51.30%**	**87.09%**
% of all females	*1.57%*	*1.17%*	*14.45%*	*0.00%*	*23.88%*	*0.02%*	*58.91%*	*100.00%*
% of race are female	83.45%	88.94%	84.95%	0.00%	93.34%	60.00%	85.38%	87.09%
Male (number)	47	22	373	1	257	2	1,520	2,222
% of total enrollment	**0.27%**	**0.13%**	**2.16%**	**0.01%**	**1.48%**	**0.01%**	**8.78%**	**12.84%**
% of all males	*2.12%*	*0.99%*	*16.79%*	*0.05%*	*11.57%*	*0.09%*	68.41%	*100.00%*
% of race are male	16.55%	11.06%	14.55%	100.00%	6.66%	40.00%	14.62%	12.84%
Unknown (number)	0	0	13	0	0	0	0	13
% of total enrollment	**0.00%**	**0.00%**	**0.08%**	**0.00%**	**0.00%**	**0.00%**	***0.00%***	**0.08%**
% of all unknown	*0.00%*	*0.00%*	*100.00%*	0.00%	*0.00%*	*0.00%*	*0.00%*	*100.00%*
% of race are unknown	0.00%	0.00%	0.51%	0.00%	0.00%	0.00%	0.00%	0.08%
Total (number)	284	199	2,564	1	3,856	5	10,399	17,308
% of total enrollment	**1.64%**	**1.15%**	**14.81%**	**0.01%**	**22.28%**	**0.03%**	**60.08%**	**100.00%**
% of sex/gender	*1.64%*	*1.15%*	*14.81%*	*0.01%*	*22.28%*	*0.03%*	*60.08%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 26B (continued). New Form: Total of All Subjects Reported Using the 1997 OMB Standards by Race and Ethnicity

II. Total Enrollment Report: All Subjects by Ethnicity (New Form, Part A)

Sex/Gender	Not Hispanic	Hispanic or Latino	Unknown/Not reported	Total
Female (number)	6,000	7,712	1,361	15,073
% of total enrollment	**34.67%**	**44.56%**	**7.86%**	**87.09%**
% of all females	*39.81%*	*51.16%*	*9.03%*	*100.00%*
% of race are female	89.45%	99.18%	48.19%	87.09%
Male (number)	695	64	1,463	2,222
% of total enrollment	**4.02%**	**0.37%**	**8.45%**	**12.84%**
% of all males	*31.28%*	*2.88%*	*65.84%*	*100.00%*
% of race are male	10.36%	0.82%	51.81%	12.84%
Unknown (number)	13	0	0	13
% of total enrollment	**0.08%**	**0.00%**	**0.00%**	**0.08%**
% of all unknown	*100.00%*	*0.00%*	*0.00%*	*100.00%*
% of race are unknown	0.19%	0.00%	0.00%	0.08%
Total (number)	6,708	7,776	2,824	17,308
% of total enrollment	**38.76%**	**44.93%**	**16.32%**	**100.00%**
% of sex/gender	*38.76%*	*44.93%*	*16.32%*	*100.00%*
Total (%)	100.00%	100.00%	100.00%	100.00%

III. Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date, by Race (New Form, Part B)

Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More than one race	Unknown/ Other	Total	Subtotal minority categories (shaded): Tables 26B.I–26B.III
Female (number)	1	0	0	0	190	0	7,521	7,712	10,306
% of total enrollment	**0.01%**	**0.00%**	**0.00%**	**0.00%**	**2.44%**	**0.00%**	**96.72%**	**99.18%**	**59.54%**
% of all females	*0.01%*	*0.00%*	*0.00%*	*0.00%*	*2.46%*	*0.00%*	*97.52%*	*100.00%*	*68.37%*
% of race are female	100.00%	0.00%	0.00%	0.00%	99.48%	0.00%	99.17%	99.18%	95.18%
Male (number)	0	0	0	0	1	0	63	64	509
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**	**0.81%**	**0.82%**	**2.94%**
% of all males	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*1.56%*	*0.00%*	*98.44%*	*100.00%*	*22.91%*
% of race are male	0.00%	0.00%	0.00%	0.00%	0.52%	0.00%	0.83%	0.82%	4.70%
Unknown (number)	0	0	0	0	0	0	0	0	13
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.08%**
% of all unknown	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*
% of race are unknown	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.12%
Total (number)	1	0	0	0	191	0	7,584	7,776	10,828
% of total enrollment	**0.01%**	**0.00%**	**0.00%**	**0.00%**	**2.46%**	**0.00%**	**97.53%**	**100.00%**	**62.56%**
% of sex/gender	*0.01%*	*0.00%*	*0.00%*	*0.00%*	*2.46%*	*0.00%*	*97.53%*	*100.00%*	*62.56%*
Total (%)	100.00%	0.00%	0.00%	0.00%	100.00%	0.00%	100.00%	100.00%	100.00%

Table 26C. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Number of protocols with enrollment data reported on old form: 11

Sex/Gender	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal minority categories (shaded): Old form
Female (number)	1	21	70	28	926	9	1,055	120
% of total enrollment	**0.03%**	**0.69%**	**2.29%**	**0.92%**	**30.27%**	**0.29%**	**34.49%**	**3.92%**
% of all females	*0.09%*	*1.99%*	*6.64%*	*2.65%*	*87.77%*	*0.85%*	*100.00%*	*11.37%*
% of race are female	20.00%	33.33%	30.43%	36.84%	34.79%	39.13%	34.49%	32.09%
Male (number)	4	42	160	48	1,736	14	2,004	254
% of total enrollment	**0.13%**	**1.37%**	**5.23%**	**1.57%**	**56.75%**	**0.46%**	**65.51%**	**8.30%**
% of all males	*0.20%*	*2.10%*	*7.98%*	*2.40%*	*86.63%*	*0.70%*	*100.00%*	*12.67%*
% of race are male	80.00%	66.67%	69.57%	63.16%	65.21%	60.87%	65.51%	67.91%
Unknown (number)	0	0	0	0	0	0	0	0
% of total enrollment	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
% of all unknown	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*0.00%*
% of race are unknown	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Total (number)	5	63	230	76	2,662	23	3,059	374
% of total enrollment	**0.16%**	**2.06%**	**7.52%**	**2.48%**	**87.02%**	**0.75%**	**100.00%**	**12.23%**
% of sex/gender	*0.16%*	*2.06%*	*7.52%*	*2.48%*	*87.02%*	*0.75%*	*100.00%*	*12.23%*
Total (%)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Tables 26B and 26C

Bold: Sex/gender and race or ethnicity as percentage of total number of participants in research protocols (old or new form)

Italic: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same sex/gender (row total)

Typeface: Sex/gender and race or ethnicity as percentage of total number of participants reporting the same race/ethnicity (column total)

Table 27. NIH Sixteen-Year Trends for Protocol and Enrollment Data: 1995–2010

Table 27A. Increases in Protocols and Enrollment Data

I. Sixteen-Year Increases in Protocols and Enrollment Data

Totals	Reported in FY 1995	Reported in FY 2010	Relative increase (2010/1995)
Total number protocols with enrollment	3,188	12,079	3.8
Total enrollment	1,021,493	23,363,635	22.9
Total minority enrollment	374,433	7,510,763	20.1
Total minority enrollment (%)	36.7%	32.1%	0.9

II. Nine-Year Increases in Protocols and Enrollment Data: Foreign and Domestic

Totals	Reported in FY 2002	Reported in FY 2010	Relative increase (2010/2002)
Total domestic enrollment	10,192,401	21,523,076	2.1
Total foreign enrollment	946,083	1,840,559	1.9

Note: Trend data vary over time because the data for each year represent the net total of data resulting from (1) studies continuing from the prior year; (2) addition of new studies reported; and (3) subtraction of studies that are no longer reported.

Table 27B. Sixteen-Year Summary of Total Number of Protocols Reported: FY 1995–2010

FY reported	FY funded	Form(s) used	Number of protocols with enrollment data	Number of domestic protocols with enrollment data	Number of foreign protocols with enrollment data	Percent domestic protocols
1995	1994	Old	3,188			
1996	1995	Old	6,036			
1997	1996	Old	5,692			
1998	1997	Old	7,602			
1999	1998	Old	8,285			
2000	1999	Old	9,390			
2001	2000	Old	10,212			
2002	2001	Old & new	8,945	8,463	482	94.6%
2003	2002	Old & new	10,216	9,578	638	93.8%
2004	2003	Old & new	10,125	9,760	365	96.4%
2005	2004	Old & new	10,233	9,862	371	96.4%
2006	2005	Old & new	10,758	10,294	464	95.7%
2007	2006	Old & new	10,914	10,463	451	95.9%
2008	2007	Old & new	11,045	10,548	497	95.5%
2009	2008	Old & new	11,171	10,263	908	91.9%
2010	2009	Old & new	12,079	11,189	890	92.6%

Figure 27A. Total Protocols by Year Reported

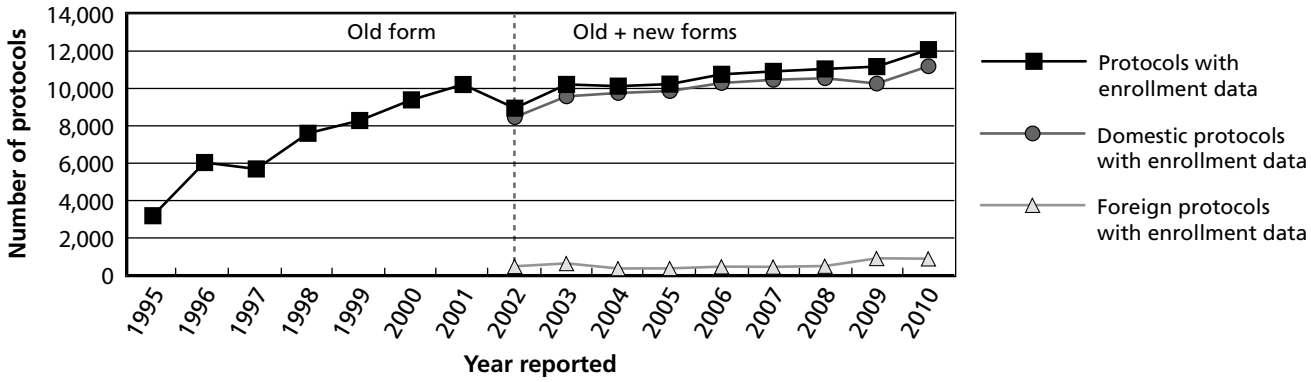


Table 27C. Comparison of Domestic and Foreign Enrollment Reported in FY 2002–2010

FY reported	FY funded	Total enrollment*	Total domestic enrollment (number)	Total domestic enrollment (%)	Total foreign enrollment (number)	Total foreign enrollment (%)
2002	2001	11,138,484	10,192,401	91.5%	946,083	8.5%
2003	2002	14,772,254	11,911,357	80.6%	2,860,897	19.4%
2004	2003	18,923,920	14,359,793	75.9%	4,564,127	24.1%
2005	2004	15,722,752	12,669,858	80.6%	3,052,894	19.4%
2006	2005	14,830,930	11,425,701	77.0%	3,405,229	23.0%
2007	2006	17,448,458	16,180,588	92.7%	1,267,870	7.3%
2008	2007	15,412,355	14,134,627	91.7%	1,277,728	8.3%
2009	2008	19,138,738	17,848,074	93.3%	1,290,664	6.7%
2010	2009	23,363,635	21,523,076	92.1%	1,840,559	7.9%

*Total enrollment data reported using the old and new forms.

Figure 27B. Relative Proportions of Domestic and Foreign Enrollment

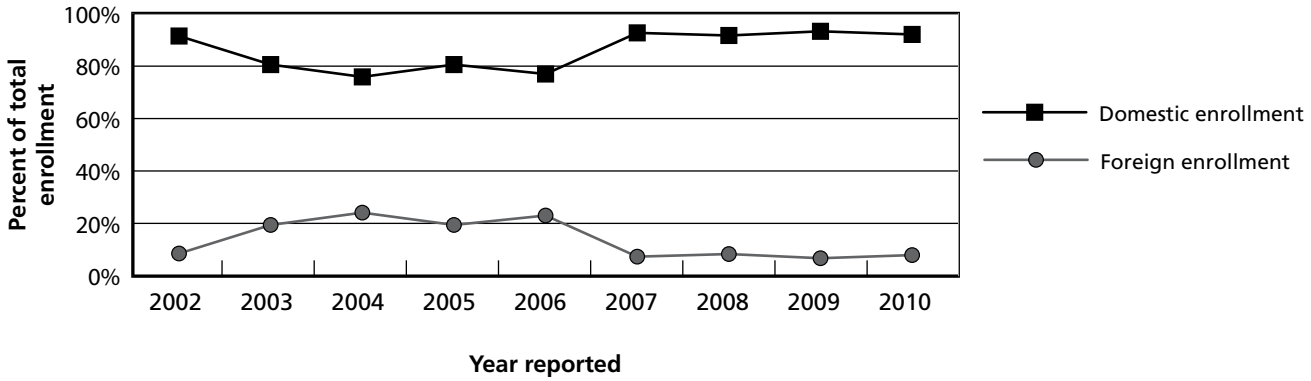


Table 28. NIH Sixteen-Year Minority Trend Summary of NIH Extramural and Intramural Clinical Research Reported for FY 1995–2010

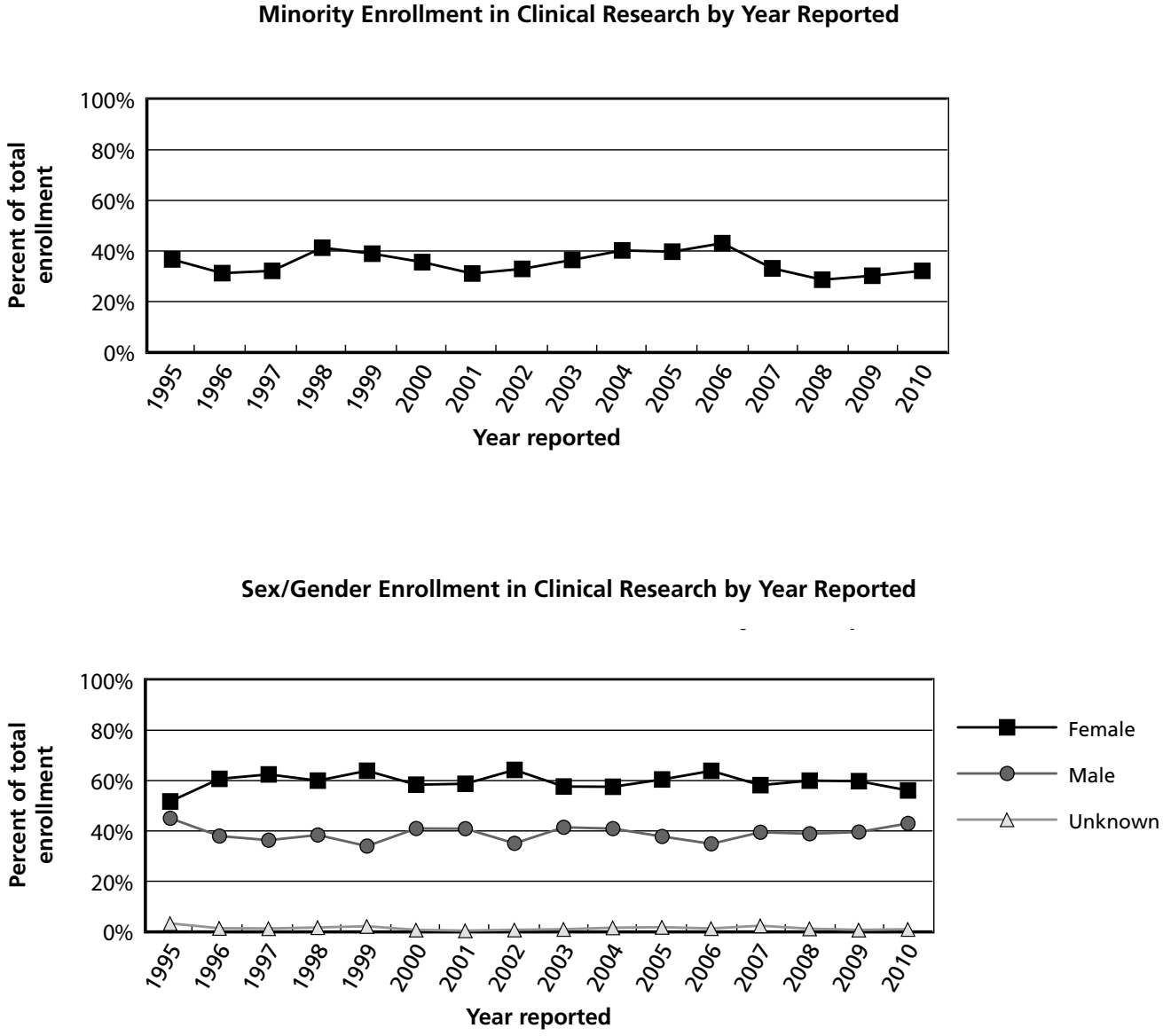
Table 28A. Sixteen-Year Summary Totals: Enrollment by Sex/Gender and Race/Ethnicity Categories in All Protocols (Old and New Forms)

FY reported	FY funded	Form(s) used	Females	Males	Unknown sex/gender	Total all subjects	Subtotal of minority subjects enrolled	Protocols with enrollment data
1995	**1994**	**Old**	**528,421**	**459,921**	**33,151**	**1,021,493**	**374,433**	**3,188**
1995	1994	Old	51.7%	45.0%	3.2%	100.0%	36.7%	—
1996	**1995**	**Old**	**4,130,385**	**2,583,865**	**91,054**	**6,805,304**	**2,125,958**	**6,036**
1996	1995	Old	60.7%	38.0%	1.3%	100.0%	31.2%	—
1997	**1996**	**Old**	**3,320,610**	**1,930,783**	**65,540**	**5,316,933**	**1,709,223**	**5,692**
1997	1996	Old	62.5%	36.3%	1.2%	100.0%	32.2%	—
1998	**1997**	**Old**	**4,246,130**	**2,716,880**	**115,566**	**7,078,576**	**2,923,662**	**7,602**
1998	1997	Old	60.0%	38.4%	1.6%	100.0%	41.3%	—
1999	**1998**	**Old**	**5,102,306**	**2,712,068**	**169,863**	**7,984,237**	**3,108,228**	**8,285**
1999	1998	Old	63.9%	34.0%	2.1%	100.0%	38.9%	—
2000	**1999**	**Old**	**5,585,042**	**3,919,065**	**64,990**	**9,569,097**	**3,406,297**	**9,390**
2000	1999	Old	58.4%	41.0%	0.7%	100.0%	35.6%	—
2001	**2000**	**Old**	**6,808,822**	**4,740,887**	**44,547**	**11,594,256**	**3,619,119**	**10,212**
2001	2000	Old	58.7%	40.9%	0.4%	100.0%	31.1%	—
2002	**2001**	**Old & new**	**7,155,549**	**3,904,560**	**78,375**	**11,138,484**	**3,666,880**	**8,945**
2002	2001	Old & new	64.2%	35.1%	0.7%	100%	32.9%	—
2003	**2002**	**Old & new**	**8,514,481**	**6,121,496**	**136,277**	**14,772,254**	**5,387,692**	**10,216**
2003	2002	Old & new	57.6%	41.4%	0.9%	100.0%	36.5%	—
2004	**2003**	**Old & new**	**10,889,097**	**7,741,892**	**292,931**	**18,923,920**	**7,611,611**	**10,125**
2004	2003	Old & new	57.5%	40.9%	1.5%	100.0%	40.2%	—
2005	**2004**	**Old & new**	**9,503,922**	**5,941,907**	**276,923**	**15,722,752**	**6,245,436**	**10,233**
2005	2004	Old & new	60.4%	37.8%	1.8%	100.0%	39.7%	—
2006	**2005**	**Old & new**	**9,473,273**	**5,172,205**	**185,452**	**14,830,930**	**6,388,316**	**10,758**
2006	2005	Old & new	63.9%	34.9%	1.25%	100.0%	43.1%	—
2007	**2006**	**Old & new**	**10,152,590**	**6,887,793**	**408,075**	**17,448,458**	**5,783,543**	**10,914**
2007	2006	Old & new	58.2%	39.5%	2.34%	100.0%	33.1%	—
2008	**2007**	**Old & new**	**9,243,966**	**5,991,739**	**176,650**	**15,412,355**	**4,412,106**	**11,045**
2008	2007	Old & new	60.0%	38.9%	1.15%	100.0%	28.6%	—
2009	**2008**	**Old & new**	**11,439,143**	**7,570,646**	**128,949**	**19,138,738**	**5,783,543**	**11,171**
2009	2008	Old & new	59.8%	39.6%	0.67%	100.0%	30.2%	—
2010	**2009**	**Old & new**	**13,102,832**	**10,044,444**	**216,359**	**23,363,635**	**7,510,763**	**12,079**
2010	2009	Old & new	56.1%	43.0%	0.9%	100.0%	32.1%	—

Note 1: Table 28A summarizes enrollment by sex/gender and race/ethnicity categories for the 16-year reporting period (1995–2010). The data are compiled from tables 28B, 28C and 28D, below, which provide the detailed distributions by sex/gender and race/ethnicity using the *old* enrollment form (table 28B) and the *new* enrollment form (tables 28C and 28D).

Note 2: Individual race and ethnicity categories in the old form and the new form cannot be combined because the categories reflect different OMB standards used in 1977 (old form) and 1997 (new form).

Figure 28A. NIH Sixteen-Year Minority Trend Summary of NIH Extramural and Intramural Clinical Research Reported for FY 1995–2010



Note: Trend data vary over time because the data for each year represent the net total resulting from (1) studies continuing from the prior year; (2) addition of new studies reported; and (3) subtraction of studies that are no longer reported.

Table 28B. Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

Note 1: The shaded portions of tables 28B, 28C, and 28D, below, show the race/ethnicity categories that are identified as minority categories. The data reported in FY 2002 and later are from the population tracking system that was deployed with data reported in FY 2002 and later that allows separate reporting using the old form and the new form, and separate reporting for foreign and domestic data.

Note 2: Data from tables 28B, 28C, and 28D are combined to provide the summary data in table 28A.

FY reported	FY funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Minority subtotal	Protocols with enrollment data
1995	**1994**	**11,221**	**38,952**	**234,976**	**89,284**	**540,313**	**106,747**	**1,021,493**	**374,433**	**3,188**
1995	1994	1.1%	3.8%	23.0%	8.7%	52.9%	10.5%	100.0%	36.7%	
1996	**1995**	**146,319**	**617,211**	**823,102**	**539,326**	**4,114,249**	**565,097**	**6,805,304**	**2,125,958**	**6,036**
1996	1995	2.2%	9.1%	12.1%	7.9%	60.5%	8.3%	100.0%	31.2%	
1997	**1996**	**36,638**	**321,479**	**864,102**	**487,004**	**3,199,778**	**407,932**	**5,316,933**	**1,709,223**	**5,692**
1997	1996	0.7%	6.0%	16.3%	9.2%	60.2%	7.7%	100.0%	32.1%	
1998	**1997**	**85,957**	**1,237,030**	**1,096,218**	**504,457**	**3,713,759**	**441,155**	**7,078,576**	**2,923,662**	**7,602**
1998	1997	1.2%	17.5%	15.5%	7.1%	52.5%	6.2%	100.0%	41.3%	
1999	**1998**	**71,436**	**1,429,022**	**1,081,210**	**526,560**	**4,470,966**	**405,043**	**7,984,237**	**3,108,228**	**8,285**
1999	1998	0.9%	17.9%	13.5%	6.6%	56.0%	5.1%	100.0%	38.9%	
2000	**1999**	**82,728**	**1,525,392**	**1,209,769**	**588,408**	**5,588,942**	**573,858**	**9,569,097**	**3,406,297**	**9,390**
2000	1999	0.9%	15.9%	12.6%	6.1%	58.4%	6.0%	100.0%	35.6%	
2001	**2000**	**105,067**	**1,495,279**	**1,199,625**	**819,148**	**7,314,449**	**660,688**	**11,594,256**	**3,619,119**	**10,212**
2001	2000	0.9%	12.9%	10.3%	7.1%	63.1%	5.7%	100.0%	31.2%	
2002	**2001**	**45,843**	**1,222,296**	**702,234**	**398,657**	**4,044,052**	**321,349**	**6,734,431**	**2,369,030**	**6,187**
2002	2001	0.7%	18.1%	10.4%	5.9%	60.1%	4.8%	100.0%	35.2%	
2003	**2002**	**36,579**	**730,542**	**472,426**	**288,523**	**3,238,284**	**278,901**	**5,045,255**	**1,528,070**	**4,903**
2003	2002	0.7%	14.5%	9.4%	5.7%	64.2%	5.5%	100.0%	30.3%	
2004	**2003**	**29,387**	**307,052**	**342,188**	**214,322**	**2,348,529**	**172,130**	**3,413,608**	**892,949**	**2,782**
2004	2003	0.9%	9.0%	10.0%	6.3%	68.8%	5.0%	100.0%	26.2%	
2005	**2004**	**22,375**	**254,598**	**229,615**	**134,972**	**1,267,089**	**102,405**	**2,011,054**	**641,560**	**1,786**
2005	2004	1.1%	12.7%	11.4%	6.7%	63.0%	5.1%	100.0%	31.9%	
2006	**2005**	**19,648**	**131,786**	**148,948**	**78,596**	**883,041**	**63,231**	**1,325,250**	**378,978**	**1,391**
2006	2005	1.5%	9.9%	11.2%	5.9%	66.6%	4.8%	100.0%	28.6%	
2007	**2006**	**5,372**	**51,742**	**238,004**	**83,192**	**1,097,387**	**48,630**	**1,524,327**	**378,310**	**1,098**
2007	2006	0.4%	3.4%	15.6%	5.5%	72.0%	3.2%	100.0%	24.8%	
2008	**2007**	**1,930**	**16,258**	**99,164**	**28,819**	**460,533**	**19,715**	**626,419**	**146,171**	**915**
2008	2007	0.3%	2.6%	15.8%	4.6%	73.5%	3.1%	100.0%	23.3%	
2009	**2008**	**1,213**	**11,652**	**42,405**	**19,301**	**299,115**	**15,780**	**389,466**	**74,571**	**843**
2009	2008	0.3%	3.0%	10.9%	5.0%	76.8%	4.1%	100.0%	19.1%	
2010	**2009**	**682**	**9,081**	**32,551**	**15,441**	**203,303**	**5,699**	**266,757**	**57,755**	**532**
2010	2009	0.3%	3.4%	12.2%	5.8%	76.2%	2.1%	100.0%	21.7%	

Table 28C. New Form Part A: Total of All Subjects Reported Using the 1997 OMB Standards

Note 1: The new form consists of parts A and B (tables 12C and 12D) for reporting years 2002–2010. This form is provided as part of the annual progress report.

Note 2: Table 12C displays the new form part A for reporting separate race and ethnicity data.

Note 3: Table 12D displays the new form part B, which is the distribution of Hispanics reported by race, using the totals from the "Hispanic or Latino" column in part A.

I. Subjects by Race

FY reported	FY funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian or Pacific Islander	White	More than one race	Unknown/ Other	Total*
2002	**2001**	**77,734**	**354,049**	**547,776**	**21,636**	**2,651,541**	**30,955**	**720,362**	**4,404,053**
2002	2001	1.8%	8.0%	12.4%	0.5%	60.2%	0.7%	16.4%	100.0%
2003	**2002**	**63,544**	**2,138,002**	**960,090**	**37,569**	**5,415,710**	**99,462**	**1,012,622**	**9,726,999**
2003	2002	0.7%	22.0%	9.9%	0.4%	55.7%	1.0%	10.4%	100.0%
2004	**2003**	**98,047**	**4,345,396**	**1,379,857**	**54,452**	**8,065,069**	**186,241**	**1,381,250**	**15,510,312**
2004	2003	0.6%	28.0%	8.9%	0.4%	52.0%	1.2%	8.9%	100.0%
2005	**2004**	**292,215**	**3,046,370**	**1,358,262**	**53,286**	**7,672,890**	**182,953**	**1,105,722**	**13,711,698**
2005	2004	2.1%	22.2%	9.9%	0.4%	56.0%	1.3%	8.1%	100.0%
2006	**2005**	**141,567**	**3,463,202**	**1,251,339**	**38,460**	**7,089,017**	**321,554**	**1,200,541**	**13,505,680**
2006	2005	1.0%	25.6%	9.3%	0.3%	52.5%	2.4%	8.9%	100.0%
2007	**2006**	**145,417**	**1,356,900**	**2,012,695**	**57,149**	**10,341,483**	**278,068**	**1,732,419**	**15,924,131**
2007	2006	0.9%	8.5%	12.6%	0.4%	64.9%	1.7%	10.9%	100.0%
2008	**2007**	**134,494**	**1,168,053**	**1,835,035**	**48,560**	**9,651,267**	**181,941**	**1,766,586**	**14,785,936**
2008	2007	0.9%	7.9%	12.4%	0.3%	65.3%	1.2%	11.9%	100.0%
2009	**2008**	**154,515**	**1,840,539**	**2,287,577**	**50,339**	**12,790,945**	**323,839**	**1,301,518**	**18,749,272**
2009	2008	0.8%	9.8%	12.2%	0.3%	68.2%	1.7%	6.9%	100.0%
2010	**2009**	**361,229**	**2,133,596**	**2,949,614**	**150,856**	**15,278,117**	**358,946**	**1,864,520**	**23,096,878**
2010	2009	1.6%	9.2%	12.8%	0.7%	66.1%	1.6%	8.1%	100.0%

* The "Total" columns of tables 28C.I and 28C.II must agree.

Table 28C (continued). New Form Part A: Total of All Subjects Reported Using the 1997 OMB Standards

II. Subjects by Ethnicity

FY reported	FY funded	Not Hispanic	Hispanic or Latino**	Unknown/ Not reported	Total*
2002	**2001**	3,071,952	292,429	1,039,672	**4,404,053**
2002	2001	69.8%	6.6%	23.6%	100.0%
2003	**2002**	8,162,259	611,641	953,099	**9,726,999**
2003	2002	83.9%	6.3%	9.8%	100.0%
2004	**2003**	13,168,842	756,339	1,585,131	**15,510,312**
2004	2003	84.9%	4.9%	10.2%	100.0%
2005	**2004**	11,804,164	773,939	1,133,595	**13,711,698**
2005	2004	86.1%	5.6%	8.3%	100.0%
2006	**2005**	11,308,244	1,054,313	1,143,123	**13,505,680**
2006	2005	83.7%	7.8%	8.5%	100.0%
2007	**2006**	13,017,124	1,169,092	1,737,915	**15,924,131**
2007	2006	81.7%	7.3%	10.9%	100.0%
2008	**2007**	11,881,644	1,116,699	1,787,594	**14,785,937**
2008	2007	80.4%	7.6%	12.1%	100.0%
2009	**2008**	16,033,547	1,302,944	1,412,781	**18,749,272**
2009	2008	85.5%	6.9%	7.5%	100.0%
2010	**2009**	18,962,836	1,958,060	2,175,982	23,096,878
2010	2009	82.1%	8.5%	9.4%	100.0%

* The "Total" columns of tables 28C.I and 28C.II must agree.

** The "Hispanic or Latino" column of table 28C.II must agree with the "Total" column of table 28D.

Table 28D. New Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled by Race

FY reported	FY funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian or Pacific Islander	White	More than one race	Unknown/ Other	Total*	Minority subtotal	Protocols with enrollment data
2002	**2001**	4,867	1,305	13,066	101	159,252	7390	106,448	**292,429**	1,297,850	**2,758**
2002	2001	1.7%	0.4%	4.5%	0.0%	54.5%	2.5%	36.4%	100.0%	29.5%	
2003	**2002**	5,400	1,953	14,566	679	350,439	28,088	210,516	**611,641**	3,859,622	**5,313**
2003	2002	0.9%	0.3%	2.4%	0.1%	57.3%	4.6%	34.4%	100.0%	39.7%	
2004	**2003**	6,408	5,040	25,276	2,037	361,112	62,909	293,557	**756,339**	6,718,662	**7,343**
2004	2003	0.8%	0.7%	3.3%	0.3%	47.7%	8.3%	38.8%	100.0%	43.3%	
2005	**2004**	22,739	7,816	19,446	1,981	388,874	51,166	281,916	**773,938**	5,603,876	**8,447**
2005	2004	2.9%	1.0%	2.5%	0.3%	50.2%	6.6%	36.4%	100.0%	40.9%	
2006	**2005**	45,074	6,641	21,712	2,193	417,495	185,477	375,721	**1,054,313**	6,009,338	**9,367**
2006	2005	4.3%	0.6%	2.1%	0.2%	39.6%	17.6%	35.6%	100.0%	44.5%	
2007	**2006**	37,581	7,414	31,239	4,310	538,216	100,197	450,135	**1,169,092**	4,356,434	**9,816**
2007	2006	3.2%	0.6%	2.7%	0.4%	46.0%	8.6%	38.5%	100.0%	29.5%	
2008	**2007**	34,335	31,616	85,548	2,369	518,825	64,979	379,027	**1,116,699**	4,265,935	**10,130**
2008	2007	3.1%	2.8%	7.7%	0.2%	46.5%	5.8%	33.9%	100.0%	28.9%	
2009	**2008**	39,198	53,546	91,184	3,103	729,355	63,934	322,808	**1,303,128**	5,708,972	**10,328**
2009	2008	3.0%	4.1%	7.0%	0.2%	56.0%	4.9%	24.8%	100.0%	30.4%	
2010	**2009**	203,106	9,836	170,553	2,824	1,015,859	72,974	482,908	**1,958,060**	7,453,008	**11,547**
2010	2009	10.4%	0.5%	8.7%	0.1%	51.9%	3.7%	24.7%	100.0%	32.3%	

*The "Total" column in table 28D must agree with the "Hispanic or Latino" column in table 28C.II.

Table 28E. Comparison of Domestic and Foreign Enrollment and Protocols With Enrollment for FY 2002–2010

Note 1: The total enrollment, total domestic enrollment, and total foreign enrollment increased overall from FY 2002 to FY 2010.

Note 2: The percent domestic enrollment decreased from more than 90% reported in FY 2002 to less than 80% reported in FY 2010. Percent foreign enrollment correspondingly increased during the same period.

FY reported	FY funded	Total enrollment data*	Total domestic enrollment	Percent domestic enrollment	Total foreign enrollment	Percent foreign enrollment	Total number of protocols with enrollment data*	Number domestic protocols	Percent domestic protocols	Number foreign protocols	Percent foreign protocols
2002	**2001**	**11,138,484**	**10,192,401**	**91.5%**	**946,083**	**8.5%**	**8,945**	**8,463**	**94.6%**	**482**	**5.4%**
2003	**2002**	**14,772,254**	**11,911,357**	**80.6%**	**2,860,897**	**19.4%**	**10,216**	**9,578**	**93.8%**	**638**	**6.2%**
2004	**2003**	**18,923,920**	**14,359,793**	**75.9%**	**4,564,127**	**24.1%**	**10,125**	**9,760**	**96.4%**	**365**	**3.6%**
2005	**2004**	**15,722,752**	**12,669,858**	**80.6%**	**3,052,894**	**19.4%**	**10,233**	**9,862**	**96.4%**	**371**	**3.6%**
2006	**2005**	**14,830,930**	**11,425,701**	**77.0%**	**3,405,229**	**23.0%**	**10,758**	**10,294**	**95.7%**	**464**	**4.3%**
2007	**2006**	**17,448,458**	**16,180,588**	**92.7%**	**1,267,870**	**7.3%**	**10,914**	**10,463**	**95.9%**	**451**	**4.1%**
2008	**2007**	**15,412,355**	**14,134,627**	**91.7%**	**1,277,728**	**8.3%**	**11,045**	**10,548**	**95.5%**	**497**	**4.5%**
2009	**2008**	**19,138,738**	**17,848,074**	**93.3%**	**1,290,664**	**6.7%**	**11,171**	**10,263**	**91.9%**	**908**	**8.1%**
2010	**2009**	**23,363,635**	**21,523,076**	**92.1%**	**1,840,559**	**7.9%**	**12,079**	**11,189**	**92.6%**	**890**	**7.4%**

*Total enrollment data and total number of protocols reported using the old and new forms.

Figure 28B. Nine-Year Trend Summary of Domestic and Foreign NIH Extramural and Intramural Clinical Research

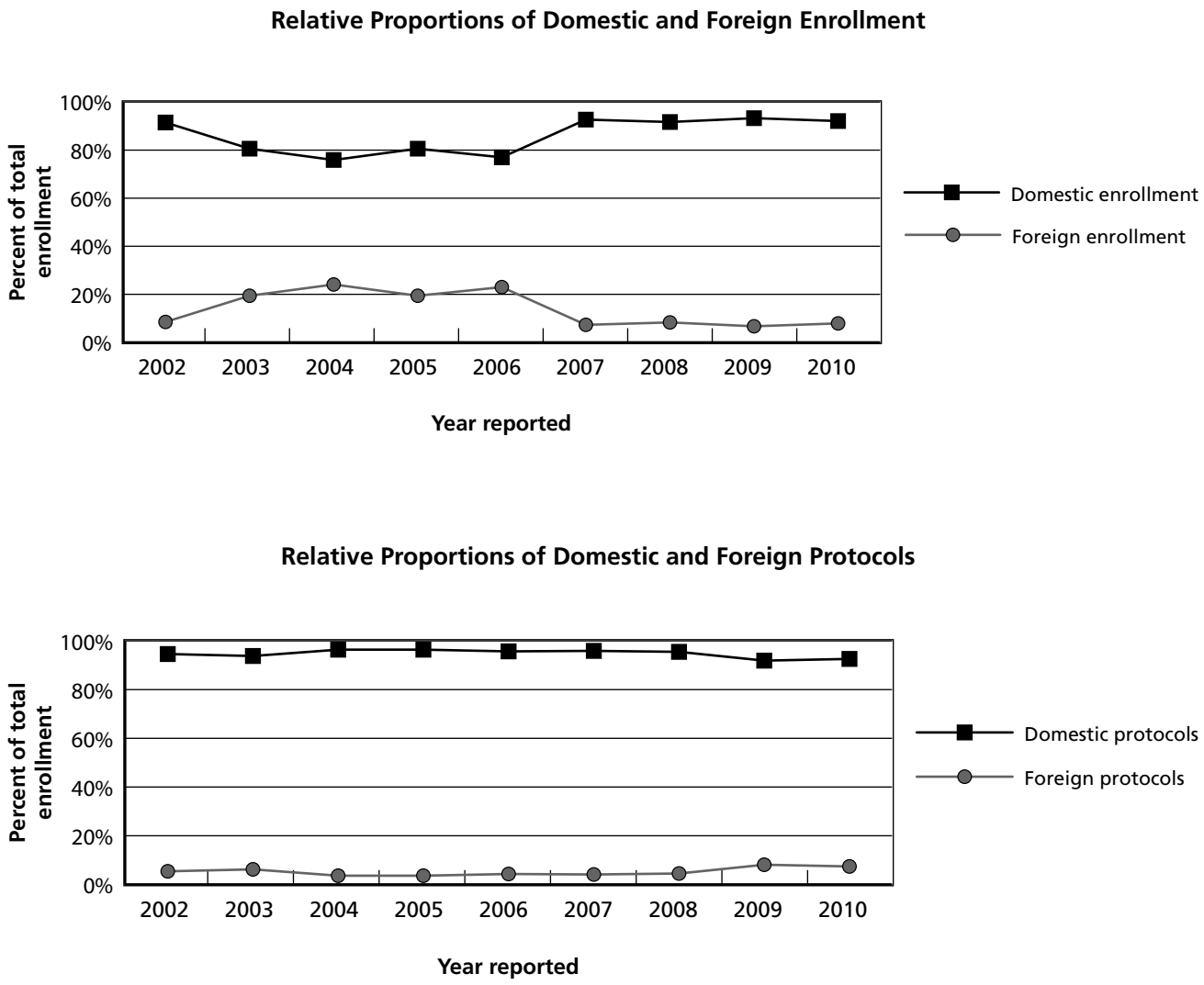


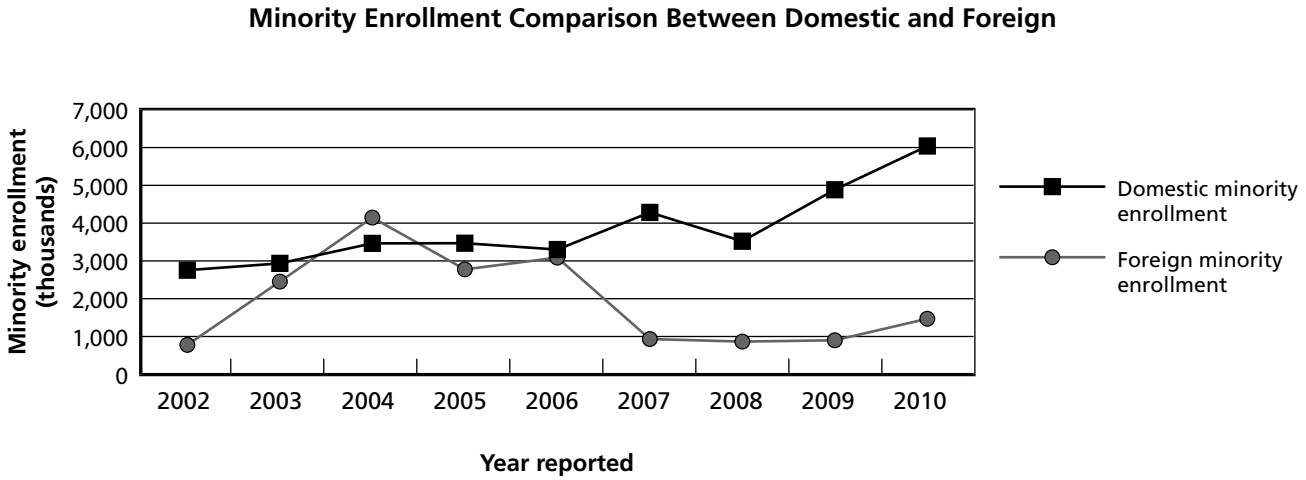
Table 28F. Minority Enrollment Comparison Between Domestic and Foreign

FY reported	FY funded	Minority enrollment in foreign protocols	Total enrollment in foreign protocols	Minority enrollment in domestic protocols	Total enrollment in domestic protocols
2002	**2001**	**777,461**	**946,083**	**2,754,820**	**10,149,869**
2002	2001	**82.2%**	100.0%	**27.1%**	100.0%
2003	**2002**	**2,452,329***	**2,860,897**	**2,935,363**	**11,911,357**
2003	2002	**85.7%**	100.0%	**24.6%**	100.0%
2004	**2003**	**4,147,255****	**4,564,127**	**3,464,356**	**14,359,793**
2004	2003	**90.9%**	100.0%	**24.1%**	100.0%
2005	**2004**	**2,776,565**	**3,052,894**	**3,468,864**	**12,669,858**
2005	2004	**90.9%**	100.0%	**27.4%**	100.0%
2006	**2005**	**3,087,181**	**3,405,229**	**3,301,135**	**11,425,701**
2006	2005	**90.7%**	100.0%	**28.9%**	100.0%
2007	**2006**	**932,686**	**1,267,870**	**4,283,738**	**16,180,588**
2007	2006	**73.6%**	100.0%	**26.5%**	100.0%
2008	**2007**	**864,945**	**1,277,728**	**3,521,691**	**14,134,627**
2008	2007	**67.7%**	100.0%	**24.9%**	100.0%
2009	**2008**	**899,749**	**1,290,664**	**4,883,794**	**17,848,074**
2009	2008	**69.7%**	100.0%	**27.4%**	100.0%
2010	**2009**	**1,469,232**	**1,840,559**	**6,041,531**	**21,523,076**
2010	2010	**79.8%**	100.0%	**28.1%**	100.0%

* In FY 2002, a single, large, foreign research study (R01TW005993) entitled "Monitoring tobacco mortality in 2 million adults in four countries" expanded enrollment to more than 1.5 million participants, causing a sharp increase in foreign minority enrollment reported in FY 2003.

** In FY 2003, a single, large, foreign research study (R01TW005991) entitled "Strengthening monitoring of Indian tobacco mortality" expanded enrollment to more than 2 million participants, causing a sharp increase in foreign minority enrollment reported in FY 2004.

Figure 28C. Comparison of Minority Enrollment in Domestic and Foreign Extramural and Intramural Protocols for FY 2002–2010



VI. NIH Budget for Women's Health Research

Summary of NIH Budgetary Expenditures for Research on Women's and Men's Health, FY 2009 and FY 2010

The amount of funding that the National Institutes of Health (NIH) invested in research during FY 2009 and FY 2010 is presented in this budget summary. This report focuses on diseases or conditions of relevance to women. The figures presented in this report were provided and submitted by the budget officials at the individual NIH Institutes and Centers (ICs), compiled by the NIH Office of Budget, and submitted to the Office of Research on Women's Health (ORWH) for inclusion in this report.

"Women's health conditions," as defined in section 141 of the NIH Revitalization Act of 1993 (42 U.S.C. § 287d), include all diseases, disorders, and conditions—

(1) that are unique to, more serious, or more prevalent in women;

(2) for which the factors of medical risk or types of medical intervention are different for women, or for which it is unknown whether such factors or types are different for women; or

(3) with respect to which there has been insufficient clinical research involving women as subjects or insufficient clinical data on women.

Research on women's health conditions includes research on preventing such conditions and applies to women of all ages and racial and ethnic groups.

ORWH has collaborated with the U.S. Department of Health and Human Services (HHS) Coordinating Committee on Women's Health (CCWH), which is convened by the Office on Women's Health in the Office of the Secretary and includes the HHS Office of Budget, Technology, and Finance and other women's health offices and programs across HHS agencies to coordinate and standardize the procedures for reporting budgetary expenditures on women's health throughout HHS. In addition to the usual congressional appropriations provided to NIH, during FY 2009 and FY 2010 additional funding was provided through the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act).

The approach to data collection for this report is similar to that employed for reports since the 1993–1994 report, *NIH Support for Research on Women's Health Issues*. However, the methodology for calculating and coding disease spending has changed, so that amounts in some women's health spending categories appear to have decreased. Changes in methodology include eliminating the multiplication of the expenditure by prevalence percentage for diseases, disorders, or conditions when enrollment data are not available. Also, new disease areas were added to streamline disease reporting.

In some of the reports prior to FY 2003 and FY 2004, the budgetary reporting on women's health expenditures focused on single-gender studies; studies to evaluate sex/gender differences; and studies of diseases, disorders, and conditions that are unique to women. Previous reporting also used prevalence data as part of the reporting criteria and included research on diseases, disorders, and conditions that are not unique to one sex, but for which there is documented evidence of greater prevalence in one sex by a ratio of at least two to one, or for which a specific gender-related consideration exists.

For the purposes of this report, budgetary expenditures are categorized as either inseparably combined or as supporting research on women's health or men's health. As a step toward establishing uniform procedures for determining the appropriate categorical allocations, and based upon discussions of the CCWH and the NIH Coordinating Committee on Research on Women's Health, ORWH requested that NIH ICs apply the criteria below:

(1) For research on diseases, disorders, or conditions that occur primarily in women (such as breast cancer and osteoporosis), the entire amount for programs in these areas should be entered under the column labeled "women." This includes clinical, applied, and basic research.

(2) For research on diseases, disorders, or conditions that occur primarily in men (such

as prostate cancer and amyotrophic lateral sclerosis), the entire amount for programs in these areas should be entered under the column listed "men." This includes clinical, applied, and basic research.

(3) For research on diseases, disorders, or conditions that affect both women and men—

a. When it can be readily determined what amount may be allocated to women or to men, those amounts should be entered in the appropriate columns. Examples would include clinical research studies where enrollment data or prevalence data give an accurate picture of the respective benefit of the study for women and men.

b. When the amount that may be allocated to men and women cannot be readily determined, the total amount should be entered in the column listed "both." Examples would include many basic research studies; research that is exploring the role of sex and gender differences; and clinical research on diseases, disorders, and conditions that affect both women and men.

For studies on diseases, disorders, or conditions that are unique to women or to men, budgetary reporting is relatively straightforward. In contrast, for the reporting of diseases, disorders, or conditions that affect both women and men, the most appropriate way to report expenditures continues to be debated. For example, the proportion of expenditures that should be considered to support research on women's health in clinical studies on lung cancer or heart disease may be determined by the proportion of women enrolled in such studies or by the relative prevalence of a condition in women. In other types of research, such as basic research studies, it may not be possible to determine what proportion of the total expenditure should be reported for women or for men. Each IC applied the criteria according to its discretion and judgment of the applicability of a single criterion or combination of criteria. ORWH, along with its advisory and coordinating committees, is aware of possible inconsistencies in the evolving methodology for collecting budget data, and will continue to carefully monitor the outcomes and to coordinate with HHS CCWH's efforts to develop best methods for budget data collection.

Starting in FY 2009, additional funding was provided to NIH through ARRA. These funds were awarded for FY 2009 and FY 2010 only, across all of the NIH ICs, using a variety of funding mechanisms. NIH worked closely with the HHS Recovery Act implementation team to ensure transparency and accountability for these funds. In order to facilitate this transparency, ARRA funding for these two years was reported separately from the rest of the NIH budget. Therefore, the budget tables presented in this section have been broken down as "non-ARRA" and "ARRA". Because these funds were used across all of the ICs, the level of funding for NIH increased accordingly, including for women only, men only, and both.

Table 29 lists the overall non-ARRA NIH expenditures in FY 2009 and FY 2010 for specific diseases, disorders, and conditions. The health categories and subcategories in table 29 were developed to accommodate all agencies in HHS. Certain subcategories are not applicable to the NIH mission; for those subcategories, the table will show a "0" across all columns. In some cases, however, a "0" may be shown even when the subcategory is relevant. This occurs because the table is additive. Funding included in each budget allocation may be listed only once, even though conceptually it applies to more than one category. For example, expenditures on infertility in cancer survivors could apply to infertility or cancer. In this example, the IC would determine the most scientifically appropriate category. Furthermore, amounts listed for each specific topic area are likely to underestimate the total expenditures for a given topic area since no overlap in reporting is allowed by the prescribed method of data collection for this report.

Table 30 shows that the percentage of ARRA funding that benefited both women and men was 85.6 percent in FY 2009 and 87.2 percent in FY 2010. The total of ARRA funding in FY 2009 was $4.77 billion and in FY 2010, the amount was $5.11 billion.

As shown in table 31 (non-ARRA funds), approximately 82.7 percent and 82.8 percent of the NIH research budget for FY 2009 and FY 2010, respectively, supported research that benefited both women and men. Because of the additional ARRA funding in FY 2009 and FY 2010, the total dollars in the research budget expended on both women's and men's health, as defined by the specific parameters for this data collection, increased from that of FY 2007 and FY 2008 (table 32).

Considering only the non-ARRA funds for sex/gender-specific research, 12.4 percent of the NIH research budget was spent on women's health research in FY 2009 and 12.0 percent in FY 2010. Sex/gender-specific research on men's health accounted for 4.9 percent of the NIH research budget in FY 2009 and 5.2 percent in FY 2010. The higher proportion expended for women's health sex/gender-specific research than for men's health sex/gender-specific research most likely stems from the fact that there are more sex/gender-specific diseases, disorders, and conditions that affect females; including menarche, menopause, pregnancy, and gynecologic neoplasms; than there are male-specific diseases, disorders, and conditions such as prostate cancer. An important observation is that the expenditures for conditions that affect both men and women increased over the last 4 fiscal years.

It should be noted that, in 2008, the NIH implemented the Research, Condition, and Disease Categorization (RCDC) process, which established a new method of categorizing funding by disease or scientific topic area to report NIH funding to Congress and the public. The RCDC process uses expert-verified category definitions and applies them uniformly, via a text-mining algorithm, to all types of research projects from all of the ICs. This methodology changed the projects included in each category, and may have altered the dollar amounts for some categories from FY 2007 to FY 2008. The RCDC data collection process is designed to yield more precise, reliable, and consistent figures. It also should be noted that the "women's health research" category definition uses a different methodology from that used by RCDC to calculate spending. These differences may help explain why women's health research funding, outlined in this report, may not be comparable to the RCDC categories published on the NIH Web site. For the period FY 2009–FY 2010, RCDC includes information on 229 conditions that affect both males and females. More complete information on these 229 conditions, as well as male-specific conditions, can be obtained from the RCDC data system online, http://report.nih.gov/rcdc/categories/.

Table 29. HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives—Non-ARRA Funding, FY 2009 and FY 2010 (Dollars in Thousands)

I. Cancer

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Breast cancer (including mammography & other service)	660,915	0	5,908	666,823	673,970	0	11,006	684,976
Reproductive cancers: Cervical	76,880	211	6,352	83,443	90,033	688	7,692	98,413
Reproductive cancers: Ovarian	109,730	0	1,036	110,766	119,247	0	1,297	120,544
Reproductive cancers: Vaginal, uterine, and other	21,108	0	0	21,108	13,002	0	212	13,214
Lung cancer	126,283	0	133,875	260,158	15,512	0	264,999	280,511
Colorectal cancer	133,951	73	164,706	298,730	249,906	0	65,104	315,010
Other neoplasms	17,013	57,719	4,115,725	4,190,457	20,729	74,290	4,170,386	4,265,406
Subtotal	**1,145,881**	**58,003**	**4,427,602**	**5,631,485**	**1,182,399**	**74,978**	**4,520,696**	**5,778,073**

II. Cardiovascular/Pulmonary

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Blood diseases	32,693	40,755	330,324	403,772	28,803	37,082	457,509	523,394
Heart disease	126,654	128,135	731,338	986,127	133,697	139,077	798,367	1,071,141
Stroke	43,989	46,695	194,257	284,941	38,823	48,504	207,711	295,038
Other cardiovascular diseases/disorders	111,561	93,391	923,329	1,128,282	90,162	97,704	960,025	1,147,891
Pulmonary diseases	66,908	73,706	379,872	520,486	64,584	69,767	433,875	568,226
Asthma	39,658	27,470	175,108	242,236	43,749	35,523	157,627	236,899
Other	4,000	14	477,950	481,964	4,542	0	664,294	668,836
Subtotal	**425,463**	**410,166**	**3,212,180**	**4,047,809**	**404,360**	**427,657**	**3,679,408**	**4,511,425**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Figures shown in this table do not include NIH Buildings and Facilities program spending.

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

III. Reproductive & Maternal/Child/Adolescent Health

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Contraception	25,286	12,738	49,343	87,367	32,142	8,812	45,783	86,737
Infertility	11,899	1,382	13,597	26,878	9,917	2,722	12,434	25,073
Female reproductive physiology	120,192	0	324	120,516	115,890	0	173	116,063
Hysterectomy	423	0	0	423	211	0	0	211
Endometriosis/leiomyomas (fibroids)	3,485	0	27	3,512	3,724	0	699	4,423
Pregnancy/pregnancy prevention/ maternal health	209,944	30	3,188	213,162	195,223	551	12,055	207,829
Diseases related to diethylstilbestrol (DES) exposure	563	0	1,704	2,267	235	0	1,727	1,962
Female genital cutting	0	0	0	0	0	0	0	0
Pelvic floor disorders*	NR	NR	NR	NR	1,860	126	66,642	68,628
Other	4,822	25,995	527,109	557,926	1,650	13,757	549,366	564,773
Subtotal	**376,614**	**40,145**	**595,292**	**1,012,051**	**360,852**	**25,968**	**688,879**	**1,075,699**

IV. Aging

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Menopause	36,278	50	0	36,328	28,393	0	155	28,548
Menopausal hormone/non-hormone therapy	14,472	0	0	14,472	15,344	0	0	15,344
Alzheimer's disease	43,813	7,515	353,187	404,515	38,310	31,989	319,410	389,709
Malnutrition in the elderly	352	337	0	689	349	123	0	472
Osteoarthritis	27,216	0	20,649	47,865	30,315	1,439	39,519	71,273
Osteoporosis (including fractures*)	114,523	4,895	7,473	125,891	122,017	6,083	18,793	146,893
Women's Health Initiative	320	0	0	320	400	0	0	400
Demography of aging*	NR	NR	NR	NR	14,088	12,016	34,089	60,193
Aging economics*	NR	NR	NR	NR	2,291	1,435	31,990	35,716
Other	70,201	14,435	680,483	765,119	22,543	0	391,173	413,716
Subtotal	**307,175**	**27,232**	**1,061,792**	**1,396,199**	**274,051**	**53,085**	**835,129**	**1,162,265**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Figures shown in this table do not include NIH Buildings and Facilities program spending.

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

Table 29 (continued). HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives—Non-ARRA Funding, FY 2009 and FY 2010 (Dollars in Thousands)

V. Metabolism/Endocrinology/Gastrointestinal†

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Diabetes	62,389	87,154	110,822	260,365	53,491	106,388	133,916	293,795
Obesity	157,983	84,477	150,965	393,425	132,498	101,260	160,181	393,939
Hepatobiliary diseases	440	2,171	211,872	214,483	349	2,409	294,395	297,152
Thyroid diseases/conditions	13,478	3,369	6,053	22,900	10,537	3,873	443	14,853
Fecal incontinence*	NR	NR	NR	NR	1,857	237	0	2,094
Irritable bowel syndrome*	NR	NR	NR	NR	4,959	805	107	5,871
Other	5,628	255	67,089	72,972	6,153	256	209,286	215,695
Subtotal	**239,917**	**177,427**	**546,802**	**964,146**	**209,843**	**215,227**	**798,328**	**1,223,399**

VI. Substance Abuse

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Etiology (unspecified)	3,992	4,873	92,017	100,882	6,562	9,501	85,959	102,022
Epidemiology (unspecified)	4,908	2,528	15,660	23,096	4,534	3,510	16,758	24,802
Prevention (unspecified)	2,201	1,367	27,701	31,269	3,543	2,856	19,733	26,132
Treatment (unspecified)	2,546	2,097	25,541	30,185	4,811	5,042	18,428	28,281
Alcohol	11,390	13,005	120,671	145,065	15,340	20,684	138,080	174,104
Illegal drugs	259,067	332,474	449,707	1,041,248	269,304	283,853	516,367	1,069,524
Prescription drugs	0	0	46	46	0	0	0	0
Tobacco products	246	176	29,630	30,052	660	481	37,262	38,403
Other substances	178	134	6,415	6,727	103	53	8,691	8,847
Co-occurring substance abuse and mental disorders	487	423	4,290	5,200	573	843	7,827	9,243
Subtotal	**285,014**	**357,077**	**771,678**	**1,413,769**	**305,430**	**326,823**	**849,105**	**1,481,358**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Figures shown in this table do not include NIH Buildings and Facilities program spending.

*Category added as of FY 2010.
†Category amended to include "gastrointestinal" as of FY 2010.
NR = Category not reported this fiscal year.

VII. Behavioral Studies/Programs

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Violence (including domestic, abused women, spousal abuse, elder abuse, violence against women, trafficking, bullying)	6,724	970	25,898	33,592	5,815	1,154	26,415	33,384
Tobacco use cessation	673	0	4,848	5,521	995	89	4,857	5,941
Physical activity/exercise†/nutrition (promoting healthy behavior)	2,021	10	88,603	90,634	9,923	6,449	197,115	213,487
Other behavior change/risk modification	9,827	3,444	217,126	230,398	13,009	3,810	474,134	490,953
Caregiving	1,019	0	7,659	8,678	671	200	7,338	8,209
Other	2,788	1,160	348,545	352,493	21,823	12,375	422,767	456,965
Subtotal	**23,052**	**5,584**	**692,680**	**721,316**	**52,236**	**24,077**	**1,132,626**	**1,208,939**

VIII. Mental Health

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Etiology (unspecified)	147	3	16,185	16,335	178	55	20,202	20,435
Epidemiology (unspecified)	0	0	103	103	0	0	3	3
Prevention (unspecified)	70	0	2,287	2,357	0	0	2,742	2,742
Treatment (unspecified)	194	175	2,239	2,608	20	0	2,030	2,050
Depression/mood disorders	21,274	576	150,207	172,057	19,305	1,882	158,154	179,341
Suicide	428	144	12,745	13,317	0	0	10,815	10,815
Schizophrenia	591	219	149,033	149,842	352	261	143,964	144,577
Anxiety disorders	255	85	45,649	45,989	308	392	42,618	43,318
Eating disorders	5,221	37	5,521	10,779	5,349	35	6,020	11,404
Psychosocial stress	8,496	101	28,190	36,786	10,844	471	25,218	36,533
Posttraumatic stress disorder (PTSD)	4,733	1,431	13,600	19,764	3,945	1,981	14,676	20,602
Other mental disorders (excluding Alzheimer's)	19,452	8,692	828,507	856,651	26,942	7,965	908,533	943,440
Autism	0	3,338	134,105	137,443	0	36,073	67,751	103,824
Subtotal	**60,860**	**14,799**	**1,388,371**	**1,464,030**	**67,243**	**49,115**	**1,402,726**	**1,519,084**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Figures shown in this table do not include NIH Buildings and Facilities program spending.

*Category added as of FY 2010
†Category amended to include "exercise" as of FY 2010.
NR = Category not reported this fiscal year.

Table 29 (continued). HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives—Non-ARRA Funding, FY 2009 and FY 2010 (Dollars in Thousands)

IX. Infectious Diseases

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
AIDS/HIV	157,583	55,877	2,340,069	2,553,529	185,069	58,591	2,296,725	2,540,385
Tuberculosis	7,345	4,629	95,562	107,536	7,367	4,501	128,686	140,554
Sexually transmitted diseases (STD)	32,839	3,656	109,709	146,204	27,922	3,811	181,752	213,485
Topical microbicides	94,405	0	3,663	98,068	91,166	1,472	8,977	101,615
Toxic shock syndrome	1,297	0	0	1,297	2,349	0	0	2,349
Tropical diseases (including malaria)	23,715	4,069	349,305	377,089	26,138	2,631	413,481	442,250
Other	455	108	482,536	483,099	2,498	1,039	592,371	595,908
Subtotal	**317,639**	**68,338**	**3,380,844**	**3,766,822**	**342,509**	**72,045**	**3,621,992**	**4,036,546**

X. Immune Disorders

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Arthritis	46,959	6,107	240,734	293,800	NR	NR	NR	NR
Rheumatoid arthritis*	NR	NR	NR	NR	38,902	0	157,171	196,073
Lupus erythematosus	60,860	3,093	34,571	98,524	57,739	3,503	30,497	91,739
Multiple sclerosis	19,948	15,127	82,793	117,868	16,013	14,728	76,199	106,940
Myasthenia gravis	175	94	270	539	234	191	0	425
Scleroderma	9,670	0	2,706	12,376	8,116	0	3,135	11,251
Sjögren's syndrome	12,898	247	150	13,295	11,043	269	0	11,312
Takayasu disease	0	0	0	0	105	0	0	105
Other	744	744	117,527	119,014	9,212	3,846	458,343	471,401
Subtotal	**151,254**	**25,412**	**478,750**	**655,416**	**141,364**	**22,537**	**725,345**	**889,246**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Figures shown in this table do not include NIH Buildings and Facilities program spending.

*Category changed as of FY 2010.
NR = Category not reported this fiscal year.

XI. Neurologic, Muscular, and Bone

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Trauma research	6,385	6,985	91,999	105,369	NR	NR	NR	NR
Trauma research: Brain*	NR	NR	NR	NR	16,105	20,785	139,822	176,712
Trauma research: Other neurologic trauma*	NR	NR	NR	NR	17	0	19,802	19,819
Trauma research: Bone-fracture (non-osteoporotic) and muscle injury*	NR	NR	NR	NR	0	0	22,118	22,118
Muscular dystrophy	4,343	25,013	26,660	56,016	4,102	31,301	24,103	59,506
Chronic pain conditions	10,138	10,883	91,320	112,341	10,332	12,848	97,755	120,935
Temporomandibular disorders	11,696	0	373	12,069	14,158	0	869	15,027
Vulvodynia	690	0	0	690	1,004	0	0	1,004
Fibromyalgia and eosinophilic myalgia	8,559	0	200	8,759	5,539	0	0	5,539
Migraine	0	0	0	0	340	517	381	1,238
Sleep disorders	6,637	4,927	41,269	52,834	9,643	6,517	47,718	63,878
Paget's disease	0	0	1,152	1,152	0	0	786	786
Parkinson's disease	16,699	18,042	97,199	131,940	12,969	16,502	108,468	137,939
Seizure disorders	14,514	15,629	67,514	97,657	13,052	16,631	74,993	104,676
Other	125,485	139,749	988,734	1,253,968	107,818	136,491	1,200,194	1,444,503
Subtotal	**205,146**	**221,228**	**1,406,420**	**1,832,795**	**195,079**	**241,592**	**1,737,009**	**2,173,680**

XII. Kidney and Urologic

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Urinary tract infections (cystitis, pyelonephritis)	12,541	303	4,929	17,773	10,205	292	8,440	18,937
End-stage renal disease (ESRD)/ transplantation	4,584	5,047	68,254	77,885	3,646	6,014	77,380	87,040
Urinary incontinence	10,408	0	729	11,137	9,138	0	517	9,655
Painful bladder, interstitial cystitis*	NR	NR	NR	NR	8,832	1,344	0	10,176
Other	8,874	9,029	351,189	369,092	7,693	10,046	439,818	457,557
Subtotal	**36,407**	**14,379**	**425,101**	**475,887**	**39,514**	**17,696**	**526,155**	**583,364**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Figures shown in this table do not include NIH Buildings and Facilities program spending.

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

Table 29 (continued). HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives—Non-ARRA Funding, FY 2009 and FY 2010 (Dollars in Thousands)

XIII. Ophthalmic, Otolaryngologic, and Oral Health

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Eye diseases and disorders	16,893	17,979	721,061	755,933	22,388	8,714	747,554	778,656
Ear diseases and disorders	14,485	0	215,950	230,435	11,951	0	233,658	245,609
Dental and oral health	2,206	0	370,882	373,088	16	2,152	374,334	376,502
Other	0	0	0	0	0	0	34,088	34,088
Subtotal	**33,584**	**17,979**	**1,307,893**	**1,359,456**	**34,355**	**10,866**	**1,389,634**	**1,434,855**

XIV. Health Effects of the Environment

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Environmental estrogens	3,435	4,560	10,305	18,300	215	1,228	10,195	11,638
Health effects of toxic exposure (excluding cancer)	462	0	45,379	45,841	139	0	245,783	245,922
Toxicological research and testing program	0	0	76,223	76,223	0	0	79,888	79,888
Chemical/biological warfare agents	0	0	805	805	0	0	1,180	1,180
Other	165	0	1,156	1,321	0	0	678	678
Subtotal	**4,062**	**4,560**	**133,869**	**142,491**	**354**	**1,228**	**337,724**	**339,306**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Figures shown in this table do not include NIH Buildings and Facilities program spending.

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

XV. Cross-Cutting Categories and Special Initiatives

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Treatment, prevention, and services	1,490	1,092	342,572	345,155	3,490	2,527	439,463	445,480
Access to health care and financing	0	0	2,790	2,790	66	0	1,184	1,250
Education and training for health care providers	316	18	11,116	11,450	785	35	61,289	62,109
Health literacy and bilingual information	944	12	20,125	21,081	954	0	21,921	22,875
Cultural influences	914	241	5,979	7,134	3,399	455	118,806	122,660
Disability research and services	1,177	5,822	167,242	174,241	962	2,875	86,063	89,900
Homelessness	0	0	114	114	0	0	0	0
Chronic fatigue syndrome	684	75	1,808	2,567	432	209	1,682	2,323
Breast feeding	1,075	0	0	1,075	1,032	0	1,753	2,785
Organ donation	217	0	959	1,176	0	0	1,787	1,787
Genetic services/counseling	0	0	4,938	4,938	0	0	2,989	2,989
Unintentional injury	0	754	19,567	20,321	321	1,338	28,680	30,339
Alternative and complementary therapies	29,816	23,801	125,499	179,116	32,654	23,213	135,859	191,726
Health statistics and data collection	951	232	7,802	8,985	2,289	389	18,192	20,870
Office of Women's Health	12,136	0	0	12,136	12,268	0	5	12,273
Global health	9,389	447	1,682,955	1,692,791	21,894	10,623	1,656,165	1,688,682
Drug metabolism (sex differences, pregnancy, etc.)*	NR	NR	NR	NR	250	0	2,300	2,550
Other cross-cutting	54,120	3,329	2,691,747	2,749,195	629	0	714,697	715,326
Subtotal	**113,229**	**35,823**	**5,085,213**	**5,234,266**	**81,425**	**41,664**	**3,292,835**	**3,415,924**

Non-ARRA	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Non-ARRA total	**3,725,297**	**1,478,151**	**24,914,488**	**30,117,937**	**3,691,013**	**1,604,558**	**25,537,591**	**30,833,163**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Figures shown in this table do not include NIH Buildings and Facilities program spending.

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

Table 30. HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives—ARRA Funding, FY 2009 and FY 2010 (Dollars in Thousands)

I. Cancer

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Breast cancer (including mammography & other service)	99,809	0	12,163	111,972	70,283	0	20,067	90,350
Reproductive cancers: Cervical	9,871	332	110	10,313	1,479	50	2,369	3,898
Reproductive cancers: Ovarian	17,298	0	676	17,974	4,095	0	565	4,660
Reproductive cancers: Vaginal, uterine, and other	2,667	0	0	2,667	0	0	0	0
Lung cancer	22,521	0	29,364	51,885	1,539	0	49,510	51,049
Colorectal cancer	21,657	0	34,734	56,391	2,175	0	26,942	29,117
Other neoplasms	2,178	10,831	716,782	729,791	1,491	14,687	425,330	441,508
Subtotal	**176,001**	**11,163**	**793,829**	**980,993**	**81,062**	**14,737**	**524,783**	**620,582**

II. Cardiovascular/Pulmonary

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Blood diseases	5,438	6,866	48,846	61,150	4,475	9,229	58,895	72,599
Heart disease	20,564	19,972	154,297	194,883	19,366	19,206	197,753	236,325
Stroke	2,557	3,130	40,197	45,884	1,226	3,149	46,272	50,647
Other cardiovascular diseases/disorders	7,622	8,377	148,947	164,946	7,299	8,025	222,601	237,925
Pulmonary diseases	8,609	9,120	82,501	100,230	7,566	7,966	56,705	72,237
Asthma	5,839	5,201	39,806	50,846	3,272	2,428	25,243	30,943
Other	0	0	92,751	92,751	0	0	356,793	356,793
Subtotal	**50,629**	**52,666**	**607,345**	**710,639**	**43,204**	**50,003**	**964,262**	**1,057,469**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Amounts exclude $500 million appropriated under the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act) to the NIH Buildings and Facilities program for the funding of infrastructure projects involving facility construction, repair, and/or renovation during FY 2009 ($50 million) and FY 2010 ($450 million).

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

III. Reproductive & Maternal/Child/Adolescent Health

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Contraception	7,571	442	15,317	23,330	2,370	244	6,865	9,479
Infertility	143	38	2,643	2,824	664	417	2,327	3,408
Female reproductive physiology	18,745	0	0	18,745	13,768	0	139	13,907
Hysterectomy	10	0	0	10	78	0	0	78
Endometriosis/leiomyomas (fibroids)	0	0	4	4	0	0	0	0
Pregnancy/pregnancy prevention/ maternal health	25,216	0	140	25,356	51,813	0	174	51,987
Diseases related to diethylstilbestrol (DES) exposure	621	0	0	621	549	0	0	549
Female genital cutting	0	0	0	0	0	0	0	0
Pelvic floor disorders*	NR	NR	NR	NR	0	0	1,881	1,881
Other	13	4,137	15	4,165	866	3,127	18,183	22,176
Subtotal	**52,319**	**4,617**	**18,119**	**75,055**	**70,108**	**3,788**	**29,569**	**103,465**

IV. Aging

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Menopause	2,968	0	0	2,968	2,434	0	0	2,434
Menopausal hormone/non-hormone therapy	384	0	0	384	901	0	0	901
Alzheimer's disease	3,913	1,115	102,653	107,681	12,784	9,100	55,272	77,156
Malnutrition in the elderly	0	0	0	0	0	0	0	0
Osteoarthritis	3,357	0	6,191	9,548	7,040	24	6,790	13,854
Osteoporosis (including fractures*)	18,089	0	2,264	20,353	21,322	0	1,677	23,000
Women's Health Initiative	0	0	0	0	1,458	0	0	1,458
Demography of aging*	NR	NR	NR	NR	32	0	2,407	2,439
Aging economics*	NR	NR	NR	NR	112	112	4,646	4,870
Other	14,535	0	70,284	84,819	14,404	0	152,229	166,633
Subtotal	**43,246**	**1,115**	**181,392**	**225,753**	**60,487**	**9,236**	**223,021**	**292,745**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Amounts exclude $500 million appropriated under the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act) to the NIH Buildings and Facilities program for the funding of infrastructure projects involving facility construction, repair, and/or renovation during FY 2009 ($50 million) and FY 2010 ($450 million).

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

Table 30 (continued). HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives—ARRA Funding, FY 2009 and FY 2010 (Dollars in Thousands)

V. Metabolism/Endocrinology/Gastrointenstinal†

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Diabetes	5,897	9,859	29,379	45,135	16,153	24,501	41,084	81,738
Obesity	14,832	9,656	33,709	58,197	24,295	11,391	35,728	71,414
Hepatobiliary diseases	734	917	25,963	27,615	341	0	44,642	44,983
Thyroid diseases/conditions	1,177	375	13	1,565	1,792	453	0	2,245
Fecal incontinence*	NR	NR	NR	NR	0	0	0	0
Irritable bowel syndrome*	NR	NR	NR	NR	0	0	313	313
Other	0	0	41,112	41,112	0	0	199,180	199,180
Subtotal	**22,640**	**20,808**	**130,176**	**173,623**	**42,581**	**36,345**	**320,946**	**399,872**

VI. Substance Abuse

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Etiology (unspecified)	1,412	918	12,245	14,575	853	782	9,514	11,149
Epidemiology (unspecified)	495	492	539	1,526	370	373	486	1,229
Prevention (unspecified)	814	280	3,565	4,658	878	192	4,274	5,344
Treatment (unspecified)	287	391	3,319	3,997	153	183	4,469	4,805
Alcohol	2,464	1,856	18,786	23,106	1,170	1,075	20,178	22,423
Illegal drugs	37,352	38,270	60,592	136,214	32,239	26,969	66,028	125,236
Prescription drugs	0	0	0	0	0	0	2,733	2,733
Tobacco products	85	85	15,105	15,275	77	83	19,608	19,768
Other substances	545	50	5,669	6,263	0	0	290	290
Co-occurring substance abuse and mental disorders	116	91	830	1,037	41	41	25,683	25,765
Subtotal	**43,569**	**42,432**	**120,651**	**206,652**	**35,781**	**29,698**	**153,264**	**218,743**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Amounts exclude $500 million appropriated under the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act) to the NIH Buildings and Facilities program for the funding of infrastructure projects involving facility construction, repair, and/or renovation during FY 2009 ($50 million) and FY 2010 ($450 million).

*Category added as of FY 2010.
†Category amended to include "gastrointestinal" as of FY 2010.
NR = Category not reported this fiscal year.

VII. Behavioral Studies/Programs

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Violence (including domestic, abused women, spousal abuse, elder abuse, violence against women, trafficking, bullying)	424	302	2,508	3,234	96	272	1,829	2,197
Tobacco use cessation	0	0	8,624	8,624	0	0	0	0
Physical activity/exercise†/nutrition (promoting healthy behavior)	212	0	12,331	12,543	13,734	5,899	17,391	37,024
Other behavior change/risk modification	1,845	0	41,268	43,113	1,960	0	51,549	53,509
Caregiving	11	0	365	376	155	149	755	1,059
Other	426	402	49,253	50,081	1,986	996	48,562	51,544
Subtotal	**2,919**	**704**	**114,348**	**117,970**	**17,931**	**7,316**	**120,086**	**145,333**

VIII. Mental Health

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Etiology (unspecified)	0	0	8,480	8,480	0	0	4,329	4,329
Epidemiology (unspecified)	0	0	0	0	0	0	0	0
Prevention (unspecified)	1	0	0	1	0	0	154	154
Treatment (unspecified)	0	0	3,257	3,257	0	0	17,957	17,957
Depression/mood disorders	234	354	20,508	21,096	28	433	24,635	25,096
Suicide	0	0	13,003	13,003	0	0	2,894	2,894
Schizophrenia	2,782	0	39,146	41,928	608	0	36,281	36,889
Anxiety disorders	0	0	1,034	1,034	0	0	925	925
Eating disorders	232	0	824	1,056	193	0	1,214	1,407
Psychosocial stress	896	268	1,356	2,520	976	278	265	1,519
Posttraumatic stress disorder (PTSD)	627	224	1,605	2,456	82	82	1,361	1,525
Other mental disorders (excluding Alzheimer's)	4,210	1,320	89,428	94,958	3,119	640	107,048	110,807
Autism	374	1,012	55,004	56,390	500	13,111	27,923	41,534
Subtotal	**9,356**	**3,178**	**233,645**	**246,179**	**5,506**	**14,544**	**224,986**	**245,036**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Amounts exclude $500 million appropriated under the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act) to the NIH Buildings and Facilities program for the funding of infrastructure projects involving facility construction, repair, and/or renovation during FY 2009 ($50 million) and FY 2010 ($450 million).

*Category added as of FY 2010.
†Category amended to include "exercise" as of FY 2010.
NR = Category not reported this fiscal year.

Table 30 (continued). HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives—ARRA Funding, FY 2009 and FY 2010 (Dollars in Thousands)

IX. Infectious Diseases

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
AIDS/HIV	17,112	8,614	246,927	272,652	14,347	7,681	285,880	307,908
Tuberculosis	223	255	23,804	24,282	283	299	35,703	36,285
Sexually transmitted diseases (STD)	5,677	53	20,324	26,054	10,060	858	11,368	22,286
Topical microbicides	4,919	0	116	5,035	4,444	0	0	4,444
Toxic shock syndrome	0	0	0	0	0	0	0	0
Tropical diseases (including malaria)	910	532	51,445	52,887	1,475	1,180	55,817	58,472
Other	3,692	0	64,823	68,515	528	28	41,554	42,110
Subtotal	**32,533**	**9,454**	**407,439**	**449,426**	**31,137**	**10,046**	**430,322**	**471,505**

X. Immune Disorders

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Arthritis	8,084	452	51,666	60,202	NR	NR	NR	NR
Rheumatoid arthritis*	NR	NR	NR	NR	5,759	0	38,635	44,394
Lupus erythematosus	12,305	772	4,322	17,399	8,435	778	5,997	15,210
Multiple sclerosis	3,119	1,408	14,583	19,110	367	673	9,670	10,710
Myasthenia gravis	121	65	243	429	92	75	3,508	3,675
Scleroderma	2,633	0	2,387	5,020	1,309	0	770	2,079
Sjögren's syndrome	2,038	0	220	2,258	1,683	0	183	1,866
Takayasu disease	0	0	0	0	0	0	0	0
Other	0	0	51,571	51,571	1,830	979	243,604	246,413
Subtotal	**28,300**	**2,697**	**124,993**	**155,989**	**19,475**	**2,505**	**302,368**	**324,348**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Amounts exclude $500 million appropriated under the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act) to the NIH Buildings and Facilities program for the funding of infrastructure projects involving facility construction, repair, and/or renovation during FY 2009 ($50 million) and FY 2010 ($450 million).

*Category changed as of FY 2010.
NR = Category not reported this fiscal year.

XI. Neurologic, Muscular, and Bone

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Trauma research	1,165	1,575	26,832	29,572	NR	NR	NR	NR
Trauma research: Brain*	NR	NR	NR	NR	5,132	1,639	15,193	21,964
Trauma research: Other neurologic trauma*	NR	NR	NR	NR	0	0	2,547	2,547
Trauma research: Bone-fracture (non-osteoporotic) and muscle injury*	NR	NR	NR	NR	0	0	2,817	2,817
Muscular dystrophy	422	4,887	9,476	14,785	46	3,120	7,325	10,491
Chronic pain conditions	483	652	10,539	11,674	559	490	18,576	19,625
Temporomandibular disorders	247	0	233	480	449	0	185	634
Vulvodynia	1,134	0	0	1,134	934	0	0	934
Fibromyalgia and eosinophilic myalgia	1,401	0	0	1,401	208	0	0	208
Migraine	0	0	0	0	0	0	0	0
Sleep disorders	940	231	7,771	8,942	571	285	8,369	9,225
Paget's disease	0	0	610	610	0	0	0	0
Parkinson's disease	1,157	1,557	19,036	21,750	286	1,186	13,389	14,861
Seizure disorders	1,364	1,748	14,005	17,117	316	1,510	14,830	16,656
Other	8,085	10,874	174,807	193,766	2,069	7,720	399,964	409,753
Subtotal	**16,398**	**21,524**	**263,309**	**301,231**	**10,570**	**15,950**	**483,195**	**509,715**

XII. Kidney and Urologic

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Urinary tract infections (cystitis, pyelonephritis)	1,021	0	1,453	2,474	1,528	0	1,902	3,430
End-stage Renal Disease (ESRD)/ transplantation	845	1,540	10,867	13,252	964	1,275	7,929	10,168
Urinary incontinence	790	0	354	1,144	1,182	0	997	2,179
Painful bladder, interstitial cystitis*	NR	NR	NR	NR	1,112	0	29,462	30,574
Other	742	3,659	34,967	39,368	2,926	2,158	5,832	10,916
Subtotal	**3,398**	**5,199**	**47,641**	**56,238**	**7,712**	**3,433**	**46,122**	**57,267**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Amounts exclude $500 million appropriated under the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act) to the NIH Buildings and Facilities program for the funding of infrastructure projects involving facility construction, repair, and/or renovation during FY 2009 ($50 million) and FY 2010 ($450 million).

*Category changed as of FY 2010.
NR = Category not reported this fiscal year.

Table 30 (continued). HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives—ARRA Funding, FY 2009 and FY 2010 (Dollars in Thousands)

XIII. Ophthalmic, Otolaryngologic, and Oral Health

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Eye diseases and disorders	3,134	2,554	108,303	113,991	1,401	3,343	92,597	97,341
Ear diseases and disorders	3,297	0	29,459	32,756	1,410	0	12,719	14,129
Dental and oral health	715	0	53,060	53,775	770	420	49,957	51,147
Other	0	0	0	0	0	0	0	0
Subtotal	**7,146**	**2,554**	**190,822**	**200,522**	**3,581**	**3,763**	**155,273**	**162,617**

XIV. Health Effects of the Environment

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Environmental estrogens	1,858	0	0	1,858	1,270	0	2,545	3,815
Health effects of toxic exposure (excluding cancer)	0	0	0	0	0	0	3,304	3,304
Toxicological research and testing program	78	0	767	845	0	0	6,218	6,218
Chemical/biological warfare agents	0	0	1,468	1,468	0	0	0	0
Other	0	0	1,357	1,357	0	0	986	986
Subtotal	**1,936**	**0**	**3,592**	**5,528**	**1,270**	**0**	**13,053**	**14,323**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Amounts exclude $500 million appropriated under the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act) to the NIH Buildings and Facilities program for the funding of infrastructure projects involving facility construction, repair, and/or renovation during FY 2009 ($50 million) and FY 2010 ($450 million).

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

XV. Cross-Cutting Categories and Special Initiatives

Disease, condition, or initiative	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
Treatment, prevention, and services	1,386	146	44,283	45,816	1,334	105	113,457	114,897
Access to health care and financing	0	0	742	742	0	0	1,536	1,536
Education and training for health care providers	0	0	3,119	3,119	500	0	8,162	8,662
Health literacy and bilingual information	262	0	1,628	1,890	163	332	2,565	3,060
Cultural influences	464	250	1,425	2,138	68	276	4,485	4,829
Disability research and services	120	410	12,708	13,238	45	371	11,008	11,424
Homelessness	114	0	0	114	105	0	0	105
Chronic fatigue syndrome	0	0	0	0	0	0	0	0
Breast feeding	260	0	0	260	0	0	0	0
Organ donation	250	0	451	701	0	0	385	385
Genetic services/counseling	0	0	913	913	500	0	2,177	2,677
Unintentional injury	0	11	3,319	3,330	0	0	982	982
Alternative and complementary therapies	6,587	0	20,860	27,447	5,421	2,646	17,330	25,397
Health statistics and data collection	116	77	14,359	14,552	930	0	31,280	32,210
Office of Women's Health	0	0	0	0	0	0	0	0
Global health	274	0	223,595	223,869	9,870	2,401	243,758	256,029
Drug metabolism (sex differences, pregnancy, etc.)*	NR	NR	NR	NR	0	0	0	0
Other cross-cutting	6,222	0	523,181	529,403	0	0	29,033	29,033
Subtotal	**16,055**	**895**	**850,583**	**867,532**	**18,937**	**6,131**	**466,158**	**491,226**

ARRA	FY 2009 Women	FY 2009 Men	FY 2009 Both	FY 2009 Total	FY 2010 Women	FY 2010 Men	FY 2010 Both	FY 2010 Total
ARRA total	**506,444**	**179,005**	**4,087,882**	**4,773,331**	**449,342**	**207,495**	**4,457,407**	**5,114,244**

Note: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas. Amounts exclude $500 million appropriated under the American Recovery and Reinvestment Act of 2009 (Pub. L. No. 111-5, ARRA, Recovery Act) to the NIH Buildings and Facilities program for the funding of infrastructure projects involving facility construction, repair, and/or renovation during FY 2009 ($50 million) and FY 2010 ($450 million).

*Category added as of FY 2010.
NR = Category not reported this fiscal year.

Table 31. NIH Research Budget Summary by Sex/Gender, FY 2009 and FY 2010—Non-ARRA (Dollars in Thousands)

Fiscal year	Women (dollars)	Women (percent)	Men (dollars)	Men (percent)	Both (dollars)	Both (percent)	Total (dollars)	Total (percent)
FY 2009	**3,725,297**	12.4	**1,478,151**	4.9	**24,914,488**	82.7	**30,117,937**	100
FY 2010	**3,691,013**	12.0	**1,604,558**	5.2	**25,537,591**	82.8	**30,833,163**	100

Table 32. NIH Research Budget Summary by Sex/Gender, FY 2007 and FY 2008 (Dollars in Thousands)

Fiscal year	Women (dollars)	Women (percent)	Men (dollars)	Men (percent)	Both (dollars)	Both (percent)	Total (dollars)	Total (percent)
FY 2007	**3,469,502**	12.4	**1,778,288**	6.3	**22,767,376**	81.3	**28,015,166**	100
FY 2008	**3,513,618**	12.4	**1,536,423**	5.4	**23,251,857**	82.2	**28,301,898**	100

VII. Committee Members and ORWH Staff, FY 2009–2010

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Report of the NIH Institutes and Centers

National Cancer Institute

Executive Summary

Advances in cancer prevention, screening, and treatment have resulted in declining rates of cancer incidence and mortality among women in recent years. These rates reflect noteworthy decreases in some of the most common cancers among women, such as breast, cervical, colorectal, and ovarian cancers, as well as in other deadly forms of the disease. Although the incidence of lung cancer—the leading cause of cancer death among women—continues to rise, it has done so at a slower pace than in years past.

Despite this undeniable progress, cancer continues to take a devastating toll on American women. The most recent figures suggest that approximately 739,940 women would be diagnosed with cancer in 2010, and 270,290 would die from the disease. Moreover, many women from minority and underserved communities continue to be disproportionately affected by various forms of cancer.

As this report highlights, the National Cancer Institute (NCI) has made notable progress by conducting and supporting research, training, health information dissemination, and other programs with respect to the prevention, treatment, and continuing care of cancer patients. Many of these programs, including clinical, basic, translational, population-based, and dissemination research, address cancers specific to or primarily affecting women, as well as cancers with high incidence or mortality rates among women.

In the past 2 years, NCI-supported clinical researchers made important strides in identifying better ways to prevent and treat cancers that commonly afflict women. Among the most promising advances was the finding that bevacizumab (Avastin), in combination with initial chemotherapy and later used alone as maintenance therapy, can significantly prolong progression-free survival in women with advanced ovarian cancer; this marks the first time that an antiangiogenic agent has demonstrated a benefit in this population. Other noteworthy findings include long-term results from the Study of Tamoxifen and Raloxifene (STAR) showing that raloxifene (Evista) substantially reduces the risk of breast cancer in women at high risk for the disease with fewer and less-severe side effects than tamoxifen. Researchers also found that women with microscopic sentinel lymph node–positive breast cancer can be treated with surgery alone—a minimally invasive procedure that reduces women's risk of immediate morbidity from surgery, speeds their recovery time, and reduces their risk of long-term complications. NCI collaborates with the Office of Research on Women's Health (ORWH), including support of Advancing Novel Science in Women's Health Research (ANSWHR), an investigator-initiated program aiming to advance studies on how sex and gender affect women's health. ORWH is supporting, with NCI, a clinical trial that studies the long-term effect of the human papillomavirus virus (HPV) vaccine in preventing cervical cancer.

NCI also is advancing both basic science and translational research projects related to women's health. Many of the most innovative of these projects involve the use of advanced mouse models that mimic human disease. In addition, NCI supports and conducts a number of population-based projects ranging from studies focused on screening and early detection to studies aimed at identifying risk factors for poor outcome. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, for example, has identified several potential early-detection biomarkers for the screening and early detection of ovarian cancer. Seminal findings from the National

Lung Screening Trial (NLST) showed 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical computed tomography compared with those who were screened with chest x rays—making this the first controlled trial to show a decreased mortality from lung cancer from any screening procedure.

NCI remains dedicated to speeding the delivery of knowledge and beneficial interventions to the community to reduce the burden of cancer experienced by women. The NCI women's health officer, in particular, is dedicated to facilitating communication across the Institute and to promoting collaboration between NCI and other NIH Institutes and Centers, Federal agencies, and nongovernmental organizations. NCI also is committed to disseminating research advances to the scientific community and the public and has numerous resources related to women's health. Additional information about women's health issues related to cancer can be found on the award-winning NCI Web site (http://www.cancer.gov).

Introduction

The American Cancer Society estimated that 739,940 women would be diagnosed with cancer and 270,290 women would die from cancer in 2010. Breast, colorectal, and lung cancers are the most commonly diagnosed cancers among women, collectively accounting for 52 percent of estimated cancer cases. Of these three cancers, breast cancer is the most common, representing 28 percent of all new cases in women. Lung cancer accounts for 14 percent of new cancer cases among women, while colorectal cancer accounts for 10 percent. These same three cancers are also the leading causes of cancer deaths in women. Although breast cancer is the most commonly diagnosed cancer among women, lung cancer surpasses breast cancer as the leading cause of cancer death in women. In 2010, breast cancer was expected to account for nearly 15 percent of all cancer deaths among women, while lung cancer was expected to account for 26 percent.

Despite these statistics, significant progress is being made in the fight against cancer. Overall cancer incidence rates among women decreased an average of 0.5 percent per year from 1998 to 2006. This decrease reflects declines in some of the most common cancers among women. Breast cancer incidence rates have decreased an average of 2 percent each year. Colorectal and ovarian cancer incidence rates have both decreased an average of 2.2 percent per year, and cervical cancer incidence rates have decreased by 3.5 percent per year. Steady declines in cancer incidence among women also have been observed in other cancer types, such as lymphoma, leukemia, and cancers of the brain, uterus, and stomach.

Overall death rates from cancer have continued to decrease in both men and women since the early 1990s. Between 1991 and 2006, cancer death rates in women decreased by 12.3 percent—which translates to about 767,000 lives saved. Declines in breast and colorectal cancer deaths accounted for 60 percent of the total decrease, with breast cancer alone accounting for nearly 40 percent of the decline. Overall, deaths from both breast and colorectal cancers declined about 28 percent. Steady decreases also were observed in many other cancers among women, including non-Hodgkin lymphoma, leukemia, and cancers of the stomach, brain, cervix, and oral cavity and pharynx. Deaths from stomach cancer decreased about 34 percent; oral cavity and pharynx cancer, 32 percent; cervical cancer, 31 percent; non-Hodgkin lymphoma, 20 percent; brain cancer, 18 percent; leukemia, 15 percent; and ovarian cancer, 10 percent.

These data indicate real progress in cancer control. Primary prevention, early detection, and treatment have resulted in the vast majority of changes. Decreases in cervical cancer deaths are primarily due to early detection; incidence rates are expected to drop dramatically in the coming years because of improvements in primary prevention, including the human papilloma virus (HPV) vaccine. The decrease in colorectal cancer incidence rates largely reflects increases in screening that can detect and remove precancerous polyps. Decreases in mortality for many cancers, particularly breast and colon cancers, also can be attributed to improved treatment strategies, such as combination therapy, targeted drugs, and genetic testing. Unfortunately, improvement has not been equal in all cancers. The incidence of lung cancer, in particular,

continues to increase, largely because of cigarette smoking habits among women, albeit at a slower rate than in years past (0.4 percent per year from 1991 to 2006 compared with 5.6 percent per year from 1975 to 1982). Moreover, with many minority and underserved women burdened by increased rates of cancer incidence and mortality, improvements have not been equal among all populations.

The National Cancer Institute (NCI) conducts and supports research, training, health information dissemination, and other programs focused on the cause, diagnosis, prevention, and treatment of cancer, as well as rehabilitation and continuing care for patients with cancer. NCI supports numerous research programs and projects that address cancers specific to or primarily affecting women, especially those cancers with high incidence or mortality among women. This research focuses on all stages of disease, from disease prevention through cancer survivorship, and ranges from molecular and subcellular basic science experiments to population-based studies and community-based interventions.

NCI also is committed to disseminating research advances to the scientific community and to the public and has developed numerous resources related to women's health. The award-winning NCI Web site, cancer.gov, is the Institute's central vehicle for dissemination of information to a diverse range of audiences; NCI also provides a Spanish-language version of its Web site, cancer.gov en español (http://www.cancer.gov/espanol). In addition, NCI produces the NCI Cancer Bulletin (http://www.cancer.gov/ncicancerbulletin/cancer-bulletin), a biweekly online newsletter that provides useful, timely information about cancer research. NCI's Cancer Information Service (CIS) provides the latest, most accurate information about cancer treatment, clinical trials, early detection, and prevention for cancer patients, their families, and the public. U.S. residents can reach English- or Spanish-speaking NCI information specialists by calling toll-free at 1–800–4–CANCER (1–800–422–6237). An instant-messaging service called LiveHelp is also available on the NCI Web site.

Although far from comprehensive, the following pages provide a representative sampling of NCI's activities and accomplishments relative to women's health in fiscal years 2009 and 2010. Disease areas included in this report are breast, cervical, ovarian, endometrial, and lung cancer, as well as AIDS-associated malignancies.

NCI Women's Health Officer

NCI's women's health officer facilitates communication across the Institute and promotes collaboration between NCI and other NIH Institutes and Centers, Federal agencies, and nongovernmental organizations. The women's health officer develops and disseminates reports and information on NCI's research and research progress on cancers in women and coordinates NCI's responses to agency requests for information.

Accomplishments

Breast Cancer

Treatment

Less Extensive Surgery in Microscopic, Node-Positive Patients Improves Quality of Life, Saves Costs. A phase III clinical trial comparing quality of life among women with microscopic sentinel lymph node–positive breast cancer who had either sentinel lymph node biopsy or axillary lymph node dissection found that axillary lymph node dissection did not add benefit over sentinel node biopsy. Findings indicated that surgery alone is an appropriate, safe, and effective therapy for breast cancer patients with microscopically positive lymph nodes. This finding will enable such women to undergo the less extensive surgery, thereby reducing their immediate morbidity from surgery, speeding their recovery time, improving their cosmetic outcome, and reducing their long-term risk of chronic lymphedema and its associated complications, while also saving health care expenditures without compromising efforts to control their cancer.

New Combination Therapy for Breast Cancer in Postmenopausal Women. Studies have shown that postmenopausal women with estrogen receptor–positive (ER-positive) breast cancer are at increased risk of recurrence and poor prognosis if their tumors also express high levels of low-molecular-weight (LMW) cyclin E. These tumors tend to become

refractory to letrozole (Femara), which normally slows cancer cell growth. However, when these tumors are treated with the cyclin-dependent kinase (CDK) inhibitor roscovitine, now under clinical development, they may become resensitized to letrozole treatment. This new combination therapy may have considerable potential for treatment of ER-positive/high-LMW cyclin-E breast cancer tumors in postmenopausal women.

Promising Drug Targets Both Estrogen Receptor–Positive and–Negative Breast Tumors. Transmembrane proteins, called mucins, form a mucous barrier that protects epithelial cells from adverse conditions. These mucins play an important role in transmitting growth and survival signals to the cell interior, and their abnormal expression is associated with a number of human cancers. One such mucin, MUC1, is overexpressed in about 90 percent of human breast cancers and promotes tumor progression. Preclinical evidence indicates that MUC1 inhibitors are active against human tumor cells that depend on MUC1 for survival. In studies performed on well-established tumors grown from human breast cancer cells in nude mice, NCI-funded investigators have identified a novel class of MUC1 inhibitors that induce complete and prolonged regression of both ER-positive and -negative mammary tumors. Notably, there was no evidence of weight loss or other toxicities associated with the treatments. Formal toxicology studies in rats and dogs for the investigational new drug application also demonstrated a highly favorable toxicity profile that was limited primarily to anaphylactoid reactions. These studies provide evidence that MUC1 is a promising target for breast cancer therapy.

Genetic Variant Associated With Resistance to Chemotherapy Drug in Women With Breast Cancer. NCI researchers have found links between individuals' genetics and their response to chemotherapy. The findings show that genetic variation in the *SOD2* gene may affect how a person responds to cyclophosphamide, a chemotherapy drug used in the treatment of breast cancer as well as other cancers. Women with a distinct variant form of *SOD2* who received cyclophosphamide-containing chemotherapy had the poorest survival. More work is needed to examine the precise mechanism by which genotype influences the response of cancer cells to cyclophosphamide.

Drug May Help Slow Development of Brain Metastases Originating From Breast Cancer. NCI investigators have examined the role of the drug vorinostat, a histone deacetylase inhibitor, as a treatment for brain metastases that originate from breast cancer. Vorinostat can cross the blood-brain barrier and has been shown to reduce the development of large brain metastases in mice by 62 percent compared with mice that did not receive the drug. Researchers also demonstrated that vorinostat coupled with radiation therapy is able to slow the growth of metastatic breast cancer cells in vivo and improve the survival of mice with brain metastases. These results are a positive step toward improved treatment for a group of patients who currently have few options.

Prevention

Raloxifene Reduces Breast Cancer Risk With Fewer Side Effects. Long-term study results of the NCI-supported Study of Tamoxifen and Raloxifene (STAR) show that raloxifene (Evista) and tamoxifen both substantially reduce the risk of breast cancer in women at high risk for the disease. Raloxifene does so with fewer and less-severe side effects than tamoxifen. These findings were a followup to STAR's initial results, released in 2006, which led to U.S. Food and Drug Administration (FDA) approval of raloxifene to reduce the risk of breast cancer in high-risk postmenopausal women. With nearly 3 more years of followup data on the more than 19,000 women who participated in the study, the new data showed that long-term raloxifene use was approximately 76 percent as effective as tamoxifen in preventing invasive disease and 78 percent as effective as tamoxifen in preventing noninvasive disease. Raloxifene also posed a lower risk of serious side effects, such as uterine hyperplasia and thromboembolic events. The average annual incidence rate of uterine hyperplasia was five times higher in the tamoxifen group than in the raloxifene group, whereas the incidence of thromboembolic events was significantly elevated in the tamoxifen group compared with the raloxifene group.

Screening and Patient Outcomes

Breast Cancer Surveillance Consortium. The Breast Cancer Surveillance Consortium (BCSC) is a resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. BCSC comprises multidisciplinary investigators, including radiologists, primary care clinicians, pathologists, epidemiologists, health services researchers, and statisticians. To date, BCSC has served as a resource for more than 65 investigator-initiated studies funded by NCI, other Federal and State agencies, and foundations. Almost 400 publications in journals across a range of disciplines have resulted from this effort. Some of the recent findings are highlighted below:

Postmenopausal Hormone Therapy Associated With Increased Risk of Atypical Ductal Hyperplasia. Researchers culled more than 2.4 million screening mammograms between 1996 and 2005 to assess risk factors and rates of atypical ductal hyperplasia (ADH) and tumor characteristics of breast cancer patients previously screened with mammography. They examined associations between age, family history of breast cancer, postmenopausal hormone therapy, and tumor pathology (ADH or cancer with or without ADH in the same breast). Data showed that hormone therapy use decreased significantly from 35 percent to 11 percent during the study period. Rates of ADH also decreased from a peak of 5.5/10,000 mammograms in 1999 to 2.4/10,000 in 2005, and rates of cancer with ADH decreased from a peak of 4.3/10,000 mammograms in 2003 to 3.3/10,000 in 2005. Researchers found that ADH and breast cancer were significantly associated with use of postmenopausal hormone therapy, noting that the ADH decrease may be partially explained by the significant reduction in use of postmenopausal hormone therapy. Cancer associated with ADH was of lower grade and stage and more likely to be ER-positive than cancer with no ADH.

Weight Linked to Breast Cancer Risk, Outcome in Postmenopausal Breast Cancer Patients. Using BCSC data, researchers found that women who are overweight or obese after menopause face an increased risk of breast cancer. Furthermore, these women are at increased risk of having large, invasive breast cancer tumors and advanced-stage disease at diagnosis. Researchers noted that increased risk is not explained by the frequency or accuracy of screening mammography before breast cancer is diagnosed. These findings suggest that postmenopausal women who are overweight or obese should be encouraged to lose weight and undergo routine screening mammography.

Prophylactic Surgery Reduces Cancer Risk in Women With BRCA Mutations. Researchers at 22 medical centers in Europe and North America tracked nearly 2,500 women with disease-associated *BRCA1* or *BRCA2* mutations. Almost half of the women had prophylactic surgery to remove their breasts (mastectomy) or ovaries (salpingo-oophorectomy). During 3 years of followup, none of the women who underwent mastectomy developed breast cancer, whereas 7 percent of the women who did not have the surgery were diagnosed with breast cancer. Only 1 percent of the women who underwent salpingo-oophorectomy developed ovarian cancer during 6 years of followup compared with 6 percent of women who did not have the surgery. The risk reduction occurred regardless of whether the mutation was located in the *BRCA1* or *BRCA2* gene or whether a woman had cancer previously. These findings suggest that prophylactic surgery may be an effective way to reduce the risk of breast and ovarian cancers among women with inherited mutations in the *BRCA1* or *BRCA2* genes. Researchers noted the challenges inherent in the design and implementation of a feasible and ethical randomized clinical trial assessing the safety and efficacy of prophylactic surgery in women with *BRCA1* and *BRCA2* mutations. Thus, by analyzing women separately by *BRCA1* and *BRCA2* mutation status, previous breast cancer, treatment medical center, and years of surgical interventions, the investigators were able to examine risks in these groups and minimize potential bias from such selection factors.

Increased Breast Cancer Risk From Hormone Therapy More Pronounced in Women With Dense Breasts. Recent studies have found that postmenopausal hormone therapy and high breast density are both

associated with increased risk of breast cancer. A report from BCSC suggests that an interaction might exist between these two risk factors. The BCSC study looked at the effects of breast density, age, menopausal status, and hormone therapy use on women's breast cancer risk. The study found that women with low breast density were at low risk of breast cancer regardless of menopausal status or whether they were using hormone therapy. Consistent with past findings, women with dense breasts were at higher risk of breast cancer than those with low breast density. In addition, use of hormone therapy, particularly estrogen plus progesterone, further increased breast cancer risk among postmenopausal women with high breast density. Although increased risk of breast cancer associated with hormone therapy should be taken into account by all women considering hormone therapy, this study indicates that postmenopausal women with high breast density should be particularly cautious.

Weight Lifting Reduces Lymphedema Symptoms After Breast Cancer. Many breast cancer survivors develop lymphedema, an uncomfortable and sometimes painful swelling in the upper arm or hand that can be debilitating and disfiguring and for which there is no cure. Contradicting past recommendations to avoid heavy lifting and repetitive movement after breast surgery, a trial involving 141 breast cancer survivors with stable lymphedema of the arm showed that slowly progressive weight lifting does not increase arm swelling and appears to be safe. Study participants were randomized into a weight-lifting group and a control group that did not lift weights. The proportion of women who experienced an increase of five percent or more in their limb swelling was similar in both groups—11 percent of the weight-lifting group and 12 percent in the control group. The women in the weight-lifting group also reported greater improvements in the severity of lymphedema symptoms and upper- and lower-body strength compared with women in the control group. In addition, a certified lymphedema specialist found that women in the weight-lifting group had a lower incidence of lymphedema exacerbations than women in the control group. There were no serious adverse events related to the intervention. This study advances understanding of lymphedema and adds a potentially important management strategy for this troubling cancer treatment side effect.

Survivorship

Characterizing Racial Disparities in Breast Cancer Mortality. Breast cancer mortality rates among Black women have been higher than those for White women since the late 1980s, and the gap has continued to widen. To further explore the underlying causes of this racial disparity, Black-to-White rate ratios for mortality, incidence, hazard of breast cancer death, and incidence-based mortality were investigated using data from NCI's Surveillance, Epidemiology, and End Results (SEER) program among women diagnosed with breast cancer between 1990 and 2003 and followed through 2004. The Black-to-White ratio for mortality increased from 1.20 in 1990 to 1.32 in 2004. Absolute hazard rates of breast cancer death declined substantially for ER-positive tumors and modestly for ER-negative tumors over this time period but were persistently higher for Blacks than for Whites. Identifying and addressing the reasons for the excess breast cancer deaths among Black women, especially during the first few years following diagnosis, may help reduce the existing racial disparity in breast cancer mortality rates.

Undertreatment in Older Women With Breast Cancer Is a Risk Factor for Recurrence, Death. Women are more likely to develop breast cancer and are also more likely to have their disease undertreated as they grow older. This undertreatment can have dire effects. A study of 1,859 women aged 65 and older with early-stage breast cancer found that undertreatment is a risk factor for recurrence and for dying of breast cancer. Although conservative treatment may be more appropriate in older women whose tumors have excellent prognostic characteristics and in those with comorbidities, standard treatment is warranted for the majority of older women. Better strategies involving collaboration between oncologists and primary care physicians are needed to identify women most likely to benefit from standard treatment and from systematic surveillance for recurrence.

Older Women With Early-Stage Breast Cancer Do Not Benefit From Adjuvant Radiation. Findings from a phase III randomized trial indicate that some older women can forgo radiation after surgery for breast cancer. Researchers found that women 70 years of age or older with early-stage breast cancer did not benefit from the addition of radiation therapy to breast-conserving surgery and tamoxifen. This clinical trial, which was made possible only through Government funding, will spare many women the side effects of unneeded treatment, without compromising their survival, and will save health care dollars.

Risk Factors

Alcohol Consumption Increases Breast Cancer Risk. Investigators studied more than 180,000 postmenopausal women aged 50 to 71 years in the National Institutes of Health/American Association of Retired Persons (NIH-AARP) Diet and Health Study to investigate the association between alcohol and breast cancer by different tumor characteristics. They assessed alcohol use, diet, and potential risk factors for cancer with a mailed questionnaire at baseline. State cancer registries identified links between breast cancer cases and estrogen and progesterone receptor status. During an average of 7 years of followup, the study identified more than 5,000 breast cancer cases. Researchers found that alcohol consumption among postmenopausal women elevated breast cancer risk regardless of the type of alcoholic beverage consumed. The significantly increased risk of breast cancer was found even among women who consumed a moderate amount of alcohol (> 10 g/day), and the risk increased linearly as alcohol consumption increased. Alcohol consumption was positively related to ductal and lobular tumors and to hormone receptor–positive tumors. These findings suggest that alcohol is a modifiable risk factor for postmenopausal breast cancer.

Genetic Variations Linked to Risk of Breast Cancer. NCI'S Cancer Genetic Markers of Susceptibility (CGEMS) project has identified new genetic variations in two regions of DNA—located on chromosomes 1 and 14—that may be associated with the risk of sporadic breast cancer. CGEMS researchers also confirmed previous reports that six other genomic regions—located on chromosomes 2, 5, 8, 10, and 16—are associated with breast cancer risk. Further study of these regions may help to identify possible mechanisms that may contribute to the development of breast cancer.

Researchers Identify Genetic Polymorphism Associated With Survival in ER-Negative Breast Cancer. Researchers in the Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH) program evaluated possible associations between overall survival after a breast cancer diagnosis and more than 10,000 germline single-nucleotide polymorphisms (SNPs) from patients with invasive breast cancer. Using patient genotype and overall survival information from 15 international case-control studies, researchers found an SNP, rs4778137 within the *OCA2* gene, to be associated with overall survival among patients with ER-negative tumors. Both the validation dataset and the combined dataset confirmed this association.

Study Replicates Breast Cancer Susceptibility Genes in Black Women. Aggressive breast cancer disproportionately affects African Americans and Africans compared with all other racial/ethnic groups. The reasons for this disparity remain unknown, and minimal data on the genetic epidemiology of breast cancer for women of African ancestry hinder the development of innovative prevention strategies to address the disparity. Because common genetic variants may play a different role in the development and progression of breast cancer in women of African ancestry than in women of European ancestry, a study of 5 breast cancer susceptibility loci, including 11 genes previously identified in genomewide association studies, will be analyzed in women of African descent. Findings from this study will help to inform future prevention strategies.

Breast Cancer Risk Related to Childhood Cancer Treatments. A long-term followup study of childhood cancer survivors evaluated the risk of developing breast cancer among survivors in relation to the radiation dose and chemotherapy they had received. Researchers recruited patients with breast cancer who were childhood cancer survivors with and without subsequent breast cancer. Participants were

matched by their age at diagnosis and the time elapsed since their initial cancers. Researchers found that breast cancer risk increased linearly with radiation dose that included the breast; the risk increased 11-fold among patients who had been given radiation dose of approximately 40 Gy (unit of absorbed radiation dose of ionizing radiation) compared with those who did not receive radiation. Researchers also noted that the risk of breast cancer associated with breast irradiation was greatly reduced among women who had in addition received 5 Gy or more to the ovaries.

Biology

BMI1 and H-RAS Cooperate To Drive Breast Cancer Metastasis. BMI1 is a transcription repressor that inhibits gene expression through modifying chromatin structure. Under normal circumstances, BMI1 participates in the maintenance of stem cells and their self-renewal by modulating the expression of tumor suppressors that reduce cell growth. NCI scientists studied the roles of BMI1 in cancer progression and metastasis using a combination of human gene expression studies and mouse models. The results show that BMI1 cooperates with H-RAS, another oncogene, to promote an aggressive and metastatic form of breast cancer. Overexpression of either BMI1 or H-RAS caused cultured human mammary epithelial cells to increase growth rate, decrease apoptosis in response to DNA damage, and increase the ability to invade neighboring tissue. When the cells expressed both proteins, the invasive and metastatic properties were further enhanced, including the development of brain metastases. This cooperation suggests that these molecules may be important targets for treatment of this disease. The development of this mouse model of breast cancer metastasis to the brain may lead to a better understanding of processes that contribute to breast cancer mortality and facilitate the development of interventions to improve outcomes in patients.

***Pdcd4* Implicated in Hypoxia-Induced Metastasis.** NCI researchers examined the role of *Pdcd4* and lysyl oxidase (LOX) in breast cancer metastasis, the primary cause of death among breast cancer patients. *Pdcd4* is a tumor suppressor gene that inhibits breast cancer cell migration and invasion in vitro. Loss of *Pdcd4* in human nonmetastatic breast cancer cells increased the expression of LOX mRNA. LOX is a hypoxia-inducible amine oxidase, the activity of which enhances breast cancer cell invasion in vitro and in vivo. Researchers identified LOX as a target of *Pdcd4* and found that the loss of *Pdcd4* augments the hypoxia induction of LOX. These findings raise the possibility that increasing the expression of *Pdcd4* might prevent cancer metastasis in response to hypoxia.

Stamp Sales Fund Breast Cancer Research

The breast cancer research stamp is a fundraising stamp—the first one issued by the United States Postal Service. The price of the stamp covers the standard first-class letter rate plus an amount to fund breast cancer research. Surplus revenue from the sale of these stamps is allocated to NIH and the Department of Defense; to date, the stamp has raised more than $71 million for breast cancer research. One project studied the potential for the protein MUC1 to assist in detecting early breast cancer. Findings from this project suggest that MUC1's expression peaks in early-stage breast cancers but levels off in more invasive stages, indicating that MUC1 is a very early marker of disease. In another project, researchers began to develop and apply functional imaging to identify early breast cancer lesions that have properties associated with progression to invasive tumors. They identified COX2 as a likely biomarker of invasive tumor potential in patients with ductal carcinoma in situ (DCIS), the most common form of noninvasive breast cancer. They are now generating a novel "turn-on" chemosensor that is able to detect COX2 via a significant increase in fluorescence. The development of an effective COX2 imaging agent would enable the observation of disease progression and the identification of early lesions that are likely to progress to invasive malignancies. As described in the Initiatives section of this report, breast cancer research stamp funds also are being used for other initiatives, including a trial that is evaluating the genetic signature linked to the risk of breast cancer recurrence.

Cervical Cancer

Therapy

Researchers Identify Potential New Biomarker for Cervical Cancer. Cancer cells undergo significant changes in carbohydrate expression, and these alterations can be useful as biomarkers and therapeutic targets. NCI researchers have shown that the altered localization and increased expression of the carbohydrate molecule GalNAcα1-3Gal is linked to patient survival in a collection of cervical cancer tumors. This finding suggests that GalNAcα1-3Gal is a potential diagnostic marker and, with further studies, may serve as a target for therapy in cervical cancer.

Prevention

HPV Vaccine Trial Assessing Duration of Protection, Evaluating Long-Term Effects. NCI researchers are conducting a randomized, controlled phase III clinical trial of a bivalent vaccine manufactured by GlaxoSmithKline (GSK; Cervarix) to prevent HPV-16 and -18 infections and their associated cervical lesions. The vaccine, based on virus-like particle technology developed by NCI intramural investigators, is effective for preventing cervical lesions and cervical cancer in women who have not previously been infected with HPV. The trial and vaccine development have received long-term funding support from the Office of Research on Women's Health (ORWH). Recruitment and 4 years of followup have been completed in the trial, which is being conducted in an area of Costa Rica with high rates of cervical cancer. Extension of followup for up to 10 years is now underway to assess the duration of protection and long-term effects of vaccination. The study has found no therapeutic effect for the vaccine in women previously infected with HPV. Evaluation of pooled data from the NCI-supported trials and independent clinical trials conducted by GSK indicates no evidence that the vaccine has an effect on pregnancies and their outcomes, but vaccination is not recommended for pregnant women or those who intend to become pregnant within 3 months of vaccination. In 2010, data from the trial also demonstrated that antibodies generated following natural infection provide partial protection against reinfection with the same HPV type. The trial also is evaluating potential prophylactic protection against other HPV types, underlying biological/immunologic mechanisms of protection, and other important public health and natural history issues.

Population-Based Cohort Studies Focus on HPV. NCI is supporting several large population-based cohort studies focusing on HPV prevention and screening, as well as gaining a better understanding of how and why the viral infection progresses to cancer. These studies, conducted in Costa Rica and Nigeria, have yielded several important findings, including the need to incorporate the full spectrum of data available on a woman's histology, cytology, and HPV status to classify cervical disease accurately; the fact that age is not a factor for predicting absolute risk of persistence of disease with new HPV infections; and the fact that women positive for HPV-16 are diagnosed much earlier with CIN3+ (high grade cervical intraepithelial neoplasia or worse) than women positive for other carcinogenic types of HPV.

HIV Association

Study Investigates Occurrence, Determinants of HIV-Associated Malignancies. The Women's Interagency HIV Study (WIHS), established in 1993, is jointly sponsored by NCI, the National Institute of Allergy and Infectious Diseases (NIAID), and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to investigate the impact of HIV infection on women. Study participants include more than 3,500 HIV-positive and HIV-negative women, with more than 80 percent representing minority populations. This cohort provides researchers an excellent opportunity to monitor the occurrence, distribution, and determinants of HIV-associated malignancies. It also allows investigation of the interplay of viruses, coinfections, and immune dysregulation in cancer pathogenesis. WIHS utilizes Pap tests, colposcopies, and biopsies to prevent and study cervical cancer in the susceptible HIV-positive population. Results have revealed that Pap test abnormalities are more common among HIV-positive than HIV-negative women; furthermore, HIV-positive women treated for cervical

intraepithelial neoplasia (CIN), sometimes a precursor to cervical cancer if left untreated, are more likely to experience a recurrence of CIN than their HIV-negative counterparts.

Ovarian Cancer

Therapy

Bevacizumab Extends Survival in Patients With Newly Diagnosed, Advanced Ovarian Cancer. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor, has demonstrated activity in women with newly diagnosed, advanced ovarian, primary peritoneal, or fallopian tube cancer. A phase III clinical trial showed that women who received bevacizumab alone for up to 10 months after receiving standard chemotherapy plus bevacizumab survived 3.8 months longer without their cancer progressing than did women who did not receive bevacizumab.

Biology

Cancer Genome Atlas Releases First Comprehensive Ovarian Cancer Data Set. The Cancer Genome Atlas (TCGA) program—started in 2005 and jointly sponsored by NCI and the National Human Genome Research Institute—was established to provide comprehensive genomic characterization of human tumors. The program began as a pilot to evaluate the genomes of glioblastoma multiforme, lung squamous carcinoma, and serous cystadenocarcinoma of the ovary. To date, TCGA has completed characterization of 500 ovarian carcinoma cases and has released all data into the public domain. Specifically, data are available for single-nucleotide polymorphisms, copy number variation, gene and miRNA expression profiles, epigenomic landscape, and whole-exome or -genome sequencing on these samples. Analyses of the data confirm that mutations in a single gene, *TP53*, were present in more than 96 percent of the cases studied. *TP53* encodes a tumor suppressor protein that normally prevents cancer formation. Mutations in the gene disrupt this protein's function, which contributes to uncontrolled cell growth. TCGA researchers also identified patterns in genes associated with differences in patient survival. Patients whose tumors had a gene-expression signature associated with poor survival lived for a 23 percent shorter period of time than patients whose tumors had the genes associated with better survival. There were also many genomic areas of increased DNA copy number and decreased copy number identified, and some areas were found to be altered in the same direction in a high proportion of cancers. Together, these data represent the first comprehensive dataset available to the wider community from this program. In addition, those areas with increased DNA copy number area are being evaluated for containing genes that may drive the oncogenic phenotype in ovarian cancer and could therefore represent potential therapeutic targets.

Endometrial Cancer

Treatment

Biomarkers Help Determine Appropriate Therapy for Endometrial Cancer. Incidence and mortality rates of endometrial cancer continue to decline, and early-stage cancers are effectively treated surgically, frequently without adjuvant therapy. However, high-risk and advanced diseases are only moderately responsive to chemotherapy, and these patients have poor prognoses. Studies have shown that mutations of *PTEN* and β-catenin are often predictive of good prognosis, whereas p53 abnormalities, DNA aneuploidy, or elevated preoperative serum CA125 are usually associated with aggressive biological behavior. Stratification of patients into categories with different risks of recurrence using these molecular biomarkers will help determine which patients would benefit from either adjuvant therapy or more aggressive primary treatment and will help stimulate the development of more biology-driven clinical treatments.

Risk

Reducing the Risk of Endometrial Cancer. Endometrial cancer is the most common gynecologic malignancy; for the 80 percent of women diagnosed with stage I or stage II disease, 5-year overall survival rates approach 85 percent. Many studies have been conducted to understand ways to reduce women's risk of developing this disease. Physical activity seems to protect against endometrial cancer, with a risk reduction of about 20 to 30 percent for

those with the highest levels of physical activity compared with those at the lowest levels; even moderate physical activity, such as housework and gardening, may reduce risk. Other studies have shown that the risk of endometrial cancer is reduced by approximately 50 percent by the use of combined oral contraceptives; the protective effect can persist for 10 to 20 years after cessation of use. Endometrial cancer is a rare but serious side effect for breast cancer patients who take tamoxifen to reduce their risk of invasive breast cancer recurrence. In postmenopausal women, the drug raloxifene is as effective as tamoxifen in reducing the risk of recurrent breast cancer but with fewer serious side effects. (See Raloxifene Reduces Breast Cancer Risk With Fewer Side Effects in this report.)

Lung Cancer

Screening

Lung Cancer Screening Trial Results Show Mortality Benefit With Low-Dose Computed Tomography. The National Lung Screening Trial (NLST) compared two ways of detecting lung cancer: low-dose helical computed tomography (CT, also known as spiral CT) and standard chest x ray. Both chest x rays and low-dose helical CT scans have been used to find lung cancer early, but the effects of these screening techniques on lung cancer mortality rates had not been determined. NLST enrolled more than 50,000 current or former heavy smokers from more than 30 sites across the United States. NLST reported initial trial results in November 2010, showing 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical CT compared with those screened with chest x rays. An ancillary finding, which was not the main endpoint of the trial's design, showed that all-cause mortality (deaths due to any factor, including lung cancer) was 7 percent lower in those screened with low-dose helical CT. A substantial portion of this lower rate was attributable to reduced lung cancer. The possible disadvantages of helical CT include the cumulative effects of radiation and surgical and medical complications in patients who prove not to have lung cancer. These risks must be weighed against the advantage of a significant reduction in lung cancer mortality. This is the first controlled trial to show a decreased mortality from lung cancer from any screening procedure. Despite this success, it still must be emphasized that not smoking is the most effective way to reduce the risk of dying from lung cancer.

Tobacco-Related Health Disparities in Women

Unintended Consequences of Tobacco Policies on Low Socioeconomic Status Women and Girls. NCI partnered with the American Legacy Foundation to form the Tobacco Research Network on Disparities (TReND). The goal of TReND is to understand and address tobacco-related health disparities by stimulating scientific inquiry, promoting scientific collaborations, and evaluating scientific evidence. In 2009, TReND published a supplement of the *American Journal of Preventive Medicine* that highlights the helpful and harmful effects of tobacco policies on low socioeconomic status (SES) women. The papers emphasize the need for strong and effective policies to curb the growing global tobacco epidemic. The papers also demonstrate the critical need to examine all aspects of policy implementation, the extent of policy enforcement, and the potential for stigmatization among women who seek to comply with policies. TReND challenges researchers and policymakers to consider the full ramifications of tobacco control policies among low SES women who have high rates of smoking and low rates of cessation.

Large Population Studies

Large-Scale Screening Study Provides Data and Biospecimens for Research. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which began in 1993 and enrolled 155,000 participants (half of whom are women), is preparing to release data on the effectiveness of screening for the four cancers. A report, currently under development, assesses the impact of screening with CA125 and concurrent transvaginal sonography on ovarian cancer mortality. The robust dataset used for PLCO is now available to the entire research community through the Etiologic and Early Markers Program (EEMS), which includes breast cancer data from the Cancer

Genetic Markers of Susceptibility (CGEMS) project as well as data from various genome-wide association studies, including those focused on ovarian and endometrial cancers. A research team studying PLCO biospecimens found that the top-performing early detection markers for ovarian cancer were CA125, HE4, CA72.4, and CA15.3. The research team is now evaluating panels of these markers to advance the goal of ovarian cancer screening and early detection. Another team of researchers is examining blood and genomic DNA samples collected from PLCO participants who later developed ovarian cancer to identify potential biomarkers for detection of the disease.

Initiatives

Several new initiatives are now underway. These initiatives, spanning the research continuum and exploring some of today's most exciting research areas, will build upon the achievements already made in cancers affecting women.

Breast and Gynecologic Cancers

Treatment

NCI Facilitates Design and Prioritization of Trials for Breast, Gynecologic Cancers. As a result of the Clinical Trials Working Group and the Translational Research Working Group, NCI is coordinating implementation of recommendations to address the design and prioritization of phase III and select phase II trials for breast and gynecologic cancers. Scientific steering committees for each disease area have been formed to leverage existing intergroup, cooperative group, Specialized Programs of Research Excellence (SPORE), and cancer center structures. This collaboration ensures a nationally coordinated effort to implement optimally designed, high-priority clinical trials.

Screening

New Early Detection Research Network Grantees Focus on Breast, Ovarian, Uterine Cancers. The Early Detection Research Network (EDRN) awarded 32 new 5-year grants, 6 of which are focused on breast and ovarian cancers, to researchers across the country for the discovery and validation of biological markers that signal the earliest stages of cancer. Breast, ovarian, and uterine cancers are under study in three biomarker developmental laboratories responsible for development and characterization of new biomarkers or refinement of existing biomarkers. These three cancers are also the focus of three clinical validation centers that conduct clinical research on the validation of biomarkers in early cancer detection and risk assessment and serve as resource centers by participating in collaborative biomarker validation studies.

Biology

Mouse Models Used To Study Women's Cancers. Mouse models developed through the NCI Mouse Models of Human Cancers Consortium (NCI-MMHCC) are used to study cancers that disproportionately affect women. Several research teams use mouse models to make progress against breast cancer, including a group that relies on mouse models to discover serum biomarkers that show promise in detecting early disease and represent targets for vaccine development. Another research group recently developed a series of mouse models that effectively mimic luminal A type breast cancer, which accounts for 70 percent of human breast cancer. This mouse model has many hallmarks of this breast cancer subtype, including tumors that start as ER-positive and progress to ER-negative, as is often observed in the clinic. Mouse models also are being used by a research group studying the role of the LKB1 pathway in the etiology and progression of uterine cancer and by a group using mouse models of HPV-related cervical cancer to develop new therapies for the disease.

Breast Cancer

Screening

Using Technology To Connect Rarely and Never-Screened Women to Mammography. Although much progress has been made in increasing breast cancer screening rates, a significant proportion of women aged 40 and older have never had a mammogram or have not had one in the past 2 years. Behavioral interventions to increase mammography use

have not been particularly effective among these women. The Centers for Disease Control and Prevention's (CDC's) Breast and Cervical Cancer Program (BCCP) provides free and low-cost screening but reaches only a small proportion of women who need its services. Finding effective interventions that connect rarely and never-screened women to BCCP could help eliminate breast cancer disparities. A new study is examining the feasibility of using telephone-equipped kiosks in laundromats and libraries to identify African-American women who have never or rarely been screened for breast cancer and connect them with local BCCP mammography services.

Molecular Loci Help Classify Aggressive Breast Cancer Tumors. Breast SPOREs conduct translational research to develop and test novel agents and technologies for prevention, early detection, diagnosis, and treatment of breast cancer. SPORE investigators have identified gains and losses of specific genomic loci that allow them to predict outcomes of patients with highly aggressive ER-negative tumors.

Prevention

Health of Women Study Takes New Approach to Cohort Studies. NCI entered into a partnership with the Dr. Susan Love Research Foundation and the City of Hope to provide the informatics, infrastructure, and tools needed to support the Health of Women (HOW) Study. Initially launched as a beta test in December 2009, HOW is the first large, Internet-based longitudinal cohort study designed to investigate the causes of breast cancer and identify ways to prevent the disease. Within the first 4 weeks of active recruitment, more than 25,000 women enrolled and completed the first secure online module of 175 questions concerning their health and family history. New online modules will be released every 2 to 3 months over the life of the study, which is anticipated to be 20 years. To facilitate the creation of new modules, forms, and questions, NCI is developing caCURE, an application for collecting, processing, and storing patient-reported health data, through the cancer Biomedical Informatics Grid (caBIG) program. CaCURE will enable researchers to create or modify module content rapidly and easily in light of new research findings, thereby accelerating the research process.

Risk Factors

Study Evaluates Breast Density as Breast Cancer Risk Factor. NCI researchers and extramural colleagues have undertaken a study to understand the determinants of breast density and the mechanisms by which it elevates breast cancer risk. The study recruited women who underwent breast biopsies, from whom risk factor data, biological specimens, and volumetric density measures were collected. Researchers are now comparing novel volumetric density measures with standard area assessments, as well as exploring whether regional variation in density is related to risk factors and pathologic diagnosis. The study is partially funded through a competitive award generated through proceeds from the sale of the U.S. breast cancer research stamp.

Black Women's Health Study Assesses Factors Contributing to Cancer Disparities. Black women in the United States develop more aggressive breast cancer tumor types and have disproportionately high breast cancer mortality rates, colorectal cancer incidence and mortality rates, and overall cancer death rates compared with White women. The Black Women's Health Study is assessing a range of novel hypotheses concerning behavioral, psychosocial, and socioeconomic factors that may contribute to these differences, from obesity and physical activity to genetic factors. A better understanding of potentially modifiable causes of the increased risks among Black women in the United States could lead to more effective preventive measures and reductions in health disparities.

Study Evaluates the Role of Socioeconomic Status on Early Puberty. Young age at onset of breast development and menarche, both early markers of breast cancer risk, has been increasingly observed over the past few decades, particularly among African-American and Hispanic girls, but remains poorly understood. These developments have spurred the creation of the Breast Cancer and the Environment Research Centers (BCERCs) to evaluate social and economic factors that may reflect upstream determinants of early puberty and account for racial/ethnic differences. BCERC

will recruit three prospective, multiethnic cohorts of girls aged 6 to 8 years old who will be followed for 4 years to determine whether previously unexplored socioeconomic factors—including household income, parental educational attainment, home ownership, residential crowding, and wealth—can explain some of the variation in the timing of pubertal outcomes across and within racial/ethnic groups.

Coordinating Center Enhances Research Into Environmental Health Aspects of Breast Cancer. BCERCs study the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer. The Breast Cancer and the Environment Research Program (BCERP) Coordinating Center acts as a central repository and clearinghouse for data produced by the BCERCs. It enhances collaborations among investigators by managing the steering committee and its components, managing an advisory Breast Cancer and the Environment Working Group, providing reports on progress and budget to NIH staff, and organizing national meetings of the BCERP. The operations of the coordinating center are expected to assist collaborations among multidisciplinary teams of researchers, breast cancer research advocates, and community partners drawn from networks or other collaborative groups to conduct high-quality, transdisciplinary research into the environmental health aspects of breast cancer.

Linking Environmental Influences to Breast Cancer Risk. NCI and the National Institute of Environmental Health Sciences jointly released an initiative to encourage basic research on gene-environment interactions that have the potential to modify a woman's lifetime risk of developing breast cancer. Eight grants were awarded in 2010 for research focused on understanding how early environmental exposures during specific windows of susceptibility influence breast development, timing of puberty, and risk of breast cancer later in life.

Biology

Research Into ER-Negative Breast Cancer. NCI awarded three grants through the Biology of Estrogen Receptor–Negative Breast Cancer in Various Racial and Ethnic Groups Program to promote systematic study of the biology of ER-negative human breast cancers. These grants, awarded for a 5-year period beginning in 2010 at a total cost of $2 million per year, will support research focused on defining characteristics of ER-negative human breast cancer, delineating signaling cascades involved in these tumors, and identifying differences in ER-negative breast cancers among various ethnic groups. The resulting information may provide unique opportunities to generate agents that target ER-negative breast cancers.

Stamp Sales Fund Breast Cancer Research

TAILORx Trial Evaluates Genetic Signature Linked to Risk of Breast Cancer Recurrence. The Trial Assigning Individualized Options for Treatment (TAILORx) is evaluating whether a specific genetic signature shown to be associated with risk of breast cancer recurrence in women with node-negative, hormone receptor–positive tumors can be used to direct patients to the most appropriate and effective treatment. The signature being tested is the 21-gene Oncotype DX panel developed by Genomic Health, Inc., in collaboration with the NCI-supported National Surgical Adjuvant Breast and Bowel Project. The trial completed accrual in 2010 after enrolling more than 10,000 participants. Funds from the U.S. breast cancer research stamp have played a critical role in making this groundbreaking trial possible.

Cervical Cancer

Prevention

Pan-HPV Vaccines Under Development. Nearly 80 percent of women diagnosed with cervical cancer live in developing countries, a disparity attributed to lack of effective screening programs to detect and treat cervical dysplasia and early cancer in these regions. The current FDA-approved preventive HPV vaccines are highly effective, but they are expensive and do not target HPV types that account for 20 to 30 percent of cervical cancer. To overcome these issues, researchers are developing candidate HPV vaccines that are less expensive to manufacture and may prevent infection and disease induced by a broader spectrum of HPV types. The candidate vaccines are based on the

discovery that sequences at the amino-terminus of the HPV L2 minor capsid protein elicit broadly cross-neutralizing antibodies and protect animals from diverse papillomavirus types. These encouraging preclinical studies should lead to human clinical trials.

HIV Association

Enhancing Research Capacity for Studies on HIV-Associated Malignancies in Sub-Saharan Africa. NCI and the Fogarty International Center sponsored an initiative comprising several grants to encourage partnerships between U.S. and African researchers that could, in turn, build multidisciplinary research teams of African physicians, clinical scientists, basic research scientists, epidemiologists, pathologists, data managers, and other required personnel to strengthen the capacity for research on HIV-associated malignancies in sub-Saharan Africa. Two of the nine awarded grants, which are described below, focus on women's health.

Collaboration Enhances Rwandan Research Capacity in Cervical Cancer and Other HIV-Associated Malignancies. A collaborative initiative between an NCI-supported cancer center and the National University of Rwanda has been formed to investigate operational, clinical, and translational questions in cervical cancer and other HIV-associated malignancies in HIV-positive women in Rwanda and to extend the population-based cancer registry to allow linkage to the computerized HIV-tracking system.

Collaboration Developed To Improve Zambian Cervical Cancer Research Capacity. A collaboration between an NCI-supported cancer center and the Centre for Infectious Disease Research in Zambia (CIDRZ) has been formed to increase cervical cancer research capacity in that country. Cervical cancer, an HIV-associated malignancy, is the most commonly diagnosed cancer in Zambia and the leading cause of cancer-related death among Zambian women. The initiative will provide training in the areas of radiation oncology, gynecologic oncology, pathology, virology, nutrition, epidemiology, and biostatistics.

Ovarian Cancer

Therapy

Animal Models Developed To Test miRNA Therapy for Ovarian Cancer. Researchers at an Ovarian Cancer SPORE performed genome-wide functional screenings of three human ovarian cancer cell lines. They identified several microRNAs (~22 nucleotide-long, non-coding RNAs negatively regulating the gene expression in a sequence-specific manner) with therapeutic potential, such as miRNAs that increase chemotherapy resistance. To further elucidate the therapeutic potential of these miRNAs, this group has generated two preclinical animal models that will help test potential anti-miRNA therapies in vivo.

Endometrial Cancer

Survivorship

Endometrial Cancer Survival Disparities in Hispanic Ethnicity. Disparities in uterine cancer survival between Whites and Blacks have been noted and studied, but little is known about disparities between non-Hispanic Whites (NHWs) and Hispanic Whites (HWs). Based on preliminary examination of data from the Surveillance, Epidemiology, and End Results (SEER) program, researchers found that HWs experience consistently worse survival than NHWs in New Mexico and California. Although the reasons for this disparity are unknown, this study is examining whether comorbidities, in particular diabetes and hypertension, may explain part or all of the survival disparities between HWs and NHWs. If it is determined that one or more comorbidities explain the survival disparity at least in part, this finding will be the basis for a future line of research to investigate interventions (therapeutic or lifestyle) to specifically reduce endometrial cancer mortality.

Lung Cancer

Treatment

Studies Explore Antiestrogen Agents in Treatment of Lung Cancer, Signaling in Lung Cancer. The University of Pittsburgh Lung Cancer SPORE, in collaboration with

investigators at the University of California at Los Angeles and the Translational Oncology Research International (TORI) network, continue to accrue patients to two randomized phase II clinical trials for the treatment of non-small-cell lung cancer. The first trial is studying erlotinib, a tyrosine kinase inhibitor, in combination with fulvestrant, an estrogen receptor inhibitor, in patients with non-small-cell lung cancer. The second trial is studying fulvestrant, the antiestrogen agent anastrazole, and the antiangiogenic drug bevacizumab as a consolidation therapy regimen for postmenopausal women with late-stage non-small-cell lung cancer. Both trials also are collecting samples for biomarker analysis. Results are expected in summer 2011 for the first trial and in fall 2013 for the second trial.

Biology

Understanding the Lung Cancer Genome To Improve Prevention, Diagnosis, and Treatment. Lung cancer is one of the first cancer types to be analyzed by The Cancer Genome Atlas (TCGA) project, a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies and large-scale sequencing. (See Cancer Genome Atlas Releases First Comprehensive Ovarian Cancer Data Set in this report.) This integrated network of clinical sites, core resources, and specialized genome characterization and genome sequencing centers is systematically exploring and publicly disseminating the entire spectrum of genomic changes involved in human cancer. Each cancer will undergo comprehensive genomic characterization that incorporates powerful bioinformatics and data analysis components. Results from TCGA are expected to lead to the most comprehensive understanding of cancer genomes and will enable researchers to further mine the data generated by TCGA to improve prevention, diagnosis, and treatment of cancer.

National Eye Institute

Executive Summary

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90–489, with the mission to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

The major causes of blindness in both men and women include glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataracts; however, several eye conditions affect women more frequently than men. These conditions are optic neuritis, a demyelinating disease of the optic nerve that may be a precursor of multiple sclerosis; dry eye, a common condition associated with decreased tear secretion that in most cases causes mild discomfort but in more severe cases may result in corneal scarring and blindness; corneal endothelial dystrophy, a slowly progressing disease that occurs when endothelial cells deteriorate as a result of cell loss from age or trauma; keratoconus, a visually disabling thinning disorder of the central cornea that results in irregular astigmatism, progressive corneal distortion, and corneal scarring; age-related macular degeneration, a deterioration of the region of the retina responsible for high-resolution vision; idiopathic intracranial hypertension, a central nervous disorder characterized by optic nerve compression; and thyroid eye disease, an autoimmune disease that leads to loss of vision.

Accomplishments

Optic Neuritis

Optic neuritis is an acute debilitating inflammation of the optic nerve that affects more that 25,000 Americans each year, primarily women between the ages of 18 and 45. People with this disease usually have rapid vision loss and ocular pain. The NEI-supported Optic Neuritis Treatment Trial (ONTT) compared oral corticosteroid, intravenous

steroid followed by oral corticosteroid, and placebo for the treatment of new cases of optic neuritis. At present, the Longitudinal Optic Neuritis Study (LONS), which follows patients originally enrolled in ONTT, is underway. Taken together, these studies have provided well-established guidelines for treating optic neuritis and established an association between optic neuritis and multiple sclerosis. Results from ONTT showed that oral corticosteroid, the most common treatment of the disease, when used alone was ineffective in treating the disease and actually increased a person's risk for future attacks, whereas intravenously administered corticosteroids promoted more rapid recovery and did not increase the rate of recurrence. However, results from LONS demonstrate that this treatment, though accelerating visual recovery, provided no long-term benefit to vision; therefore, not treating is a viable option. Based on data collected from 2 years of followup with patients enrolled in ONTT, researchers found that treating first-time optic neuritis patients with a combination of intravenous and oral corticosteroids lowers their risk of developing multiple sclerosis in the short term. The results from this research offered the first scientific evidence that intravenous corticosteroids help to delay the short-term progression of multiple sclerosis. However, long-term followup provided by LONS revealed that the effect of corticosteroids in reducing the rate of development of multiple sclerosis was diminished after 3 years of followup. Results from ONTT also demonstrated that the presence of multiple enhancing lesions on the brain MRI scan performed at the time optic neuritis was diagnosed was the single most important predictor of the development of multiple sclerosis within 5 years, and confirmation of these results was provided by LONS. LONS investigators have completed 15-year followup examinations of enrolled patients and are in the process of analyzing study data.

Dry Eye

Tears are necessary to maintain the health and comfort of the eye. A lack of sufficient tear fluid is a very common and frequently debilitating condition. Dry eye can result from insufficient secretion of fluid by the lacrimal glands or from defects in the surface of the eye, mucin or mucous production, or the lipid or fatty components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders such as Sjögren's syndrome but also occurs in association with aging, nerve dysfunction, radiation therapy, and antidepressant and antipsychotic drug therapy. Lacrimal insufficiency is characterized by complaints of eye irritation, eye pain, foreign-body sensation, chronic red eyes, photophobia, fluctuation in vision, and/or loss of vision.

Lacrimal insufficiencies affect roughly 2 million Americans, and dry eye is the most common complaint to present in the ophthalmologist's office, with 10 to 20 percent of adults in the United States suffering from it. It appears to be more common in women than in men, particularly in postmenopausal women.

Corneal Endothelial Dystrophy

Corneal endothelial dystrophy is a slowly progressing disease of the endothelium that usually affects both eyes and is more common in women than in men. Although physicians often can see early signs of the disease in people in their 30s or 40s, the disease rarely affects vision until a person reaches his or her 50s and 60s.

The corneal endothelium is a layer of cells that line the inner surface of the cornea. The endothelial cells are responsible for pumping fluid out of the cornea. The cornea is normally clear despite being bathed in tears on the outer surface and in aqueous humor on the inner surface. This clarity is maintained by the endothelial cell layer. If endothelial cells are diseased or absent, permanent corneal edema, loss of corneal transparency, and eventual blindness may occur.

NEI-supported scientists are attempting to determine why endothelial function deteriorates following cell loss, age, or trauma. Delineating the optimal conditions for the tissue culture of corneal endothelium will help evaluate the problems involved in transplanting these cultured cells and ensuring their survival. With further refinement of endothelial culture techniques, it will be possible to determine whether cell-cycle stimulatory and inhibitory factors arise from other cells

and whether the endothelium can be induced to repair itself. Parallel gene therapy studies are being pursued in animals with the aim of developing vectors to deliver factors therapeutically to the eyes of patients with the disease.

Keratoconus

Keratoconus arises when the middle of the cornea thins and gradually bulges outward, forming a rounded cone shape. This abnormal curvature changes the cornea's refractive power, producing moderate to severe distortion (astigmatism) and blurriness (near- and farsightedness) of vision. These changes also may disrupt the normal, light-conducting arrangement of corneal protein, causing swelling and a sight-impairing scarring of the tissue. Keratoconus has become better understood through investigations into the genetic predisposition of the disease, detection of early forms of the disorder through computerized topographic analysis, and advances in understanding the enzymology that underlies corneal thinning. Microarray technology is proving to be highly valuable in developing profiles of diseased tissue and comparing them with those of normal tissue.

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study is a NEI-supported multicenter observational study designed to characterize the progression of keratoconus over a broad spectrum of disease severity. Information on participants' vision, quality of life, corneal shape, and corneal scarring was collected to characterize the disease across its course and to identify risk factors and protective factors that determine the severity and progression of the disease. Study findings demonstrate an association between corneal scarring and decreased vision in keratoconus. Researchers found a causal contribution of contact lens wear to corneal scarring, thus suggesting that modifying lens fit can reduce this risk factor. Investigators are continuing to analyze data and publish study results.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is not only the leading cause of blindness in patients older than age 65 but is now the most common cause of blindness in the United States. The incidence of AMD continues to rise in the population as the result of the increasing percentage of elderly persons, with women at 50 percent greater risk than men.

The macula is a specialized region near the center of the retina responsible for the high-resolution vision that permits activities such as reading. Degeneration of this region is believed to be the result of a complex set of interactions involving genes/gene products and environmental factors. A high priority has been placed on identifying predisposing genes and their products and then determining what environmental factors affect these gene products to produce or protect against the disease. One of these factors may be estrogen. According to a recent report in the *Archives of Opthalomology* looking at AMD in women participating in the Nurses' Health Study (NHS), women who received hormone replacement therapy after menopause had a 48-percent lower risk of neovascular AMD compared with those who had never used postmenopausal hormone therapy. In contrast, risk of early AMD was 34 percent higher among current users of postmenopausal hormone therapy. These findings suggest a role for estrogen in the pathogenesis of AMD that requires further research in specific early and late signs of disease.

The Age-Related Eye Disease Study (AREDS) is a multicenter clinical trial/epidemiologic study designed to assess the clinical course, prognosis, and risk factors of AMD and to evaluate the effects of antioxidants and zinc in slowing the progression of the disease. The study demonstrated that high-dose antioxidant supplements (beta-carotene, vitamins C and E, and zinc) can slow the progression of AMD. Data from AREDS and other studies suggest that lutein/zeaxanthin and omega-3 long chain polyunsaturated fatty acids also might have benefit in AMD and cataract. A second study, AREDS 2, is currently underway to test this hypothesis. A multicenter clinical trial called the Complications of Age-Related Macular Degeneration Prevention Trial assessed the safety and efficacy of laser treatment in preventing vision loss in patients in whom the disease is manifested bilaterally. This study recently reported that low-intensity laser treatment was ineffective in preventing complications of AMD or loss of vision.

Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) typically occurs in women of childbearing age, and the incidence is 1/100,000 in normal-weight women and 20/100,000 in obese women. The disease is characterized by an increase in intracranial pressure (> 250 mm H2O); the cause of IIH is unknown but involves obstruction of cerebral venous outflow. This obstruction, in turn, results in transient blurred vision, diplopia, and permanent vision loss. The role that obesity and hormonal changes play in contributing to this disorder is currently being investigated. Although some medications and surgical treatments are available, there is no consensus regarding treatment strategies.

Thyroid Eye Disease

Thyroid eye disease is a manifestation of Graves' disease, an autoimmune disease that causes hyperthyroidism and tends to affect 2 percent of all women (7:1 compared with men) between the ages of 20 and 40. Excessive thyroxine causes swelling of the muscle and other tissues around the eye resulting in proptosis (bulging of the eye), corneal exposure, optic nerve compression, and ultimately loss of vision. Current treatments of thyroid eye disease are only marginally effective; therefore, research into the pathogenic mechanisms and discovery of potential new therapeutic targets is underway.

Glaucoma

Primary open angle glaucoma (POAG) is a leading cause of irreversible blindness worldwide, yet the pathogenesis of this condition remains unknown. NHS, supported by various branches of NIH, has contributed considerably to research on POAG. NHS started in 1976 when 121,000 registered female nurses from across the United States agreed to complete biennial questionnaires regarding lifestyle and health. Among women 65 years of age or older, entering menopause at age 54 years or later was associated with a 47-percent reduced risk of POAG compared with entering menopause between ages 50 and 54. Furthermore, postmenopausal hormone (PMH) use consisting of estrogen and progesterone was associated with a 42-percent reduced risk of high-tension POAG (intraocular pressure [IOP] > 21 mm Hg at the time of diagnosis). Circulating estrogen strongly modulates the expression of endothelial nitric oxide synthase (NOS3). In a gene association study involving participants in NHS and the Health Professionals Follow-up Study (HPFS), researchers found significant relationships between common NOS3 gene variants and POAG in women but not in men. Furthermore, they noted significant interactions between four NOS3 gene variants and PMH use in high-tension POAG. Finally, anthropometric studies indicate an inverse relationship between body mass index (BMI) and the risk of normal-tension variant of POAG (IOP ≤ 21 mm Hg at diagnosis) in women but not in men. Perhaps higher circulating estrogen levels in women with higher BMI contribute to this inverse relationship. Collectively, these data support the notion that circulating estrogen levels play a role in the pathogenesis of POAG.

Women in NHS and the Genetic Etiology of POAG (GEP) database contributed DNA specimens to a project aimed at new gene discovery for POAG. GEP is a clinic-based sample of POAG cases and controls located mostly in New England. Specimens from NHS and GEP contributed to a genomewide association study (GWAS) of POAG as part of the Glaucoma Genes and Environment Initiative (GLAUGEN). NEI funded the formation of the GLAUGEN case control group, and the National Human Genome Research Institute supported genotyping efforts. Genotyping in GLAUGEN is complete, quality-control filters have been applied, and data analysis is ongoing.

A second GWAS within the NEI Glaucoma Human Genetics Collaboration (NEIGHBOR) consisting of approximately 2,000 POAG cases and 2,000 controls is currently underway. The NEIGHBOR consortium is located at Harvard and Duke Universities, with contributing centers at the University of Pittsburgh, University of West Virginia, Johns Hopkins University, University of Miami, University of Michigan, University of California San Diego, and Stanford University. Vanderbilt University serves as a data analysis center for the NEIGHBOR project. The high-throughput genotyping efforts in GLAUGEN and NEIGHBOR

will help define the genetic architecture of POAG. Members of the Women's Health Study (WHS), which consists of more than 26,000 women who completed a genomewide scan and biennial questionnaires regarding lifestyle, behavior, and health, will serve to confirm some of the new gene discoveries in GLAUGEN and NEIGHBOR. The identification of POAG cases in WHS is ongoing.

Initiatives

Strategic Plan

NEI and the National Advisory Eye Council (NAEC) have established a strategic plan called *A National Plan for Eye and Vision Research*. The plan, which sets out goals, objectives, and research priorities for improving visual health and preventing blindness, includes a consideration of the following diseases that have a higher incidence and prevalence for women than for men.

Optic Neuritis. Research priorities are to (1) develop an animal model of this disease to better understand its pathogenesis, (2) develop immunomodulating therapies to limit optic nerve damage from inflammation, and (3) understand the relationship between optic neuritis and multiple sclerosis.

Dry Eye. The overall objective is to determine the role of sex hormones on lacrimal gland function. A body of experimental evidence supports the notion that androgen sex hormones and prolactin modulate lacrimal gland function, thus providing an explanation for the observed gender bias of this condition and suggesting hormone modulation as a possible treatment.

Corneal Endothelial Dystrophy. Research priorities are aimed at understanding the biologic and functional structures of endothelial cells.

Keratoconus. An overarching objective is to understand the genetic basis of kerataconous. Identification of gene loci and their encoded proteins should provide clues to the pathogenesis of the disease and suggest new therapies.

Age-Related Macular Degeneration. Research priorities are aimed at identifying the cellular, molecular, and systemic factors involved in the pathophysiology of AMD. Because of the complexity of this disease, researchers are engaged in studies that use a combination of epidemiology, basic cellular and molecular biology approaches, and genetics.

Glaucoma. Functional tests used to measure vision loss due to glaucoma can be affected by estrogen. Alongside these tests, retinal nerve fiber layer thickness appears to be influenced by estrogen levels. Researchers are conducting a longitudinal study to determine the effects of female hormones on these measures of glaucomatous damage.

Cataracts. Researchers have observed a role for estrogen in the pathophysiology of cataract formation. However, the evidence is unclear whether this role is protective or deleterious. Studies are underway to determine how estrogen influences the development of cataracts.

Carotenoids and Age-Related Eye Disease Study

The Women's Health Initiative Observational Study affords NEI the opportunity to pursue epidemiologic studies in women-only cohorts. This study has allowed gender-specific analyses of risk factors in major blinding and debilitating diseases. Approximately 2,000 women from 3 sites participating in the Women's Health Initiative Observational Study were enrolled in the Carotenoids and Age-Related Eye Disease Study (CAREDS). Women aged 50 to 79 were selected to participate in the study if their dietary intake of lutein plus zeaxanthin was judged to be either high or low. The presence of AMD was assessed by fundus photography. Findings from the CAREDS study include the following:

- Diets rich in lutein and zeaxanthin among women younger than 75 years may be protective against intermediate AMD.
- High-serum vitamin D (25(OH)D) among women younger than 75 years may be protective against intermediate AMD.

Essential Fatty Acids and Dry Eye Disease

NEI has funded a clinical study planning grant to design a clinical trial examining the role of essential fatty acids (EFAs) in the treatment of moderate-to-severe dry-eye disease (DED). Despite being a widespread, growing problem with serious consequences, at present DED is inadequately treated. Because EFAs have been shown in laboratory studies, animal models, and some human studies to ameliorate inflammatory reactions and they are widely available over the counter, they are gaining in popularity to combat or prevent diseases associated with inflammation, including DED. But as with any treatment, results of a large, randomized double-blind clinical trial are needed to assess efficacy and safety. The current project is attempting to lay the groundwork for a definitive trial.

International Sjögren's Syndrome Registry

NEI is working with NIDCR and ORWH to enhance research opportunities in the diagnosis, epidemiology, and treatment of Sjögren's syndrome. NEI is cofunding an NIDCR initiative for the development of an International Sjögren's Syndrome Registry. The ultimate goal of the registry is to promote cutting-edge research in the area of Sjögren's syndrome with emphasis on diagnosis, epidemiology, causes, prevention, and treatment. The coordinating center is at the University of California San Francisco, and multiple international sites (Argentina, China, Denmark, Japan, and the United Kingdom) have been established. There is a plan to add India as a site pending approval of the Indian government. All sites have started accruing patients, which includes the use of a standardized baseline eye exam form and baseline eye exam standard operating procedures.

Neuro-Ophthalmology Research Disease Investigator Consortium

NEI is working with ORWH to evaluate diagnostic and treatment options for IIH and Graves' disease. NEI is supporting the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC), which is prepared to conduct clinical studies on these two neuro-opthalmology-related diseases that occur predominantly in women. The objective is to provide a unique opportunity to recruit and study statistically significant numbers of hard-to-find patients in order to evaluate different diagnostic and treatment options.

National Heart, Lung, and Blood Institute

Executive Summary

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives. To achieve this vision, NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public. NHLBI creates and supports a robust collaborative research infrastructure in partnership with private and public organizations, including academic institutions, industry, and Government agencies. NHLBI collaborates with patients, families, health care professionals, scientists, professional societies, patient advocacy groups, community organizations, and the media to maximize the use of research results and leverage resources to address the public health needs of the Nation.

NHLBI places high priority on enhancing the health of women by reducing the burdens of cardiovascular, lung, and blood diseases. As articulated in its strategic plan (http://apps.nhlbi.nih.gov/strategicplan/Default.aspx), the Institute's broad goals are to improve understanding of the molecular and physiologic basis of health and disease and use that knowledge to develop better approaches to disease diagnosis, treatment, and prevention; improve understanding of the clinical mechanisms of disease and thereby enable better prevention, diagnosis, and treatment; and generate a clearer understanding of the processes

involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.

For many years, NHLBI has been diligent in ensuring that its clinical research projects include adequate representation of women and that its overall research portfolio addresses gaps in knowledge of how to diagnose, prevent, and treat disease in women. This effort has included not only careful monitoring of recruitment for clinical trials and other studies but also support of certain studies conducted entirely in cohorts of women. This report describes a variety of research results, new programs and solicitations, and educational campaigns in cardiovascular, lung, and blood diseases that illustrate the Institute's recent activities of importance to women's health. Also included are highlights of NHLBI efforts to address the health consequences of overweight and obesity that are relevant to the Institute's mission and to develop and evaluate approaches to prevent inappropriate weight gain, facilitate weight loss where needed, and promote overall fitness.

In addition to supporting its own extensive portfolio of activities of importance to women's health, NHLBI has had administrative responsibility for the NIH Women's Health Initiative since fiscal year (FY) 1998.

NHLBI Entities With a Designated Focus on Women's Health

The NIH Women's Health Initiative is administered by NHLBI through its Division of Cardiovascular Sciences.

The NHLBI Office of Communications has responsibility for *The Heart Truth*.

Accomplishments

Cardiovascular Diseases

The Women's Ischemia Syndrome Evaluation

In 1996, NHLBI began the Women's Ischemia Syndrome Evaluation (WISE,) a study of more than 900 women referred for angiography because they experienced symptoms of ischemic heart disease (chest pain or shortness of breath) and were suspected of having coronary heart disease (CHD). The study found that half of these women did not, in fact, have CHD, yet many of them continued to experience debilitating symptoms or went on to have heart attacks. WISE also showed that microvascular dysfunction (impaired functioning of the small arteries of the heart, which is generally not detected by angiography) was often associated with ischemia in women who did not have CHD. Since 2006, research has focused on developing new and improved approaches for diagnosis of microvascular disease as well as on studies to improve understanding of microvascular disease and its relationship to heart attack and other cardiovascular diseases (CVDs).

A 2009 report from three of the WISE investigators reiterated the need for new diagnostic approaches to identify microvascular disease and discussed the importance of thoroughly testing women with persistent chest pain for microvascular disease and other underdiagnosed cardiac conditions. The report included two case studies describing the use of coronary reactivity testing to evaluate women with persistent chest pain but no CHD. In one case, such testing revealed that the patient suffered from microvascular dysfunction. In the other, test results enabled clinicians to rule out microvascular dysfunction and suggested that the patient's pain was caused by abnormal cardiac nociception (pain perception). The report demonstrates how coronary reactivity testing could be used to improve diagnosis of women with symptoms of ischemia who do not have CHD (Phan, Shufelt, & Merz, 2009).

In 2010, WISE published additional findings that shed light on the relationship between CVD outcomes and microvascular dysfunction caused by problems with the smooth muscle cells that form the outer layer of the microvasculature. Investigators tested 189 of the WISE participants for microvascular smooth muscle cell dysfunction. After approximately 5 years of followup, women with such dysfunction were found to have an increased risk of life-threatening cardiac events (e.g., heart attack, stroke, hospitalization for heart failure). Furthermore, knowing whether the microvascular smooth muscle cells were functioning properly greatly

improved the researchers' ability to predict a woman's risk for serious CVD events. The results indicate that women with ischemic symptoms should be evaluated for microvascular dysfunction, including dysfunction associated with microvascular smooth muscle cells (Pepine et al., 2010).

Women's Health Study (WHS)

WHS is a randomized, placebo-controlled clinical trial designed primarily to evaluate the use of low-dose aspirin and vitamin E to prevent CVD and cancer. About 40,000 women 45 years of age or older were enrolled from 1992 to 1995 and were followed for 10 years. In FY 2005, WHS was extended through 2010 to enable further evaluation of clinical issues related to CVD risk in women. WHS constitutes a rich source of data for exploring a range of important research questions, and investigators have reported many significant findings.

According to WHS, obesity may increase a woman's risk of developing atrial fibrillation (AF), a common arrhythmia. Over the past 30 years, the prevalence of AF has increased rapidly. Although population aging is a contributing factor, the increase has been greater than would be expected based on demographic changes alone. The number of overweight and obese individuals also has increased dramatically in recent years, and small studies have suggested a relationship between AF and excess weight. To investigate this relationship, WHS researchers analyzed data from more than 34,000 of the study's participants. Women who were overweight or obese were more likely to develop AF than women who were not, and risk increased progressively with higher body mass index (BMI). Weight gain also was a risk factor; women who gained weight over a 5-year period were more likely to develop AF than women whose weight remained stable. The findings suggest that women who maintain a healthy weight may reduce their risk for developing AF (Tedrow et al., 2010).

Studies have shown that the consumption of moderate to large amounts of alcohol increases the risk of AF in men, but fewer data have been available about the effects of alcohol intake in women. WHS investigators found that consumption of fewer than two drinks per day did not affect a woman's risk of developing AF. However, consumption of two or more drinks per day appeared to increase AF risk slightly, suggesting that women could reduce their risk of AF by limiting alcohol intake (Conen et al., 2008).

WHS collected blood samples from more than 28,000 participants to enable studies of the role of genetics in health and disease. The samples have been made available to other investigators who are combining genetic data from the blood samples with the wealth of data collected about diet, behavior, environmental exposures, and health outcomes.

One of the largest genetic studies involving WHS participants is the Women's Genome Health Study (WGHS), which is performing blood-based analyses to identify genetic factors that influence disease susceptibility. Its goal is to improve understanding and prediction of CVD and CVD outcomes and of health conditions that constitute major CVD risk factors (i.e., hypertension, metabolic syndrome). WGHS also seeks to evaluate genotype–phenotype interactions and shed light on interrelationships among multiple CVD risk factors in the prediction of CVD events.

Although a number of published studies have reported links between common genetic variants and the risk for developing prevalent diseases such as CVD, a genetic risk score developed by WGHS based on a woman's profile of CVD-associated genetic variants did not enable researchers to predict that individual's risk of developing CVD. Furthermore, incorporating the genetic risk score into traditional risk prediction strategies that use family history and assessment of known risk factors (e.g., blood pressure and cholesterol) did not improve the predictive value of those strategies. Although additional research may lead to the development of a genetic risk score that facilitates prediction of CVD risk, the traditional method of predicting CVD risk is still the most useful approach. The study highlights the difficulty in interpreting the results of analyses that link genetic variation to common diseases and underscores the need for research that assesses the clinical relevance of such results (Paynter et al., 2010).

Studies have suggested that men with a particular variant of the beta 2-adrenergic receptor (*ADRB2*) gene may have a reduced risk of heart attack. Results from WGHS showed that white women with a similar *ADRB2* variant also appeared to be at reduced risk for heart attack. However, the variant did not seem to reduce heart attack risk when non-White women were included in the analysis, raising the possibility that the protective effect of the *ADRB2* variant may not be generalizable to women of all racial backgrounds (Schürks, Kurth, Ridker, Buring, & Zee, 2009).

WGHS researchers identified four genes associated with an increase in blood levels of the amino acid homocysteine, a molecule linked to the development of heart disease. When the researchers attempted to replicate their findings using data from another cohort that included both women and men, they discovered that one of the four genes identified in the WHS participants had a gender-specific effect—it was associated with increased homocysteine levels in women but not in men. Although more work is needed to determine the way in which the four genes affect homocysteine metabolism, the discovery provides new opportunities to improve understanding of the role of homocysteine in CVD risk in women (Paré et al., 2009).

Other CVD Topics

Although the number of women entering the workforce grew steadily over the past few decades, little research has investigated the effects of employment status on women's health. To determine whether working outside the home affects a woman's risk of CHD or ischemic stroke, researchers analyzed employment history data from more than 7,000 middle-aged women enrolled in the Atherosclerosis Risk in Communities Study. Results showed that women employed outside the home had a lower risk of CHD and ischemic stroke than women who were homemakers. Homemakers were more likely to have CVD risk factors (e.g., diabetes, high LDL cholesterol) than women who worked outside the home. The less favorable CVD risk profile observed in homemakers appeared to account for their increased risk of ischemic stroke. However, even after taking into account differences in CVD risk factors, homemakers were still more susceptible to CHD than women who worked outside the home (Carson et al., 2009).

Premenopausal women are less likely than men the same age to have CVD, but the molecular basis of this gender difference is unknown. Gender differences in CVD also are seen in mice, leading researchers to investigate differences in survival of heart muscle cells of young male and female mice. Compared with male cells, female heart muscle cells were better able to survive exposure to a cytotoxic chemical. Estrogen receptor alpha, a protein that promotes cell survival, was expressed at higher levels in female heart muscle cells than in male cells, and other cell-survival proteins were more active in female cells. The finding indicates that female heart muscle cells may have a survival advantage over male cells and provides insights into the molecular basis for the gender difference. Additional research is needed to determine how these basic research findings could be applied to improve clinical outcomes in humans (Wang, He, Sun, Dai, & Yang, 2010).

Pre- and postmenopausal women with hypertension are equally likely to be treated with blood pressure–lowering drugs, but achieving adequate blood pressure control is more difficult in postmenopausal women than in younger women. Researchers explored this phenomenon in a rat model. They treated postmenopausal rats and young female controls with losartan, a drug that modulates the rennin-angiotensin system, a key element in blood pressure regulation. Although losartan lowered blood pressure in both postmenopausal and control animals, it failed to completely normalize blood pressure in the older animals. The results suggest that the rennin-angiotensin system contributes to hypertension after menopause but other important factors also are involved (Yanes et al., 2010).

The long-running Nurse's Health Study recently reported that depression is linked to both CHD and sudden cardiac death (SCD) in women. The research analyzed data on depressive symptoms, antidepressant use, and CVD outcomes from more than 63,000 women with no history of CHD or stroke. Results showed a link between depression reported at baseline

and the development of CHD (heart attack, angina, or coronary artery bypass graft surgery) and also revealed an association between antidepressant use and SCD (Whang et al., 2009).

Young women hospitalized with heart attacks are twice as likely as young men to die before discharge, but the reasons for this gender difference are unknown. Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO), an NHLBI-sponsored observational study, is examining factors that may predispose younger women to heart attacks and poorer outcomes. The study is following 2,000 women and 1,000 men, 18 to 55 years of age, hospitalized with a heart attack. The researchers are collecting data on biologic, demographic, psychosocial, environmental, and behavioral factors that may affect CHD and recovery after a heart attack. They also are seeking to determine whether women and men receive different care following a heart attack (http://clinicaltrials.gov/ct2/show/NCT00597922; Lichtman et al., 2010).

Adults who suffer from type 2 diabetes are two to four times more likely to die of some form of CVD than adults without diabetes, and they often have other conditions that elevate CVD risk, such as unfavorable lipid profiles. Data from various sources supported the hypothesis that CVD risk could be reduced by improving levels of other blood lipids in addition to LDL cholesterol. The NHLBI Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial evaluated the merits of a combination treatment that entailed raising HDL cholesterol and lowering blood triglycerides in addition to lowering LDL cholesterol versus standard treatment—lowering only LDL cholesterol. The aggregate results showed no evidence that patients with type 2 diabetes would benefit more from the combination therapy. When the data were analyzed by gender, however, the combination treatment appeared to reduce risk of CVD events in men but to increase the risk in women. This finding requires further study because it is not definitive (Ginsberg et al. 2010).

Critical limb ischemia—a potentially fatal condition that can cause pain, infection, gangrene, and limb loss—is caused by blockages in arteries that supply blood to the lower extremities and can be treated with vein bypass surgery to restore blood flow to the affected limb. A number of studies have suggested that women and minorities are more likely to experience adverse outcomes from this surgery, such as failure of the implanted bypass graft. To investigate vein bypass surgery outcomes in different demographic groups, investigators analyzed data from the Project of Ex Vivo Vein Graft Engineering via Transfection III (PREVENT III), a randomized trial that tested a strategy to improve vein bypass surgery outcomes. The analysis revealed that Black patients were more likely than White patients to experience complications such as blockages in the implanted blood vessel graft or to require limb amputation. Black women were at the highest risk for poor outcomes after the surgery. Although the researchers were unable to determine the reason for the variable outcomes, they concluded that the findings support the need for aggressive medical management and close monitoring in high-risk demographic groups (Nguyen et al., 2009).

Preeclampsia, a hypertensive disorder that develops during pregnancy, can have devastating consequences such as maternal kidney, liver, and central nervous system damage and fetal and maternal death. Oxidative stress, a biological reaction that damages tissues and cells, has been suggested as a potential cause of preeclampsia. Because the antioxidant vitamins C and E counteract oxidative stress, their ability to prevent preeclampsia has been of interest to researchers, but the small studies conducted to date produced conflicting results. To resolve the discrepancies, NHLBI and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) sponsored a large trial of vitamin C and E supplementation in more than 10,000 pregnant women. It concluded that daily high doses of vitamins C and E started early in pregnancy do not reduce the risk of preeclampsia and its complications. The results offer useful clinical information that will enable health care providers to avoid giving unnecessary treatments to their patients (Roberts et al., 2010).

Women's Heart Disease Awareness Campaign

The Heart Truth (http://www.nhlbi.nih.gov/educational/hearttruth), an NHLBI-sponsored national awareness campaign about heart disease in women, continues to spread the word to millions that heart disease is a major women's health concern. Since *The Heart Truth* began in 2002, awareness among women that heart disease is their leading cause of death has risen from 30 to 54 percent. *The Heart Truth* encourages women to talk with their doctors about their personal risk of heart disease and take steps to reduce it; a 2009 survey conducted by the American Heart Association found that 48 percent of women reported discussing heart disease with their doctors, up from 30 percent in 1997.

As part of *The Heart Truth* campaign, NHLBI publishes a portfolio of science-based health education materials, many of which are available in both English and Spanish, about heart disease in women and ways to prevent it. These materials are complemented by NHLBI's Diseases and Conditions Index (http://www.nhlbi.nih.gov/health/dci/index.html), which includes the topics "Heart Disease in Women" and "Coronary Microvascular Disease," a form of heart disease found more commonly in women than in men.

The Red Dress continues to be one of the most recognizable health symbols in the United States. An April 2010 survey showed that 58 percent of U.S. women recognized the Red Dress as the symbol for women and heart disease, up from 25 percent in 2005. National Wear Red Day—the first Friday in February—has become an annual event during which Americans wear red to promote awareness about heart disease in women.

More than 100 corporate partners are helping spread the campaign message by featuring *The Heart Truth* and Red Dress symbol on grocery store displays, newspaper coupon inserts, corporate Web sites, and billions of product packages. In addition, a wide range of community organizations and media groups actively contribute to the campaign. Almost 4 billion media impressions have been made to date.

The Heart Truth Road Show helps participants learn about heart disease risk factors, provides free health screenings, and disseminates educational materials. From April 2005 to October 2010, the Road Show reached tens of thousands of women in 28 cities across the United States and screened 17,200 individuals for heart disease risk factors. *The Heart Truth* Champions program, initiated in 2006 to recruit health advocates and educators in local communities, has trained 340 activists in 26 States to organize heart-health activities in their communities. Since the start of *The Heart Truth* Women of Color Initiative in early 2005, campaign messages have reached thousands of African-American and Hispanic women throughout the United States. From 2007 to 2010, *The Heart Truth* Community Action Program, implemented in partnership with the Foundation for the National Institutes of Health, has funded 17 community organizations to undertake activities designed to increase awareness of heart disease among underserved women, particularly woman of color, low-income women, and women in rural areas.

The Heart Truth is conducted in partnership with the American Heart Association, Office on Women's Health of the U. S. Department of Health and Human Services, WomenHeart–The National Coalition for Women with Heart Disease, and other organizations committed to the health and well-being of women.

Lung Diseases

Asthma

More than 24 million people in the United States have asthma. Asthma prevalence is higher in boys than in girls before puberty and higher in women than in men in adulthood.

Basic research is increasing our understanding about gender-based differences in asthma development. Studies of animal models of asthma development, as well as human cell interactions in the laboratory, are shedding light on the pathogenesis of asthma and how it may differ between females and males.

Researchers induced airway inflammation in mice and studied the resulting numbers and function of several types of lung cells as the mice developed asthma. They found that one type of macrophage was more numerous in

the lung tissue of females than in males and seemed to be involved in exacerbating airway inflammation in the females. Increased understanding of the role of such macrophages may help explain some of the gender-based differences found in the development of asthma in humans (Melgert et al., 2010).

Other investigators looked at peripheral blood lymphocytes taken from asthmatic and nonasthmatic individuals. They found two T cell subtypes that, under certain stimulative conditions, proliferated markedly in blood from asthmatics but not nonasthmatics. Further investigation showed that one of these T cell subtypes, known as type 2 T cells, increased significantly more in blood from female asthmatic patients than from male patients (Loza, Foster, Bleecker, Peters, & Penn, 2010).

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is now the third most common cause of death in the United States and the only major chronic disease for which death rates are increasing. More American women than men die of COPD annually. More than 12 million people are currently diagnosed with COPD, and another 12 million are thought to have COPD but have not been diagnosed.

Gender differences in symptoms and disease progression among COPD patients are widely recognized. Women manifest disease symptoms earlier, probably because they generally have a smaller airway size and seem to develop COPD with less exposure to tobacco smoke. In addition, women require tailored smoking cessation approaches if quitting is to be as successful as in men.

Recently published results from a large clinical study of COPD shed further light on gender differences in lung function and effects of smoking. Researchers focused on two subgroups of current or former smokers with COPD—those who developed COPD before 60 years of age and those who had a relatively low level of exposure to cigarette smoke. In both subgroups, women had significantly lower lung function than men and their COPD was more severe (Sorheim et al., 2010).

The *COPD Learn More Breathe Better* campaign, led by NHLBI in partnership with professional societies and advocacy organizations, is directed toward women and men older than 45 years of age. The campaign seeks to increase awareness of COPD and understanding that the disease is treatable, and it encourages people at risk to get a simple breathing test and talk with their doctors about treatment options. The campaign emphasizes that COPD is now as much of a problem for women as for men. In March 2009, NHLBI held a meeting of organizations active in COPD education to encourage information sharing and identify needs for expansion of the campaign. The resulting recommendations led to establishment of the Breathe Better Network to support organizations representing States, cities, or communities engaged in COPD education and awareness through the campaign. In fall 2010, the campaign also launched new print and radio public service announcements to raise awareness among women and men about the symptoms of COPD.

The Institute has worked to ensure that its clinical and population-based studies involving COPD include women in substantial numbers so that results apply to the full range of patients. For example, in an ancillary study to the NHLBI Multi-Ethnic Study of Atherosclerosis, researchers analyzed the heart and lung structure and function of more than 2,800 generally healthy adults, half of whom were women, and found that even mild COPD can diminish the heart's ability to pump effectively. These findings support the importance of increased awareness and early diagnosis of COPD in women as well as in men (Barr et al., 2010).

Cystic Fibrosis

Although cystic fibrosis (CF), an inborn error of metabolism that is inherited in an autosomal recessive manner, affects an equal number of females and males, gender is now recognized as a factor influencing CF severity. Women with CF experience accelerated declines in lung function, acquire infections earlier, have more frequent exacerbations, develop more diffuse lung disease, and die younger than men with CF. NHLBI-supported researchers are investigating the reasons for these gender differences.

New research has shown that high levels of the major circulating estrogen 17β-estradiol, which occur shortly before ovulation, may be implicated in mucus buildup in women with CF. Specifically, fluctuations in 17β-estradiol during the menstrual cycle may contribute significantly to the excess burden of CF in women by worsening the degree of airway surface dehydration and decreasing mucociliary clearance, an important defense mechanism in CF lung disease. Research in cell cultures showed that tamoxifen, which acts on estrogen receptors, reversed the adverse effects of high 17β-estradiol levels and, therefore, may potentially constitute a useful therapy for treating CF in women (Coakley et al., 2008).

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare lung disease that mostly affects women in their mid-30s and 40s, causing abnormal muscle-like cells to grow out of control in certain organs or tissues, especially the lungs, lymph nodes, and kidneys. Over time, these LAM cells can proliferate throughout the lungs and destroy normal tissue. NHLBI efforts to improve treatment of LAM encompass several approaches. Research underway includes development of a LAM Genome Atlas, exploration of a new research paradigm on the ability of LAM cells to metastasize, and investigation of the role of estrogens in this disease. These and other projects seek to identify additional treatment targets, discover molecular markers, and determine the mechanisms of lung destruction. The MILES (Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus) trial, conducted through the NIH Rare Lung Diseases Consortium, is in progress. Other therapeutic options also are being investigated because sensitivity to sirolimus varies and the drug has significant side effects, including lung inflammation, that are worrisome in LAM patients. Reproductive hormones (e.g., prolactin) that stimulate the growth of LAM cells are being studied as potential drug targets. NHLBI intramural investigators have developed procedures for stabilizing cells from blood and other body fluids to facilitate their distribution to investigators for research. A new effort is underway to make existing LAM databases more accessible to investigators. NHLBI continues to cofund the annual LAM scientific conference and participate in meetings of the trans-NIH Tuberous Sclerosis Coordinating Committee.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a particularly insidious and devastating syndrome resulting from increased pulmonary vascular resistance, which causes restricted flow through the pulmonary arterial circulation and, ultimately, death from right-heart failure. PAH development involves an imbalance of cell proliferation, cell death, and genetic factors analogous in many respects to cancer. The predominance of PAH among women has been recognized for several decades. Estimates of a 4-to-1 female-to-male ratio among patients with either idiopathic PAH or PAH associated with an identifiable cause have been reported.

In light of this gender-specific pattern of disease, NHLBI-supported researchers are studying the effects of sex hormones on lung vascular biology and development of PAH. Basic science studies have actually demonstrated protective effects of estrogens on the health of the pulmonary circulation. However, further investigation has suggested that PAH development may not be related solely to the presence or absence of estrogen. Rather, altered or cyclical levels of estrogen, altered metabolism of estrogens, and differential estrogen metabolite signaling are important determinants of lung vascular function. One line of evidence suggests that the balance between two metabolites (known as E2 and 2ME) is an important regulator of lung vascular growth and cellular repair. During conditions of chronic hypoxia, inflammation, exposure to certain drugs, and changing environmental factors, an abnormal E2-to-2ME metabolic profile might precipitate PAH disease development in women who have a genetic predisposition. Further translational and clinical studies are needed to explore this possibility and develop targeted diagnostics and therapeutics for women who have been diagnosed with PAH or are at risk of developing it (Tofovic, 2010).

Blood Diseases

Clotting Abnormalities

Women have special concerns involving increased risk of venous blood clots throughout life. Oral contraceptives, pregnancy, and postmenopausal hormone therapy all confer a heightened risk of deep vein thrombosis and pulmonary embolism, and other factors also have been implicated in the higher susceptibility experienced by women.

A recent review of studies addressing sex-based differences in thrombosis and antithrombotic therapy highlighted a number of possible biological explanations for such differences. Differences between women and men in procoagulant protein expression and platelet function may account for some of the variation, explaining, for example, why women react differently than men to aspirin therapy for prevention of CVD and why women with AF seem to suffer more strokes than men with the same condition (Bailey, Scantlebury, & Smyth, 2009).

Another study documented the extent to which older women are affected by venous thromboembolism (VTE) and identified a number of factors that exacerbate risk. Researchers linked data from the Iowa Women's Health Study with Medicare records of hospitalizations for VTE from 1986 to 2004 and found substantial morbidity and mortality associated with VTE. Women who smoked, were physically inactive or overweight, or had diabetes experienced higher rates of VTE (Lutsey et al., 2010).

Other NHLBI-supported efforts in this area include studies of damage to veins and valves following deep vein thrombosis; development of innovative treatment approaches to prevent long-term damage to the veins, including use of an image-guided strategy to dissolve clots; and research to improve the health and well-being of elderly patients at risk of developing clots.

Treatment with low-dose warfarin can safely and effectively prevent clinical events associated with inappropriate clotting, but establishing a therapeutic dosage is tricky because individuals can vary markedly in their response to the drug. A large randomized multicenter clinical trial—Clarification of Optimal Anticoagulation Through Genetics—is testing a new approach to the initiation of warfarin therapy. Building on previous research that identified genetic variants associated with warfarin sensitivity, the trial will evaluate dosing guided by genotype and clinical information compared with dosing guided by clinical information alone (http://clinicaltrials.gov/ct2/show/NCT00839657?term=COAG&rank=1).

In September 2008, the Acting Surgeon General issued a call to action to reduce the number of cases of deep vein thrombosis and pulmonary embolism in the United States. NHLBI supported this effort by emphasizing its commitment to support research to improve understanding about and treatment of these disorders. The Institute also drafted scripts for public service announcements on deep vein thrombosis for use by the Acting Surgeon General's office.

Von Willebrand Disease Guidelines

In February 2008, NHLBI issued the first guidelines ever published in the United States for the diagnosis and management of von Willebrand disease (vWD), the most common inherited bleeding disorder. Developed by an expert panel convened by NHLBI in consultation with the American Society of Hematology, the complete guidelines and a pocket guide for health professionals are available on the NHLBI Web site and as printed documents (http://www.nhlbi.nih.gov/guidelines/vwd). They also were published in the journal *Haemophilia* (Nichols et al., 2008).

VWD affects 1 in every 100 to 1,000 people. The guidelines focus attention on the special challenges faced by women with vWD. They offer advice for diagnosing vWD in women and for addressing the special risks that pregnancy and childbirth present.

The guidelines have been disseminated by expert panel members and partner organizations. Recently, one expert panel member coauthored a journal article to increase understanding among obstetricians and gynecologists about vWD and other bleeding disorders in women and to recommend steps

for diagnosing and managing the disease in women (James et al., 2009).

Sleep Disorders

Sleep apnea is a common disorder in which sleep is disrupted due to episodic dips in blood oxygen levels. Gender differences in symptoms have been observed—men generally have traditional apnea manifestations (e.g., snoring), whereas women are more likely to report sleep disturbances, longer sleep latency, and greater difficulty remaining asleep. Data show that sleep apnea before middle age is more common in men, but after menopause women are as likely as men to suffer from the disorder.

Sex differences in specific CVD risks have been associated with untreated sleep apnea. For example, middle-aged men with mild to severe apnea have three times the stroke risk of comparable women. However, impaired sleep presents serious health risks for women as well as men. WHI found that in otherwise healthy women the risk of ischemic stroke was 22 percent higher among those who typically slept less than 6 hours per night. CVD risks are associated with sleep apnea during pregnancy, and sleep disturbances, including apnea, are associated with polycystic ovary syndrome. Studies have demonstrated a 2.5-fold increase in gestational high blood pressure and preeclampsia rates in women who report habitual snoring during pregnancy.

NHLBI-supported researchers continue to study sex differences in sleep disorders. For instance, some investigators are exploring the effects of age, gender, and fat distribution on an individual's susceptibility to changes in neuromuscular control of upper airway mechanical load, an important factor in the pathogenesis of obstructive sleep apnea.

Data from more than 6,000 women and men in the Sleep Heart Health Study indicated that sleep-disordered breathing was associated with a higher risk of death from any cause, even when factors such as age, sex, BMI, smoking, and other medical conditions were taken into account. Restricting the analysis to deaths from CVD showed similar results—those with sleep-disordered breathing were more likely to die of CVD than those without. Analyzing the data by age and sex, researchers found these associations with mortality to be most apparent in men 40 to 70 years of age whose breathing was severely affected (Punjabi et al., 2009).

Research on Overweight and Obesity

NHLBI efforts in this area address health consequences of excess body weight that are relevant to the Institute's mission and the development and evaluation of approaches (e.g., healthy eating patterns, physical activity) to prevent inappropriate weight gain, facilitate weight loss where needed, and promote overall fitness.

Medical Correlates/Consequences of Overweight and Obesity

Obesity is a major risk factor for the development of hypertension, but the mechanisms by which excess weight raises blood pressure are not well understood. Researchers studied neutrophils (cells that can promote inflammation) and other markers of blood-vessel inflammation in subcutaneous fat of women who were normal weight, overweight, or obese. Obese women had the greatest number of neutrophils and highest levels of inflammatory markers, and elevations in both were correlated with increasing BMI and blood pressure in the overall group of women. These findings indicate that the hypertension observed in obesity may be mediated by inflammation (Shah, Leik, & Walsh, 2010).

Data from the Multi-Ethnic Study of Atherosclerosis were used to examine the relationship between obesity and remodeling of the left ventricle of the heart. Left ventricular size and function, as well as a variety of measures of obesity, were assessed in 5,098 individuals without apparent CVD, more than half of whom were women. An increased mass-to-volume ratio of the left ventricle was associated with several measures of obesity in both women and men. This finding, which indicates that obesity is associated with concentric remodeling of the left ventricle, may help to increase understanding of the mechanisms by which obesity influences heart disease (Turkbey et al., 2010).

Obesity is associated with low levels of growth hormone and increased risk of developing insulin resistance. A recent study compared

lipid and growth hormone levels in 21 obese and 17 normal-weight premenopausal women. The obese women had significantly higher lipid levels and lower growth hormone levels, suggesting that a paucity of growth hormone may contribute to insulin resistance in obesity through its effect on lipid levels (Bredella et al., 2009).

Research on Prevention and Treatment of Overweight and Obesity

The Food, Fun, and Fitness Internet Program for Girls tested the efficacy of an intervention for increasing physical activity and consumption of fruits, juices, and vegetables among Black girls at risk for obesity. Eighty girls from 8 to 10 years of age who had a home computer, Internet access, and an email address were enrolled in the 8-week program. They received rewards for completing all activities either immediately or after completing the entire program. Both amount of physical activity and intake of fruits, juices, and vegetables increased significantly from their baseline levels. These findings suggest that Internet-based interventions may be useful tools to prevent obesity in at-risk youth (Thompson et al., 2008).

Another intervention for obesity examined whether improvements in problem-solving abilities could increase treatment adherence and weight loss. Problem-solving entails actions such as defining a problem, generating alternatives, making decisions, and following through. Healthy but sedentary obese women 50 to 75 years of age from medically underserved rural areas participated in a 6-month lifestyle modification program that involved problem-solving therapy. On average, they lost 8.8 percent of their body weight. Women with large weight reductions (≥10 percent) showed a greater improvement in problem-solving skills than those with smaller reductions (<5 percent). These findings suggest that improving problem-solving skills may help overcome barriers to intervention adherence and thus facilitate weight loss (Murawski et al., 2009).

Although the benefits of walking as a means of weight control have been well documented, the effects of bicycling have been largely unexplored, especially in women. Data from the longitudinal Nurses Health Study II, which tracked weight change between 1989 and 2005 as well as information about exercise habits in premenopausal women, have shed light on this topic. On average, the women gained about 20 pounds during that time period. Those who engaged in bicycling, like those who walked briskly, tended to gain less weight. The magnitude of the effect was related to the amount of bicycling, particularly among women who were overweight or obese. These findings suggest that making bicycling more accessible (e.g., for commuting or running errands) could help to facilitate weight control (Lusk, Mekary, Feskanich, & Wilett, 2010).

Using WHS data on a large cohort of healthy women, investigators examined the relationship between amount of exercise and weight gain during various intervals from 1992 through 2007. Women were classified in three physical activity groups—low (equivalent to <150 minutes per week of moderate-intensity activity), medium (150 to 420 minutes), and high (>420 minutes). Greater physical activity was associated with less weight gain only in normal-weight women. These findings suggest that the amount of weekly moderate-intensity physical activity currently recommended by Federal guidelines (150 minutes) may be insufficient to prevent weight gain over time. They also highlight the importance of controlling caloric intake to prevent weight gain in women who are already overweight (Lee, Djoussé, Sesso, Wang, & Buring, 2010).

The Supporting Healthy Activity and Eating Right Everyday (SHARE) trial tested the effects of culturally specific social support for weight loss in a cohort of Black participants, most of whom were women. No differences in weight loss were observed between the high- and low-support strata. The analysis suggested that having family members or friends involved in one's weight-loss efforts is effective only when they also participate in a program and succeed in losing weight as well (Kumanyika et al., 2009).

A new program, initiated in FY 2009 by NHLBI in partnership with several other NIH entities, is using findings from basic research on human behavior to develop more effective interventions to reduce obesity, focusing on high-risk populations. One NHLBI-supported study in menopausal women seeks to increase physical activity and reduce chronic stress and

depression by reaching out to the individual, her social network, and the community. Another study will develop strategies to reduce stress-induced eating in lower-income pregnant women, focusing on the influence of reward and stress-response systems.

Another NHLBI initiative comprising several clinical trials seeks to help young adults (18 to 35 years of age) to achieve healthy weights through healthy eating and physical activity. More than half of the participants are expected to be women. The trials combine behavioral weight management programs with technologies such as text messaging, online social networking, and Bluetooth-enabled scales. One of the studies, cofunded with NICHD, will test Internet-based programs to promote the health of pregnant and postpartum women, focusing on issues such as diet, physical activity, and weight; the trial expects to enroll about 3,500 ethnically and socioeconomically diverse women in their first 20 weeks of pregnancy.

Another new NIH program led by NHLBI will evaluate methods for preventing excessive weight gain in nonoverweight or moderately overweight children and methods for reducing weight in obese children. The program is innovative in that it will test long-term intervention approaches and address multiple levels of influence, including community youth organizations, schools, primary care providers, and families. At least half the participants in the NHLBI-supported studies are expected to be girls.

The Women's Health Initiative (WHI)

WHI is a major long-term research program designed to address the most frequent causes of death, disability, and diminished quality of life in postmenopausal women—CVD, cancer, and osteoporosis. It enrolled more than 160,000 women in clinical trials and an observational study, all of which have been completed.

The original protocol allowed for followup until March 2005, but participants were subsequently invited to enroll in the WHI Extension Study for followup through 2010. More than 115,000 women opted to participate.

In January 2007, WHI began providing support for solicited research using blood, DNA, and other biological samples and clinical data from WHI participants. The studies will help explain the clinical trial findings and will investigate the impact of genetic and biological markers on common diseases affecting postmenopausal women. A second solicitation for research projects was funded in January 2009. Ten 2-year contracts were awarded that address the following topics:

- Sex hormones in colorectal cancer
- Predictive modeling for CVD
- Predictors of non-Hodgkin lymphoma
- Biomarkers and risk factors for lung cancer in smokers and nonsmokers
- Biomarkers for pancreatic cancer
- Serum protein markers for early detection of ovarian cancer
- Inflammation and thrombosis in CVD
- Genetic risk factors for hip fracture
- Omega-3 fatty acid biomarkers and cognitive decline
- Markers of rheumatoid arthritis, inflammation, thrombogenesis, and CVD risk

In January 2010, the WHI SNP Health Association Resource (SHARe) dataset was made available for research use. It includes extensive data on 12,008 Black and Hispanic women 50 to 79 years of age who enrolled in 1 or more components of the WHI program. WHI SHARe is included in the NIH Database of Genotypes and Phenotypes (dbGaP), a Web-based resource for archiving and distributing data from genomewide association studies (GWAS)—studies that explore associations between genetic variations and observable traits (phenotypes) such as weight, cholesterol level, or the presence or absence of a disease. Launched in December 2006, dbGaP was developed and is operated by the National Center for Biotechnology Information, a division of the National Library of Medicine. To protect the confidentiality of study participants, dbGaP includes only deidentified data (i.e., data stripped of names, Social Security numbers, and other personal information) from participants who have consented to genetic research and to allowing their data to be shared. Although summary data and analyses are available to any researcher,

individual-level data can be used only by authorized investigators who meet requirements for access outlined in the NIH GWAS policy (http://grants.nih.gov/grants/gwas/index.htm). Researchers are prohibited from redistributing data or trying to determine the identity of participants.

An additional 5-year extension of WHI began October 1, 2010. Its main objectives are to take advantage of the large WHI cohort to explore factors contributing to CVD burden in aging women; increase data sharing; launch a new generation of ancillary studies, consortium studies, and clinical trials; and increase mentoring of new investigators. This initiative will emphasize opportunities to apply newer technologies such as genomics, proteomics, telomere length measures, metabolomics, expression studies, and epigenetics to serial blood samples.

Main Findings on Postmenopausal Hormone Therapy

WHI included two randomized clinical trials of postmenopausal hormone therapy—a study of estrogen plus progestin (E+P) in women who had an intact uterus and a study of estrogen alone in women who had undergone a hysterectomy. Both were designed to test the hypothesis that long-term use of hormone therapy could reduce risk of CHD. The E+P trial was halted ahead of schedule in July 2002. Compared with women taking a placebo, study participants taking hormones experienced higher rates of heart attack, stroke, blood clots, and invasive breast cancer. Although the women taking hormones had a lower incidence of colon cancer and fewer hip fractures, the overall balance of risks and benefits was unfavorable. In March 2004, the estrogen-alone trial also was halted ahead of schedule. After an average of nearly 7 years of treatment, estrogen therapy had no effect on CHD risk, but it increased risk of stroke and blood clots in the legs. No evidence of elevated breast cancer risk was found, and a favorable effect on bone health emerged. On balance, however, the trial indicated that postmenopausal hormone therapy should not be prescribed for chronic disease prevention.

Following release of these findings, use of postmenopausal hormone therapy in the United States declined dramatically. Thereafter, the incidence of breast cancer also dropped, but the cause of the decrease remained controversial. Subsequent analysis of additional data from women enrolled in the E+P trial showed that the elevated breast cancer risk at the end of the trial decreased rapidly after stopping hormone therapy. In the concurrent observational study, users of E+P initially had a twofold increased risk of breast cancer compared with nonusers, but this difference also decreased rapidly in about 2 years, coinciding with large reductions in hormone therapy use after 2002. The declines in breast cancer incidence were unrelated to changes in the frequency of mammograms (Chlebowski et al., 2009a).

Extended followup of clinical trial participants confirmed that E+P users experienced a greater incidence of invasive breast cancer than women taking placebo pills. Moreover, the cancers were relatively more advanced (e.g., they more frequently involved positive lymph nodes) when diagnosed. In addition, death rates from breast cancer were higher among E+P users and more deaths from any cause occurred among the cohort of women who developed breast cancer. These new data suggest that future reductions in breast cancer can be expected as a result of declines in postmenopausal hormone use, and they add to the body of evidence to be considered by women and their doctors as they weigh the risks and benefits of treatment for menopausal symptoms (Chlebowski et al., 2010a).

Continued study of the cardiovascular effects of postmenopausal hormone therapy confirmed the short-term risks associated with E+P treatment. Researchers reported a trend toward an increased risk of heart disease during the first 2 years of hormone therapy among women who began therapy within 10 years of menopause, and a more marked elevation of risk among women who began hormone therapy more than 10 years after menopause. Analyses indicated that, overall, the risk of heart disease more than doubled within the first 2 years of taking E+P. The difference in the initial level of risk did not appear related to age, based on findings that the increased risk was similar among women in their 50s and

60s (Toh, Hernández-Diaz, Logan, Rossouw, & Hernán, 2010).

Selected Reports on CVD

An analysis of data from WHI participants found that a simple measurement—the pulse rate of a woman at rest—predicts heart attack or CHD death independently of common risk factors such as smoking. Although previous studies had found this to be the case in men, the relationship between heart rate and cardiovascular events in women was unclear. Women with high heart rates were significantly more likely to experience a coronary event than women with low rates, regardless of their level of physical activity. The correlation was stronger among women 50 to 64 years of age than among older women, but it did not differ between White women and women of other races or between women with and without diabetes (Hsia et al., 2009).

Long-term followup of participants in the WHI observational study documented the usage and benefits of aspirin among 8,928 women with stable CVD. Forty-six percent of the women reported taking aspirin, of whom 30 percent took 81 milligrams and the remainder 325 milligrams. Black study participants and Medicaid beneficiaries were less likely than others in the group to be taking aspirin. After adjustment for confounding variables, aspirin use—regardless of dosage—was associated with significantly lower risk of mortality from any cause and of CVD mortality in particular (Berger et al., 2009).

Treatment with moderate doses of calcium plus vitamin D (CaD) did not seem to alter the amount of coronary artery calcified plaque (a marker for atheromatous plaque burden and a predictor of future risk of CVD events) among postmenopausal women (Manson et al., 2010).

Although some short-term studies had found that CaD supplementation appeared to lower levels of total cholesterol, LDL cholesterol, and triglycerides and to raise levels of HDL cholesterol somewhat, CaD supplementation was not associated with lipid changes over 5 years in the WHI clinical trial cohort (Rajpathak et al., 2010).

CaD supplementation did not reduce either blood pressure or the risk of developing hypertension over 7 years of followup (Margolis et al., 2008).

Analysis of women 50 to 59 years of age who participated in the hormone trials found that higher levels of pulse pressure and systolic blood pressure were strong determinants of coronary artery calcium, whereas diastolic blood pressure was inversely related (Allison et al., 2008).

A strong, positive, independent association was found between current or past smoking, as well as the amount smoked, and clinically important abdominal aortic aneurysm events (repairs and ruptures). Diabetes and postmenopausal hormone therapy were negatively associated (Lederle et al., 2008).

Current drinking was associated with a lower risk of total mortality among White women, regardless of hypertensive status, and among Black women with hypertension but not those without (Freiberg et al., 2009).

Selected Reports on Other Topics

Breast Cancer

No relationship was found between dietary vitamin D or calcium intake and mammographic density, a strong predictor of breast cancer risk, in postmenopausal women (Bertone-Johnson et al., 2010).

New-onset breast tenderness that occurred during E+P therapy was associated with increased breast cancer risk, a finding that suggests the appearance of this symptom may identify high-risk women (Crandall et al., 2009).

High levels of fasting insulin and of circulating estrogen were independent risk factors for postmenopausal breast cancer and largely explained the association between obesity and the risk of breast cancer in postmenopausal women (Gunter et al., 2009).

A history of migraine was associated with a lower risk of breast cancer, and this relationship was independent of recent nonsteroidal anti-inflammatory drug (NSAID) use (Li et al. 2010b).

Alcohol use at study entry was associated with higher breast cancer risk overall and

higher risk of hormone receptor–positive disease. Among women with hormone receptor–positive breast cancers, the association between alcohol use and increased breast cancer risk was observed for invasive lobular carcinoma but not for invasive ductal carcinoma (Li et al., 2010a).

Stressful life events were not independently associated with breast cancer risk (Michael et al., 2009).

Time spent outdoors during daylight hours throughout the year was associated with a reduced risk of breast cancer, a finding that supports the hypothesis that vitamin D may protect against breast cancer (Millen et al., 2009).

Use of oral bisphosphonates was associated with significantly lower invasive breast cancer incidence, suggesting that these drugs may have inhibiting effects on the disease (Chlebowski et al., 2010c).

Assignment to a low-fat diet was associated with a lower subsequent rate of breast cancer among women who reported hot flashes at the outset of the study but not among women without hot flashes, suggesting that hot flashes may identify a subgroup of women whose breast cancer risk might be lessened via dietary modification (Caan et al., 2009).

Cigarette smoking was not associated with development of ductal carcinoma in situ (DCIS), a risk factor for subsequent breast cancer and the postulated penultimate stage preceding invasive breast cancer (Kabat et al., 2010a).

Although other research has shown a modest association between alcohol intake and breast cancer risk, in this study, alcohol intake was not related to DCIS, suggesting that alcohol may exert its effect later in the carcinogenic process (Kabat et al., 2010b).

Recreational physical activity and anthropometric factors (BMI, waist circumference) showed no association with risk of DCIS in postmenopausal women (Kabat et al., 2010c).

Other Cancers

No association was found between high dietary intake of carbohydrates and increased risk of pancreatic cancer (Simon et al., 2010).

Multivitamin use had little or no influence on the risk of common cancers in postmenopausal women (Neuhouser et al., 2009).

Although use of E+P did not increase incidence of lung cancer in postmenopausal women, it increased the number of deaths from lung cancer, particularly non-small-cell lung cancer. (Chlebowski et al., 2009b).

Use of estrogen alone did not increase incidence of lung cancer, and, unlike the case with E+P, it also had no effect on lung cancer deaths (Chlebowski et al, 2010b).

Bone Health

Although use of loop diuretics at any time in the past was not associated with falls, fractures, or changes in bone mineral density (BMD) in postmenopausal women, prolonged use of these drugs was associated with higher fracture risk (Carbone et al., 2009).

Use of proton pump inhibitors (potent gastric acid–suppressing medications) was not associated with hip fractures but was modestly associated with fractures of the spine, forearm, or wrist and with total fractures (Gray et al., 2010).

High blood levels of the amino acid homocysteine were associated with an increased risk of hip fracture, regardless of dietary folate, vitamin B-6, or vitamin B-12 intake; the association could therefore be accounted for by poor renal function (Leboff et al., 2009).

A low-fat diet with increased consumption of fruits, vegetables, and grains modestly reduced the risk of multiple falls, but slightly lowered hip BMD did not change the risk of osteoporotic fractures. (McTiernan et al., 2009).

Cognitive Function

Cognitive decline, on average, preceded or occurred simultaneously with physical performance decline in older women (Atkinson et al., 2010).

Postmenopausal women who suffered from one or more psychiatric disorders were more than twice as likely to be diagnosed with cognitive impairment as those with no psychiatric disorder. Older age, White race, and diabetes were also associated with cognitive impairment (Colenda et al., 2010).

Small decrements in global cognitive function associated with postmenopausal estrogen therapy persisted after estrogen was stopped, but the differences in cognitive function were small and would not be detectable or have clinical significance for an individual woman (Espeland et al., 2010).

Estrogen therapy, either alone or with progestin, was not associated with a significant increase in subclinical cerebrovascular disease, which had been hypothesized to be a cause of the higher risk of dementia seen in estrogen users (Coker et al., 2009).

Other Health Issues

Despite early preservation of lean body mass with postmenopausal hormone therapy, the therapy did not ameliorate long-term age-associated loss of lean body mass (Bea et al., 2011).

Hormone therapy provided no overall protection against functional decline (measured by grip strength, chair stands, and timed walk) in nondisabled postmenopausal women 65 years or older (Michael et al., 2010).

Higher protein consumption was associated with a strong, independent, dose-responsive lower risk of developing frailty (low physical function or activity, exhaustion, unintended weight loss) in older women (Beasley et al., 2010).

Consumption of a healthy diet that included foods rich in a variety of vitamins and minerals was associated with lower occurrence of the most common type of cataract in the United States (Mares et al., 2010).

High-fat diets were associated with risk of intermediate age-related macular degeneration, but diets high in monounsaturated fatty acids appeared to be protective (Parekh et al., 2009).

Middle-aged and older women who reported prior-year abuse (physical, verbal, or both) had significantly higher mortality risk, even when other factors were taken into account, than women who did not report abuse (Baker et al., 2009).

Residential and workplace insecticide exposures were associated with risk of autoimmune rheumatic diseases (i.e., rheumatoid arthritis, systemic lupus erythematosis) in postmenopausal women (Parks et al., 2011).

Women who had received breast implants decades earlier were generally healthier, more physically fit, and less likely to be obese, but they reported more social and psychological disability (Rubin et al., 2010).

Being overweight or obese was associated with progression of pelvic organ prolapse, and weight loss did not appear to affect regression (Kudish et al., 2009).

Estrogen use increased risk of kidney stones, the risk was independent of progestin coadministration, and the effects did not vary significantly according to whether the women had a history of kidney stones before entering the trial (Maalouf et al., 2010).

Gender Analysis

As noted under Accomplishments, researchers have uncovered a number of gender differences with regard to various aspects of cardiovascular, lung, and blood diseases and sleep disorders. The findings encompass differences in risk factors, symptoms, diagnosis, response to preventive and therapeutic interventions, and prognosis. The long-running Framingham Heart Study continues to yield comparisons of CVD risk in three generations of women and men, and the Jackson Heart Study and the Hispanic Community Health Study are expected to provide sources of data on gender differences in minorities.

Initiatives

Broad Agency Announcements

Toward Maximizing the Scientific Value of the Biological Specimens From the Women's Health Initiative II. This initiative solicited proposals for investigations using blood, DNA, and other biological samples and clinical data from WHI participants. (BAA-NHLBI-WH-09-01).

Studying Community Programs To Reduce Childhood Obesity. This program will examine outcomes associated with community programs to reduce childhood obesity through policy, environmental, and educational activities that address achievement of energy balance through diet and physical activity (BAA-NHLBI-HC-10-15).

Request for Applications

Childhood Obesity Prevention and Treatment Research Consortium. This initiative supports multiple controlled trials to test innovative interventions to prevent excess weight gain in nonoverweight or overweight young people and/or to achieve healthy weight in those who are obese (RFA-HL-10-004&005, with NICHD).

Program Announcements

Exploratory/Developmental Clinical Research Grants in Obesity. Projects funded via this solicitation will conduct exploratory/developmental clinical studies to accelerate the development of effective interventions for prevention or treatment of overweight or obesity in adults or children (PA-09-124, with NIDDK, NCI, NCCAM, ODS).

Community-Based Partnerships for Childhood Obesity Prevention and Control: Research To Inform Policy. This program seeks to enhance childhood obesity research by forming local, State, or regional teams of researchers, policymakers, and other relevant stakeholders such as community representatives, public health practitioners, and educators (PA-09-141, with NCI, OBSSR, CDC NCCDPHP).

Improving Diet and Physical Activity Assessment. This initiative supports research to improve measurements of diet and physical activity through development of better instruments, innovative technologies, and/or applications of advanced statistical/analytic techniques (PAR-09-224, with NCI, NIA, NIDDK, NICHD, NINR, ODS).

Nutrition and Physical Activity Research To Promote Cardiovascular and Pulmonary Health. This program supports research to improve knowledge of the influences of diet, physical activity, and sleep on cardiovascular and pulmonary conditions; increase the evidence base for public health recommendations and clinical guidelines regarding these lifestyle behaviors; and develop and test strategies to improve adoption of the recommendations (PA-09-243&244, with NCCAM, NINR).

Obesity Policy Research: Evaluation and Measures. The goals of this program are to conduct evaluation research on obesity-related "natural experiments" (i.e., community- and other population-level public policy interventions that may affect diet and physical activity behavior) and develop and validate instruments and methodologies to assess the food and physical activity environments at the community level (PA-10-027. 028, 029, with NCI, NIDDK, OBSSR, NICHD, CDC NCCDPHP).

Diet Composition and Energy Balance. This solicitation will support investigations of the role of diet composition in energy balance, ranging from basic studies of the impact of micro- or macronutrient composition on appetite, metabolism, and energy expenditure through clinical studies evaluating the efficacy of diets differing in nutrient composition, absorption, dietary variety, or energy density for weight loss or weight maintenance (PA-10-152, NIDDK, NICHD, NCI, NCCAM, NIA, NIAAA, ODS).

Conferences and Working Groups

Sleepiness and Health-Related Quality of Life, April 13–14, 2009. The purpose of this workshop was to characterize the extent of sleep problems and examine evidence that they are an emerging threat to health.

Converging Concepts in Cellular Therapy, April 23–24, 2009. This workshop was designed to stimulate discussions about advances made in cellular therapy research and development, consider the benefits and risks associated with the clinical use of these therapies, and provide a venue for information exchange.

Thalassemia: Clinical Priorities/Clinical Trials, May 20–21, 2009. The overall goal of the workshop was to identify needs for clinical research and trials to reduce the burden of thalassemia.

Translational and Clinical Research in Thrombosis and Hemostasis, June 19, 2009. This working group brought together expert scientists and clinicians to discuss the status of translational and clinical research in thrombosis and hemostasis and identify research priorities.

COPD 2009: Assessment of the Current State of the Art for Basic and Clinical Research, June 29–30, 2009. This workshop was convened to evaluate the current state of basic and clinical research in COPD and identify important areas of research to be addressed.

Clinical Research in the Critically Ill Patient: Beyond Mortality, August 5–6, 2009. The goal of the workshop was to assess the current state of clinical research addressing acute lung injury and acute respiratory distress syndrome, identify research needs, and develop recommendations for clinical research in the near future.

Getting From Genes to Function in Lung Disease, September 3–4, 2009. This workshop addressed genetic variance in lung disease risk, the function of the associated genetic variations, and the mechanisms by which they alter individual risk for disease or pathogenesis.

International COPD Genetics Workshop, July 13–14, 2010. This workshop focused on contributions of genetic factors to the development and progression of COPD.

Virtual Reality Technologies for Obesity and Diabetes Education and Behavior Change, July 15–16, 2010. This workshop explored the research potential of virtual reality technologies as tools for behavioral and neuroscience studies in diabetes and obesity.

Nutrition and Diet in Registry and Surveillance Studies of Hemoglobinopathies, August 23–24, 2010. This working group met to identify priorities for basic, clinical, translational, and population-based research on nutrition and diet in individuals with sickle cell disease or thalassemia.

Sickle Cell Disease Clinical Research, August 25–27, 2010. This annual meeting provides updates on clinical trials, basic and translational research, and associated activities.

Infection, Immunity, Inflammation, and Atherothrombosis: New Directions for Improving Patient Care, September 6–7, 2010. The objectives of the conference were to assess what is known about the role of infection, immunity, and inflammation in the development and progression of atherothrombotic diseases, review emerging technologies, and identify research needs.

Defining Molecular Pathways and Mechanisms That Predict CVD Risk Associated With Sleep-Disordered Breathing, September 7–8, 2010. The purpose of this workshop was to identify molecular mechanisms and pathways associated with CVD risk in patients with sleep-disordered breathing.

Personalized Approaches to Cardiovascular Medicine: New Directions for Improving Patient Care, September 28–30, 2010. The purpose of the meeting was to evaluate the prospects for using genetic and genomic research to generate new knowledge that might reduce CVD morbidity and mortality.

Comparative Effectiveness Research for Lung Diseases, September 30–October 1, 2010. This meeting was convened to identify and evaluate the various management options (e.g., drugs, devices, procedures, behavioral interventions, implementation methods) used to treat lung diseases.

Special Populations

Heart disease and stroke remain the first and fourth most common causes of death of all Americans, and African Americans suffer disproportionately from these diseases. For example, in Mississippi, the age-adjusted CVD mortality for African-American women is 75 percent higher than for White women, and African-American men have rates 47 percent higher than those of White men. To investigate disparities in CVD prevalence, severity, and mortality among African Americans, the Jackson Heart Study (JHS) was initiated in 1998. The ongoing project has enrolled 5,500 African-American women and men living in the Jackson, MS, area. It is uniquely positioned to identify factors that influence the development and worsening of CVD in African Americans, with an emphasis on manifestations related to hypertension such as coronary artery disease, heart failure, stroke, peripheral arterial disease, and renal disease.

During FY 2006, NHLBI awarded contracts for the Hispanic Community Health Study, a long-term population study analogous to JHS, in Latinos. As many as 16,000

individuals—4,000 at each of 4 sites—are undergoing a series of physical examinations and interviews to identify the prevalence of a wide variety of conditions, including heart disease, stroke, asthma, COPD, sleep disorders, dental disease, hearing disorders, diabetes, kidney and liver disease, and cognitive impairment. The study is assessing risk factors such as diet, physical activity, obesity, smoking, blood pressure, blood lipids, acculturation, social and economic disparity, psychosocial factors, occupation, health care access, the environment, and medication and supplement use. It also will determine the role of cultural adaptation and disparities in the prevalence and development of disease. Participants will range in age from 18 to 74 years and be Mexican Americans, Puerto Ricans, Cuban Americans, and Central/South Americans.

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Online Resources

NHLBI Strategic Plan
http://apps.nhlbi.nih.gov/strategicplan/Default.aspx

Examining Heart Attacks in Young Women (VIRGO)
http://clinicaltrials.gov/ct2/show/NCT00597922

The Heart Truth
http://www.nhlbi.nih.gov/educational/hearttruth

Clarification of Optimal Anticoagulation Through Genetics
http://clinicaltrials.gov/ct2/show/NCT00839657?term=COAG&rank=1

NHLBI, *Diseases and Conditions Index*
http://www.nhlbi.nih.gov/health/dci/index.html

NHLBI, The Diagnosis, Evaluation and Management of von Willebrand Disease
http://www.nhlbi.nih.gov/guidelines/vwd

U.S. Department of Health and Human Services, *Genome-wide Association Studies (GWAS)*.
http://grants.nih.gov/grants/gwas/index.htm

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National Institute on Aging

Executive Summary

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer's disease and other dementias, menopause and menopausal hormone therapy, osteoporosis, physical disability, and other diseases and conditions. During fiscal year (FY) 2009–2010, NIA-supported researchers made important progress in a number of women's health-related areas, including the following:

Reproductive Health/Menopause

Research continued through the Study of Women's Health Across the Nation (SWAN) and other studies on the etiology and treatment of menopause-related symptoms. For example, SWAN investigators have found that patterns of hormonal activity fluctuate across the menopausal transition and that specific hormonal patterns are not related to the presence or absence of hot flashes. However, gains in body fat were associated with increased reporting of hot flashes. A variety of interventions for the most common symptoms of the menopausal transition are currently under study through the MS FLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) initiative, and a phase I clinical trial of ER2-selective phytoestrogens (phytoSERMS) in women experiencing hot flashes has been initiated. NIA investigators also identified genetic variants associated with age at menarche and menopause.

Cognitive Health and Alzheimer's Disease

Although in previous studies, menopausal hormone therapy (MHT) has been associated with an increased risk of cognitive decline and dementia, some recent research suggests that a "window of opportunity" exists during which MHT exerts a protective effect on the brain and after which such treatment is ineffective or even dangerous with regard to cognition. NIA-supported investigators continue to study the effects of different forms of menopausal hormone therapy on cognition, as well as the mechanisms through which estrogen and related hormones work on the brain.

Sex and Gender Differences

American women lag significantly behind their counterparts in other higher income nations in terms of longevity, and since 1980, the pace of gains in life expectancy of older U.S. women has slowed markedly compared with other industrialized countries. An NIA-sponsored National Research Council panel found strong evidence that smoking is responsible for a good deal of the divergence in female life expectancy. Other factors, including obesity, diet, exercise, and economic inequality, also may play a role, but the evidence is less clear cut. Investigators continued to explore the reasons behind the sex differentials in disability and mortality across the life span, including divergent levels of longevity among women in high-income nations.

New and ongoing research initiatives focusing on women's health include the following:

- A solicitation for research applications to study the etiology and/or mechanisms regulating bone mass that are regulated by a "central relay" in the brain
- A study of intermittent energy restriction (IER)—brief periods of dramatically reduced caloric intake—versus continuous reduction in caloric intake to reduce breast cancer risk and improve insulin tolerance
- The Women's Health Initiative Study of Cognitive Aging (WHISCA), which investigates both on-trial and long-term posttrial effects of exposure to MHT on cognitive aging within the context of the Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative (WHI) more generally
- A study of raloxifene to treat Alzheimer's disease in women
- The SWAN Sleep Study, in which investigators from four SWAN sites are examining sleep patterns and factors that may affect sleep during the menopausal transition

In addition, NIA supports a number of communication and education activities aimed at women, career development activities, and research pertaining to the specific health concerns of minority women.

Introduction

Older women outnumber older men in the United States, and the proportion of the population that is female increases with age. In 2008, women accounted for 58 percent of the population age 65 and older and for 67 percent of the population age 85 and older. Despite living longer, however, older women are more likely to report depressive symptoms or limitations in physical function, are more likely to live alone (a potential indicator or risk factor for isolation, lack of caregivers, or lack

of support), and live in poverty at a disproportionately high rate (Federal Interagency Forum, 2010). American women also lag significantly behind their counterparts in other higher income nations in terms of longevity, and since 1980, the pace of gains in life expectancy of older U.S women has slowed markedly compared with other industrialized countries (National Research Council, 2011).

The National Institute on Aging (NIA) supports a diverse portfolio of research on older women's health, including studies on the following topics:

- Cognitive aging, including Alzheimer's disease and other types of dementia
- Menopause and menopausal hormone therapy
- Osteoporosis and hip fracture
- Physical disability
- Caregiver burden
- Decline in function of older women
- Age-related muscle loss
- Cancer in older women
- Demography and economics of aging
- Ovarian hormone influences on brain structure and function
- Premature ovarian failure
- Sex differences in aging and age-related health conditions

A Women's Health Liaison in the Office of Planning, Analysis, and Evaluation coordinates NIA activities related to women's health and serves as liaison to the NIH Coordinating Committee on Research on Women's Health. Recent accomplishments in women's health, as well as ongoing and new research initiatives with a particular emphasis on women, are described below.

Accomplishments

Menopause and Beyond: The Study of Women's Health Across the Nation

NIA's flagship study of women's health is the Study of Women's Health Across the Nation (SWAN), an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from pre- to postmenopause. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in White, African-American, Chinese, Japanese, and Hispanic women. Funded initially in 1994, SWAN is a cooperative agreement consisting of seven clinical field sites, a central reproductive hormone laboratory, a coordinating center, an advisory panel, and a repository of blood, urine, and DNA specimens. The study is supported by NIA, the National Institute of Nursing Research, and the NIH Office of Research on Women's Health (ORWH).

Selected findings from SWAN in 2009–2010 include the following:

Depression. Although most women do not become depressed at midlife, high levels of depressive symptoms are more common in peri- and postmenopausal women than in premenopausal women. SWAN investigators have found that higher testosterone levels are associated with greater risk of depressive symptoms during the menopausal transition and that an increased level of C-reactive protein, a marker for inflammation, is modestly associated with an increase in depressive symptoms. Investigators also found that a lifetime history of major depression is a strong predictor of the metabolic syndrome, an interrelated group of risk factors for heart disease, diabetes, and stroke, and that recurrent major depression may be a risk factor for progression of atherosclerosis, with African-American women particularly vulnerable to the effects of depression on early atherosclerotic disease.

Obesity. SWAN investigators found that higher androgens, lower sex hormone-binding globulin, surgical menopause, and early hormone therapy use predict incident obesity (body mass index ≥ 30) and/or severe obesity (body mass index ≥ 35). Hostility is associated with increased visceral fat (fat that lies deep within the abdomen and is associated with an increased risk of cardiovascular disease), as are higher levels of bioavailable testosterone.

However, higher levels of physical activity are associated with reduced visceral fat in both African-American and White women.

Cardiovascular disease. SWAN investigators found that women experience a unique increase in lipids at the time of the final menstrual period, suggesting that monitoring lipids in perimenopausal women and treating high levels as appropriate could be part of efforts to prevent coronary heart disease.

Vasomotor symptoms. Investigators found that patterns of hormonal activity fluctuate across the menopausal transition and that specific hormonal patterns are not related to the presence or absence of hot flashes. However, gains in body fat are associated with increased reporting of hot flashes.

Cognitive Health and Alzheimer's Disease

Some change in cognitive function is normal with advancing age, although the mechanisms underlying these changes are not fully understood in either men or women. However, for some people, cognitive change can be the harbinger of a more serious underlying condition. Alzheimer's disease (AD) is the most common cause of dementia among people age 65 and older and is a major public health issue for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. Estimates of how many people in the United States currently have AD differ, with numbers ranging from 2.4 million to 5.1 million, depending on how AD is measured. But scientists agree that unless the disease can be effectively treated or prevented, the numbers will increase significantly if current population trends continue (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). Risk of developing AD at any specific age is similar for women and men; however, because women live longer, there are significantly more women than men with AD, and in a recent epidemiologic study, the overall lifetime risk of developing AD for a woman was nearly twice that for a man (32 percent vs. 18 percent) (Hebert, Scheer, McCann, Beckett, & Evans, 2001). At the same time, in a recent study, amnestic mild cognitive impairment (MCI), often a precursor condition to AD, was more common in men than in women, suggesting that sex differences in disease course may exist; for example, the investigators hypothesize that women may transition from MCI to dementia later in life than men but more abruptly (Petersen et al., 2010).

Menopausal Hormone Therapy and Alzheimer's Disease

Some previous studies have suggested that postmenopausal women using hormone therapy may have a reduced risk of developing cognitive decline. However, results from the Women's Health Initiative Memory Study (WHIMS), a substudy of the Women's Health Initiative, contradicted these previous findings, with results suggesting that women age 65 and older receiving either conjugated equine estrogens alone or Prempro, a particular form of estrogen plus progestin hormone therapy, could be at increased risk of developing dementia, including AD. These studies were stopped earlier than planned when researchers found that the hormone therapy increased health risks and failed to prevent heart disease.

However, some research suggests that a "window of opportunity" exists during which menopausal hormone therapy exerts a protective effect on the brain, and after which such treatment is ineffective or even dangerous with regard to cognition. NIA-supported investigators continue to study the effects of different forms of menopausal hormone therapy on cognition, as well as the mechanisms through which estrogen and related hormones work on the brain:

- In one recent study, the most commonly prescribed estrogen therapy in the United States, conjugated equine estrogens (Premarin), impaired cognitive performance in a rat model of naturally occurring menopause but benefited cognition in rats whose ovaries were surgically removed ("induced" menopause).
- Several recent studies implicate the use of MPA (medroxyprogesterone acetate), the most commonly used progestin component of menopausal hormone therapy, in age-related cognitive decline. In one study, investigators found that MPA impaired learning, delayed memory retention, and exacerbated overnight forgetting in a rat

model of surgical menopause. In another, ovariectomized rats were placed on one of several hormone regimens for 6 months. The rats receiving 17β-estradiol, a form of estrogen, in combination with MPA performed significantly worse on a spatial memory task than all other groups receiving hormone replacement. However, the rats receiving regular doses of 17β-estradiol performed better on the task than the rats receiving the drug cyclically and a control group of rats receiving no treatment.

- In a study of postmenopausal women, longtime (10+ years) users of menopausal hormone therapy (conjugated equine estrogens with or without MPA) demonstrated increased activation of brain regions used for visual working memory and increased performance task compared with women who had never used hormone therapy.
- Basic research conducted by NIA intramural investigators in collaboration with extramural colleagues has revealed that multiple brain regions outside the neuroendocrine reproductive axis are sensitive to ovarian hormone status, including areas such as the prefrontal cortex that are critical for cognitive health. Recent studies indicate that menopause potently regulates synaptic structure in the prefrontal cortex and other memory-related brain regions, potentially comprising a key mechanism by which aging affects cognitive aging. Identifying treatment strategies that promote optimal cognitive outcomes is an important focus of ongoing research efforts.

Genetics of Menopause and Menarche

NIA-supported investigators participated in major genomewide association studies to identify the genetic variants associated with age of menarche and age of menopause. Thirty new loci for age at menarche were identified by a meta-analysis of genomewide association studies. Further analysis revealed that four of the genes had previously been associated with body mass index, three were implicated in energy homeostasis, and three are involved in hormonal regulation. The analysis of the age-of-menopause genes is in progress and should be published in the coming months.

Migraines With Aura in Middle Age Associated With Late-Life Brain Lesions in Women

Women who suffer from migraine headaches in middle age accompanied by neurologic aura (visual disturbances, dizziness, or numbness that can precede migraines) are more likely to have damage to brain tissue in the cerebellum later in life. The investigators noted that many people have these types of "silent" brain lesions, but their effect on physical and cognitive function in older people is not well understood.

Sleep in Older Women

Sleep disturbance and insomnia are commonly reported by postmenopausal women. However, the relationship between hormone therapy and sleep disturbances in postmenopausal women is poorly understood. In a recent study, the relationship between hormone therapy and sleep-wake cycle was assessed using data from the Study of Osteoporotic Fractures (SoF), a long-running study of osteoporosis and other age-related conditions in older women. The authors demonstrated that postmenopausal women currently using hormone therapy had significantly better sleep quality. SoF investigators also found that older women with weak circadian activity rhythms have higher mortality risk.

Intermittent Caloric Restriction: An Effective Weight Loss Strategy?

Excess weight and weight gain during adulthood increase the risk of an array of health conditions; however, poor compliance with strict weight loss regimens is common among both men and women. Recently, NIA intramural investigators conducted a randomized clinical trial comparing the feasibility and effectiveness of two different diets in premenopausal women: intermittent energy restriction (IER)—brief periods of sharp reduction in calorie intake—and continuous energy restriction (CER)—a long-term reduction in calorie intake. They found that both diets resulted in significant weight loss, improved insulin sensitivity, and improvements in other health

biomarkers. Participants reported that the IER diet was much easier to adhere to and maintain than the CER diet. These findings suggest that IER diets could be an effective strategy for improving long-term overall metabolic health in women.

Risk/Benefit Index for Breast Cancer Chemoprevention

Previous studies have shown that the drug raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women. However, both drugs are associated with significant health risks. Investigators from NIA and the National Cancer Institute, working in partnership with extramural researchers, have developed a comprehensive index to quantify risks and benefits of chemoprevention with tamoxifen and raloxifene. Tables describe the risks and benefits of raloxifene and tamoxifen and can help identify groups of women for whom the benefits outweigh the risks. This index can complement clinical evaluation in deciding whether to initiate chemoprevention and in comparing the benefits and risks of raloxifene versus tamoxifen.

Premature Ovarian Failure

Genetic analyses have shown that mutations in the transcription factor FOXL2 cause blepharophimosis epicanthus inversus syndrome, with attendant premature ovarian failure in affected women. Subsequent work demonstrated that FOXL2 is the only gene known to be uniquely expressed in ovaries and is required both for ovarian follicle formation and for the determination and maintenance of female somatic sex. Its action can help to preserve female fertility and also prevents partial conversion of a developing ovary into a testis.

Gender Analyses

Females generally have lower mortality than males at every age. At the same time, women have worse self-rated health and more hospitalization episodes than men. Two recent NIA-supported studies examined sex differences in health at older ages. The first compared older adults in Denmark, the United States, and Japan and found that sex differences in mortality rates, handgrip strength, and physical disability at older ages are broadly similar across the three populations. Women tend to score higher on measures of depression than men, and women and men have similar cognitive function and self-rated health in all three countries. Japan is an outlier among rich countries in the magnitude of older women's mortality advantage, most likely because of large differences in cohort smoking experience between men and women. (Japanese men smoke more, and Japanese women less, than elsewhere.) (Oksuzyan et al., 2010).

The population for the second study was a representative sample of Danes born in 1905 and still alive in 1998. Three examinations were performed when they were 95, 98, and 100 years old, and mortality has been followed up through age 103. Nonagenarian men had greater initial grip strength but a faster rate of decline than did the women. Initial grip strength was inversely related to mortality, and there was no sex difference in the predictive value of grip strength. Contrary to some previous studies, the rate of decline was not significantly associated with mortality; therefore, the faster rate of physical decline among men does not emerge in this study as an explanation for men's mortality disadvantage (Oksuzyan, Maier, McGue, Vaupel, & Christensen, 2010).

Sex and gender analyses are included in many NIA clinical studies, and several studies focus specifically on sex and gender differences in older age:

- The Rancho Bernardo Study, a long-running study of sex-specific rates of and risk factors for bone loss and fracture in community-dwelling men and women
- A study assessing the extent to which sex hormones exert gender-specific and age-related effects on the respiratory control system
- Studies of gender differences and individual variability in human aging

Explaining Divergent Levels of Longevity in High-Income Countries

As noted above, American women do not live as long as women in other high-income nations, and since 1980, the pace of gains in life expectancy of older U.S. women has slowed markedly compared with other industrialized countries. To explore potential explanations for divergent longevity trends, NIA sponsored a National Research Council (NRC) panel. The panel found strong evidence that smoking is responsible for a good deal of the divergence in female life expectancy. Other factors, including obesity, diet, exercise, and economic inequality, also may play a role, but the evidence is less clear cut (Crimmins, Preston, & Cohen, 2011a; Crimmins, Preston, & Cohen, 2011b)

Initiatives

New Initiatives in 2009–2010

Mechanisms Mediating Changes in Central Regulation of Bone Mass (RFA AG-11-006). Recent basic research findings have indicated that the regulation of bone mass is highly complex, involving not just the bones themselves but also a "central relay" involving serotonergic neurons in the brain. For example, patients treated with selective serotonin reuptake inhibitors (SSRIs) have been shown to have significantly higher fracture risk than age-and sex-matched patients not taking SSRIs. In FY 2010, NIA issued a research solicitation for applications to study the etiology and/or mechanisms regulating bone mass that are regulated by a central relay. These studies will significantly enhance our understanding of the integrated nature of the age-related changes in bone mass and, in all likelihood, will identify novel therapeutic targets to prevent bone loss in older women and men.

Trends in Morbidity and Mortality: Sex Differences and Cross-National Research (RFA-AG-11-004). NIA is supporting research aimed at advancing knowledge about the reasons behind the divergent trends observed in health and longevity at older ages, both across industrialized nations and across geographical areas in the United States. Sex and gender differences in health and longevity are an important aspect of this initiative.

Window of Opportunity of Estrogen Therapy for Neuroprotection. This January 2010 conference brought together experts in the field of aging and endocrinology to discuss the development of translational research models and focused on the critical period to achieve optimal neuroprotection with hormone/estrogen therapy. A report of the workshop appeared in the *New York Times* (Gorney, 2010; http://www.nytimes.com/2010/04/18/magazine/18estrogen-t.html). An upcoming special issue of *Brain Research* titled "The Window of Opportunity: Menopause and Hormone Replacement Therapy" will contain the papers presented during this meeting.

12th Biennial Graylyn Conference on Women's Cognitive Health. The theme of this October 2009 conference was "Improving the Trajectory of Cognitive Aging in Women Through Innovative Translational Research." Invited speakers presented and critically reviewed the current knowledge from basic to clinical research and health services research in order to guide efforts toward developing an innovative research agenda about hormonal and other therapies relevant to the advancement of knowledge in women's cognitive aging.

Intermittent Versus Continuous Caloric Restriction To Reduce Breast Cancer Risk. Animal and human studies suggest that intermittent energy restriction (IER)—brief periods of dramatically reduced caloric intake—may be superior to continuous energy restriction (CER) for preventing breast cancer and improving insulin tolerance (linked to breast cancer). NIA intramural investigators have initiated a study to test the hypothesis that IER not only is more effective than CER in reducing biomarkers of breast cancer risk but also will be more acceptable as a long-term preventive strategy for women. Study participants––women at increased risk of breast cancer because of a family history of the disease and adult weight gain of > 10 kg—will be placed on one of two dietary regimens (600 kcal/day for 2 days/week and 1800 kcal for 5 days/week) for 6 months; at the end of the intervention period, investigators will assess and compare a number of biomarkers of risk. The relative

acceptability of IER and CER also will be evaluated. In addition, the investigators are elucidating the molecular mechanisms by which alterations of dietary energy intake can influence breast cancer development. The results of these studies will inform future research on weight loss interventions to prevent breast cancer.

Estrogen Receptor-Beta PhytoSERMs for Management of Menopause and Age-Associated Memory Decline. Selective estrogen receptor-2 (ER2) targeting may be a novel therapeutic approach for the development of therapies for symptoms of menopause, as well as for Alzheimer's and other dementias. The pathophysiology of AD may be modifiable or preventable by estrogens. NIA-supported investigators have initiated a phase I clinical trial of ER2-selective phytoestrogens (phytoSERMS) in perimenopausal and menopausal women experiencing hot flashes. Although the trial was established to determine safety, tolerance, and best dose of phytoSERMs, it also will explore potential efficacy.

Ongoing Research Initiatives

MsFLASH Initiative. In 2008, NIA, in collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Center for Complementary and Alternative Medicine (NCCAM), and ORWH, established the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) initiative, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition. The MsFLASH network is composed of five clinical research centers and a data coordinating center. Different approaches are being studied for efficacy against hot flashes and night sweats in diverse groups of women in trials with either placebo or usual-care control groups. Investigators also will look at possible effects on other symptoms at middle age, including sleep disturbance, mood disorder, vaginal dryness, and sexual function. A number of different treatment strategies are being studied, including antidepressants, paced respiration (slow deep breathing), yoga, low-dose estrogen gel, and exercise.

SWAN Sleep Study. SWAN investigators from four sites are examining sleep patterns and factors that may affect sleep during the menopausal transition. Although sleep disruptions, insomnia, and breathing-related sleep disorders increase as women age, little is known about how their sleep changes as women progress through the menopausal transition. The goals of Sleep I, the baseline phase, were to (1) characterize sleep disturbances in a large, multiethnic sample of mid-life women; (2) characterize relationships among menopausal characteristics (e.g., vasomotor symptoms and bleeding) and sleep disturbances; (3) evaluate the influence of psychobiological factors on the sleep-menopause relationship; and (4) establish baseline data for Sleep II, the longitudinal phase of this research study. The major goals of Sleep II, currently in progress, are to identify (1) potential predisposing, precipitating, and perpetuating factors for chronic sleep disturbances during the menopausal transition and (2) adverse effects of sleep disturbances on subsequent health status during the early postmenopausal period. Recently, investigators on the SWAN Sleep Study have found that African-American women experience lower sleep quality than White women and that financial strain is associated with decreased sleep quality. Women in a stable relationship (marriage or long-term cohabitation) tend to sleep better than unpartnered women.

Women's Health Initiative Study of Cognitive Aging. The Women's Health Initiative Study of Cognitive Aging (WHISCA) investigates both on-trial and long-term posttrial effects of exposure to menopausal hormone therapy on cognitive aging within the context of the Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative (WHI) more generally. Whereas WHIMS focuses on the effects of menopausal hormone therapy on the risk and progression of Alzheimer's disease and other dementias, WHISCA assesses the effects of hormone treatment on memory, cognition, and mood in nondemented WHIMS volunteers age 65 and older who had been randomized to hormone therapy or placebo within the WHI trial. More than 12,000 longitudinal assessments have been performed for 2,302 WHISCA participants. In addition to allowing

assessment of hormonal effects on cognitive aging, this database also allows more general investigation of risk and protective factors for cognitive decline in older women. Because almost half of the women have participated in the WHIMS-MRI study, this database also allows investigation of variation in brain volumes and brain lesion burden in relation to cognitive change.

A new study involving the WHISCA cohort is exploring the complexity between genetic background and cognitive decline as an intermediate phenotype of dementia. The study also will examine how cognitive decline is modified by hormone therapy. The study will measure variations in candidate genes with known involvement in certain aspects of cognition and will probe the relationship between these candidate genes and incidence of MCI and dementia. Secondary analysis will examine the relationship between candidate gene variants and cognitive decline as a function of hormone therapy, and volumetric brain changes as an intermediate phenotype in the gene-to-behavior pathway.

Estrogen, Menopause, and the Aging Brain: How Basic Neuroscience Can Inform Menopausal Hormone Therapy Use in Women. Several large studies on steroid hormone neurobiology may provide insights into the basis of disparities between basic science outcomes and clinical trial outcomes in hormone therapy regimens, and thereby lay the groundwork for more informed approaches to hormone use in humans in order to help promote successful brain aging:

- **Progesterone in Brain Aging and Alzheimer's Disease.** Investigators are working to enhance our knowledge of the neurobiology of progesterone action in brain regions required for cognition and vulnerable to age-associated degenerative disease such as Alzheimer's. The hypothesis under study is that the sex steroid hormone progesterone promotes the brain's molecular, synaptic, cellular, and behavioral plasticity and reduces its vulnerability to the development of AD via direct effects mediated by progesterone receptors in hippocampus and indirect effects via interaction with estrogen pathways.
- **Novel Mechanistic Targets of Steroid Hormones in the Brain.** The overall goal of this study is to identify and characterize new and alternative targets by which estrogens and progestins are neuroprotective. Investigators will study a variety of receptors as potentially critical players in neuroprotection and neurogenesis.

KEEPS Cognitive and Affective Study. The KEEPS (Kronos Early Estrogen Prevention Study) Cognitive and Affective Study is the first multisite, randomized, placebo-controlled, double-blind, parallel-group design clinical study to address major issues related to use of menopausal hormone therapy raised by WHI and WHIMS. Specifically, this study evaluates the differential efficacy of conjugated equine estrogen (CEE, e.g., Premarin) and transdermal 17β-estradiol (tE2) on comprehensive measures of cognition and mood in perimenopausal women over an extended therapy of 4 years. Study participants also will be treated with progesterone to counteract overproliferation of endometrial tissue, which can be a side effect of menopausal hormone therapy. The goals of the study are to (1) characterize the potential differential efficacy and adverse effect profile of extended therapy with CEE and tE2 on cognitive function of perimenopausal women, (2) identify the effects of micronized progesterone on the proposed battery of cognitive and affective tests in perimenopausal women, (3) establish the relationship between estrogen-induced changes in markers of atherosclerosis, heart disease, and measures of mood and cognition, (4) characterize the relationship between estrogen-related changes in proposed markers of inflammation, blood hypercoagulability, and tests of cognition and mood, and (5) determine whether ApoE genotype will influence cognitive responsivity to menopausal hormone therapy.

Raloxifene in Women With AD: A Randomized Controlled Trial. Raloxifene, a selective estrogen receptor modulator (SERM), is used for treatment and prevention of osteoporosis in postmenopausal women. In animal studies, raloxifene affects neural activity in ways that might be expected to improve cognitive function, and clinical data suggest that it could improve dementia symptoms in women

with AD. NIA is currently supporting a randomized, double-blind, placebo-controlled pilot trial of raloxifene for the treatment of women with AD. Results from this pilot trial, if positive, will inform future larger scale trials.

Cognition in the Study of Tamoxifen and Raloxifene. Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) evaluates the effects of these SERMs on cognition and mood as an ancillary study to the STAR breast cancer prevention trial. Co-STAR enrolled 1,532 participants age 65 years and older who have been followed with annual assessments of global and domain-specific cognitive function. Since the unblinding of the main STAR trial on April 17, 2006, Co-STAR participants have received a final posttrial assessment, with posttrial assessments available for more than 1,000 participants. In addition to allowing assessment of the effects of these SERMs on cognitive aging in older women, this database also allows more general investigation of risk and protective factors for cognitive decline in older women.

Ovarian Cancer Pathogenesis and Drug Resistance. NIA intramural investigators are working to elucidate clues to the pathogenesis of ovarian cancer, one of the most common gynecologic malignancies in women, with particular attention to a family of proteins known as claudins. Evidence is mounting that the proteins claudin-3 and claudin-4 may represent useful markers for the detection and diagnosis of ovarian cancer. The same research team also is identifying genes associated with resistance to drugs that are commonly used to treat ovarian cancer.

Communications and Education Initiatives

Many of the topics covered by NIA publications are of special interest to women. Several booklets were updated this past year, including *Osteoporosis AgePage* and *Hormones and Menopause—Tips from the National Institute on Aging.* The Institute's booklet *Menopause: Time for a Change* remains NIH's primary source for detailed information on the menopausal transition.

Most caregivers are women, and NIA recently completely redesigned and updated a 44-page booklet to help them tackle some of the difficult issues they face. *So Far Away: Twenty Questions and Answers About Long-Distance Caregiving* provides advice and resources to help caregivers assess what kind of help is needed, coordinate with family members, keep up with medical care, decide when a move is needed, and more.

NIA continues to complement its research initiatives by supporting two information centers for older people and their families, the public, health care providers, and others interested in health and aging research. The NIA Information Center responds to inquiries received on its toll-free phone number and distributes NIA's free publications on a variety of topics, which can be viewed on the Web at http://www.nia.nih.gov/healthinformation. The NIA Alzheimer's Disease Education and Referral (ADEAR) Center provides free information and publications for families, caregivers, and professionals on research, diagnosis, treatment, patient care, caregiver needs, and education and training related to AD, at http://www.nia.nih.gov/alzheimers.

Health Disparities

Demographic projections predict a substantial change in the racial and ethnic makeup of the older population, heightening the need to examine and reduce differences in health and life expectancy. NIA is committed to addressing health disparities, with many initiatives supported in partnership with the National Center on Minority Health and Health Disparities. Minority aging research is conducted throughout the Institute's programs, and much of this research has relevance to the health needs of minority women. Examples of current programs and projects include the following:

- The Study of Women's Health Across the Nation (SWAN), which explores a number of health parameters among White, African-American, Chinese, Japanese, and Hispanic women
- The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study, a community-based research effort designed to focus on evaluating health

disparities in minority and socioeconomically diverse populations

- A study of variability in socioeconomic status (SES) trajectories for both White and African-American women as they age, as well as how these SES trajectories influence both overall mortality and mortality from specific diseases such as heart disease and cancer for women of different races
- A clinical trial of vitamin D supplementation to prevent osteoporosis in older African-American women
- A study of genetic factors related to Alzheimer's disease among African-American men and women

Career Development

NIA actively encourages participation by women in its training and career development initiatives. In addition, the Institute supports a research study examining the barriers women face in careers in biomedical research in universities and research centers and cofunds the University of Maryland BIRCWH (Building Interdisciplinary Research Careers in Women's Health) program, which has a research emphasis on women and aging.

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National Institute on Alcohol Abuse and Alcoholism

Executive Summary

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports research on both the behavioral and medical causes and consequences of alcohol use and abuse and alcoholism, and on new ways to prevent and treat these significant public health problems. In the United States, alcohol consumption is among the 10 leading causes of disability-adjusted life years and ranks as the third

leading preventable cause of death. Alcohol abuse and alcoholism are among the major medical problems afflicting both men and women. Epidemiologic evidence suggests that nearly 20 percent of adult males suffer from alcohol abuse or alcoholism-related complications. On the other hand, only about 5 to 6 percent of adult females are alcoholics or abuse alcohol on a regular basis. Although men display a higher prevalence for alcoholism, it is women who suffer a much greater risk for alcoholism-associated physical damage. Whereas women generally consume less alcohol compared with men, females usually suffer more severe brain, liver, and other organ damage following binge or chronic alcohol abuse. Over the past several years, NIAAA-supported research has shown that these sex-based differences arise partially from the complex interactions between genetic background and other physiologic processes. For example, numerous physiologic differences between men and women in the rate of alcohol absorption and metabolism are likely to be genetic in origin and may influence the development of alcoholism and alcohol-associated tissue injury. In addition, complex environmental and social factors significantly influence the differences in men's and women's drinking behaviors and related health problems. Continued research focused on these gender/sex differences in alcohol dependence is needed to better our understanding of this devastating health problem and to develop appropriate individualized treatment for both men and women.

NIAAA continues to expand its research portfolio on the impact of alcohol and alcohol misuse on women's health. Research related to women's health is found in each programmatic division of the Institute. Because of the multidimensional and interdisciplinary nature of alcohol use disorders and their prevalence worldwide, collaborative research endeavors on a national and international scale are required for progress toward the goal of reducing alcohol abuse disorders and alcoholism among women. NIAAA develops and supports several collaborations with foreign scientists, including the longest running United States-South African project and new United States-Ukraine study, to understand the role of prenatal alcohol exposure and causes of sudden infant death syndrome and adverse pregnancy outcomes, such as stillbirth and fetal alcohol spectrum disorders (FASD). The long-term goals of this initiative are to decrease fetal and infant mortality and improve child health in the affected communities.

To increase the impact of research findings related to women's health and alcohol, NIAAA takes a multimedia approach to reach the public, clinicians, educators, and other professionals. For example, NIAAA's public education materials targeting a diverse audience of women provide evidence-based, easy-to-read information about the negative effects of alcohol consumption on the female body, discuss the potential harm posed by alcohol use during pregnancy, and encourage a healthy life style.

Significant scientific advances in understanding the causes, consequences, prevention, and treatment of alcohol use, abuse, and dependence among women have occurred in the past 2 fiscal years. The following pages highlight NIAAA's recent activities and accomplishments in biomedical and behavioral research related to women's health. The accomplishments fall into six major research categories: (1) psychosocial determinants of drinking in women; (2) gender differences; (3) alcohol and pregnancy; (4) alcohol use and fetal alcohol spectrum disorders; (5) treatment of women with alcohol use disorders; and (6) alcohol and violence. This report consists of contributions from the Divisions of Epidemiology and Recovery, Metabolism and Health Effects, Neuroscience and Behavior, and Treatment and Prevention Research.

Accomplishments

Psychosocial Determinants of Drinking in Women

Trends in Women's Drinking Patterns. A study using data collected from 1981 to 2001 from the National Study of Health and Life Experiences of Women (NSHLEW) examined 12-month drinking trends among women and found that (1) different patterns of childhood sexual abuse (CSA) predict different long-term drinking outcomes, (2) quantity-frequency

methods of alcohol consumption may overestimate women's reports of alcohol use, (3) recalled ages of drinking onset predict subsequent drinking and may have implications for prevention of early onset of drinking, and (4) alcohol is significantly involved in the number of episodes as well as severity of physical partner aggression. The effects of more severe CSA appeared to increase as women aged, pointing to an important or delayed sleeper effect in which continued or increased drinking may be attributable to unresolved psychological factors or trauma.

Interventions To Reduce Drinking-Related Harm in College Women. Heads UP! Women was a cooperative agreement project in NIAAA's Rapid Response to College Drinking Initiative that tested the efficacy of a multicomponent motivational interview-based intervention for freshman women, females sanctioned by the university's judicial affairs, and general members of the college campus community. Findings from this cooperative agreement are notable because the intervention significantly reduced alcohol consumption, number of binge drinking episodes, and drinking-related consequences among all participant groups. In addition, the intervention effect was greatest among women with stronger social and enhancement motivations for drinking. This work has implications for designing effective interventions that target college women. Furthermore, booster or maintenance sessions may promote more enduring effects.

Effects of Service Agency Utilization and Drinking Trajectories. Preliminary findings from a longitudinal study of gender differences in drinking trajectories among treated versus untreated dependent and problem drinkers found that recovery-oriented social networks, Alcoholics Anonymous attendance, and contact with the mental health system were significantly related to decreased consumption for both genders, with welfare contacts additionally related to less drinking for women only. This work has implications for service agencies that intervene and treat individuals with drinking problems.

Gender Differences

Sex Differences in Alcohol Withdrawal. Clinical experience has shown that women alcoholics experience fewer alcohol withdrawal symptoms than men. NIAAA is supporting a research study, initially cofunded by the Office of Research on Women's Health (ORWH) through the Research Enhancement Awards Program (REAP), to establish mechanisms responsible for gender differences in the typical brain hyperexcitability that occurs during alcohol withdrawal. These neurochemical and behavioral studies are being conducted in an animal model of chronic alcohol exposure, with the objective of examining the role of specific synaptic proteins involved in the sex differences. The primary hypothesis is that sex differences in recovery from ethanol withdrawal involve sex-selective changes in inhibitory (GABAergic) and excitatory (glutamatergic) neurotransmission that occur as a result of the differing hormonal milieu between males and females. The project has identified significant sex differences in withdrawal recovery, in the effectiveness of GABAergic neuroactive steroids to moderate withdrawal seizure risk, and in chronic ethanol-induced alterations of GABA receptor subunit levels. Findings generated from this proposal have important clinical implications by predicting neurobiological differences in the sequelae of withdrawal between men and women. This information also will enable tailoring of treatments of alcoholics according to gender and hormonal status.

Sex-Specific Differences in Alcoholic Gut and Liver Injury. Women are at a greater risk for alcohol-induced liver injury than men, but underlying mechanisms are poorly understood. Many publications indicate that chronic alcohol consumption dramatically changes the hormonal milieu of both the blood and liver in both sexes. The liver is a key player in this scenario because, in addition to being the site of steroid hormone metabolism, the liver is responsive to sex hormones. One proposed link between female sex hormones and alcoholic liver injury is through gut-derived endotoxin, a component of the outer wall of Gram-negative bacteria that causes hepatic tissue injury. Estrogen enhances liver sensitivity to endotoxin and may therefore worsen liver injury,

especially in alcoholics who show elevated levels of endotoxin. To understand the interactions among alcohol, gut-derived endotoxin, sex hormones, and liver injury, this project investigates sex-specific differences in alcoholic gut and liver injury. Successful completion would add important information on how hormones and alcohol interact.

Ethanol-Induced Cardiac Injury in Aged Females. Postmenopausal women have higher mortality rates after myocardial infarction than aged men, and it is unclear whether the effects of aging and estrogen (E2) deficiency are additive with regard to ethanol-induced cardiac ischemia/reperfusion (I/R) injury. Since mitochondria play a pivotal role in cell survival and cardioprotection, it is conceivable that ethanol and age-associated increases in I/R injury may arise from the altered mitochondrial proteome. To address this issue, this project employs in vitro isolated heart and in vivo mitochondrial respiration studies in conjunction with a novel high-throughput proteomics approach and ontological analysis to characterize alterations in mitochondrial signaling occurring with aging and E2 deficiency in the female rat myocardium following chronic ethanol ingestion. The high throughput proteomics approach will provide critical and novel mechanistic insight on the role of female sex in the development of alcohol-related cardiac dysfunction in aged and adult rats. In addition, the proposed comprehensive and novel approach will identify proteins that comprise the functional sequelae of complex cardiac phenotypes of chronic ethanol ingestion and will further characterize possible targets for therapeutic intervention in the postmenopausal women. This project is supported with funds from the American Recovery and Reinvestment Act of 2009.

Neuroendocrine Effects of Alcohol on Puberty. This research, which is relevant to adolescent health and development, is intended to further identify consequences of alcohol consumption with regard to hormonal events and their actions that can alter female pubertal maturation. The studies are a logical extension of previous work and dissect out the effects of both chronic and acute alcohol on the factors that regulate hypothalamic hormone release. A series of well-designed experiments performed in vitro and in vivo on rat and primate models has demonstrated the effect of alcohol exposure on the expression and secretion of specific protein receptors and peptide hormones involved in the signaling process. The studies assess influences of specific puberty-related peptides, demonstrate the involvement and activation of important genes critical to brain events leading to mammalian puberty, and discern the effects of alcohol on their actions and interactions. Resolving mechanisms mediating alcohol effects on the secretion of peptide hormones during pubertal development will provide important insights into alcohol-induced disturbances of a broad spectrum of other reproductive processes and pathologies.

Myocardial Protein Synthesis After Alcohol Intoxication. Cardiomyopathy is typically diagnosed in about 35 percent of individuals who chronically consume excessive amounts of alcohol, and cardiomyopathy significantly contributes to premature mortality among alcoholics. There are discrepancies among investigators regarding sex and the toxic effects of chronic alcohol on the myocardium. However, only selected candidate proteins have been investigated; therefore, the full extent to which myocardial proteins are affected by chronic alcohol across the sexes remains unresolved. The purpose of these studies is to understand the pathophysiologic steps involved and to characterize the effects of other factors including gender differences. The investigators found that prolonged feeding of a diet containing ethanol resulted in a reduced heart weight as well as a significant decrease in structural and functional parameters, including cardiac output and end-diastolic diameter, in male rats but not in female rats. In addition, long-term alcohol intake demonstrated more significant alterations in the structural and functional parameters of the heart in males compared with females, suggesting that male myocardium is more susceptible to the toxic effects of alcohol abuse.

Alcohol-Induced Bone Resorption: The Role of Oxidative Stress. Chronic alcohol abuse results in osteoporosis and increased fracture risk in both pre- and postmenopausal women. This research using animal models has demonstrated that alcohol treatment results

in analogous bone loss and reduced mineral density in both rats and mice as a result of an imbalance between the actions of osteoclasts, which remove old bone, and osteoblasts, which are responsible for forming new bone. The researchers have shown that, in cycling female rats and mice, alcohol-enhanced bone resorption is associated with increased osteoclast cell numbers and the induction of specific signaling factors (e.g., RANKL) in bone marrow and significantly reduced plasma estradiol concentrations. In contrast, in pregnant females where plasma estradiol levels remain elevated (and unaffected) by alcohol consumption, alcohol-induced bone loss was significantly attenuated. Finally, these studies demonstrated that estradiol replacement prevents alcohol-induced bone loss by opposing the induction of RANKL mRNA in osteoblasts and ethanol-induced osteoclastogenesis. Therefore, these studies offer a window into the mechanisms by which chronic alcohol consumption exacerbates osteoporosis and fracture risk in women, while also suggesting a protective role for estrogens.

The Alcohol Pharmacology Education Partnership. This educational grant supports the development of six computer-based instructional modules that use principles of biology, chemistry, and math to describe the actions of alcohol in the body and an interactive Web site for high school teachers and students to access these materials. Approximately 300 high school biology and chemistry teachers nationwide will field-test the Web sites, and then a series of evaluations and recursive workshops will be used to evaluate changes in the students' understanding of the target goals of the program. Evaluations of test score changes will determine significant differences that may emerge among the gender and ethic/racial categories.

Astrocytes, a Type of Brain Cell, Are More Susceptible to Damage After Alcohol Withdrawal in Females Than in Males. This study utilizes sex-specific brain astrocytes as a model to elucidate how alcohol influences cell viability, gene expression, and brain function in males versus females. This study extends the previous work by these investigators that compared neuroadaptive changes in males versus females using gene expression transcriptional profiling associated with withdrawal from chronic ethanol exposure. The prior studies demonstrated that sex is a more powerful determinant of neuroadaptation than genotype or withdrawal severity phenotype. The gene expression differences revealed that females were more vulnerable to alcohol-induced brain damage, consistent with some clinical studies. The current study will determine whether chronic exposure to ethanol and withdrawal alters the survival of astrocytes, a type of nonneuronal cell in the brain, in a sex-specific fashion. Results from these studies will lead to a better understanding of the specific effects of alcohol on astrocyte function and potentially to identifying therapeutic targets for the sex-specific treatment or amelioration of brain damage associated with chronic alcohol abuse in both males and females. This research is supported with funds from the American Recovery and Reinvestment Act of 2009.

Females Are More Susceptible Than Males to Alcohol-Induced Activation of the Stress Axis. Brain injury is among the most prominent effects of prolonged alcohol use or abuse, and evidence suggests that females may be more sensitive than males to the neurotoxic effect of prolonged alcohol intake. Thus, examination of biochemical pathways involved in this form of brain injury may be of value in identifying therapeutic targets to be exploited in treating alcohol-related brain injury. This proposal examines the hypothesis that alcohol-induced activation of the stress (hypothalamic pituitary) axis promotes NMDA receptor-mediated seizure and/or neurotoxicity during alcohol withdrawal in a sex-dependent manner. Using in vitro and in vivo rodent models, this study will determine whether alcohol exposure activates glucocorticoid receptor and increases the expression of polyamine-sensitive subunit (NR2B) of NMDA receptor. This action will promote NMDA channel opening and neuronal excitation and neurotoxicity in a glucocorticoid receptor-dependent manner. These findings may suggest a role for glucocorticoid receptor antagonists in the treatment of ethanol detoxification or maintenance of abstinence, especially in females.

Role of Gonadal Hormones in HPA Responses to Alcohol Administration. Maladapation of the stress response can cause long-term health problems. The hypothalamus-pituitary-adrenal (HPA) or "stress" axis responds differently in male and females to stressors and to alcohol. The purpose of this project is to investigate whether gonadal hormones determine the HPA response to alcohol. If ovarian hormones produce greater modification of alcohol-activation of the HPA axis in women than testicular hormones do in men, this situation may explain some of the differences seen in response to alcohol in women compared with men. Results would permit the development of sex-specific treatments for alcohol abuse.

Interactive Effects of Ethanol and Estrogen on the Brain During Puberty. Women who abuse alcohol are twice as likely to develop anxiety disorders compared with men, a phenomenon in which the underlying biological mechanisms are unknown. The overall objective is to identify the interactive effects of alcohol and estrogen on arginine vasopressin (AVP), a well-established key molecular mediator of anxiety, in order to elucidate the molecular mechanisms predisposing women to increased risk of anxiety disorder. The proposal is focused on a specific candidate gene (AVP) and its downstream signaling pathways that are developmentally shaped during puberty. Using adolescent female rats, this study is examining whether AVP is permanently altered, either as a direct target for alcohol or indirectly through steroid hormone receptor signaling pathways. The value of this research lies in the potential for therapeutic approaches that would target specific genes and perhaps reverse brain damage caused by alcohol consumption during pubertal development as well as strengthen reasons for abstaining from alcohol during that time. This research is supported with funds from the American Recovery and Reinvestment Act of 2009.

Alcohol, Puberty, and Sex Differences in Alcohol Intake. Despite the marked hormonal and neural changes associated with puberty and the other physiologic transitions of adolescence, little is known about how these factors might contribute to the ontogeny of sex differences in ethanol intake and sensitivity. Using a rat model, this proposal examines both the organizational and activational effects of the rise in gonadal hormones at puberty on expression of sex differences in ethanol intake, ethanol sensitivity (indexed by ethanol-induced social suppression), and ethanol stress interactions. To date, notable activational effects of gonadal hormones are evident among males in terms of ethanol intake and preference, with perhaps some role of ovarian hormones among females in the elevation of stress hormone levels following ethanol challenge and in social interactions. Differences between males and females in their response to kappa receptor stimulation may be a possible neural contributor to ethanol-related sex differences. This research will increase our understanding of the role of pubertal hormones in promoting the emergence of sex-typical patterns of alcohol use, consequences, and abuse.

Sex Differences in Learning and Memory in the Adolescent Rat: Role of Gonadal Hormones. Adolescence represents a critical window of vulnerability for initiating alcohol use and in a large number of cases leading to increased alcohol intake. It is well documented that adolescents differ from adults in their sensitivity to alcohol. Previous research has shown that male rats exposed to alcohol during adolescence exhibit significant deficits in spatial learning and memory that persist into adulthood. Alcohol in female adolescent rats also causes profound deficits in spatial learning and memory, but these deficits do not persist beyond the alcohol exposure period. This proposal will explore the nature, mechanisms, and consequences of alcohol exposure during adolescence on learning and memory in male and female rats and the influence of pubertal gonadal hormones on sex differences in alcohol behavior. The overarching goal is to determine whether, during adolescence, pubertal gonadal hormones influence alcohol-induced behavioral deficit by modulating the NMDA receptor. Understanding age-related changes in the brain as it transitions from adolescence to adulthood, and the effects of pubertal gonadal hormones on alcohol-induced behavioral deficits, will provide clues as to why the adolescent period is particularly vulnerable to use and abuse of alcohol and lead to novel therapeutic

targets that may be used for prevention and/or treatment of adolescent alcohol use and abuse.

Neurophysiologic and Behavioral Factors Underlying Attention to Alcohol Cues in Mexican-American College Freshmen Women. This recently funded study will investigate attentional changes to alcohol in first-generation Mexican-American women during their freshmen year of college. The transition from a traditional home environment to a college campus where drinking alcohol may be much more prevalent provides an opportunity to study shifts in perceptions, acculturation, and neurophysiologic responses about drinking. The study will measure attention to alcohol cues (a picture of a glass of wine, for example) at baseline and again later near the end of the freshmen year of college. Event-related brain electrical activity will be recoded to track the brain's neurophysiologic response to alcohol cues during the first year in a college environment. This study also will test whether the P300 electrical brain wave could be used as a neurophysiologic marker of risk for subsequent alcohol abuse in this unique population of women. Understanding the neural and behavioral changes related to exposure to alcohol cues will be important for the design of attention training programs to prevent or treat abusive drinking of alcohol.

Gender Differences in Brain Structure and Function in Chronic Alcoholism. This study has been funded for many years to investigate the changes in brain structure and cognitive and affective behaviors associated with the development of chronic alcoholism. Based on emerging findings from this study showing differences between men and women, the investigators will now begin focusing on gender differences and their potential causative role in the trajectory toward chronic alcoholism. The study will measure differences in brain structural integrity and functional activation (changes in brain blood flow) during performance of emotional or affective behaviors, reward processing, and conative (i.e., intentional) behaviors. The guiding hypothesis is that alcoholic men and women may differ in the structural integrity of certain brain areas and that different patterns of functional brain activation will occur during performance of the behavioral tasks. Understanding the neurobehavioral consequences of chronic alcoholism in terms of gender differences may help in the recognition of predisposing risk factors that are gender specific.

Gender Differences and Menstrual Cycle Effects on Brain Neurotransmitter Levels and Cognitive Functioning. This recently funded study will investigate differences in the levels of the neurotransmitters, GABA and glutamate, in the hippocampus of the brain and their relationship to spatial and verbal learning and memory (functions dependent on the hippocampus) in young adult males and females. The study also will test women in both the follicular phase (low hormone levels) and the midluteal phase (high hormone levels) of the menstrual cycle to investigate possible changes in GABA and glutamate levels and memory function influenced by hormonal changes. This information, particularly of the influence of the menstrual cycle in females, will be used to design a longitudinal study of changes in neurochemistry (e.g., neurotransmitter levels) and hippocampal-mediated learning and memory functions in alcoholic men and women. Knowledge of the neurochemical correlates of hippocampal memory and learning functioning could be useful as markers of recovery during abstinence from alcohol and as potential predictors of risk for relapse.

Brain Imaging of Appetitive Decisionmaking in Alcohol-Dependent Young Women. NIAAA recently funded an application to study the interaction between alcohol and the brain processes underlying sexual decisionmaking that may bias alcohol-dependent women towards risky sexual behavior. Whether a woman's hormonal state is likely to be a relevant factor mediating alcohol and brain interactions, possibly creating windows of acute vulnerability for young women, also will be investigated. Using functional magnetic resonance imaging, this study will test the hypothesis that alcohol-dependent young women have a more sensitized reward brain circuitry in general and that the hormonal state close to ovulation further enhances vulnerability to sexual risk taking. An understanding of menstrual cycle interactions with neural activation and sexual decisionmaking in alcohol-dependent and

nondependent women can enhance our ability to intervene to promote safer sexual behavior in at-risk young women.

Genetic Factors Play a Role in Alcohol Problems in Young Women. Although many studies have determined the degree to which genetic factors contribute to alcoholism in males, there is a paucity of data on how genetic factors play a role in vulnerability towards alcoholism in women. NIAAA is supporting a research study that aims to identify the genetic factors that contribute to alcoholism in women and how certain environmental exposures influence vulnerability. This study is a prospective study of a birth cohort of female like-sex twin pairs born in Missouri to Missouri-resident parents. During previous years of funding, information was obtained from twin pairs who were in adolescence. The focus of the current funding is on female twin pairs who have reached young adulthood. Recent findings have identified genes involved in serotonin neurotransmission as contributing to vulnerability towards alcoholism in these young women. In addition, it was found that peer substance involvement modifies genetic influences on regular substance involvement in these young women. This work has significant implications for understanding the risk factors associated with alcohol use and abuse specifically in women, who have traditionally been an understudied population. Finally, the information gained from this study will help the design of better treatments for women with alcohol problems and thus improve public health.

Alcohol and Pregnancy

Prenatal Alcohol Exposure Among High-Risk Populations: Relationship to Sudden Infant Death Syndrome and Stillbirth. A cooperative agreement was established jointly between NIAAA and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) to conduct community-linked studies on the underlying causes of sudden infant death syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and fetal alcohol syndrome (FAS), and the role of prenatal alcohol exposure. The Prenatal Alcohol in SIDS and Stillbirth (PASS) Network consists of two comprehensive clinical sites in the Northern Plains and Western Cape of South Africa, a developmental biology and pathology center, a physiology assessment center, and a data coordinating and analysis center. At the time of this report, the PASS Network had enrolled nearly 5,000 pregnant women (towards an enrollment goal of 12,000) in a comprehensive longitudinal cohort study in which their infants will be followed for up to 1 year. The network also is recruiting known cases of SIDS and stillbirth for a retrospective study. In addition, embedded studies have been designed to explore the role of (under-) nutrition in exacerbating the effects of maternal alcohol exposure on fetal and offspring development. The long-term goals of this initiative are to decrease fetal and infant mortality and improve child health in the affected communities.

Alcohol's Effects on Conception and Pregnancy. Alcohol consumption during gestation produces a variety of adverse pregnancy outcomes and birth defects. However, the influence of acute alcohol consumption near the time of conception is relatively unknown. The goal of this research is to determine how alcohol exposure influences genomic modification and function during the oocyte-to-embryo transition and leads to susceptibility towards disease. This project will identify candidate genes whose expression and epigenetic status are influenced by the presence of ethanol during the oocyte-to-embryo transition. Previous studies have shown that mice specifically exposed to alcohol during in vitro maturation of oocytes have a higher incidence of metabolic disease, such as obesity and diabetes, in adulthood. The investigators will first identify the critical genes altered by acute alcohol exposure during in vitro maturation in oocytes and embryos. Then they will test the effects of ethanol exposure on the establishment of initial epigenetic patterns in preimplantation embryos as a mechanism for altered gene expression. This research will eventually help us to understand the molecular consequences of the pregnancies under the influence of alcohol. This research is cofunded by ORWH and also is supported with funds from the American Recovery and Reinvestment Act of 2009.

Utility of Novel Biomarkers for Identification of Fetal Alcohol Exposure. This work addresses the difficulties of confirming maternal drinking during pregnancy as well as diagnosing less severe cases of FASD through the development of better biomarkers for prenatal alcohol exposure. The project attempts to validate phosphatidylethanol (PEth) as a novel biomarker for prenatal alcohol exposure, as measured in the blood of pregnant women collected by venipuncture and that of their newborn children from Guthrie cards collected by heel-prick. This research is an extension of an ABMRF (Foundation for Alcohol Research)-supported prospective study of 150 pregnant women (moderate drinkers and light drinkers/abstainers) recruited from the University of New Mexico-affiliated clinic dedicated to pregnant women with a present or past history of substance abuse. The sensitivity and specificity of PEth will be compared with traditional ethanol biomarkers, screening questionnaires, and other direct ethanol metabolites of the mother and the fetus. If successful, routine screening for PEth may allow for the identification of women whose drinking places the fetus at risk and may lead to the earlier use of intervention strategies to minimize FASD-associated deficits.

Alcohol Use and FASD

Collaborative Initiative on FASD. Ongoing research within this consortium comprising multiple international sites with high incidence of FAS and FASD includes a cooperative agreement with the Ukrainian Omni-Net Centers to screen more than 20,000 pregnant women who come to regional health care facilities for routine prenatal visits. A sample of moderate-to-heavy drinkers and controls will be selected for longitudinal followup, including expanded prenatal ultrasound measures, physical examination, and neurobehavioral testing of offspring. An embedded study examines the effects of maternal micronutrient status and other markers of oxidative stress at midpregnancy and in the third trimester and the effects of maternal vitamin and mineral supplementation on the growth, neurobehavioral development, and alcohol-related physical features of the alcohol-exposed offspring. In addition, some consortium members are developing animal models of FAS and FASD with the aim of clarifying mechanisms, improving diagnostic methods, identifying genetic and molecular markers of these disorders, and testing potential interventions. The long-term goals of this research consortium are to refine the diagnostic criteria for FAS/FASD, explore the underlying mechanisms of the disorder, and develop therapeutic interventions to provide relief to those affected with the most debilitating features of the disease.

Differences in the Serotonin System in Animals Exposed to Prenatal Ethanol. Prenatal ethanol exposure may affect an individual's brain function later in life, and some effects may be specific to females. NIAAA is funding a research program to investigate fetal programming of the stress and hormonal response after exposure to prenatal ethanol. Adult female rats that were exposed to ethanol prenatally show an altered stress hormone response to drugs that attach to the serotonin receptor in the brain. Males show no hormonal effect to these drugs. Publications from this research show that prenatal ethanol exposure has differential long-term effects on the brain stress system in males and females. The changes induced by prenatal ethanol exposure may alter the way women respond to stress later in life and may have implications for depression and other related mental health disorders.

Neurocircuit Targets of In Utero Ethanol Intoxication and of Therapies for FASD. There are currently no treatments to prevent or reverse cognitive deficits in children caused by ethanol intoxication during pregnancy. One NIAAA-funded project aims to identify and test therapies that could protect the developing brain from ethanol injury and preserve cognitive functioning in children at risk for FASD. One possible mechanism for these learning and memory deficits is a defect in the signaling of gamma-aminobutyric acid (GABA), one of the major neurotransmitters in the brain. A recent study found that during a period equivalent to human third-trimester brain development, binge-like intoxication in rat pups distorts maturation of GABA synapses in certain brain regions. This action could be largely prevented by finasteride, a drug that blocks formation of modulators of the GABA synapse. This work has the potential to provide

a model for testing treatments aimed at offering hope for preventing or limiting cognitive injury in children with FASD.

Alcohol's Effects on Teratogenesis. Women who consume alcohol during pregnancy place their offspring at risk for a number of teratogenic effects. In the United States, an estimated 130,000 women per year expose their fetuses to high levels of alcohol, and the estimated associated costs are $4 to $11 billion. Genetic factors, both maternal and fetal, are known to play a role in susceptibility to ethanol during teratogenesis. NIAAA is currently supporting a study on the genetic mechanisms mediating differential susceptibility to the teratogenic effects of ethanol. A maternal effect mediating different teratogenic outcomes following prenatal ethanol exposure has been identified using mouse models. The study has examined genomic imprinting as an epigenetic mechanism for the teratogenic effect. The researchers in this study have examined several imprinted genes known to play a role in growth and development. The examination includes DMA methylation, histone modifications, and changes in gene expression in embryos and placentae following prenatal ethanol exposure. In addition, they examined global gene expression changes in fetuses exposed to alcohol in utero. The epigenetic modifications and/or gene expression changes identified in imprinted genes following prenatal alcohol exposure in mice can be potential targets for future human studies. The study of the effects of a methyl-supplementation diet on some of the teratogenic effects of ethanol may allow for the design of rational treatment and, ultimately, prevention strategies.

Maternal Risk Factors for FAS: A Population-Based Study in South Africa. A comprehensive prevention study in five matched urban and rural communities in the Western Cape Province of South Africa screened and diagnosed grade-school children for FASD and partial FASD. The study found that mothers of children with FASD had a higher prevalence of current drinking and history of drinking during pregnancy compared with control mothers. A significantly greater proportion of mothers of FASD children reported drinking before becoming pregnant than control mothers (92 percent and 25 percent, respectively), and more FASD mothers continued to drink throughout the first, second, and third trimesters of the index pregnancy. Although differences in current drinking patterns were not significant, the mean number of drinks consumed per week during pregnancy was significantly higher among mothers of FASD children compared with control mothers. Higher reported levels of drinks per day were associated with poorer IQ and verbal scores among the FASD children, and heavier drinking during pregnancy (e.g., three drinks or more per drinking occasion) was associated with behavioral problems among the women's children. Characteristics of the mothers of FASD children included rural residence; farm worker status; and lower height, weight, head circumference, and body mass than control mothers. The predominant beverage of choice among these mothers was beer.

Treatment of Women With Alcohol Use Disorders

Prenatal Drinking and Knowledge of FAS: A Randomized Trial in Russia. The overarching aim of the study is to reduce risk for alcohol-exposed pregnancy (AEP) and alcohol-related neurodevelopmental disorder/FASD by testing a prevention model specifically targeted to large numbers of women in obstetrics/gynecology (ob/gyn) clinics in Russia. The study will conduct a randomized trial to determine whether physicians, trained to conduct brief motivational intervention, can foster (1) changes in childbearing-aged Russian women's health beliefs regarding risk for AEP and (2) greater reduction of women's AEP risk behaviors (e.g., through abstinence from alcohol use and consistent contraception use) compared with standard ob/gyn care. Preliminary studies have suggested that although many Russian women reduce alcohol consumption after pregnancy recognition, before the diagnosis of pregnancy, few women recognize the risks of combining alcohol use with the potential to become pregnant. Therefore, substantial numbers of women of childbearing age may be at high risk for fetal alcohol exposure during the early weeks of pregnancy. Knowledge gained from the study can contribute to FASD prevention research throughout the world.

Reducing Alcohol-Exposed Pregnancy Risk. Although most women discontinue drinking after learning that they are pregnant, approximately one-half of all pregnancies are unplanned, and most women do not know they are pregnant until 4 to 6 weeks after conception. This means that, even among women who are inclined and able to discontinue drinking after learning they are pregnant, a high percentage of pregnancies are alcohol-exposed. Thus, although it is known that approximately 15 percent of women continue to drink after learning they are pregnant, the actual total number of alcohol-exposed pregnancies is probably significantly higher than this number suggests. One of the strongest predictors of substance use during pregnancy is substance use before pregnancy. In an ongoing behavioral therapy development project, investigators are seeking to develop and test the feasibility and efficacy of a brief, theory-based intervention to reduce the risk of AEP in high-risk community women. The EARLY intervention is based on social learning theory, with counseling components including personalized feedback on risks related to drinking and ineffective contraception, health information, decisional balance exercises, discussion of readiness to change, eliciting of goal statements, and development of change plans. Participants are a high-risk community sample of women who drink frequently or who binge and who use contraception ineffectively, drawn from sexually transmitted disease and public health clinics and alcohol/drug treatment settings. Investigators anticipate that women who receive the EARLY intervention will show significantly greater reductions in high-risk behavior, including risky drinking and ineffective use of contraception, than women in the information/attention control group. The study includes analysis of correlates of change, including, among other factors, alcohol/drug use and severity, psychiatric comorbidity, and motivation for change, to increase understanding of how the intervention works and what factors may predict response. Findings from this study will inform the development of brief interventions that effectively reduce the risk behaviors for AEP and that may be transferred to a variety of public health treatment and intervention settings. This research is supported with funds from the American Recovery and Reinvestment Act of 2009.

Reducing Alcohol and Risks Among Young Females. One recent intervention study examined and addressed the combined effect of early alcohol use and risky behavior within a population of urban African-American and Latina adolescent females at high risk for HIV/AIDS and other infections. Past research by the investigative team documented that nearly 10 percent of females in their target population are at risk in 7th grade and more than half by spring of 10th grade. This study, involving parents and their sixth grade daughters, examined the effectiveness of "Especially for Daughters," an audio-CD intervention to promote attitudes and behaviors associated with reduced alcohol consumption and sexual risk taking among adolescent girls. Investigators also sought to determine whether changes in the girls' attitudes and behaviors were mediated by changes in certain parenting mechanisms, including parental monitoring, household rule setting, and communication. Results from this study indicate that girls who received the intervention reported fewer sexual risks and less drinking at followup than those in the control group. In addition, their parents reported greater self-efficacy to address alcohol and sex and more communication on these topics. Findings from this study have advanced understanding of the link between early alcohol initiation and risky sexual behavior and may have important implications for the design and implementation of school-based programs to reduce alcohol, drug, and HIV-related risks among adolescent girls.

Brief HIV and Alcohol Combined Interventions for Women. A recent randomized clinical trial focused on reducing HIV risk behaviors among women seeking help for alcohol problems. This study is evaluating the relative effectiveness of Combined Behavioral Intervention (CBI), a state-of-the-art, empirically based treatment for addressing alcohol problems in dependent drinkers, followed by an HIV risk reduction intervention (HIV-RR) and CBI, followed by an intervention limited to dissemination of HIV information (HIV-I). Investigators had predicted that women who responded favorably to alcohol treatment and who received HIV-RR, an enhanced intervention including both HIV-related information and elements to increase motivation and behavioral

skills necessary to reduce HIV risk behavior, would fare better than their counterparts in HIV-I. However, preliminary results indicate that by the last followup points, all participants, regardless of condition, improved across time on many sexual risk and substance use measures. The research team has hypothesized that, among other factors, these results may have been influenced by the severity of alcohol use disorders (high rate of alcohol dependence) among women in the study, the fact that women were seeking treatment for their alcohol and other drug use while not seeking to change sexual behavior, and the effect of reduced drinking on sexual risk. Thus, although it appears that there was a null result for the HIV risk reduction intervention, these results may add to a growing body of evidence that alcohol and other substances are the most important drivers of the high-risk sexual behavior that is fueling the HIV epidemic and that providing treatment for alcohol and substance use disorders is the key to reducing HIV risk related to both substance use and sexual behavior.

Testing Cognitive-Behavioral Therapy Models and Change Mechanisms for Alcohol-Dependent Women. Limited research exists on alcohol-dependent women and, in particular, on the change mechanisms that enable alcohol-dependent women to reduce drinking and maintain sobriety. Furthermore, there is a paucity of clinical research to develop and test cost-effective group therapy models for alcohol-dependent women. One ongoing study is adapting an existing Individual Female Specific Cognitive Behavioral Therapy (I-FSCBT) approach to treating women with alcohol dependence to a group format (GFSCBT) and comparing the relative efficacy of the two approaches. Both the group and individual treatments are abstinence based and include motivational enhancement, coping skills training, management of negative effect, skills to manage heavy drinkers in the social network, relapse prevention, and discussions of personal autonomy. In addition to determining their relative efficacy, investigators are examining hypothesized mechanisms of change in drinking that are common to both the group and individual treatments. The study also is examining the relative cost-effectiveness of the individual and group treatments in an effort to inform decisionmaking by health service policymakers and administrators. The research team also has developed a plan for transdisciplinary collaboration to explore genetic and environmental interactions that may influence the course of alcohol dependence among women, as well as women's response to treatment.

Behavioral Couples Therapy for Women Alcoholic Patients. One recent study examined the effect of behavioral couples therapy for women alcoholic patients seeking treatment. The study also evaluated the effects of comorbidities, including anxiety, depression, and posttraumatic stress disorder (PTSD), and the male partners' substance use on the alcohol-related outcomes. Preliminary results show a decrease in substance use and problems, including violence of the female patients towards their partners, in the women receiving the couples therapy compared with the control treatment group. It is anticipated that this research will advance understanding of best approaches to improving communication in couples affected by alcohol dependence.

Alcohol and Violence

Brief Intervention for Problem Drinking and Partner Violence. Intimate partner violence (IPV) remains a major source of morbidity and mortality in the United States, with women suffering the majority of adverse long-term consequences. Although both men and women perpetrate IPV at similar rates, an ongoing randomized clinical trial (RCT) will focus on IPV-involved women drinkers (victims, perpetrators, or both). IPV and heavy drinking (four or more drinks/day for women) are commonly seen as co-occurring conditions in emergency department (ED) settings, but these two conditions are rarely addressed together. Interventions that take a collaborative treatment approach to IPV and substance abuse have focused almost exclusively on male perpetrators, even though heavy drinking also is associated with IPV victimization and perpetration in women. Advised by international experts on gender and alcohol use and motivational enhancement therapy, a multidisciplinary group of investigators is conducting an RCT with 600 women ED patients who self-disclose co-occurring problem drinking

and IPV. The project will assess whether a brief motivational intervention can decrease episodes of heavy drinking and incidents of IPV, assessed weekly for 12 weeks. The 25-minute manual-guided motivational intervention will be delivered by trained social workers at the time of the ED visit, followed by a 15-minute phone booster at 10 days. Both the intervention and control groups will be contacted at 3, 6, and 12 months following the ED visit. Secondary outcomes include IPV severity, alcohol quantity/frequency, self-rated health, health behaviors, quality of life, and relationship satisfaction. This model could be generalizable to other acute health care settings.

Longitudinal Study of Social Support, PTSD, and Drinking in Rape Victims. Research shows that PTSD and problem drinking are common sequelae experienced by women victims of adult sexual assault, yet the role of social support in understanding these outcomes is unclear. An ongoing study is testing a theoretical model of the relationship between social support received by sexual assault victims and their postassault adjustment, including PTSD, problem drinking, and positive adaptation. Approximately 1,832 women who experienced either attempted or completed rape and disclosed their experience to at least 1 informal support provider will be recruited from the local community, universities, and victim service agencies to complete a series of 4 mail surveys distributed at 6-month intervals over the course of 2 years. The researchers are investigating how women's experiences of general and assault-specific social support relate to their coping and behavioral responses and postassault adjustment over time. Also explored is the prospective influence of women's experiences of social support on risk for sexual and nonsexual revictimization and whether such effects are mediated by women's coping and behavioral responses and postassault adjustment. The research team also is examining how revictimization influences women's subsequent coping and behavioral responses and postassault adjustment. These processes will be compared in victims of alcohol-related as well as non-alcohol-related sexual assaults. Finally, qualitative data gleaned from interviews with victims and informal support providers will yield a new understanding of how social support influences victims' postassault adjustment, whether any differences are a function of the victim being a problem drinker, and whether alcohol was involved in the assault.

Alcohol Use, Relationship Conflict, and IPV. Although alcohol consumption has long been recognized as a risk factor in IPV, few studies have addressed whether acute alcohol consumption is a causal factor in episodes of relationship conflict or aggression. An ongoing study is addressing the proximal relationship between alcohol consumption and relationship aggression among a community sample of young married and cohabiting couples. In one component of the study, the effect of alcohol use—administered independently to male and female partners—on communication behaviors and verbal aggression is experimentally explored within a conflict-resolution paradigm. It is hypothesized that alcohol consumption by either partner will increase behavioral negativity and verbal aggression. In addition, a daily diary study will allow an examination of whether the likelihood of relationship conflict or aggression occurring on a given day is increased when the man, the woman, or both have consumed alcohol earlier that day. Indepth, event-based interviews, conducted at the conclusion of the 8-week diary period, will provide insight into how alcohol may contribute to the initiation, escalation, and desistance of conflict. There are several unique aspects to the research. First, although the majority of research has focused on the role of men's drinking in their perpetration of aggression, women's drinking also may contribute to relationship conflict and aggression. Thus, the role of women's drinking on relationship conflict and aggression—both within the laboratory and in naturally occurring conflict episodes—will be explicitly considered. Second, the diary study is the first to examine the daily relationship between alcohol use and episodes of relationship conflict in a nonclinical sample and is expected to address the relative importance of alcohol in naturally occurring relationship conflict. Third, recognizing that alcohol may not facilitate conflict or aggression for all couples, both studies will consider the role of potential moderating variables, including propensity toward aggression, behavioral

self-control, and alcohol expectancies. This study is expected to provide important insight into the causal mechanisms underlying the relationship between alcohol and IPV.

Alcohol and Aggression in Women. Aggression is a major public health concern, with devastating effects to perpetrators, victims, and society and with associated costs of more than $100 billion dollars in the United States alone. Alcohol is most commonly linked to violent behavior, with the majority of serious violent acts occurring under the influence of alcohol. Although the effect of alcohol on aggression has been studied in men, there has been little research on women. This controlled laboratory study is the first to examine the effects of alcohol intoxication on physically aggressive behavior in women with intermittent explosive disorder (IED) and women without IED. In addition, the study examines cognitive executive functioning as a moderator of alcohol-facilitated aggression in women. With the significant economic and social costs resulting from aggression, much of which occurs under the influence of alcohol, furthering our understanding of the inter-relationship between physical aggression, executive functioning, and alcohol-facilitated aggression in women would help identify alcohol as a risk factor for female aggression. Furthermore, this study will open up a new avenue of research into other possible risk factors for alcohol-facilitated aggression in women and guide the development of treatment and intervention programs, in much the same way as such research is currently doing for men.

Brief Intervention To Reduce Drinking and IPV in Women. This research project is evaluating the effects of adding a brief intervention combining alcohol intervention with standard batterer intervention compared with individual interventions provided on their own. Specifically, it is examining the effects of the intervention on alcohol use and perpetration and victimization among these women. In addition, the study aims to evaluate the relationship between women's alcohol use and IPV by examining the relationship between use and violence on women's drinking versus nondrinking days. The study fits under the NIAAA Strategic Plan goal to elucidate the relationships between alcohol and violence.

Reducing Violence Against Women With Alcoholic Partners. An ongoing research project is focusing on coping-skills training for women with alcoholic partners. The study develops and compares a coping-skills training program with standard 12-step facilitation treatment. The project will evaluate and compare outcomes of the treatments, including levels of interpartner violence, negative affect, and negative marital behaviors among the partners. The study also will evaluate the women's skill levels and drinking patterns and their relationships to the behavioral outcomes.

Developing Web-Delivered Coping-Skills Training for Women With Alcoholic Partners (ARRA-Related Application). Nearly 1 in 20 adult women in the United States lives with an alcoholic or problem-drinking partner. To address this problem, this project will develop and test an empirically supported, clinic-based coping-skills training program for women with alcoholic/problem-drinking partners. The coping-skills training program will be developed as a Web-accessible version. The aim is to develop an easily accessible, confidential, low-cost, evidence-based treatment for a large segment of the population who otherwise would not or could not receive or seek care for this widespread problem.

Initiatives

Requests for Applications (RFAs)

Advancing Novel Science in Women's Health Research (ANSWHR). NIAAA participated in this ORWH initiative. The overall purpose of ANSWHR is to stimulate and support innovative research that will advance new concepts in women's health research and the study of sex/gender differences (PAS-10-226).

Building Interdisciplinary Research Careers in Women's Health (BIRCWH). ORWH and cosponsors, including NIAAA, issued this RFA to support Ph.D. and M.D. junior faculty members, known as BIRCWH scholars, to receive mentored research career development in interdisciplinary research on women's health or on sex/gender differences

related to biology, health, or disease. NIAAA provides cofunding for one grant that focuses on understanding the interplay between women's health and addictive behaviors, specifically involving tobacco, alcohol, overeating, and illicit drugs (RFA-OD-09-006).

Novel Interventions for Neurodevelopmental Disorders. The purpose of these RFAs was to encourage development and evaluation of novel interventions to improve functioning in neurodevelopmental disorders. NIAAA joined this National Institute of Mental Health initiative in order to foster the development of therapeutic interventions for neurobehavioral deficits associated with fetal alcohol exposure. Four new FASD projects (detailed below) were funded in fiscal year 2009 as a result of this RFA. These grants will provide the opportunity to test interventions in children affected by prenatal alcohol exposure and provide the foundation for increasing NIAAA's investment in intervention and treatment approaches (RFA-MH-09-161 [R21/R33], RFA-MH-09-160 [R34]).

Limited Competition, Role of Prenatal Alcohol Exposure in SIDS and Stillbirth (U01). This limited competition funding opportunity announcement (FOA) issued by NICHD and NIAAA invited cooperative agreement applications from investigators participating in the PASS Network for phase II. The purpose of this FOA is to invite applications to complete enrollment, followup, and primary data analysis of the Safe Passage Study to investigate the role of prenatal alcohol exposure in the risk for SIDS and adverse pregnancy outcomes such as stillbirth and FASD, including FAS, and how they may be interrelated (RFA-HD-10-018).

Program Announcements (PAs)

Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence. NIAAA is continuing to participate with the National Institute on Drug Abuse (NIDA) in an initiative to promote research on women and sex/gender differences in drug/alcohol abuse and dependence. This initiative, which was recently reissued, encourages research from basic studies of molecular genetics and neurotransmitters to studies of epidemiology, etiology, and prevention/treatment interventions that focus on sex/gender differences. Studies on sex/gender-based interventions related to HIV/AIDS and crosscutting issues related to stages of the life cycle, health disparities, methodological approaches, and gender-specific recruitment issues also are encouraged. Under the previous FOA, NIAAA received 23 applications of which 4 received funding in the past 2 years (PA-11-047, PA-11-048, PA-11-049).

Medications Development for the Treatment of Pregnant/Postpartum Women With Substance-Related Disorders and/or In Utero Substance-Exposed Neonates. The purpose of this PA is to foster the development of novel pharmacologic strategies for the treatment of pregnant/postpartum women with substance-related disorders and/or in utero substance-exposed neonates. Thus, this program is suitable for the development of therapeutics that address alcohol abuse by pregnant women, as well as the consequences to the alcohol-exposed infant (PA-09-106 [R01], PA-09-107 [R21]).

Genetic Susceptibility and Variability of Human Structural Birth Defects (R01). NIAAA participated with several Institutes and Centers in this PA issued by NICHD inviting research project applications designed to study fundamental developmental processes using animal models in conjunction with translational/clinical approaches, with the goal of advancing our understanding of the etiology of structural birth defects. Alcohol is a known teratogen, capable of causing FASD, a collection of birth defects and developmental disabilities that occur in individuals whose mothers drank alcohol during pregnancy (PA-11-085).

Chronic Fatigue Syndrome: Pathophysiology and Treatment. NIAAA has a shared interest in two ORWH initiatives on the pathophysiology and treatment of chronic fatigue syndrome (CFS) that extend until September 2011. The objective of these PAs is to encourage research into the etiology, diagnosis, pathophysiology, and treatment of CFS in diverse groups and across the lifespan, the environmental and biological risk factors, the determinants of heterogeneity among patient populations, and the common mechanisms influencing the multiple

body systems affected in CFS. Interdisciplinary research is highly encouraged (PA-08-246, PA-08-247).

Multimedia Products From NIAAA

Drinking and Your Pregnancy. NIH Publication No. 05-5610 (revised version).

Rethinking Drinking. NIH Publication No. 10-3770 (revised version).

Alcohol: A Women's Health Issue. This booklet has been updated to include new information and statistics. Available in English and Spanish, it is also available in full text on the NIAAA Web site.

Preventing Alcohol, Tobacco, and Other Substance-Exposed Pregnancies. In December 2009, NIAAA published a report on the symposium titled "Preventing Alcohol, Tobacco, and Other Substance-Exposed Pregnancies," which was cohosted by the Work Group on Women, Drinking, and Pregnancy of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders, NIAAA, and the American Legacy Foundation in Rockville, MD, on September 23–24, 2008. The report summarizes key information from each of the 22 presentations and from the highly interactive and informative discussions that followed. Plans are in place for wide distribution of the report through collaborating Federal agencies and State public health departments.

National Institute of Allergy and Infectious Diseases

Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated diseases, including diseases that affect the health of women and girls. NIAID involves women in many of its clinical studies on treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and sexually transmitted infections (STIs). NIAID also collaborates with other organizations on research initiatives within NIAID's mission areas that aim to improve women's health.

This biennial report provides an overview of selected NIAID-sponsored women's health activities. The first section describes scientific accomplishments in research on HIV/AIDS, STIs, and immunology and immune-mediated diseases. The accomplishments include the sponsorship of clinical trials that test possible antiretroviral (ARV) drugs or topical microbicides to prevent the transmission of HIV to women or their partners; epidemiologic studies to explore the cardiovascular health of women infected with HIV; therapeutic studies to optimize ARV regimens and to examine the effects of ARV drugs during pregnancy and breastfeeding; basic research to understand the mechanisms of autoimmune diseases to guide future treatment research; sponsorship of clinical trials to test promising immunotherapies for autoimmune diseases; research to identify treatments to block reactivation of latent herpes virus infections; and development of improved preclinical models for the study of STIs. The second section on related accomplishments in women's health research includes research training and the activities of NIAID's Women's Health Research Work Group. Additional sections address research initiatives for HIV/AIDS, STIs, and autoimmune diseases; conferences and workshops; sex/gender analysis studies; and research on health disparities in special populations.

Accomplishments

HIV/AIDS

The United Nations Joint Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that 33 million people worldwide are infected with HIV. Women face the greatest risk of acquiring HIV because of substantial mucosal exposure to seminal fluids, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners. Most women are infected with HIV through sex with men or injection drug use.

According to UNAIDS, in 2009, women accounted for almost 52 percent of all adults living with HIV worldwide and for 60 percent in sub-Saharan Africa. The Centers for Disease Control and Prevention (CDC) reported that the rate of new HIV diagnoses in women in the United States leveled off from 2005 to 2008, after increasing in previous years. This trend was accompanied by a slight decline in the rate of new AIDS diagnoses in women in the United States. However, HIV/AIDS and associated comorbidities and co-infections continue to cause substantial illness and death in the United States and worldwide. In 2009, for example, WHO reported that HIV/AIDS is the leading cause of death globally among women of reproductive age.

In addition to the complications of HIV/AIDS that affect men, infected women also suffer gender-specific manifestations of HIV disease, such as recurrent vaginal yeast infections, pelvic inflammatory disease (PID), genital ulcer disease, severe herpes infections, abnormalities related to infection with human papillomavirus (HPV), and vulvar and vaginal carcinomas. Drug metabolism differs in women compared with men, potentially resulting in differential responses to ARV therapy and an increased incidence of drug toxicities in women. Frequently, women with HIV infection have difficulty accessing health care and carry a large burden of caring for children and other family members who also may be HIV-infected. They often lack social support and face other challenges that may interfere with their ability to adhere to treatment regimens.

NIAID is supporting investigations of the course of HIV/AIDS in women through multiple initiatives including intramural studies; unsolicited research; the Women's Interagency HIV Study (WIHS), a long-term cohort study; and clinical trials to investigate gender-specific differences in HIV disease progression, complications, and/or treatment. These clinical trials are being conducted by the Microbicides Trials Network (MTN), AIDS Clinical Trials Group (ACTG), International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), HIV Interdisciplinary Network for Pathogenesis Research in Women (WHPN), HIV Prevention Trials Network (HPTN), HIV Vaccine Trials Network (HVTN), and International Network for Strategic Initiatives in Global HIV Trials (INSIGHT).

Epidemiologic Research

NIAID supports epidemiologic research in the following areas:

- The long-term natural history of HIV infection in women, in particular, research that evaluates the impact of ARV therapy on the clinical course of HIV disease
- The effect of hormonal, endocrine, and local factors on HIV viral load and sexual transmission
- Studies of older populations of HIV-infected women to investigate what pathogenic processes are related to HIV, ARV therapy, and/or the aging process
- Characterization of acute clinical events and co-infections and their impact on HIV disease progression
- Studies of the female genital tract compartment, including the microenvironment, HIV virology, and immunology of the female genital tract compared with blood

Women's Interagency HIV Study

The Women's Interagency HIV Study (WIHS) is the largest observational study of HIV-infected women and includes participants living in six U.S. metropolitan areas. The majority of the more than 3,500 women enrolled in the study are African-American and Latina women living in urban areas. The size of the study, the number of recently diagnosed patients, and the availability of stored biospecimens allow the evaluation of clinical outcomes in the era of highly active antiretroviral therapy (HAART). Researchers are investigating factors such as the development of AIDS, drug resistance, co-infections, therapy use and treatment effects, metabolic abnormalities and toxicities, hormonal factors, aging, neurocognitive functioning, and physical impairment. This study has yielded discoveries that have led to a better understanding of how HIV is spread, how HIV disease progresses, and how it can best be treated. More information is available at http://statepiaps.jhsph.edu/wihs.

Scientific Advances

The Risk of Cardiovascular Disease (CVD) Among Women in the WIHS Study Initiating Abacavir. Earlier research has shown that women infected with HIV tend to have a higher risk for CVD compared with the general population, partly due to HIV-specific factors. This NIAID-funded study was designed to analyze specimens and associated data from the WIHS biorepository to study risk factors for the development of CVD in HIV-infected women who are taking abacavir, which is used to treat HIV/AIDS. For example, the investigators tested for several plasma proteins, hsCRP, IL-6, and D-dimer, that are known to be associated with inflammation. Because women taking abacavir showed no increases in these proteins, the investigators concluded that mechanisms other than increased systemic inflammation may account for abcavir's reported association with increased CVD (*AIDS*. 2010 Jul 17;24(11):1657-65).

Protease Inhibitor Levels in Hair Strongly Predict Response to Treatment. ARV therapies fail when behavioral or biologic factors lead to inadequate medication exposure. The currently available methods to assess a patient's exposure to ARVs are limited. NIAID-funded investigators have found a way to measure ARV exposure levels by testing small samples of hair. The researchers looked for an association between levels of protease inhibitors (PIs), a type of ARV, in hair and successful suppression of HIV in the patient. They found that PI levels in hair were the strongest independent predictor of successful viral suppression in a diverse group of HIV-infected adults. This noninvasive method for measuring ARV exposure may prove useful in resource-poor settings (*AIDS*. 2009 Feb 20;23(4):471-8).

Prevention Research

Topical Microbicides

There is an intensified need for the development of a safe, effective, and acceptable topically applied chemical and/or biologic barrier to prevent sexually transmitted HIV infection. NIAID-sponsored research goals focus on the development of topical microbicides that (1) prevent HIV infection and/or viral replication, (2) are safe and noninflammatory (i.e., cause no irritation to the vaginal/cervical/urethral/rectal epithelium), and (3) reduce HIV transmission and acquisition, including potentiation of HIV acquisition by other STIs.

Microbicide Trials Network (MTN)

In 2006, MTN was formed to develop and evaluate microbicide products aimed at reducing the sexual transmission of HIV. MTN carries out its mission through a strong network of expert scientists and investigators from domestic and international sites. The network uses a focused microbicide research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission. More information is available at http://www.mtnstopshiv.org.

Scientific Advances

- **The Effects of Intercourse and Ejaculation on a Microbicide Gel (0.5% PRO 2000 Gel): Implications for Future Clinical Trials.** NIAID-supported research has shown that it is possible to conduct a well-controlled clinical study to measure the effects of intercourse and ejaculation on innate vaginal immunity and to assess the antiviral activity and safety of a microbicide candidate. This study also provides conclusive evidence that the activity of certain classes of microbicides can be altered significantly when mixed with ejaculate. Future research to develop and test topical microbicides may need to take these findings into account (*PLoS One*. 2010 Jan 22;5(1):e8781).
- **High Resolution Imagining Provides a Promising Model for Testing the Safety of Microbicides.** NIAID-funded researchers developed the Rambouillet sheep as a new preclinical animal model that has significant advantages over existing models for assessing the safety of microbicide candidates. They also provided proof-of concept that optical coherence tomography, a type of high-resolution imaging, is a sensitive and accurate method to assess subclinical effects of microbicides on cervical and vaginal mucosa (*Sexually Trans. Dis.* 2009 May 36(5) 312-318).

Clinical Trials

- **Vaginal and Oral Interventions to Control the Epidemic (VOICE) Trial (MTN-003).** This large randomized phase IIb clinical trial is comparing the safety and effectiveness of two approaches to HIV prevention in 5,000 African women. Investigators are studying the use of an oral ARV pill, either tenofovir (TFV) or Truvada, once a day compared with daily use of the ARV-based vaginal microbicide TFV gel. VOICE also will examine (1) the potential for and prevalence of drug resistance in women who acquire HIV while participating in the study, (2) bone mineral density in study participants, and (3) the impact of individual and community factors on trial retention and treatment adherence. More information is available at http://www.niaid.nih.gov/news/newsreleases/2009/pages/voice.aspx.
- **Additional Studies To Support the VOICE Trial.** Three additional NIAID-supported studies are evaluating the safety, acceptability, and adherence of 1% tenofovir (TFV) gel: HPTN 059 (completed in 2009), MTN-001, and MTN-002.
- **Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women (HPTN 035).** This international study evaluated the safety and efficacy of BufferGel and 0.5% PRO2000/5 Gel (P) when applied vaginally by women at risk for sexually transmitted HIV infection. The investigators found that BufferGel had no detectible effect on preventing HIV infection, but PRO2000 gel was safe and approximately 30 percent effective (not statistically significant). A larger study known as MDP-301 later showed that, although safe, PRO2000 gel was not effective at reducing the risk of HIV infection. More information is available at http://www.niaid.nih.gov/news/newsreleases/2009/pages/hptn_035_gel.aspx and http://www.niaid.nih.gov/news/newsreleases/2009/Pages/IneffectiveGel.aspx.
- **Phase I Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel™) Applied Vaginally in Sexually Active Young Women (MTN-004).** This ongoing MTN clinical trial seeks to enroll a total of 60 women at two study sites, one in Tampa and one in San Juan. Both sites are part of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)-funded Adolescent Trials Network. This study will evaluate the safety of Vivagel applied twice daily for 2 weeks in sexually active 18- to 24-year-old women. More information on this study and other MTN research is available at http://www.mtnstopshiv.org/node/studies.
- **Rectal Microbicide Safety and Acceptability Studies.** Two NIAID-supported studies are evaluating microbicides for rectal use: RMP02/MTN 006 (enrollment completed) and MTN-007 (enrolling in the United States).
- **Evaluating Outcomes of Women Enrolled in Microbicide Trials.** NIAID is supporting two studies (MTN-015, EMBRACE/MTN-016) to better understand the impact of microbicides/preexposure prophylaxis (PrEP) for women who either become infected with HIV or become pregnant while participating in a clinical trial. These studies are currently enrolling participants.
- **Integrated Preclinical/Clinical Program HIV Topical Microbicides Awards.** Several studies funded through this program were developed, initiated, and/or completed in 2010. They include an ongoing trial of rectal health, behaviors, and microbicide acceptability; a safety and acceptability study of UC-781, a vaginal microbicide gel for rectal application in individuals not infected with HIV; a study of the pharmacokinetics and pharmacodistribution of oral TFV and vaginally formulated TFV gel used rectally; a comparative study of the mucosal toxicity, colorectal distribution, and participant acceptability of three different preparatory enemas; use of optical coherence tomography as an imaging system to assess microbicide safety; postcoital antiviral activity of cervicovaginal secretions following vaginal application of the microbicide 0.5% PRO 2000/5 Gel (P); use of antimicrobial peptides for prevention of genital herpes

simplex virus (HSV) and HIV co-infection; user-acceptability studies of long-acting microbicidal vaginal gels and intravaginal rings; and a study to explore the sensory perceptions of vaginal product users. More information is available at http://www.niaid.nih.gov/topics/hivaids/research/prevention/pages/topicalmicrobicides.aspx.

Prevention of Mother-to-Child Transmission of HIV

According to WHO, the vast majority of all HIV-infected infants and children acquire the virus from their mothers before or during birth or through breastfeeding. Most mother-to-child-transmission (MTCT) occurs late in pregnancy or during birth. Currently, the United Nations Children's Fund (UNICEF) and WHO recommend that infants born to HIV-infected mothers who do not have access to acceptable, feasible, affordable, sustainable, and safe replacement feeding should be exclusively breastfed for at least 6 months. NIAID is conducting studies for prevention of mother-to-child transmission (PMTCT) in HIV-infected pregnant women. NIAID-sponsored PMTCT research focuses on the following goals:

- Defining the mechanisms and risk factors for HIV transmission to children and adolescents and from mother to infant as well as risks for disease progression within the framework of clinical studies and trials
- Developing and testing additional ARV strategies for PMTCT of HIV infection through clinical trials in the United States and international settings
- Developing interventions for PMTCT of HIV via breast milk in settings where breastfeeding is the best assurance for infant nutrition

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), which is sponsored by NIAID and NICHD, is a network dedicated to significantly decreasing the mortality and morbidity associated with HIV disease in children, adolescents, and pregnant women. IMPAACT develops and evaluates safe and cost-effective approaches for the interruption of mother-to-infant HIV transmission; evaluates treatments for HIV-infected children, adolescents, and pregnant women; investigates strategies for treatment and prevention of co-infections and comorbidities; and evaluates vaccines for the prevention of HIV sexual transmission among adolescents. More information is available at http://impaact.s-3.com.

Scientific Advances

ARV Regimens in Pregnancy and Breastfeeding in Botswana. The Mma Bana Study/BHP 016 study was designed to determine which of two treatment regimens is more effective in reducing HIV viral load and preventing MTCT among HIV-infected pregnant and breastfeeding women in Botswana. One group of participants received Trizivir (TZV), a single pill containing abacavir sulfate, lamivudine, and zidovudine, and a second group received lopinavir/ritonavir and lamivudine/zidovudine. A third group of women received nevirapine plus zidovudine-lamivudine (the observational group). The investigators found that all regimens of HAART used during pregnancy and through 6 months postpartum resulted in high rates of viral suppression, with an overall rate of MTCT of 1.1 percent (*N Engl J Med* 2010; 362:2282-2294).

ARV Treatment of Mothers or Infants To Reduce HIV Transmission. NIAID-supported investigators compared the safety and efficacy of a maternal triple-drug ARV regimen and infant nevirapine administered during 28 weeks of breastfeeding to reduce postpartum HIV transmission in Malawi. The investigators found that both prevention strategies were effective in reducing HIV transmission during breastfeeding (*N Engl J Med* 2010; 362:2271-2281).

The Effects of Single-Dose Nevirapine (SD NVP) on Future Treatment Options for Women and Children. NIAID-supported investigators recently published results from two major studies: OCTANE/A5208 and P1060. Both studies demonstrated that SD NVP used for PMTCT can hamper the drug's future effectiveness as part of a later HIV treatment regimen for either the mother or the child. More information is available at http://www.niaid.nih.gov/news/newsreleases/2010/Pages/P1060OCTANE.aspx (*N Engl J Med*

2010; 363:1499-1509), N Engl J Med 2010; 363:1510-1520).

Clinical Trials

- **Promoting Maternal-Infant Survival Everywhere (PROMISE) Study.** In early 2010, NIAID-supported investigators initiated a large, multinational clinical trial to determine how best to reduce the risk of HIV transmission from infected pregnant women to their babies during pregnancy and breastfeeding while preserving the health of these children and their mothers. The study aims to enroll about 8,000 HIV-infected women who are pregnant or have recently given birth and about 6,000 HIV-exposed infants of these women. The participants are being recruited from as many as 18 countries whose levels of resources range from high to low. More information is available at http://www.niaid.nih.gov/news/newsreleases/2010/pages/promise.aspx.
- **Additional Studies on the Effects of SD NVP on Future Treatment Options for Women and Children.** Two studies—ACTG 5207 in Africa, India, and Haiti and PACTG 1032 in Thailand—are exploring strategies to minimize viral resistance to ARV therapy and assess the impact of viral resistance after SD NVP.
- **HIV Treatment Reinitiation in Women Who Received Anti-HIV Drugs To Prevent Mother-to-Child Transmission of HIV (ACTG 5227).** This study is examining whether the impact of HAART in women for treatment of HIV is affected by prior exposure to HAART for PMTCT.
- **Studies to Evaluate Approaches for PMTCT.** Several trials are investigating use of ARVs in infants and mothers to prevent MTCT. HPTN 040 is assessing two different combinations of anti-HIV medications compared with a one-drug standard regimen given at birth. HPTN 046 is assessing daily use of NVP for 6 months in infants to prevent HIV transmission in breastfeeding women. An investigator-initiated clinical trial (R01 AI 087139) is assessing the impact of maternal HAART on transmission of HIV resistance to the infant during breastfeeding.

Vaccine Research

Vaccines contain dead or modified microorganisms or parts of microorganisms that can stimulate an immune response in the body to prevent future infection with the same or similar microorganisms. They serve as the foundation of preventive measures to curtail infectious disease epidemics, with a historically demonstrated positive impact on public health. NIAID conducts and supports basic research in areas such as infectious diseases, microbiology, and immunology to generate the knowledge essential for developing safe and effective vaccines for the prevention of HIV infection. The recent positive findings from the RV144 HIV vaccine efficacy trial in Thailand, which showed that a vaccine candidate was partially effective at preventing HIV infection, have provided renewed energy in the field. NIAID is building on this achievement through a sustained commitment to pursuing both basic and vaccine discovery research while continuing to advance the most promising HIV vaccine candidates into testing. Even a partially effective HIV vaccine could have a significant positive impact on the health of women, particularly in resource-limited settings.

HIV Vaccine Trials Network

The NIAID-sponsored HIV Vaccine Trials Network (HVTN) is an international collaboration of scientists searching for an effective and safe HIV vaccine. HVTN's mission is to facilitate the process of testing preventive vaccines against HIV/AIDS, conducting all phases of clinical trials, from evaluating experimental vaccines for safety and the ability to stimulate immune responses to testing vaccine efficacy. More information is available at http://www.hvtn.org.

Clinical Trial

- **Longitudinal Studies of Women at High Risk for HIV-1 Infection To Inform HIV Vaccine Trial Participation (HVTN 906; HVTN 907).** HVTN is conducting two studies on the feasibility of identifying, recruiting, and retaining women at high risk for HIV infection for participation in vaccine trials. The research also will estimate HIV incidence in study participants over a period of 18 months. HVTN 906 has enrolled a total of 800 women with

multiple risk behaviors who are living in New York City, Philadelphia, and Chicago. HVTN 907 has enrolled 800 women with high-risk behaviors who are living in the Caribbean (Haiti, Dominican Republic, and Puerto Rico). Study investigators are conducting followup studies of women who contracted HIV during the trials, analyzing the success of enrollment strategies, assessing factors that predict HIV prevalence, and identifying factors that predict willingness to participate in future HIV vaccine trials.

Other Prevention Research—HIV Prevention Trials Network

Established in 2000, the HIV Prevention Trials Network (HPTN) is a worldwide collaborative clinical trials network that develops and tests the safety and efficacy primarily of nonvaccine interventions designed to prevent the transmission of HIV. The HPTN research agenda focuses on the use of ARV therapy; treatment and prevention of sexually transmitted infections; treatment of substance abuse, particularly injection drug use; and behavioral risk reduction interventions to reduce HIV transmission and acquisition. HPTN studies are conducted in various populations, such as women, and geographical regions that bear a disproportionate burden of HIV infection. More information on HPTN is available at http://www.hptn.org.

Clinical Trial

- **Women's HIV SeroIncidence Study (ISIS) (HPTN 064).** This multisite observational study is designed to estimate the overall HIV incidence in 2,000 women at high risk for HIV acquisition in the United States. Investigators also will evaluate laboratory assays for HIV; estimate study recruitment and retention rates; describe sexual behaviors, alcohol and drug use, prevalence of domestic violence, and mental health indicators of women at risk for HIV; assess women's preferred recruitment and retention strategies for future studies; describe social, structural, and contextual factors to inform future intervention studies; and explore facilitators and barriers to HIV testing among men residing in high-risk areas. In 2009, this HPTN study began enrolling participants from 10 geographically distinct high-risk areas of the United States.

Therapeutics Research

AIDS Clinical Trials Group

Established in 1987, the AIDS Clinical Trials Group (ACTG) is a multicenter clinical trials network that conducts translational and therapeutics research in the United States and internationally. Research priorities include translational research and optimization of clinical management, including management of co-infection and comorbidities. In collaboration with other clinical trials networks, ACTG also pursues research and development of therapeutic vaccines and research on HIV treatment in pregnant women. More information is available at http://actgnetwork.org.

Scientific Advances

ARV Therapy in Treatment-Naïve Premenopausal and Postmenopausal HIV-Infected Women. The investigators from ACTG 5001 compared the treatment responses of treatment-naïve premenopausal and postmenopausal women who were enrolled in two ARV therapy studies. The investigators demonstrated that postmenopausal women benefit from ARV therapy, with responses similar to those seen in premenopausal women. They also reported that responses to ARV therapy were maintained through 2 years of followup. These findings suggest that treatment-naïve women should respond to ARV therapy regardless of menopausal status (*Clin Infect Dis.* 2009 Aug 1;49(3):473-6).

Use of a Transdermal Hormonal Contraceptive Patch in HIV-1 Infected Women Treated With PIs. An ACTG trial (A5188) studied the use of an estrogen/progesterone-containing hormonal contraceptive patch in HIV-infected women who were taking the PI lopinavir-ritonavir as part of an ARV therapy regimen. Among women using the patch, estrogen levels were higher and progesterone levels were lower in women on the PI-containing ARV therapies, compared with levels in women who were not on ARV therapy. Nevertheless, the concentrations of the contraceptive drugs in the women taking PIs suggest that the contraceptive patch is likely to

remain effective. The investigators also noted a trend for the concentration of lopinavir-ritonavir to be decreased slightly in women using the contraceptive patch (*J Acquir Immune Defic Syndr.* 2010 Dec 1;55(4):473-82).

Clinical Trials

Optimizing Treatment for Treatment-Experienced HIV-Infected People (A5241). This phase IV study is designed to determine whether there is a benefit of adding a nucleoside reverse transcriptase inhibitor (NRTI) to a new anti-HIV drug regimen. Twenty-two percent of study participants are women, which will allow investigators to perform subgroup analyses on outcomes in women.

Once-Daily PI/Non-NRTI (NNRTI) Therapy Combinations for Treatment-Naïve HIV-Infected Patients in Resource-Limited Conditions (A5175). This study, which was completed in 2010, compared the effectiveness of three different drug combinations in HIV-infected individuals starting their first HIV treatment regimens. Participants, 47 percent of whom were women, were recruited from the United States, South Africa, Malawi, Zimbabwe, India, and Thailand. The trial includes neurology and genital compartment substudies. Data analysis is underway.

Osteoporosis in HIV-Infected Postmenopausal Women (R01 AI 065200). This ongoing clinical trial is examining the impact of traditional risk factors for osteoporosis, as well as HIV infection and ARV therapy, on the prevalence of osteoporosis and the rate of bone loss in HIV-infected postmenopausal African-American and Hispanic women.

Sex and Disease-Dependent Nucleoside Analog Toxicity (R01 AI 064029). This clinical trial is comparing concentrations of nucleosides in the cells of men and women taking an ARV therapy regimen that contains a nucleoside analog. The study seeks to explain gender differences in adverse events such as localized loss of fat tissue and fat accumulation in individuals taking these drugs. Researchers also will examine the effects of nucleoside analogs on the mitochondria, a cellular organelle that provides the cell with energy.

Centers for AIDS Research

Centers for AIDS Research (CFAR) is a unique trans-NIH program that provides infrastructure to support interdisciplinary, peer-reviewed HIV/AIDS research in an environment that coordinates studies, promotes communication, provides shared services/expertise, and funds short-term feasibility studies that cannot be funded easily by other mechanisms. There are currently 21 CFARs (17 standard and 4 developmental) located at academic and research institutions throughout the United States. Several of the CFARs are actively supporting research activities in women. In 2010, 6 CFARs awarded 16 pilot projects through the CFAR Developmental Cores in the area of HIV research in women. In addition, the Inter-CFAR Collaboration on HIV Research in Women is a network of CFAR investigators dedicated to promoting cutting-edge science in HIV research and women. The collaboration develops new strategies for future research to address HIV-related issues unique to women and promotes career development and professional growth among junior investigators interested in this field. The overall goal of the program is to identify gaps in knowledge in research on HIV and women and generate collaborative activity between CFARs and other research networks. More information on CFAR research is available at http://www3.niaid.nih.gov/research/cfar.

Sexually Transmitted Infections

The prevention and treatment of STIs are critical global and national health priorities because of their disproportionate and devastating impact on women and infants and their inter-relationships with HIV/AIDS. CDC reported in 2009 that about 19 million new STIs occur in the United States each year at a cost of nearly $16.4 billion. The CDC report titled *Sexually Transmitted Disease Surveillance 2009* shows persistent racial disparities for chlamydia and gonorrhea and a particular burden of STIs among women in the United States.

NIAID supports a broad array of biomedical research for more effective prevention and treatment approaches to control STIs:

- Research for safe and effective vaccines, topical microbicides, therapeutics, and

strategies for preventing and treating STIs and resulting conditions

- Basic research on the pathogenesis, immunity, molecular and structural biology of sexually transmitted pathogens, and impact of STIs in various populations
- Development of better and more rapid diagnostics

Genital Herpes

There are two types of herpes simplex virus (HSV) and both can cause genital herpes. HSV type 1 (HSV-1) most commonly infects the lips, causing sores known as fever blisters or cold sores, but it also can infect the genital area and produce sores. HSV type 2 (HSV-2) is the usual cause of genital herpes, but it also can infect the mouth. HSV-2 is more common in women than in men. Genital HSV infections can present serious health consequences, including lifelong recurrent episodes of painful genital lesions; increased likelihood of HIV transmission and acquisition; and for women, possible transmission to fetus or neonate that can result in neonatal brain damage or death.

Scientific Advance

Monoamine Oxidase Inhibitor (MAOI) Blocks HSV Replication and Reactivation From Latency. HSV infection can remain latent for the life of some individuals but can be reactivated to cause symptoms in others. NIAID scientists showed that reactivation of HSV in cells grown in the laboratory can be prevented by MAOIs. The researchers investigated the role of LSD1, a cellular enzyme involved in HSV infection. They showed that LSD1 interacts with another cellular protein, HCF-1, which plays an essential part in the HSV infection process. Because LSD1 is similar to a family of proteins that can be inhibited by MAOIs, the researchers investigated the effect of these drugs on HSV infection. They found that two MAOI drugs were able to prevent HSV infection of cells and one of the drugs also prevented HSV reactivation from a latent state. These observations identify a novel therapeutic target for herpesvirus infections (*Nature Medicine 2009* Nov;15:1312-7).

Clinical Trial

Herpevac Clinical Trial for Women. This phase III clinical efficacy trial of a vaccine for the prevention of genital herpes has enrolled more than 8,300 women at approximately 50 sites in the United States and Canada. Although the vaccine was generally safe and well-tolerated, it proved to be ineffective in preventing genital herpes disease. This study was a public-private partnership with GlaxoSmithKline. More information is available at http://www.niaid.nih.gov/news/QA/Pages/HerpevacQA.aspx.

Human Papillomavirus

Human papillomavirus (HPV) is a group of viruses that includes more than 100 different strains. HPV is of clinical and public health importance because persistent infection with certain oncogenic (cancer-causing) types of HPV can lead to cervical cancer, which is one of the most common cancers in women worldwide. Non-oncogenic HPVs do not cause cancer but are responsible for genital warts, respiratory papillomatosis, and cutaneous warts. These lesions can be especially problematic in individuals who are immunocompromised by HIV infection or organ transplantation.

The vaccine Gardasil is licensed for the prevention of cervical cancer, precancerous genital lesions, and genital warts due to HPV types 6, 11, 16, and 18 in females ages 9 to 26 years. It also is licensed for the prevention of genital warts in males ages 9 to 26 years. Cervarix is licensed for the prevention of cervical cancer due to HPV types 16 and 18 in women ages 10 to 26 years.

Scientific Advance

New Long-Term Method for Growing Cells Will Aid HPV Research. HPV, like other viruses, can be grown in cell cultures for use in laboratory research. Because cell cultures of oncogenic strains of HPV are long lived, they are easier to study than non-oncogenic HPVs, which are short lived in cell culture. However, NIAID scientists have discovered a way to create long-term cultures of non-oncogenic HPV-infected cells. They developed a method that immortalizes a type of cell known as a primary keratinocyte. These cells, which are found in

foreskin and vaginal and cervical epithelium, are natural hosts for all HPV types. This finding makes possible long-term studies of non-oncogenic HPV in cell culture (*J Clin Invest.* 2010 Jul 1;120(7):2619-26).

Clinical Trial

HPV Vaccine in HIV-Infected Females. The A5240 study is evaluating the safety and tolerability of a HPV vaccine in HIV-infected women. NIAID is supporting a similar study for HIV-infected girls (PACTG 1047).

Chlamydia

Chlamydia trachomatis infections are among the most prevalent of all STIs. In women, chlamydia infections may result in PID, which is a major cause of infertility, ectopic pregnancy, and chronic pelvic pain. The rate of reported chlamydia infection is greater among women than men, and adolescent women have the highest risk of infection.

Scientific Advance

An Improved Mouse Model of Chlamydia. Chlamydia vaccine research has been hampered by the lack of a suitable small-animal model that mimics chlamydia infection in humans. NIAID scientists have isolated a human *Chlamydia* strain that produces an infection in female mice similar to chlamydia infection in humans. They also identified a *C. trachomatis* gene that is associated with the ability of this strain to cause infection. This work will advance small-animal modeling for the study of human STIs, provide novel insights into the genetic epidemiology of chlamydia in humans, and may help to identify individuals at increased risk of postinfection complications (*Infect Immun.* 2010 Sep;78(9):3660-8).

STI-Associated Cervicitis

Cervicitis is most often caused by an infection, usually an STI such as chlamydia, gonorrhea, HSV, HPV, or trichomoniasis. Cervicitis is very common, affecting more than half of all women at some point during their adult life. Simple cervicitis usually heals with treatment if the cause is found and there is a treatment for that cause (http://www.nlm.nih.gov/medlineplus/ency/article/001495.htm).

Scientific Advance

***Mycoplasma genitalium* and Cervicitis.** NIAID investigators examined a possible association between cervicitis and several organisms that cause STIs, including C. trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, and M. genitalium. They discovered a strong association of M. genitalium with cervicitis. This investigation highlights the need for studies on the potential etiology of M. genitalium in cervicitis in more diverse populations (Sex. Transmit. Dis. 36:598-606, 2009).

Immunology and Immune-Mediated Diseases

NIAID supports investigations of immunology and immune-mediated diseases and their effect on women's health. The goal of this research is to increase the health and well-being of women by developing new methods to prevent and treat autoimmune diseases, enhance graft survival in women, and prevent the immunologic causes of infertility.

Autoimmune Diseases

Autoimmune diseases are a group of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. Some of the more common autoimmune diseases include rheumatoid arthritis (RA), type 1 diabetes, multiple sclerosis (MS), celiac disease, and inflammatory bowel disease. Many autoimmune diseases disproportionately affect women, and this group of diseases is among the leading causes of death for young and middle-aged women. NIAID supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs.

Lupus

Systemic lupus erythematosus (SLE), more commonly known as lupus, is a chronic inflammatory autoimmune disease. Inflammation caused by lupus can affect many body systems, including the joints, skin, kidneys, blood cells, heart, and lungs. An estimated 1.5 million Americans and more than 5 million individuals worldwide have a form of

lupus. Ninety percent of the people with lupus are women, and generally the age of onset is between 15 and 45 years. Lupus in more common in Black, Hispanic, Native American, and Asian women than in White women.

Scientific Advances

- **High Lupus Prevalence in Women of African Descent May Have Roots in a Malaria-Protective Mechanism.** NIAID scientists discovered that mice with a genetic difference in the *FcγRIIB* gene are more susceptible to SLE but are protected from death due to cerebral malaria. The protection appears to be caused by immune mechanisms that allow SLE-prone mice better control of overall inflammatory responses to parasite infections. These findings suggest that the high prevalence of SLE in women of African descent living outside Africa may result from the inheritance of genes that are beneficial in the control of cerebral malaria but that also contribute to autoimmune disease (*Proc Natl Acad Sci U S A.* 2011 Jan 18;108(3):1122-7. Epub 2010 Dec 27).
- **Role for Autoantibodies in Learning Disorders of Lupus Offspring.** NIAID-supported research has identified a possible explanation for why children of mothers with lupus have higher rates of learning disorders. The researchers used a mouse model of lupus in which pregnant females have autoantibodies that react with NMDAR, a receptor protein present on brain neurons. They found that autoantibodies to NMDAR were transported from the mothers through the fetal circulation to the fetal brain. Mothers with high levels of NMDAR-specific autoantibodies had mice pups with more abnormalities in the formation of the brain cortex during development and in cognitive function in adulthood. With this knowledge, researchers may be able to target treatments to minimize cognitive impairments in offspring of mothers with lupus. This study also suggests an approach for studying the possible role of maternal autoantibodies in other congenital, neurodevelopmental disorders (*Nat Med* 2009: 15(1): 91-6).

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory disease that causes pain, swelling, stiffness, and loss of function in the joints. It occurs when the immune system, which normally defends the body from invading organisms, turns its attack against the membrane lining the joints. RA affects about 1.3 million Americans, and women are affected about two times more frequently than men. The course of RA can range from mild to severe, and in most cases it is chronic.

Scientific Advances

Gut Microbe Can Drive Autoimmune Arthritis. NIAID-supported researchers found that a specific species of intestinal bacteria, segmented filamentous bacteria, may induce arthritis in a mouse model prone to autoimmune arthritis. The investigators found that, when raised in a germ-free environment, the mice developed a much less severe form of arthritis, had low levels of autoantibodies, and had none of a type of cell (Th17 cells) known to be associated with inflammation. However, the introduction of the segmented filamentous bacteria into the gut of the germ-free mice caused a rapid onset of arthritis, the appearance of Th17 cells, and high levels of autoantibodies. This research improves understanding of how intestinal bacteria affect autoimmune disease (*Immunity* 2010: 32: 815-827).

Blood Test Allows Prediction of Time of Onset of RA in At-Risk Individuals. Most people who will develop RA have certain autoantibodies present in their blood several years before the actual onset of disease. In this study, NIAID-supported investigators tested blood samples collected over many years from at-risk individuals who subsequently developed RA. They found a clear correlation between the levels of immune system signaling proteins, called cytokines and chemokines, and the time to onset of disease. This discovery may facilitate improved individual prognoses and may help researchers develop therapies that delay the onset of RA in at-risk individuals (*Arthritis Rheum* 2010: 62: 3161-72).

Systemic Sclerosis

Systemic sclerosis (or scleroderma) is a group of autoimmune diseases in which the immune system is thought to stimulate cells called fibroblasts, which then produce too much collagen. Systemic scleroderma is the form of the disease that not only includes the skin but also involves the tissues beneath the skin, the blood vessels, and the major organs. The excess collagen forms thick connective tissue that can interfere with the function of affected organs. An estimated 40,000 to 165,000 people in the United States have this disease, and women—especially middle-aged women and African-American women—are affected more than men.

Clinical Trial

- **High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Severe Systemic Sclerosis.** This study—Scleroderma Cyclophosphamide or Transplantation (SCOT)—is assessing the safety and potential usefulness of high-dose immunosuppressive therapy followed by hematopoietic stem cell transplant compared with monthly pulse cyclophosphamide for systemic sclerosis. The hypothesis is that high-dose immunosuppressive therapy will destroy the malfunctioning immune system and replacement with immature immune cells will permit the development of a healthy immune system, inducing a long-term remission or even eradication of the disease.

Understanding the Causes of Autoimmune Diseases

NIAID supports research to elucidate the causes of autoimmune diseases. This research is critical to inform the development of interventions to prevent, diagnose, and treat these illnesses.

Scientific Advance

- **A New T Cell Regulatory Circuit.** Autoimmune diseases can arise from loss of control over two types of immune cells: T cells or B cells. T-cell responses typically result in inflammatory disease and B-cell responses result in the production of autoantibodies. Much immunology research over the past decade has focused on specialized T cells capable of regulating other T cells and thereby dampening inflammatory responses. NIAID-funded researchers have now described another set of regulatory T cells that control the generation of autoantibodies. Mice that are genetically unable to properly stimulate this new subset of regulatory T cells spontaneously produce autoantibodies similar to those seen in humans with SLE and other rheumatic diseases (*Nature* 2010: 467: 328-33).

Related Accomplishments in Women's Health Research

Research Training and Career Development

Mentoring International Investigators on HIV Research and Women's Health. Mentored Career Development Awards focus on pharmacologic interventions available to HIV-infected women to increase treatment responses and to decrease infectiousness; the impact of the menstrual cycle on ARV pharmacokinetics; and antiviral therapy and HIV in the genital tract of women.

Developing Minority and Women Scientists in AIDS Research. The Chicago Developmental CFAR provides mentoring, training, and resources for minority and women scientists participating in AIDS research. A number of women scientists, including several young investigators, have been encouraged to submit research grants. Some of the mentors are also women scientists. In addition, the University of Washington CFAR's Sociobehavioral and Prevention Research Core strongly supports women and minority researchers. The core director facilitates a mentoring group for junior faculty and fellows; the group comprises a majority of women minority researchers.

Trans-NIAID Women's Health Research Work Group

The Trans-NIAID Women's Health Research Work Group (1) focuses on women's health and gender-based research activities that advance the mission and research priorities

of NIAID, (2) identifies gaps in research, and (3) provides recommendations for future women's health research opportunities. The work group performs the following functions:

- Advises NIAID on the coordination of women and gender-based research across the Institute
- Develops a common framework for identifying and assessing women and gender-based research
- Encourages trans-NIAID and trans-NIH collaborations on women and gender-based research activities
- Coordinates a seminar series highlighting issues and advances in women's health research

Research Initiatives

Initiatives in HIV/AIDS Research

Program Announcement

HIV Interdisciplinary Network for Pathogenesis Research in Women (WHPN). NIAID released this program announcement (PA) in June 2008 to enhance knowledge of the transmission and pathogenesis of HIV infection in women through the study of biologic mechanisms that affect HIV transmission, acquisition, progression, and manifestations in women. In fiscal year (FY) 2010, NIAID funded three major projects and two American Recovery and Reinvestment Act (ARRA) supplements to existing projects. Funded projects aim to explore viral and host interactions that affect HIV transmission in the female reproductive tract; define mechanisms and cofactors of HIV transmission in pregnant and postpartum women; examine HIV susceptibility and pathogenesis in the female genital tract; and explore whether antibodies against HIV may help prevent infection in HIV-exposed but uninfected women (PAR-08-170).

Requests for Applications

Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM). This request for applications (RFA), sponsored by NIAID and the National Institute of Mental Health (NIMH), was reissued in 2010 to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. New awards will examine the activity and pharmacodynamics of long-acting acceptable microbicides; support basic and comparative studies of HIV prevention through inhibition of CCR5, a protein known to be involved in HIV infection; and pursue development of a practical microbicide based on HIV entry inhibitors (RFA-AI-10-006).

Microbicide Innovation Program (MIP). NIAID supports MIP in coordination with the Office of AIDS Research (OAR) and the NIH Office of Research on Women's Health (ORWH). MIP supports research to advance the development of new microbicide approaches through preclinical and basic research; discovery and exploration of microbicides (singly or in combination) to prevent HIV or STIs that increase risk for HIV acquisition; emerging technologies or models to improve assessment of microbicide safety, efficacy, and acceptability; and exploration of complex prevention strategies that use microbicides in combination with other prevention strategies (RFA-AI-10-011).

Methods for Prevention Packages Program (MP3). This program, sponsored by NIAID, NIMH, and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), is designed to foster interdisciplinary teams to formulate and assess prevention packages (combination interventions including both biomedical and behavioral components) for specific populations. Funded projects include a protocol to examine the safety and efficacy of the prevention package and feasibility studies that include adherence and acceptability in the target population (RFA-AI-10-005).

Contract

Partnerships for Topical Microbicides Program. Through these contracts, industry and academic or other nonprofit organizations work together in consortiums to develop and bring promising topical microbicide candidates to the point of preparation for clinical trials. The focus is to develop a potential microbicide with a proposed dual indication

(i.e., prevention of HIV and an STI or prevention of two STIs) (RFP-AI-04-047).

Initiatives in STI Research

Request for Applications

Partnerships for Point-of-Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings (U01). In FY 2008, NIAID released an RFA calling for applications targeting product development activities that will lead to new or improved POC diagnostic technologies for infectious disease-causing pathogens or toxins in nontraditional health care settings. Nontraditional health care settings include the home, rural and urban community public health care clinics, and temporary health care clinics established in response to a natural or man-made disaster. NIAID made five awards in FY 2009 (RFA-AI-08-003).

Research Enhancement Awards Program

Biochemical Analysis of Papillomavirus Replication. This investigation of papillomavirus genome replication received an ORWH Research Enhancement Awards Program (REAP) award in 2007 and is now funded by NIAID. The investigators are using genetic, biochemical, and structural analyses of the viral proteins and DNA segments called sequence elements that are required for viral DNA replication. Papillomaviruses are very important causative agents of human disease, including cervical cancer. A deeper understanding of the life cycle in general, and DNA replication in particular, is critical to the understanding of this disease, its transmission, and ultimately the development of effective therapeutic measures. The viral DNA replication machinery to be elucidated in this research presents one of the few potential targets for drug therapy (1 R01 AI072345-01A2).

Initiatives in Autoimmune Disease

Program Announcement

Advancing Novel Science in Women's Health Research. NIAID is a cosponsor of this ORWH-led initiative that supports a number of scientific areas that advance women's health research. In 2010, NIAID funded an award that focused on a mouse model study designed to investigate sex differences in influenza (PAS-07-381).

Requests for Applications

Autoimmunity Centers of Excellence (ACEs). The nine ACEs conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials of drugs called immune modulators that act on the immune system. The centers support close interaction between clinicians and basic researchers to facilitate identification of effective strategies for inducing immune tolerance and developing immune modulation strategies to treat or prevent disease. This interaction also accelerates the translation of scientific advances to the clinic. Completed, ongoing, and planned clinical trials address lupus, Sjögren's syndrome, RA, MS, ulcerative colitis, scleroderma, pemphigus, and type 1 diabetes. Created by NIAID, the ACEs are currently cofunded by the National Institute of Dental and Craniofacial Research (NIDCR) and the NIH ORWH. More information is available at http://www.autoimmunitycenters.org (RFA-AI-08-010).

Immune Defense Mechanisms at the Mucosa (R21/U01). These initiatives support research projects on immune defense mechanisms and immune regulation at respiratory, gastrointestinal, and genital tract mucosal surfaces. The exploratory/developmental research initiative (R21) is supporting more than 50 investigator-initiated projects. In addition, the research project cooperative agreement (U01) program will support collaborative research to promote new ideas, approaches, and technologies to address the difficult questions remaining in mucosal immune defense. The long-term goal is to develop the knowledge base needed to design mucosal vaccines and therapeutics for mucosal pathogens and mucosal inflammation. The program includes basic, applied, and clinical research projects (RFA-AI-08-020 and RFA AI-10-008).

Ancillary Studies in Immunomodulation Clinical Trials (R01). This program, cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Diabetes and Digestive

and Kidney Diseases (NIDDK), and National Institute of Neurological Disorders and Stroke (NINDS), supports mechanistic studies in clinical trials of immunomodulatory interventions for immune system-mediated diseases and preventative and therapeutic vaccines for non-HIV/AIDS infectious diseases. This program uses patient samples from clinical trials to study and define the underlying immunologic mechanisms of the tested intervention, the mechanisms of disease pathogenesis, and biomarkers of disease activity and therapeutic effect. Through this RFA, NIAID supports mechanistic studies in polyarticular juvenile idiopathic arthritis (JIA), RA, and MS (RFA-AI-08-011).

The NIH Roadmap Human Microbiome Project

NIAID is actively participating in the NIH Roadmap Human Microbiome Project (HMP) along with the National Human Genome Research Institute (NHGRI), NIDDK, National Cancer Institute (NCI), and NIDCR as the lead Institutes (http://nihroadmap.nih.gov/hmp). The objective of the project is to characterize the human microbiota and demonstrate the feasibility of this strategy to determine whether changes in the microbiome can be correlated with human disease, response to vaccines and treatment, or healthy phenotype. The project is supporting the generation of reagents, reference data sets, and other research resources for the scientific community and can be used to conduct Institute and Center-specific basic and applied research, leading to new strategies for diagnosis and treatment of human diseases and prevention strategies to maintain or reestablish the healthy microbiome.

NIH HMP has funded projects to examine the relationship between changes in the human microbiome in health and disease. The following activities focus on women's health research:

- Changes in the composition of the human vaginal microbiome are being examined in women with bacterial vaginosis to shed light on the cause of this disease. In a related study, investigators are examining human genetic markers that may be associated with the disease.
- NIH HMP-funded investigators are studying the vaginal microbiome in reproductive-age women to examine changes in the composition that may be predictive of occurrence and remission of bacterial vaginosis.

Conferences and Workshops

CFAR Joint Symposium on HIV Research in Women. **This meeting was held October 27–28, 2010, in Chicago,** to identify gaps in knowledge in HIV and women's research and develop strategies to move the field forward. The meeting also focused on opportunities for collaborative activity between CFARs and other research networks, highlighting cutting-edge science and opportunities for young investigators. The meeting consisted of three sessions: (1) HIV Across the Female Life Course, (2) HIV Treatment and Comorbidities, and (3) Primary Prevention of HIV in Women. The meeting brought together basic, clinical, and behavioral scientists in a setting designed to facilitate interdisciplinary research collaboration. More than 100 individuals participated in the event, and their activities have resulted in submission of several grants. More information is available at http://www.chicagocfar.org/CFARWomen.html.

Best Practices for Phase I Safety Assessment of Microbicide Candidates. This workshop was convened in November/December 2009 to bring together clinical researchers to address issues critical to phase I safety evaluation of microbicide products. Workshop participants engaged in discussions to examine the strengths and weaknesses of current practices and deliberations for developing best practices to enhance future clinical evaluation of microbicide safety.

Haematopoietic Stem Cell Transplantation for Severe Autoimmune Diseases. NIAID, the Gruppo Italiano Trapianto di Midollo Osseo (GITMO), and the European Group for Blood and Marrow Transplantation (EBMT) cosponsored this workshop in November 2009. Meeting participants held critical discussions on basic and clinical research of haematopoietic stem cell transplant for treatment of autoimmune diseases, including MS, systemic sclerosis, SLE, Crohn's disease, type 1 diabetes,

and cytopenias. Participants also reviewed current data and considered future directions for clinical studies. The content and recommendations of this workshop are in preparation for publication in *Bone Marrow Transplantation*.

NIAID Women's Health Research Seminar Series 2009–2010. The NIAID Women's Health Research Work Group hosted its quarterly seminar series in 2009–2010. The goal of the series is to highlight infectious and immune-mediated research that advances women's health. Presentations included research on the HPV vaccine and the challenges of adolescent immunization, sex differences in influenza, sex differences in HIV prevention, and cholera and climate change from a gender perspective.

Sex/Gender Analysis

NIAID supports research to analyze sex/gender differences in disease susceptibility, pathology, or response to prevention or treatment strategies. The following scientific advances and ongoing and planned activities are highlighted in this report:

- The Risk of CVD Among Women in the WIHS Study Initiating Abacavir
- Optimizing Treatment for Treatment-Experienced HIV-Infected People
- Sex and Disease-Dependent Nucleoside Analog Toxicity
- Trans-NIAID Women's Health Research Work Group
- Advancing Novel Science in Women's Health Research

Research on Health Disparities Among Special Populations

NIAID supports research to understand and eliminate health disparities among special populations, including minorities, rural women, lesbians, women of lower socioeconomic status, and women with disabilities. The following scientific advances and ongoing and planned activities are highlighted in report:

- WIHS
- Vaginal and Oral Interventions to Control the Epidemic (VOICE) Trial
- Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women
- Phase I Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel™) Applied Vaginally in Sexually Active Young Women
- ARV Regimens in Pregnancy and Breastfeeding in Botswana
- ARV Treatment of Mothers or Infants To Reduce HIV Transmission
- Promoting Maternal-Infant Survival Everywhere (PROMISE) Study
- Additional Studies on the Effects of SD NVP on Future Treatment Options for Women and ChildrenLongitudinal Studies of Women at High Risk for HIV-1 Infection To Inform HIV Vaccine Trial Participation
- Once-Daily PI/NNRTI Therapy Combinations for Treatment-Naïve HIV-Infected Patients in Resource-Limited Conditions
- Osteoporosis in HIV-Infected Postmenopausal Women
- High Lupus Prevalence in Women of African Descent May Have Roots in a Malaria-Protective Mechanism
- Partnerships for Point of Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings (U01)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Overview

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, clinical, and epidemiologic research, research training, and information programs on many of the more debilitating diseases affecting Americans. NIAMS funds studies on a number of diseases that affect

women disproportionately, including osteoarthritis, osteoporosis, rheumatoid arthritis, fibromyalgia, scleroderma, and systemic lupus erythematosus (lupus). Scleroderma and lupus are diseases in which health disparities have been clearly identified. NIAMS is committed to uncovering the bases of these gender, racial, and ethnic disparities and to devising effective strategies to treat or prevent them.

Program Highlights

The anticipated increase in the U.S. elderly population will probably be accompanied by a larger group of osteoporosis patients. Researchers are developing new diagnostic methods to assess bone quality and predict its impact on individuals' health status in order to prevent morbidity from osteoporosis. These approaches include monitoring bone mineral density and bone microstructure. In addition, an active pipeline of basic and translational research is in the process of developing drugs that improve bone quality.

Research has led to a new understanding of rheumatoid arthritis and has increased the likelihood that, in time, scientists will find even better ways to treat the disease. Several genetic and molecular components have been identified that may become diagnostic indicators and therapeutic targets.

Genomewide association studies (GWAS) have yielded important results for complex disorders, such as rheumatoid arthritis, lupus, and scleroderma. This research has identified potential risk genes and pathogenic pathways for targeted drug development. Very large cohorts are needed for GWAS in order to determine subtle genetic differences across patients' entire genomes (genetic makeup) relative to control populations without the disease. Reaching this goal has been aided by the persistence of research networks in collecting a substantial number of patient samples over many years and by collaborations between U.S. and non-U.S. researchers supported by government agencies, private foundations, and industry.

Accomplishments

Osteoarthritis

Osteoarthritis, or degenerative joint disease, is the most common form of arthritis. Nearly 27 million Americans ages 25 and older have osteoarthritis. It is most common in older people; by 2030, an estimated 20 percent of Americans—about 70 million people—will have passed their 65th birthday and will be at increased risk for osteoarthritis. Before age 45, more men than women have osteoarthritis; after age 45, it is more common in women. Healthy cartilage, which allows bones to glide over one another, absorbs energy from the shock of physical movement. In osteoarthritis, the surface layer of cartilage breaks down and wears away. This erosion results in bones under the cartilage rubbing together, causing pain, swelling, and stiffness. Bone spurs develop, permanently changing the joint's shape.

Potential Biomarkers for Knee Osteoarthritis From the Osteoarthritis Initiative Images. The Osteoarthritis Initiative is a prospective natural history cohort established to provide clinical and imaging data and associated biospecimens for the discovery of biomarkers of onset and progression of knee osteoarthritis. The initiative has collected biological specimens (blood, urine, and DNA), images (x rays and magnetic resonance scans), and clinical data from nearly 5,000 participants ages 45 to 79, 58.5 percent of whom are female. Women constitute 50 to 59 percent of all groups, including minorities; therefore, the cohort is well powered for any analysis of gender differences in the onset and progression of osteoarthritis. The magnetic resonance imaging (MRI) component of the Osteoarthritis Initiative allows investigators to examine knee cartilage for changes between each annual visit. Researchers hypothesize that the layers of cartilage surrounding the knee joint become disorganized as osteoarthritis develops and progresses. Scientists are developing methods of image alignment and comparison for use in quantitative analysis of MRI data. Preliminary results show that quantitative analyses using strategies to measure the exact same knee region over time can detect subtle changes, indicating disruption of the integrity of the

materials that make up cartilage. These findings indicate that this methodology has the potential to provide a noninvasive means to assess the early development and worsening of osteoarthritis of the knee.

"Sturdy Shoes" May Not Be Better for the Knee. Knee osteoarthritis is a significant source of disability and reduced quality of life worldwide. Because there is no cure, traditional management aims to reduce pain, improve function, and enhance quality of life while minimizing the adverse effects of therapy. Nonpharmacologic interventions, such as physical activity, are considered the first-line approach to disease management. Research over the past decade has demonstrated that increased knee joint loading is an important risk factor for disease progression. Because load across the knee is affected by footwear, a person's shoes may contribute to the progression, if not the development, of knee osteoarthritis. Prior studies have shown that women's high-heeled shoes, even with moderate heel height, resulted in greater loads across the medial knee compartment and the patellofemoral joint compared with barefoot walking. In a recent study, flat, flexible footwear (flip-flops or light-weight walking shoes) was associated with less loading on the knee during walking compared with supportive, stable shoes with less flexible soles (clogs or shoes designed to stabilize the foot). Thus, types of shoes worn by patients with knee osteoarthritis should be evaluated more closely in terms of their contribution to the disease. Long-term intervention trials are needed to evaluate the clinical effects of shoe design on pain and disease progression in knee osteoarthritis.

Strength Training or Self-Management Improves Outcomes for People Who Have Knee Osteoarthritis. Very few randomized trials have tested the efficacy of nonpharmacologic approaches to osteoarthritis pain and disability. A recent study of robust size and duration showed that physical activity and self-management separately improve both pain and physical function in middle-aged people with early osteoarthritis. Surprisingly, there was no added benefit to combining the physical activity and self-management, but the proof that both are safe and effective should enhance the recommendations that physicians can make to their patients with early osteoarthritis.

Cost-Effectiveness of Total Knee Replacement in the United States. Total knee replacement is a highly successful treatment for end-stage osteoarthritis of the knee joint when other treatments fail to alleviate pain and improve or maintain function. Approximately 500,000 total knee replacements are performed in operating rooms across the United States each year, at a cost in excess of $11 billion (HCUPnet. National statistics on all stays. http://hcupnet.ahrq.gov/HCUPnet.jsp.) Although the procedures generally are successful, certain patients and certain hospitals have better outcomes than others, influencing the procedure's overall cost-effectiveness. A recent study confirmed that total knee replacement is a cost-effective surgical procedure for end-stage knee osteoarthritis based on a patient's risk of complications and postoperative mortality and a hospital's experience with total knee replacements. A computer simulation demonstrated that the procedure is clinically effective and cost-effective across all risks groups. Moreover, total knee replacements are particularly cost-effective at hospitals conducting more than 200 procedures per year and for people who have the surgery shortly after their osteoarthritis progresses to the point of needing it. This information should help health care providers and patients as they make informed decisions regarding treatment options for worsening knee osteoarthritis.

Osteoporosis

Osteoporosis is a disease that alters the mechanical strength of bone, leading to increased risk for fracture. In the United States today, 10 million individuals already have osteoporosis and 34 million more have low bone mass, placing them at increased risk for this disease. Although the risk for osteoporosis increases as people get older, it can strike at any age and affects both men and women.

New Approaches to Understanding Osteoporotic Fractures. A new computational modeling method may lead to improvements in identifying individuals at high risk of fracture who might benefit from interventional strategies to prevent bone loss or improve

bone mineral density and bone quality. Current imaging methods are outstanding at screening for low bone mineral density but are not sufficiently discriminatory with regard to fracture risk. Newer imaging techniques and secondary analyses reveal bone characteristics that appear to be related to bone strength and risk of fracture, as well as the role of "microcracks," or "microfractures," and their repair as determinants of bone strength. Enormous amounts of data have been collected in these studies, but it has been difficult to relate them to bone quality. This new approach combines analyses of quantitative computed tomographic scans of bone structure with estimates of bone loading to develop a model to explain how these parameters influence microfracture susceptibility. Comparing results from the model with actual human bone indicated that shape and alignment of bone structure have some effect on bone quality, but more research is needed on the influence of other factors, such as bone matrix composition and the presence of microfractures.

Even Mild Spine Deformities in Some Postmenopausal Women Represent Osteoporotic Fractures. Vertebral fractures in older adults due to osteoporosis have major medical and economic impacts. Because strategies to preserve bone health and prevent fractures exist, early detection and prediction of vertebral fractures could profoundly improve the lives of many people. Severe vertebral deformities are associated with an increased likelihood of future fractures. The correlation between milder defects and the development of osteoporosis is less clear. Using several sensitive imaging techniques and sophisticated mathematical and biomechanical modeling and analyses, recent research has correlated the degree of vertebral deformity with measures of bone quality and determined that many postmenopausal women who have mild vertebral deformities actually have early osteoporotic spine fractures. The findings suggest that women with mild spine defects could benefit from lifestyle changes or medical treatments that allow them to retain their bone health. However, improved criteria and techniques are needed to distinguish the mild deformities that reflect true osteoporotic fractures from those due to normal, nonpathologic anatomical variations so that women with healthy bones are not subjected to unnecessary treatments.

Genes Influencing Bone Mineral Density and Fracture Risk Revealed. Recent technological advances have enabled scientists to conduct GWAS in which they scan the entire human genome for common genetic variations associated with disease. Most of these common genetic variations are individual changes in the genetic code called single nucleotide polymorphisms (SNPs). If particular SNPs are found more often in individuals with the disease than in those without, the SNPs are said to be "associated" with the disease. Such SNP associations can lead to the identification of gene variants involved in the development of disease and can reveal new targets for therapeutic development. For bone mineral density, the most commonly used predictor of osteoporotic fracture risk, GWAS to date have suggested that many different genes can influence bone mass and fracture risk. NIH-supported scientists in the United States, in collaboration with researchers from several other countries, combined information on bone mineral density and SNPs from more than 19,000 people. They identified 20 SNPs consistently associated with variation in bone mineral density and located near genes involved in building or maintaining healthy bone. The results suggest that certain SNPs confer increased risk for low bone mass and fracture and that the total number of "risk SNPs" in an individual's genome can be a useful predictor of bone health.

Soy Isoflavones Fail To Prevent Postmenopausal Bone Loss. The decrease in natural estrogen at menopause leads to the loss of bone mass and can increase a woman's risk of fracture. Postmenopausal hormone therapy alleviates certain symptoms of menopause, such as hot flashes, and prevents bone loss. However, the NIH Women's Health Initiative demonstrated that long-term use of some estrogen therapy formulations can increase a woman's risk of breast cancer and stroke. Isoflavones from soy, which are structurally similar to estrogen, have gained attention as a potential alternative to reduce menopausal symptoms and bone loss without the risks of estrogen therapy. Observations that Asian women (whose diets are rich in soy)

have lower rates of hip fractures, and results from other short-term human intervention studies, suggest that soy and its derivatives may be beneficial in protecting postmenopausal women from osteoporosis. However, study results have been equivocal because of small sample sizes and short interventional periods. Recently, researchers reported results of a more robust trial involving more subjects (more than 200 healthy, postmenopausal, nonosteoporotic women) who were followed for a longer period (3 years). The participants were randomly assigned to groups receiving no isoflavone or one of two doses of isoflavone. During the 36-month study period, the investigators found no effect of isoflavones on bone mineral density measurements at the spine, hip, and whole body. After 3 years of regular monitoring, the researchers concluded that isoflavones did not protect against bone loss in postmenopausal women.

Wrist Fractures Are Associated with Increased Functional Declines in Older Women. Wrist fractures are one of the most common fractures in older adults and the most common upper extremity fracture in this population. They occur more frequently than hip fractures in women younger than age 75, can be disabling, and affect the various daily activities of independent living. A recent study found that women who broke a wrist are 50 percent more likely than their uninjured counterparts to see their ability to function independently diminish in the years following the injury. Wrist fractures remain an important predictor of future functional decline, even after adjustment for common risk factors such as age, body mass index (BMI), health status, lifestyle, comorbidities, and neuromuscular function. The effects of wrist fractures on functional decline are similar to those seen with falls, arthritis, and diabetes, although not as dramatic as the impact of hip fractures.

Bone Biology

Identification of a Major Molecular Factor for Balanced Bone Resorption and Formation. Bone is under constant remodeling in response to damage caused by normal and weight-bearing activities. Bone remodeling requires two opposite, sequential processes: bone resorption, which entails removal of old, damaged bone by bone cells called osteoclasts, followed by bone formation, when bone cells called osteoblasts lay down new bone. These processes must be precisely controlled and coordinated so that when old bone is resorbed, the proper amount of new bone replaces it at the correct location. Disruption of this choreography, such as the net bone loss seen in osteoporosis, can have significant pathologic consequences, namely, bone fractures. Investigations to understand the mechanisms that go awry—leading to an imbalance of bone resorption and bone formation—identified a role for transforming growth factor beta 1 (TGF-β1), a well-characterized molecule involved in numerous other events in the body, such as regulation of cell growth (e.g., tumor suppression), and a variety of diseases. Investigators studying bone remodeling in the laboratory showed that bone-resorbing osteoclasts activate TGF-β1 in the vicinity of resorbed bone, and, in turn, TGF-β1 attracts cells that become bone-forming osteoblasts to the site. The *TGF-β1* gene was mutated in a mouse model similar to a human disease that is characterized by aberrant bone remodeling. The gene modification caused excessive TGF-β1 activation, resulting in widespread migration of the osteoblast precursor cells throughout the bone instead of only at sites of bone resorption. This occurrence could be partially corrected by injecting molecules that could inhibit TGF-β1's activity. This research identifies the critical role of TGF-β1 in linking the bone resorption and bone formation processes and its potential as a therapeutic target for bone diseases.

Inactivation of Single Gene Affects Bone, Bone Marrow Function, Fat Distribution, and Energy Metabolism. Osteoporosis, diabetes, and obesity are common diseases, and a recent discovery contributes to the growing recognition that these problems are not independent but rather are linked through molecular pathways that are still largely unknown. In recent years, scientists have come to understand that the regulation of bone remodeling is intricately connected to other processes in the body, including the utilization and storage of energy that comes from dietary sugar and fat. For example, osteoblasts and adipocytes (fat cells)

arise from the same precursor cell, the mesenchymal stem cell, which is found in bone marrow. Researchers also have noticed that the fat content of bone may increase as people get older, at the same time that bone mass decreases, with an associated risk for osteoporosis. In another link to energy metabolism, osteocalcin, a protein made by osteoblasts, can influence insulin levels, a critical regulator of blood glucose (sugar). Scientists showed that the activity of a single gene—early B cell factor 1, or *Ebf1*—influences bone formation, bone marrow composition, fat distribution, and energy metabolism in a mouse model. Removing the *Ebf1* gene with genetic engineering resulted in an increased number of osteoblasts, but also greater numbers of bone marrow adipocytes, and significantly less fat in other parts of the mice, suggesting that the overall regulation of energy metabolism was altered. Further examination revealed that the mice had lower than normal blood levels of glucose and fats, although they ate more than normal mice. Thus, an improved understanding of this complex web of metabolic pathways, with new therapeutics based on that knowledge, could advance the prevention and treatment of a broad range of health problems.

Caloric Restriction During Growth Leads to Weaker Bone. Achieving maximal peak bone mass is important for reducing the risk of osteoporosis and fractures later in life. Humans acquire up to 90 percent of peak bone mass in the first two decades of life, during the period of rapid growth in childhood and adolescence. Caloric restriction has been shown in a few species to increase longevity and improve the health of older animals. However, recent studies on anorexia in humans have suggested that starvation poses osteoporosis risks later in life by decreasing several hormones important for bone and at the same time increasing fat content in the bone marrow. Caloric restriction during rapid bone growth leads to lower bone mass and weaker bone, which could predispose an individual to develop osteoporosis later in life. Researchers investigated the effect of reduced food consumption on bone in young, growing mice. In addition to having lower body mass and body fat than the mice on the normal diet, calorie-restricted mice also had lower bone mineral density, smaller bones, thinner and more porous bone cortex, and decreased bone strength. Subsequent studies showed that the calorie-restricted mice were forming less bone than normal mice and that their bone tissue was being resorbed more quickly than that of the control animals. These results show that caloric restriction during adolescence can have damaging effects on overall bone health. The knowledge that postnatal diet (a modifiable factor) affects the skeleton during the period of peak bone acquisition may lead to public health awareness of the deleterious effects of anorexia on bone, and ways to improve skeletal health through better nutrition throughout life.

Rheumatoid Arthritis

Rheumatoid arthritis affects an estimated 0.6 percent of Americans. It is a debilitating autoimmune disease characterized by chronic joint inflammation, in which the body's natural defense system attacks its own tissues. Rheumatoid arthritis occurs more frequently in women than in men.

Platelet-Derived Microparticles Can Amplify Inflammation in Rheumatoid Arthritis. The chronic joint inflammation associated with rheumatoid arthritis involves aberrant activities of several types of cells, such as immune cells in the joint. Platelets are highly abundant in the bloodstream, outnumbering other blood cells by about 100-fold. Beyond their normal role in the formation of blood clots and wound repair, platelets may adhere to the cells that line blood vessels (endothelial cells) in disease conditions and promote inflammation by recruiting inflammatory cells to the vessels. Recently, scientists investigated whether platelets play a role in rheumatoid arthritis by looking for them in the synovial (joint) fluid of patients with the disease. They detected the characteristic platelet molecular markers on the surface of platelets, but they were on smaller particles ("microparticles") than normal platelets. These smaller, platelet-derived microparticles, which sprout from activated platelets, were abundant in synovial fluid and stuck to the inflammatory cells also present in the synovial fluid. In tests with a mouse model of rheumatoid arthritis, the disease severity was reduced when mice received a platelet-depleting drug, suggesting

that platelets are involved in arthritis development. Furthermore, the researchers observed that the platelet-derived microparticles activate synoviocytes (cells that form the lining of the joint) to produce a range of inflammatory proteins in both human and mouse cell culture systems. Together, these results support a new mechanism of disease in rheumatoid arthritis, in which platelets are activated locally in the arthritic joint to generate microparticles that, in turn, activate resident synoviocytes, leading to the amplification and perpetuation of joint inflammation. This study also identified a molecular target that plays a critical role in this pathway. Inhibition of this molecule may represent a novel therapeutic approach for treating rheumatoid arthritis.

Identification of Molecular Targets of Rheumatoid Arthritis Autoantibodies. Autoantibodies, which attack the body's own tissues, are a feature of autoimmune diseases. Many of these autoantibodies are detectable in the blood of rheumatoid arthritis patients, but little is known about the disease's autoantigens, the molecules recognized by specific autoantibodies that set off and sustain the immune response. Alpha-enolase is a potential autoantigen for rheumatoid arthritis; large amounts of it are found in rheumatoid joints. Alpha-enolase is also a highly conserved protein, meaning that it has maintained its molecular constitution through evolution so that it is very similar in bacteria and humans. Recently, investigators found that a form of alpha-enolase in rheumatoid arthritis patients is modified by a process called citrullination. The citrullinated autoantigen is recognized specifically by disease-associated autoantibodies. Interestingly, the enzyme responsible for citrullination is made by *Porphyromonas gingivalis,* a bacterium known to be the major cause of periodontal (gum) disease. Infectious agents have long been proposed as potential environmental triggers of autoimmune disease, and it has been shown recently that periodontal disease is a risk factor for rheumatoid arthritis. These findings suggest that, in some rheumatoid arthritis patients, an antibody response to a bacterial pathogen may cross-react with a human protein, which could lead to the autoimmune inflammation seen in rheumatoid arthritis.

The Role of Gut-Residing Microbes in Arthritis Development in an Animal Model. The microbiome is the population of microbes that lives mutualistically in different parts of the body. Among the various body locations, the gut is a particular site where the microbiome is tightly associated with the immune system, where it can promote normal immune function by regulating the balance of immune cell subsets. However, an imbalance in these cell populations and the immune activities that they control may result in inflammatory and autoimmune diseases. In particular, one of these immune cell subsets, Th 17 cells, is stimulated in mice by their resident (commensal) gut bacteria (the gut microbiome). In a mouse model of rheumatoid arthritis, joint inflammation was directly associated with the appearance of high levels of autoantibodies against one of the animal's own proteins, glucose-6-phosphate isomerase (GPI). Some mice were kept in conditions that would allow them to develop a gut microbiome through exposure to nonpathogenic bacteria, whereas others lived in germ-free conditions so that they did not collect commensal bacteria. The mice with a gut microbiome had higher levels of anti-GPI autoantibodies, Th 17 cells in their intestines, and they developed severe arthritis at a young age. In contrast, the germ-free mice had lower levels of autoantibody-producing immune cells, almost no Th 17 cells in their guts, and milder, late-onset arthritis. These findings provide a model in which gut microbes are capable of inducing Th 17 cells, leading to production of autoantibodies that drive arthritis development. This work has provided the basis for further investigations into the role of human microbiome in rheumatoid arthritis.

Pain May Contribute to Development, Expansion, and Worsening of Arthritis. Rheumatoid arthritis is usually characterized by significant pain that often affects physical function and quality of life. Recent evidence suggests that chronic rheumatoid pain involves not only the joints but also parts of the brain and nervous system. The pain pathway involves nerve cells (neurons) that send sensory input to the brain, where it is processed and may result in a motor neuron-muscle response to the pain stimulus (e.g., pulling your finger from the fire). This pain processing

pathway is complex and includes sensitization of the primary sensory nerves that innervate the joint and transmit signals to the spine. This stimulation from the sensory nerves can lead to neuroinflammation in the spine and central nervous system, including the production of molecular mediators of inflammation, such as interleukin-1β (IL-1β). To understand the role of the central nervous system in rheumatoid pain, researchers stimulated the localized production of IL-1β in the spinal area in a mouse model of arthritis. They showed that arthritis, and subsequent pain, can be induced by the release of IL-1β in the spinal cord rather than in the joints. These unique findings suggest a bidirectional communication between the joints and the central nervous system that may contribute to the worsening of arthritis in the joints by processes that originate in the nervous system—not just the joint.

Common Disease Risk Factors Shared Between Diabetes and Rheumatoid Arthritis Patients. Certain autoimmune diseases, such as rheumatoid arthritis and type 1 diabetes, are found to cluster in families and sometimes occur in the same patient. These co-occurrences suggest shared disease susceptibility involving genetic or environmental risk factors or even the interaction of both. A risk association between rheumatoid arthritis and type 1 diabetes also suggests common disease processes for these two very distinct clinical conditions. A recent study of Swedish patients with rheumatoid arthritis, diabetes, or both looked for molecular indicators (biomarkers) of rheumatoid arthritis, including a genetic risk factor (the PTPN22 variant) across the patient groups. Rheumatoid arthritis patients who were positive for the disease-associated biomarkers sometimes had type 1 diabetes—the autoimmune form of the disease, which usually occurs early in life and requires insulin injections. There was no association between the development of any form of rheumatoid arthritis and patients with type 2 diabetes (which is not an autoimmune disease, is more common in adult patients, and is usually treated with oral medications). These findings suggest that patients with this combination of biomarker-positive rheumatoid arthritis, type 1 diabetes, and the PTPN22 gene variant share common disease mechanisms. The findings also offer unique insights into fundamental autoimmune mechanisms of disease, including new approaches to their prevention and treatment.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (lupus) is an autoimmune disease affecting approximately 240,000 Americans. Nine of 10 people who have lupus are women. African-American women are three times more likely to get lupus than White women, and it is also more common in Hispanic/Latino, Asian, and American Indian women.

An X-Chromosome Gene, IRAK 1, Involved in Risk and Pathogenesis of Lupus. Although the cause of lupus is unknown, several lines of evidence support a complex interaction of multiple genes and environmental factors. The high prevalence of the disease in women has led to an investigation of potential risk genes on the X chromosome, including the gene encoding interleukin-1 receptor associated kinase 1 (IRAK1)—a critical mediator in the immune system's ability to recognize and respond to pathogens. Through its multifunctional role, the IRAK1 molecule can initiate a cascade of signaling events, leading to expression of genes associated with inflammation. Recently, scientists examined the genomes of a large group of lupus patients. They found several variants in the *IRAK1* gene, which were more common to patients of multiple ethnic backgrounds, at a significantly higher frequency than in healthy controls, indicating an association with the disease. To examine the biological relevance of *IRAK1* in lupus, the investigators generated *IRAK1*-deficient mice through genetic engineering in a mouse population that is prone to developing the disease. Symptoms associated with lupus, including kidney abnormalities and autoantibody production, disappeared in the absence of *IRAK1*. These results provide compelling evidence that *IRAK1* is a disease gene in lupus, and its location on the human X chromosome is a possible explanation for female predominance of the disease.

Intracellular Receptors Play a Role in Lupus and May Hold Clues to Treatment. New information about the immune system could eventually lead to ways to block its

components that initiate or perpetuate lupus. Under normal circumstances, the immune system is able to distinguish foreign microorganisms from our bodies' own components and, when necessary, trigger the production of antibodies against them. However, in the case of some autoimmune diseases, a flaw in the process leads to the development of autoantibodies, which react with the body's own molecules. Researchers have known that people with lupus produce autoantibodies to their own DNA, and their findings suggest that a class of receptors, called toll-like receptors (TLRs), located on and within the body's cells, plays a role in the development of these autoantibodies. Endosomal TLRs (eTLRs), a TLR subset, are expressed in intracellular compartments called endosomes, specifically recognize DNA and RNA of an invading organism or, in the case of autoimmune disease, a person's own—followed by production of antibodies. Recently, scientists have confirmed this role for eTLRs by blocking eTLR activity in a mouse model of lupus, which abolished autoantibody production. However, these lupus-prone mice were able to make antibodies to infectious agents, showing that blocking eTLRs might not lower normal immune responses in these mice. The findings suggest that it may be possible to block eTLRs that cause autoimmunity without interfering with the protection from infection that other TLRs provide.

Antimalarial Drug May Protect Kidneys in Lupus Patients. The kidneys are among the multiple organ systems that can be affected in lupus, particularly in the most severe cases. Hydroxychloroquine, a drug originally developed as an antimalarial agent, has been used to treat many manifestations of lupus. Studies have shown that hydroxychloroquine is safe to use in most patients with lupus during the whole course of their disease, including pregnancy. Recently, researchers analyzed the medical records of Hispanic, African-American, and White lupus patients in the Lupus in Minorities, Nature versus Nurture (LUMINA) database to evaluate the effect of chloroquine on lupus nephritis, a kidney condition. Their findings reinforce the very favorable benefit-to-risk relationship of hydroxychloroquine use in patients with lupus and suggest that this drug may prevent renal damage and the impact of such damage on long-term morbidity and mortality.

Scleroderma

Scleroderma is a disabling autoimmune disease that affects approximately 50,000 U.S. adults and is characterized by fibrosis and hardening of tissues. Its cause is unknown. There is no cure, and there are few effective treatments. Systemic sclerosis is one form of scleroderma and involves many parts of the body, such as skin, internal organs, and blood vessels.

Human Genome Scan Reveals New Gene Influencing Risk for Systemic Sclerosis. A recent GWAS expanded its search for potential systemic sclerosis risk genes to patients in the United States as well as Europe. Previously identified genetic risk factors were confirmed in the immune system's major histocompatibility complex, as well as in gene regions encoding for other immune-related molecules, namely STAT4 and interferon regulatory factor 5 (IRF5). A significant, new systemic sclerosis-associated genetic difference also emerged in the *CD247* gene region, which encodes a molecule involved in regulating the immune response. A complete understanding of all systemic sclerosis-associated genetic markers should aid in the diagnosis of patients at risk, provide important insights into mechanisms of the disease, and contribute to the development of novel therapeutic interventions.

Identification of a Potential Target for Treating Tissue Fibrosis. Fibrosis is a disorder of the extracellular matrix, the mesh of proteins like collagen that makes up the body's connective tissue. It is a factor in scleroderma, among other diseases, and can affect many of the body's organs, including the lungs, liver, and skin. Its consequences can be devastating, even leading to death. Recent research has shown that cells in fibrotic tissue receive the wrong molecular signals, causing too many extracellular proteins to be made. One possible way to approach the fibrosis problem, scientists say, might be to try to interrupt such signals at critical points in cellular processes. Two research groups used separate approaches to uncover the importance of the molecule early growth receptor 1 (EGR-1) in regulating genes involved in fibrosis. Both research teams found

that the experimentally produced fibrosis was associated with abnormally elevated EGR-1 activity. Furthermore, when they induced fibrosis in cells or mice lacking EGR-1, the amounts of fibrosis were dramatically reduced. One of the groups found that EGR-1 levels were higher in lung tissues and connective tissue cells of people with pulmonary fibrosis compared with healthy controls. The scientists concluded that EGR-1 is essential for the development of fibrosis, making it a potential target for therapy.

Fibromyalgia

Fibromyalgia syndrome is a chronic disorder characterized by widespread pain and tenderness. It is frequently accompanied by other symptoms, such as fatigue, insomnia, depression, and anxiety. Fibromyalgia affects approximately 2 percent of the U.S. population; it is much more common in women than men, and it is associated with substantial morbidity and disability. The precise cause of fibromyalgia is not known, but research suggests its relationship to a problem with the central nervous system's processing of pain. As with some other chronic pain conditions, people with fibromyalgia often develop a heightened response to stimuli, experiencing pain that would not cause problems in other people.

The Effect of Obesity in Fibromyalgia Syndrome Patients. Researchers hypothesize that obesity is a risk factor for fibromyalgia and may amplify related symptoms. Elements contributing to the pathophysiology of both obesity and fibromyalgia include abnormal regulation of the central pain modulation system, dysregulated interactions between glands in the endocrine system, and a weakened immune system. In addition, obesity is often accompanied by increased levels of molecules associated with chronic inflammation. In a recent pilot study, researchers evaluated a group of fibromyalgia patients (5 men and 33 women), of which 50 percent had BMIs in the obese range (greater than 30) and another 21 percent were overweight. High BMI was correlated with increases in molecular indicators of inflammation, maximal heart rate, and sleep disturbance. Inadequate sleep is known to influence fibromyalgia symptoms, which may be exacerbated in fibromyalgia patients with high BMI because of a higher rate of sleep disturbances. This study provides preliminary evidence that obesity plays a role in fibromyalgia-related dysfunction.

Affective Self-Awareness Can Reduce Fibromyalgia Pain. In addition to pain and fatigue, people who have fibromyalgia may experience a variety of other symptoms, including difficulties expressing anger or distinguishing negative from positive emotions (emotional awareness). Some studies have suggested that deficits in emotional awareness may be linked to increased pain in fibromyalgia and that an individual's pain experience can be reduced through improved self-awareness. In a randomized controlled trial of fibromyalgia patients, the intervention group received education about chronic pain, wrote emotional disclosures about stress, learned awareness techniques, and reengaged in previously avoided activities. In comparison with a control group that received education but not the intervention, the "treated" group showed reduced pain and improved physical functioning. This self-awareness intervention shows the significance of the mind-body relationship in trying to empower individuals with fibromyalgia to more effectively control their pain and associated symptoms. Furthermore, this relatively inexpensive intervention does not require much equipment or increase in provider burden, which enhances its accessibility to a broad patient population.

Health Disparities Among Special Populations of Women

Traffic Pollution, a Newly Identified Environmental Risk Factor for Rheumatoid Arthritis. Although the precise etiology of rheumatoid arthritis has not been established, it is thought to develop in genetically predisposed individuals who are exposed to certain environmental factors. Epidemiologic research has revealed the impact of strong environmental factors on rheumatoid arthritis risk, including cigarette smoking, hormone use, and female reproductive factors, and a significant increase in rheumatoid arthritis risk in areas of the United States with higher levels of air pollution. These observations led to the hypothesis that inhaled particulate

matter, similar to cigarette smoke, may induce local lung inflammation and systemic inflammation. Recently, the potential association of rheumatoid arthritis and the proximity of residences to road traffic was assessed in the Nurses' Health Study, a long-term prospective cohort initiated in 1976 (with biennial followup questionnaires) to capture information on risk factors and the occurrence of major illnesses. After adjustment for a number of potential confounding factors, the results show that women living within 50 meters of a road are at a 31-percent increased risk for rheumatoid arthritis compared with women living 200 meters or more from a road. This association also was observed in analyses of nonsmokers. These findings suggest that extended exposure of adults to traffic pollution may be an environmental risk factor for rheumatoid arthritis.

Understanding Why Rheumatoid Arthritis Patient Treatment Preferences Differ by Race. There has been a perception that White rheumatoid arthritis patients are more likely to receive aggressive care than African-American patients. Past health disparities studies suggest that access to care, insurance, quality of care, and social determinants of health may explain those racial differences. Physician practice environments and lack of training or resources to provide optimal care for minority populations may be factors. Recently, researchers tested the hypothesis that disparities in rheumatoid arthritis treatment among racial groups are independent of differences in access to care and are related to patient treatment preferences and perceived risks and benefits of treatment options. A study of 136 rheumatoid arthritis patients (83 percent female) revealed significant differences between African-American (49 percent) and White (51 percent) patients in the evaluation of risk due to adverse events and toxicity and potential benefits related to delays in disease progression and improvement of symptoms. More African-American participants (52 percent) were found to be risk-averse compared with Whites (12 percent). In the risk-benefit assessment of treatments, African-American patients put more emphasis on the risk of toxicity and less emphasis on the likelihood of benefit than Whites. Because aggressive care of rheumatoid arthritis is known to result in improved outcomes, it will be important to reassess how health care providers communicate risk and benefits to patients of all races, to ensure that patients can make informed decisions about their treatment choices.

Information Dissemination

Bone Health Information

http://www.bone.nih.gov

A new Web resource providing people with the latest science-based information on bone health and bone disease is available through the NIH Osteoporosis and Related Bone Diseases National Resource Center.

New Fact Sheets: Understanding Autoimmune and Autoinflammatory Diseases

http://www.niams.nih.gov/Health_Info/Autoimmune/default.asp

http://www.niams.nih.gov/Health_Info/Autoinflammatory/default.asp

These publications are geared for patients and families and have easy-to-read information on autoimmune and autoinflammatory diseases such as rheumatotoid arthritis, lupus, and familial Mediterranean fever.

NIAMS Multimedia Web Page

http://www.niams.nih.gov/News_and_Events/Multimedia/default.asp

The new NIAMS multimedia page provides a centralized place on the NIAMS Web page where visitors can access videos, images, and audio publications in both Spanish and English.

U.S. Department of Health and Human Services Lupus Awareness Campaign

http://www.couldihavelupus.gov

The Office of Women's Health at the U.S. Department of Health and Human Services partnered with the Ad Council, with input from patient advocacy groups and Federal Agencies involved in lupus research and treatment, including NIAMS, to produce a lupus awareness campaign titled "Could I Have Lupus?" The main message of the campaign

is that lupus is a life-altering disease that primarily affects young women who may be experiencing symptoms of lupus but have not been diagnosed.

NIAMS Multicultural Outreach and Information

http://www.niams.nih.gov/about_Us/Mission_and_Purpose/Community_Outreach/Multicultural_Outreach/default.asp

NIAMS has created a Web page to serve as a single location for health information related to multicultural groups. NIAMS also is leading a trans-NIH initiative to engage underserved multicultural communities in accessing information and materials for disease management through a network of partners.

Initiatives

NIAMS participated in the following funding opportunity announcements:

PA-08-246, Chronic Fatigue Syndrome (CFS): Pathophysiology and Treatment (R01); PA-08-247, Chronic Fatigue Syndrome: Pathophysiology and Treatment (R21) (fibromyalgia comorbidity). This ORWH-led solicitation was created to stimulate research on the epidemiology, diagnosis, pathophysiology, and treatment of CFS. Applicants were encouraged to address age, environmental, and biological risk factors for CFS and the common mediators influencing multiple body systems affected by the disease.

PAS-07-381, Advancing Novel Science in Women's Health Research (ANSWHR) (R21), PAS-07-382, Advancing Novel Science in Women's Health Research (ANSWHR) (R03). Another funding announcement led by ORWH emphasized support of pilot or small, self-contained projects that promoted innovative, interdisciplinary research to advance new concepts in women's health research and research in sex/gender differences.

National Institute of Biomedical Imaging and Bioengineering

Executive Summary

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) was established by law in December 2000 and received its first appropriation and grant-funding authority in fiscal year (FY) 2002. As the NIBIB continues to mature and establish programs, funding opportunities have been developed to support a variety of scientific areas, including programs aimed at fostering women's health research.

NIBIB serves as the hub within the National Institutes of Health (NIH) for coordination of biomedical imaging and bioengineering efforts. NIBIB (1) fosters, conducts, supports, and administers research and research training programs in biomedical imaging and bioengineering by means of grants, contracts, and cooperative agreements; (2) provides coordination, integration, and review of progress and planning of biomedical imaging and bioengineering research; (3) formulates research goals and long-range plans with the guidance of the National Advisory Council for Biomedical Imaging and Bioengineering; and (4) sponsors scientific meetings and symposia, collaborates with industry and academia, and fosters international cooperation regarding biomedical imaging and bioengineering.

NIBIB recognizes the significant potential of improved imaging technologies in early disease detection. During FYs 2009 and 2010, NIBIB funded grants focused on women's health research or technologies aimed at improving devices for female populations. These projects range from advanced imaging methodologies to tissue engineering activities designed specifically for women's diseases, such as breast cancer; disorders and diseases with profound consequences for women, such as sexually transmitted diseases; and conditions that predominate in women, such as temporomandibular joint (TMJ) disorder.

During FYs 2009 and 2010, NIBIB supported research on women's health in the

following areas: factors that influence careers of women in science and engineering, technologies to reduce health disparities, aging, breast cancer, solid tumors, sexually transmitted infections, reproduction and fetal health conditions, and temporomandibular joint (TMJ) disorder.

Introduction

Dr. Roderic Pettigrew, the first director of NIBIB, began his tenure at NIH in September 2002. Since his arrival, NIBIB has reorganized the Institute to facilitate the support of interdisciplinary research in areas of relevance to the missions of NIH and NIBIB.

In December 2004, Dr. Anthony Demsey joined NIBIB as director of the Office of Extramural Policy and subsequently of the Office of Research Administration. Under his purview, Dr. Demsey has the overall responsibility of managing and monitoring all NIBIB activities that focus specifically on women's health research. In February 2007, Dr. Valery Gordon (formerly of the Office of the NIH director, Office of Extramural Research) joined NIBIB. She has direct day-to-day responsibility for women's health research oversight. Dr. Demsey and Dr. Ruth Grossman serve as NIBIB's representatives to the Coordinating Committee on Research on Women's Health.

Accomplishments

Highlighted below are significant NIBIB research accomplishments related to women's health.

Breast Cancer

Bioimaging With Nanopyramids. This project aims to apply nanopyramids, a new type of nanoparticle with unique and tunable optical properties, to the detection of breast cancer. Nanopyramids will be targeted to the epidermal growth factor receptor (EGFR) and the tyrosine kinase receptor (ErbB2, or HER2 in humans). Biofunctionalized nanopyramids will bind to EGFR and HER2 and will be bright and easily visible in dark field microscopy. The targeted nanopyramids also will be conjugated to a contrast agent for magnetic resonance imaging (MRI), potentially enabling whole-body detection of breast cancers. Early detection of EGFR and HER2 in breast cancer cells facilitates targeted treatment and may increase survival rates.

Breast Cancer Diagnosis by Electrical Impedance Imaging. Noninvasive electrical impedance measurements that are made using a handheld probe have been shown to improve the specificity and sensitivity of mammography for breast tumor diagnosis in patients with ambiguous mammograms. This noninvasive technology poses no known risks to the subject and provides a new diagnostic parameter to assess suspicious anomalies. This project seeks to refine electrical impedance tomography as a diagnostic modality and to develop a scientific basis to justify a large-scale clinical trial of the technique. Success of such a trial would reduce the need for biopsy and increase the detection of tumors at an earlier stage, which would reduce the morbidity and mortality of breast cancer.

Dual-Drug High-Dose PLGA-Lipid Hybrid Nanoparticles for Drug Delivery. The objective of this project is to develop a nanoparticle, using a unique and novel lipid-polymer hybrid nanoparticle platform, which can contain two chemotherapy drugs, doxorubicin and paclitaxel, with sufficiently high drug loading that a single or a few nanoparticles can kill a drug-resistant cancer cell. Concurrent delivery of the two clinically approved anticancer drugs at high dosage to the same breast cancer cells in a targeted manner is expected to overcome chemoresistance to cancer drugs.

Evaluation of Digital Breast Tomosynthesis as a Method for Routine Breast Cancer Screening. Digital breast tomosynthesis (DBT) is considered a very promising development in breast cancer imaging. Clinical pilot studies have demonstrated that DBT yields higher sensitivity and specificity than projection mammography, the current breast cancer screening tool of choice. However, there is concern regarding the use of DBT for routine breast cancer screening because DBT generates approximately 50 times more images than projection mammography and, thus, requires extensive review time for the radiologist. An NIBIB-funded investigator is trying to gain insight into the likely success of DBT as the

population breast cancer screening modality of choice by comparing the performance of radiologists in detecting breast cancer when interpreting DBT cross-sectional images with their performance in interpreting digital mammography images, with the comparison done using time-controlled viewing experiments.

High-Resolution Whole-Breast MRI at 3.0T. The applicants proposed to develop, implement, and validate breast MRI methods with very high spatial-resolution at 3T. Although breast MRI has recently been shown to be cost-effective in screening high-risk patients or patients with a contralateral breast cancer, its sensitivity to ductal carcinoma in situ, its ability to assess small lesions, and its positive predictive value limit increased use. Higher resolution MRI can address all of these limitations, providing a more accurate tool for assessment of breast cancer. Improved specificity may reduce the rate of unnecessary biopsy while also making MRI effective for screening lower risk patients. Increased sensitivity for small lesions will allow for earlier detection of cancer and result in increased survival rates and a reduced screening frequency.

Low-Dose Breast Computed Tomography With Photon-Counting Detector. This study focuses on a breast computed tomography (CT) system with the capability of producing images of higher quality at a reduced dose compared with current breast CT systems. The key to the system involves a photon-counting and energy-resolving x ray detector. Properties of low noise and high quantum efficiency translate to higher image signal-to-noise ratio (SNR) at a lower dose. SNR of breast CT systems utilizing a photon-counting detector can be improved by 30 percent compared with those with a charge-integrating flat panel detector. An SNR improvement of 30 percent equals a dose reduction of 40 percent in breast CT. Thus the project aims to provide clinicians with images of higher quality while exposing patients to lower dosages.

Parallel Detection and Computation for Diffuse Optical Tomography of Breast. The aim of this work is to develop and assess near-infrared diffuse light imaging schemes for tumor detection and characterization. The researchers used a combination of experimental, theoretical, and computational tools and techniques to develop computational schemes for improving the accuracy of three-dimensional (3D) reconstruction and recruiting more high-risk patients for in vivo measurements. Diffuse optical tomography (DOT) reconstruction images of total hemoglobin concentration and scattering have been correlated by radiologists specializing in MRI and categorized into well-correlated, intermediate, and poorly correlated cases in terms of tumor position. DOT has successfully distinguished benign from malignant invasive carcinomas in optical contrast studies.

Development of Practical Midinfrared Spectroscopic Imaging Technology for Cancer. The project proposes to develop a new chemical imaging instrument to image biopsy tissues to achieve early decisions and accurate diagnoses. The goal is to develop techniques for processing breast and prostate cancer biopsy samples. Using imaging technology, the investigators propose to accomplish these goals without using dyes, stains, or human supervision, which could transform standard practices used for histologic assessment.

MRI Evaluation of Tumor Growth and Treatment Response. This project addresses the quantitative evaluation of tumor growth and treatment response by MRI by integrating dynamic contrast–enhanced MRI (DCE-MRI) measurements with quantitative metrics derived from other imaging modalities such as diffusion-weighted MRI (DW-MRI), fluorodeoxyglucose positron emission tomography (FDG-PET), computed tomography (CT), and optical methods. The performance of these methods in serving as reporters on tumor growth and treatment response will be evaluated when used separately or in combination to evaluate human breast cancer treatment response.

Nanocrystal Delivery of Hydrophobic Anticancer Drugs. Recent advances in nanotechnology have made it possible to design drug carriers with nanometer-scale features that have the potential to deliver insoluble or poorly soluble drugs to improve their pharmacokinetics. For example, the drug paclitaxel has a significant impact on solid tumors and is currently approved by the Food and Drug Administration (FDA) for the treatment of

breast and ovarian cancer. The clinical application of paclitaxel, however, is limited by its low solubility in water. The goal of this project is to develop safe and cost-effective nanocrystals for the delivery of poorly soluble anticancer drugs that can be effectively scaled up and commercialized to treat breast cancer. The team has developed unique nanocrystals that encapsulate more than 99 percent of the paclitaxel drug and has shown antitumor activity and low toxicity in a murine breast cancer model. Studies also are underway to scale up and commercialize this technology using a three-phase engineering method that results in significantly lower acute toxicity than commercial paclitaxel formulations and lowers drug dosing with improved efficacy.

Nanodevice for the Clinical Breast Examination. NIBIB is supporting the development of an inexpensive, noninvasive, handheld screening tool for early detection of breast cancer. This nanodevice will be able to digitally image the palpability of a tumor and the nature of its attachment to surrounding tissue. It will enable family physicians and other clinicians to screen patients who do not have access to the more expensive screening tool and avoid unnecessary exposure to radiation used in mammography. The quantitative image, including the size, hardness, and palpability of the mass, will provide a set of orthogonal measurements that will significantly improve the procedure of clinical breast examination and improve specificity (i.e., low false positives) to help physicians make well-informed decisions to perform further testing and initiate therapy at the earliest stages of breast cancer.

Phage-Mimetic Nanorods for Targeted Breast Cancer Treatment. The objective of this research is to develop a new tumor-homing anticancer agent for breast cancer therapy. Researchers are using a biomimetic strategy to bring together tumor-homing proteins and tumor-destructing nanomaterials to develop this agent. The goal is to mimic the self-assembly of proteins onto DNA immobilized gold nanorods, inject them, and then heat them to destroy breast tumors. The targeting peptides are identified by a process known as phage display technology that specifically recognizes receptors of breast tumors. The results to date demonstrate that the new therapeutic agent was engineered and does target tumors and could also destroy them in response to a tissue near-infrared penetrating light.

Reversing Electrostatic Interactions for Improved Gene Delivery. Improved or alternative treatment options are needed for breast cancer. Currently, there is no standard of care for metastatic breast cancer. All of the first-line combination therapies are regarded as equally efficacious and have a 60-percent response rate. A team of investigators is developing a new approach to deliver tumor-suppressor genes by reversing electrostatic interaction in amphiphilic systems. With this approach, functional amphiphiles undergo transition from cationic to anionic in cells and release DNA from supramolecular assemblies. The overall goal of these studies is to design, synthesize, and evaluate new charge-reversal amphiphiles to enhance gene transfection efficiency. The results from delivering the p53 gene indicated 50-percent knockdown of the gene and that the endocytosis is the pathway responsible for transfection, unlike that used by conventional liposomal delivery systems.

Speckle-Free Transmission Ultrasound for Breast Imaging. The goals of this project are the development and implementation of a breast ultrasound fluoroscopy system (BUFS), which includes image acquisition and postprocessing for C-scan ultrasound images; generation of preliminary tests with laboratory prototype; redesign and fabrication of a premarket system suitable for imaging the human breast; and development of an interface mechanism for the C-scan ultrasound camera and the breast. Scientists and engineers successfully built a higher dynamic range complementary metal-oxide semiconductor (CMOS)-base ultrasound sensor. Two different C-scan systems were built. The first is a C-scan ultrasound attenuation system designed to examine breast phantoms and breast specimens; there are plans to begin small-animal and ultrasound CT studies. The second system is a "dry" BUFS prototype whose design was modified to enable better coupling of the transducers and capabilities for sensing small-image areas integrated into a larger breast image using "stitching" algorithms. The stitching algorithms were

developed as a set of Fourier composition techniques for integration of C-scan images. The investigators plan to perform a series of physical tests and imaging performance studies to evaluate the quality of the ultrasound images and to conduct a limited clinical trial (premarket testing) to compare conventional mammography and conventional ultrasound for imaging breast tissue. The investigators expect that a clinically viable system will soon be available for diagnosis of breast cancer.

Time-Resolved Breast Imaging Using a Combined MRI and Optical Tomography Approach. A breast cancer patient's response to primary systemic therapy is important in deciding whether to switch to a different treatment regime or progress to surgery immediately. The overall goal of this proposal is to combine MRI and near-infrared spectroscopy and tomography to characterize the predictive value of compression-enabled measurements of tissue hemodynamics, blood flow, and oxygen consumption as new biomarkers sensitive to therapy progress and quantify their relationship to final pathologic outcome. The use of fast optical tomography during breast compression to investigate biomechanical and metabolic characteristics of normal and lesion tissues, with the goal of improving specificity for cancer diagnosis and noninvasively monitoring chemotherapy progress.

Volumetric Mapping of Breast Cancer Biomarkers Using High-Speed Magnetic Resonance. This project is aimed at developing a novel ultra-high-speed 3D magnetic resonance spectroscopic imaging (MRSI) exam to map total choline (tCho), a sensitive biomarker of breast tumor status. Although MRI plays an increasingly important role in screening, clinical diagnostics, and treatment followup of breast cancer, the overall specificity is still low, resulting in a considerable number of benign biopsies. Recent studies have reported that quantitative MRSI measurements of tCho added to a DCE-MRI exam produce improvements in the sensitivity, specificity, and accuracy for all readers and improve the interobserver agreement between the readers. A second promising application of breast MRSI involves predicting response to treatment, possibly within 24 hours after the first dose of chemotherapy for locally advanced breast cancer. The much higher spatial resolution and shorter measurement time of the technology compared with conventional magnetic resonance spectroscopic methods will enable clinically feasible mapping of tCho to enhance the limited specificity of routine DCE-MRI.

Highly Fluorescent Magnetic Nanoprobes for Enhanced Cancer Imaging and Therapy. The broad objective of this proposal is to develop new multifunctional nanoprobes with superior optical and magnetic properties for enhanced molecular cancer imaging and therapy. An electromagnetic device for producing a controllable magnetic field gradient will be designed and used in the guiding of the nanoprobes to target cells. The targeting efficacy of the fluorescent nanoprobes (also incorporating drug load) will be evaluated in the imaging and treatment of breast cancer in model systems.

Breast CT Scanner for Earlier Cancer Detection. Based on initial tests, breast CT has demonstrated enormous potential to detect breast cancer early and lead to more timely treatments for breast cancer patients. While breast CT would probably improve cancer detection in all women, some women may have risk factors (dense breasts, genetic markers, etc.) that require additional screening using breast CT. Investigators have designed and constructed the first dedicated breast CT scanner, using a breast CT table that eliminates the need for compression of the breast, is capable of 10-second breast imaging, and produces 3D images of the breast. The team also found that breast CT may be able to routinely detect breast tumors that are smaller than those that can be detected by mammography. More important, the radiation dose of breast CT studies was found to be comparable to that of mammography.

A high-quality prototype breast CT scanner was built in 2004 during the first funding period. Also, a phase II clinical trial evaluated the efficacy of breast CT for the early detection of breast cancer in a group of women likely to have breast cancer. A second, more sophisticated prototype breast CT scanner was fabricated in 2007, adding the capability of simultaneous positron emission tomography

(PET) imaging. Researchers are investigating other enhancements to breast CT technology and are conducting further clinical trials in a second funding period. A third prototype with several improvements will be built in the current funding period.

Receiver Operating Characteristic Analysis for Computer-Aided Breast Cancer Diagnosis. NIBIB funds several projects on receiver operating characteristic (ROC) analysis for computer-aided diagnosis of breast cancer. ROC analysis is used to evaluate a diagnostic method for sensitivity (the fraction of positive cases that are properly identified) and specificity (the fraction of negative cases that are properly identified). Improved sensitivity means fewer cases of cancer missed during screening, whereas improved specificity means fewer false alarms that can cause undue stress and worry for women. One such project is working to improve the software used to analyze data from experiments conducted to evaluate the diagnostic performance of imaging modalities. The software will be improved to manage situations in which some of the radiologists read all of the clinical cases while others read only a portion of the cases or situations in which there are many more positive cases than negative cases in an experimental data set.

Nanodevice for Digital Imaging of Palpable Structure at Human-Finger Resolution for Breast Cancer Detection. The investigators propose to develop an inexpensive, noninvasive, handheld screening tool for early detection of breast cancer that can image the palpability of a tumor and the nature of its attachment to surrounding tissue. The overall goal of this research is to develop a thin-film nanodevice (i.e., electronic skin) that will convert the pressure distribution on physical contact to light that can be imaged directly on a digital camera at a resolution on par with the human finger (~20 μm). This tool will enable family physicians and other clinicians to screen patients who do not have access to the more expensive screening tools and avoid unnecessary exposure to radiation used in mammography.

Magnetic Resonance Elastography. The goal of this research is to develop, validate, explore, and identify high-impact applications of a new diagnostic imaging technology for quantitatively assessing the mechanical properties of tissues, a technique called magnetic resonance elastography (MRE). Mechanical waves are generated in tissue, and a remarkably sensitive phase-contrast MRI technique, using synchronous motion-sensitizing gradients, is used to directly image the pattern of wave propagation. Specially developed mathematical algorithms are used to analyze the wave images and generate quantitative images depicting the stiffness and other mechanical properties of tissue. Using magnetic resonance to palpate tissues will allow clinicians to identify breast lesions and will distinguish benign lesions from malignant ones.

Advanced High-Resolution Two-Dimensional X-Ray Detector for Mammography. The goal of this project is to improve the image quality and reduce the cost of digital mammography. The research team will develop a computed radiography (CR) system for mammography based on novel glass ceramic materials. These glass materials will be used to develop a transparent phosphor material that is less expensive and can attain better performance than existing phosphor materials. Because they are transparent, they do not suffer from loss of resolution and increase in noise due to light scattering from grain boundaries, as do polycrystalline materials. Specifically, the researchers plan to (1) perform structural investigations, (2) optimize transparent phosphor material for application in CR mammography, (3) design and construct a readout system for transparent phosphor material, and (4) characterize and benchmark the new computed radiography.

Near-Infrared Diffused Light Imaging With Ultrasound Guidance. The goals of this project are to explore the utility of a novel hybrid ultrasound/optical imaging technique for (1) accurate diagnosis of breast lesions that could result in the reduction of benign biopsies and (2) assessing chemotherapy response and evaluating treatment efficacy. Investigators have developed a novel hybrid ultrasound/optical imaging system that uses simultaneous

optical (infrared) and ultrasound sensors in a handheld probe. This method provides accurate detection of tumor angiogenesis (i.e., formation of new blood vessels) and the distribution of these new blood vessels, which helps distinguish benign lesions from early-stage cancers. This method will be tested in a large number of patients who also will receive ultrasound-guided biopsy. Early results indicate that this method may be promising as an adjunct to mammography and may help to reduce the number of benign breast biopsies compared with methods that have been in use for more than 20 years.

Ultrasound Imaging of Breast by Use of a Hemispheric Array and Inverse Scattering. Investigators are developing a high-resolution, quantitative 3D ultrasound breast imaging method using a hemispheric transducer array. This system is designed to achieve high-resolution image reconstruction and quantitative measurements of normal versus malignant tissues. Successful completion will result in a screening method for breast cancer without the use of x rays. In addition, this method will overcome x-ray mammography limitations such as low resolution, low contrast in dense breasts, and poor imaging of breasts with implants and will eliminate the need for breast compression. This device may ultimately change the way screening for breast cancer is performed and significantly improve detection, diagnosis, and monitoring for cancer recurrence or response to treatment. The system may replace mammography and radiation-based methods as the standard of care.

Robotic Haptic Feedback System for Breast Biopsy /Radiofrequency Ablation of Breast Tumor Under Continuous MRI. This project proposes to develop an image-guided robotic system that will be able to perform breast biopsy and deliver radiofrequency ablation (RFA) at the site of the breast tumor. The investigators will incorporate continuous MRI during the procedure so that sampling errors will be minimized during the biopsy. Furthermore, the haptics in the teleoperated robotic system will provide force feedback to the clinicians to guide the biopsy and RFA needle with wider areas of access to various regions of the breast.

Design Studies and Optimization of Phase-Contrast Mammography. A new form of x-ray imaging called phase contrast imaging allows visualization and differentiation of soft tissues that is much greater than conventional x-ray imaging but at considerable reduction in radiation dose. Investigators plan to adapt this method to breast mammography and to improve the ability to image dense breasts, which are challenging to visualize using conventional mammography. This study is in a very early stage. Prototype imagers will be built by the end of the current funding period and will be evaluated objectively for improvements in image quality, improved detection capabilities, and reduction in radiation exposure. If successful, this new imaging modality will improve a radiologist's ability to detect subtle cancer features and allow earlier treatments.

Other Cancers

Multifunctional Protein Nanocapsules for Targeted Delivery. Recent advances have applied nanotechnology and nanoparticles as diagnostic and therapeutic agents toward the treatment of cancer. The goal of this investigation is to incorporate multiple functionalities into 25-nm protein nanoparticles and test their potential for the targeted delivery of doxorubicin in treating breast cancer cells. The synthesis involves the genetic engineering of chimeric proteins that encapsulates the drug molecule and dissociates at a specific pH to release the drug. The quaternary protein assembly comprises 60 subunits, and its modular structure enables the nanoscale architecture with cell-targeting peptides to be specifically tailored in a straightforward manner. Studies thus far have shown an increase in the effectiveness of this drug at a lower dose compared with synthetic drug delivery systems and a decrease in side effects.

Optical Coherence Tomography Image-Guided Surgical Resection of Solid Tumors. Image-guided surgical interventions have the potential to improve surgical outcomes by providing improved visualization and differentiation of normal and pathologic tissue intraoperatively and in real time. A critical need exists for an image-guided interventional technology capable of real-time intraoperative imaging for

the complete resection of a tumor mass, for the detection and removal of individual tumor cells that have migrated across tumor margins, and for the detection of cells that have metastasized to lymph nodes. Optical coherence tomography (OCT) is an emerging high-resolution real-time biomedical imaging technology capable of intraoperative imaging for tumor detection and intervention. This project will use OCT for high-resolution image-guided surgical interventions for the identification and resection of solid tumors, suspicious regions around the tumor, and lymph nodes that show evidence of metastatic cancer. To do this, the investigators are developing a high-speed surgical microscope-based OCT system with fast image processing hardware that will be tested in an animal model of breast cancer. The use of OCT for image-guided surgical interventions has the long-term goal of improving surgical outcomes by enabling complete resection of tumors with real-time, high-resolution visualization of the surgical field.

Thermally Targeted Drug Delivery by Elastin Biopolymers. Cancer describes a collection of diseases caused by multiple genetic mutations arising from environmental insults, somatic DNA replication error, and inherited genetic defects. The modern treatment of cancer typically includes various combinations of radiation, chemotherapy, and surgery or drug-based therapies. A critical failure in such therapies/treatments can ultimately lead to metastases. A team of investigators is developing a new combination strategy to treat ovarian cancer using a novel drug delivery approach. The dual targeting delivery strategy described in this proposal attacks both the tumor vasculature and the cancer cells directly when applying a localized hyperthermia approach. Here, scientists have developed elastin-like polypeptide nanoparticles (ELPs) that undergo a transition from a solid to a liquid when heated. This change causes the delivery vehicles to aggregate in targeted regions of tumors. In the first stage of therapy, the tumor vasculature is ablated by irradiating the aggregated ELPs that are formed, and in the second stage, the doxorubicin is then released to kill the remaining cancer cells. Studies thus far have shown that these thermally triggered ELPs result in increased tumor accumulation and better distribution in tumors to improve overall therapeutic efficacy compared with conventional therapeutic approaches such as a single drug delivery modality or nonthermally targeted systems.

Reproductive Health

Center for Point-of-Care Technologies Research for Sexually Transmitted Diseases. The goal of this project is to develop point-of-care (POC) tests for sexually transmitted diseases (STDs), with *Chlamydia trachomatis* being a main focus as the most common bacterial STD. The STD area is optimal for development of POC tests given the stigma, privacy, and confidentiality issues that limit the effectiveness of current approaches to testing and followup treatment. These infections have serious long-term consequences for women because many, if not most, STD infections are asymptomatic. The center is developing a range of technologies for detection of *C. trachomatis*, including immunoassay and molecular diagnostic approaches, with assessment of the acceptability of sample collection by patients and the ability of patients to obtain accurate results compared with testing by trained health care professionals.

Temporal-Spatial Biomagnetic Fields of the Fetus. The primary goal of this research is to develop an integrated computer environment for the analysis and display of biomagnetic signals recorded from pregnant women, including anatomical information obtained by 3D ultrasound. Thus far, the major achievement has been the ability to improve the SNRof the acquired biomagnetic signals using optimal signal analysis technique. A significant outcome of this achievement has been the reliable detection of fetal ST segments, which is potentially valuable because electrocardiography studies in labor have shown that analyses of fetal ST segments are highly correlated with a positive predictive value of fetal distress.

Development of Advanced Techniques for Magnetic Resonance of the Newborn Brain. This project is focused on developing both imaging and metabolic assessment techniques through MRI and spectroscopy in neonates. With the extraordinarily high premature birth rate of more than 540,000 per year in the United States and its extremely high human

and economic costs, neonatal MRI is a critically important advance in radiological care. These investigators propose to develop and translate new specialized 3T MRI tools for the noninvasive characterization of brain maturation and injury in premature and term newborns.

Fetal Functional Magnetic Resonance Imaging. Fetal functional MRI (f-fMRI) has immense potential to further the understanding of normal and pathologic fetal neurofunction and development. Studies of the development and application of f-fMRI are motivated in part by the need for monitoring fetuses at risk for intrauterine growth restriction (IUGR). The purpose of this study is to design, implement, and optimize a technique for f-fMRI that depends on blood-oxygen level. These techniques involve novel approaches for reducing the field of view of the MRI image and will substantially reduce major artifacts due to fetal and maternal motions. The imaging techniques will be used to compare normal fetuses and fetuses at risk for IUGR.

Molecular and Cellular Transport in Mucus. STDs and unwanted pregnancy create tremendous burdens on individuals, on U.S. society, and on national health care costs. The goal of this project is to understand the biological barriers to protein and DNA transport at mucosal surfaces and to produce new polymeric delivery systems to enhance immune protection within the female reproductive tract. The team has designed and synthesized biodegradable nanoparticles that can cross the human cervical mucus layer, enter specific cells, and release complex agents such as siRNA and DNA to treat or protect against infectious diseases such as genital herpes and specific pathogens.

MRI of Fetal Ventriculomegaly: Morphology and Outcome. Ultrasound is the imaging modality of choice for fetal evaluation. However, there are many cases in which ultrasound is nonspecific, and further development of ultrasound techniques is needed, especially for fetuses with ventriculomegaly (VM). Fetuses with VM are a heterogeneous population, and it is likely that using additional MRI data will facilitate improved counseling and management of these patients. This research is based on the hypothesis that, when compared with ultrasound data alone, the use of MRI with ultrasound will improve the diagnostic utility for patients with VM and the ability to predict outcomes.

Point-of-Care Ultrasound for Maternal Health. Ultrasound has become an integral part of prenatal care. However, many patients in rural or underserved areas do not have access to this diagnostic equipment. System costs and the need for trained operators limit the use of ultrasound to hospitals, clinics, and doctor's offices. Researchers at General Electric's Global Research Center in Niskayuna, NY, are tackling both challenges. First, they developed a low-cost method to fabricate ultrasound transducers—the probes that generate and receive sound waves—and now they are developing software that automatically adjusts image quality, reducing the need for specialized operator training.

Development of Spatial-Temporal Analysis Tools for Uterine Biomagnetic Signals. The proposed study will record the magnetic field corresponding to the electrical activity of uterine contraction and provide requisite spatial-temporal information. To take advantage of the spatial-temporal resolution in uterine magnetomyographic (MMG) signals, the investigators will further enhance computational and analysis tools and develop this system as a clinical device to predict the onset of labor both in the case of term and preterm patients. The goal is to develop techniques to improve extraction, recognition, and validation process of uterine MMG activity. This ability would be of great clinical benefit for the management of the term patient and especially for the management of patients at high risk for premature delivery.

Development of Analysis Tools To Enhance Fetal Neurologic Assessment. The ultimate goal of this proposal is to develop a clinical neurologic assessment tool for the developing fetus. This proposal has two specific aims: one is to improve fetal spontaneous magnetoencephalography signal extraction by using advanced spatial filter processing methods, and the other is to apply this technology to assess the spontaneous brain activity in a specific group of fetuses who are at risk for developing neurologic problems. The

investigators will specifically investigate IUGR fetuses because their compromised intrauterine environment affects potential growth and brain development. The spontaneous brain activity characteristics of IUGR fetuses will be compared with fetuses with normal growth.

Temporomandibular Joint Disorder

Tissue engineering TMJ Articular Fibrocartilage. Temporomandibular joint (TMJ) disorders are painful conditions that disproportionately affect women and for which there are few (if any) successful treatments. TMJ is the small, complex joint that forms the articulation of the lower and upper jaws, and it is characterized by an unusual hybrid-type of cartilage. Several major technical hurdles have barred the development of clinically useful engineered cartilage, particularly optimization of mechanical properties and obtaining an appropriate cell source. The investigators have been utilizing advances (cell sourcing, bioreactor growth systems, scaffolds with functional tensile strength) to generate TMJ articular cartilage appropriate for implantation and repair of TMJ. They have identified several scaffolds with high-tensile strength that may support tissue engineering of TMJ cartilage. These studies are intended to lead to translational research, in which these tissue engineered constructs will be assessed in preclinical models.

Initiatives

In FY 2009–2010, NIBIB participated in initiatives that addressed areas relevant to women's health.

Joint Initiatives

RFA-GM-09-012, Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (R01). NIBIB participated in a trans-NIH funding opportunity for research on (1) causal factors explaining the current patterns observed in the careers of women in biomedical and behavioral science and engineering and variation across different subgroups and (2) the efficacy of programs designed to eliminate sex/gender disparities and promote the careers of women in these enterprises. This program is designed to better understand the factors that influence existing outcomes, the identification of new principles that would inform the development and adaptation of existing intervention strategies, the analysis of differences in the career activities of men and women scientists and engineers that could inform the development of interventions for remediation, and the analysis of career patterns to further support new programs.

PAS-10-226, Advancing Novel Science in Women's Health Research (ANSWHR) (R21). With the Office of Research on Women's Health, NIBIB cosponsored a trans-NIH investigator-initiated exploratory developmental program designed to promote innovative, interdisciplinary research to advance new concepts in women's health research and the study of sex/gender differences. Published research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. The ANSWHR program is focused on stimulating and supporting innovative research that will advance new concepts in women's health research and the study of sex/gender differences.

NIBIB Initiative

RFA-EB-10-002, Development and Translation of Medical Technologies That Reduce Health Disparities (SBIR [R43/R44]). NIBIB sponsored a funding opportunity focused on reducing health disparities through the development and translation of appropriate medical technologies, new or existing, that can have a significant impact on health care access and health outcomes for health disparities in populations. The RFA supports a wide range of research aimed at the development of innovative diagnostics, treatments, and preventative strategies to reduce, and eventually eliminate, health disparities.

Health Disparities Among Special Populations of Women

NIBIB is continuing to develop and support a research portfolio that pursues cutting-edge science in the area of women's health research. NIBIB increased its commitment to women's

health research from more than $10 million in 2008 and more than $15 million in 2009 (American Recovery and Reinvestment Act [ARRA] + non-ARRA) to almost $17 million in 2010 (ARRA + non-ARRA).

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Executive Summary

The mission of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is to ensure that every child is born healthy and wanted; that women suffer no harmful effects from reproductive processes; that all children can achieve their full potential for healthy and productive lives, free from disease or disability; and that the health, productivity, independence, and well-being of all people be ensured through optimal rehabilitation. Within this mission, NICHD supports essential research that plays a unique role in women's health, aiming to overcome many of the complex challenges that women encounter over their lifetimes. NICHD is home to much of the Nation's leading science related to women's overall health, gynecologic health, pregnancy, and childbirth, as well as studies of diseases and conditions related to these topics.

To improve the lives of women around the world, NICHD supports a wide-ranging research portfolio in women's health, including research on preconception care, fertility preservation, maternal obesity, oogenesis, ovarian failure, uterine fibroids, pelvic floor disorders, endometriosis, vulvodynia, infertility, contraception, HIV, menopause, violence, obstetrical pharmacology, preterm birth, stillbirth, assistive reproductive technologies, and many other aspects of women's health. The Institute not only supports research on women's health but also conducts outreach and dissemination activities and develops press releases and publications to share research results and health information with the general public. Because women's health issues are related to a variety of other research areas, the Institute partners with many Institutes, Centers, and Offices at the National Institutes of Health (NIH), as well as other Federal Agencies, to support its women's health research, training, and outreach activities.

NICHD's commitment to maintain and improve women's health during pregnancy has led to many research advances in women's health, including encouraging women of childbearing age to take proactive steps to increase the chances of a healthy pregnancy. Recent research findings strongly suggest that by losing weight before they become pregnant, obese women may reduce the chance that their infants will be born with heart defects. NICHD-supported scientists also provided the first conclusive evidence that treating pregnant women who have even the mildest form of gestational diabetes can reduce the risk of common birth complications among infants as well as blood pressure disorders among mothers.

NICHD's research accomplishments in women's health also encompass reproductive sciences, where scientists are moving forward new options to improve pregnancy outcomes, restore fertility in women undergoing cancer treatment, and develop methods to treat reproductive conditions such as endometriosis and primary ovarian insufficiency (POI). For example, NICHD has released a comprehensive plan to help health care professionals diagnose and treat POI, where the ovaries stop releasing eggs and producing estrogen and other reproductive hormones at an early age.

NICHD's accomplishments in women's health research are wide-ranging and address conditions across the life stages. Highlighted in this report are just *some* of NICHD's recent activities related to women's health. The report is organized to (1) briefly summarize the NICHD organizations that focus on women's health, (2) highlight some of the Institute's recent accomplishments and activities across categories affecting women's health, such as training and special populations, and (3) list and briefly describe initiatives and conferences related to women's health, again across categories. Outreach and dissemination activities also are included throughout the report. When available, hyperlinks are included for more information about specific activities.

Additional information about the Institute's research on women's health is also available on the NICHD Web site at http://www.nichd.nih.gov/womenshealth/womenshealth.cfm.

Introduction

NICHD supports research and activities that promote women's health across five major research components and through the NICHD Office of the Director (http://www.nichd.nih.gov/about/org/orgchart/).

The NICHD Office of the Director (OD) provides leadership for the scientific direction of the Institute. NICHD's director and deputy director are committed to improving the lives of women, children, and families and have launched multiple initiatives dedicated to improving women's health. With the appointment of a new Institute director in 2010, NICHD launched a new scientific visioning process. The purpose of the process is for NICHD, in collaboration with its external communities, to identify the most promising scientific opportunities of the next decade across the breadth of the Institute's mission. The aim of this process is to develop a scientific vision that sets an ambitious agenda and inspires the Institute, its many partners, and the research community to achieve critical scientific goals and meet pressing public health needs, including those related to women's health (http://www.nichd.nih.gov/vision).

The NICHD OD continues to support the breadth of women's health research and women's health education. In 2009, NICHD also launched the National Children and Maternal Health Education Program (NCMHEP), created to provide a forum for reviewing, translating, and disseminating new research in the field of maternal and child health. NCMHEP is designed to achieve its goals by leveraging a coalition of the Nation's most prominent health care provider associations, Federal Agencies, nonprofit maternal and child health organizations, and other partners. More information about the program can be found at http://www.nichd.nih.gov/ncmhep.

The Center for Developmental Biology and Perinatal Medicine supports a broad range of research to advance fundamental and clinical knowledge about maternal health and problems of child development. Research efforts include studies on the factors that affect pregnant women and their unborn infants, such as the causes and consequences of fetal growth restriction, preterm labor and birth, and stillbirth. In 2009–2010, the center supported studies in, among other areas, promoting healthy weight in pregnancy and in the postpartum period among overweight/obese women, reducing preterm births in underserved pregnant women, and evaluating diet, glycemic load, and metabolism in obese pregnant women (http://www.nichd.nih.gov/about/org/cdbpm).

The Center for Population Research supports a diverse range of research, including studies to understand reproductive health and biology, with the goal of alleviating human infertility and reproductive disorders. Reproductive sciences research includes studies to expand fundamental knowledge of the processes that underlie fertility and infertility in women, leading to the development of more effective strategies to diagnose, treat, and prevent conditions that compromise reproductive health. For example, the Center supports a clinical research network, along with independent studies, to better understand, prevent, and treat pelvic floor disorders. A pelvic floor disorder occurs when the pelvic muscles and connective tissue in the pelvis weaken or are injured. Pelvic floor disorders may result in incontinence or pelvic floor prolapse, which can require surgery. An estimated one-third of all U.S. women are affected by one type of pelvic floor disorder at some time in life. The Center also continues to expand funding opportunities to study vulvodynia, a type of chronic pelvic pain. Another reproductive condition emphasized in the Center's portfolio is uterine fibroids, the most common noncancerous tumors for women of childbearing age. In addition, a research program on contraception and reproductive health supports the development of contraceptive methods that are safe, effective, inexpensive, readily available, preferably reversible, and meet the diverse needs of women throughout their reproductive lives, including the need to prevent the spread of sexually transmitted diseases. More information on the center can be found at http://www.nichd.nih.gov/about/org/cpr.

The Center for Research for Mothers and Children supports a vast array of maternal and child health research, including studies of gestational diabetes, obesity, and HIV/AIDS in children, adolescents, and women. The Center also funds research that examines the mechanisms of cognitive, social, emotional, and neurobiological development, as well as the influences of genetics, nutrition, the environment, and life experiences on overall physical growth and development, health promotion, and disease prevention. Such research may show gender differences during development. The center is home to unique clinical networks that specifically target research in obstetrical pharmacology. Also critical in protecting women's health is a program that supports research in the epidemiology, natural history, pathogenesis, transmission, and treatment of HIV infection and disease in women of childbearing age and pregnant women, as well as in infants, children, adolescents, and families (http://www.nichd.nih.gov/about/org/crmc).

The NICHD Division of Epidemiology, Statistics, and Prevention Research conducts epidemiologic and other types of research in the areas of fertility, pregnancy complications and adverse pregnancy outcomes, childhood injuries, and birth defects. The division also conducts behavioral research in health promotion; its primary interests involve preventing problem behaviors among adolescents, including those factors that increase risks of motor vehicle crashes for girls and boys, and coping with diseases such as diabetes in a family context. In 2009, the National Standard of Normal Fetal Growth Study, a project of the division, was selected as one of NIH's Signature Projects and thereby received supplemental funding under the American Recovery and Reinvestment Act (ARRA) of 2009. The division created the study to address a critical data gap in contemporary obstetrical practice. ARRA funds will permit the recruitment of 500 twin pregnancies as well as the addition of 4 new clinical sites. The study also will examine healthy development of fetuses in pregnant women by assessing nutrition and dietary supplementation during pregnancy; collecting blood samples for a prospective study of gestational diabetes mellitus and for a prediction study of fetal growth restriction and/or overgrowth; and collecting placental tissues and umbilical cord blood for studies on the etiology of idiopathic fetal growth restriction (http://www.nichd.nih.gov/about/org/despr).

The NICHD Division of Intramural Research conducts interdisciplinary and interactive research to answer basic biomedical research questions and solve difficult clinical problems, including problems in female reproduction and development. This effort includes research in genetics, genomics (the study of how genes function), and epigenetics (DNA-associated, heritable switches that can affect gene function) and how these areas influence normal and abnormal development. The intramural program also studies the basic biophysical mechanisms underlying cell and tissue function, early development, and the prevention and treatment of conditions of female reproduction, through innovative diagnostics and therapies. The division continues to conduct groundbreaking research in women's health issues through its research components that address issues such as ovarian function and processes that lead to successful fertilization and infertility treatment. For example, the Program in Reproductive and Adult Endocrinology examines research areas such as endometriosis, fibroids, infertility, and endocrine aspects of disease—both basic and clinical. More information about the studies being conducted in this and other women's health-related research programs is available on the NICHD Division of Intramural Research Web page.

Accomplishments

Pregnancy

Vitamin C and E Supplements Do Not Reduce Risk for Blood Pressure Disorders of Pregnancy. The largest study to date of vitamin supplements and hypertension in pregnancy found that taking vitamin C and E supplements starting in early pregnancy does not reduce the risk for hypertensive disorders and their complications in pregnant women. The supplements notably failed to reduce the risk of preeclampsia, a potentially fatal form of hypertension in pregnancy. NICHD provided major funding for the study. Other funding

contributors were the National Heart, Lung, and Blood Institute (NHLBI) and the National Center for Research Resources' Clinical and Translational Science Awards program. The study was conducted at 16 sites within NICHD's Maternal-Fetal Medicine Units (MFMU) Network. The findings appeared in the April 8, 2010, issue of the New England Journal of Medicine (http://www.nichd.nih.gov/news/releases/040710-vitaminC-and-E.cfm?from=women).

Study Finds Link Between Preeclampsia and Reduced Thyroid Function. Women who experience preeclampsia, a serious complication of pregnancy, may have an increased risk for reduced thyroid functioning later in life. The analysis combined two separate studies, each of which suggested a link between preeclampsia and reduced thyroid function. In the first study, women who developed preeclampsia were more likely to have slightly reduced thyroid functioning during the last weeks of their pregnancies. The second study found that women who had preeclampsia during their pregnancies were more likely to have reduced thyroid functioning more than 20 years after they had given birth compared with women who had not had preeclampsia during pregnancy. The study authors advised physicians treating women with a history of preeclampsia to be aware that this group of patients may be at increased risk for reduced thyroid functioning. Funding for the research was provided in part by NICHD and NHLBI (http://www.nichd.nih.gov/news/releases/111709-preeclampsia.cfm?from=women).

Treating Even Mild Gestational Diabetes Reduces Birth Complications. Researchers provided the first conclusive evidence that treating pregnant women who have even the mildest form of gestational diabetes can reduce the risk of common birth complications among infants as well as blood pressure disorders among mothers. The researchers found that, compared with the women's untreated counterparts, women treated for mild gestational diabetes had smaller, leaner babies less likely to be overweight or abnormally large and less likely to experience shoulder dystocia, an emergency condition in which the baby's shoulder becomes lodged inside the mother's body during birth. Treated mothers also were less likely to undergo cesarean delivery, to develop high blood pressure during pregnancy, or to develop preeclampsia, a life-threatening complication of pregnancy that can lead to maternal seizures and death. The study was conducted by researchers in NICHD's MFMUNetwork and appeared in the October 1, 2009, *New England Journal of Medicine*. In addition to funding from NICHD, the study was supported by NIH's National Center for Research Resources (http://www.nichd.nih.gov/news/releases/112109-gestational-diabetes.cfm?from=women).

Study Indicates Stress May Delay Women Getting Pregnant. This study is the first of its kind to document, among women without a history of fertility problems, an association between high levels of a substance indicative of stress and a reduced chance of becoming pregnant. The researchers showed that women who had higher levels of a substance called alpha-amylase were less likely to get pregnant than women with lower levels of the substance. Alpha-amylase is secreted into saliva by the parotid gland, the largest of the salivary glands. Although alpha-amylase digests starch, in recent years many researchers have used it as a barometer of the body's response to physical or psychological stress. The substance is secreted when the nervous system produces catecholamines, compounds that initiate a type of stress response. The study results suggest that finding safe ways to alleviate stress may play a role in helping couples become pregnant. In addition to researchers at NICHD and the University of Oxford, England, the study also includes an author from the Ohio State University College of Medicine, Columbus (http://www.nichd.nih.gov/news/releases/081110-stress-delay-women-getting-pregnant.cfm?from=women).

Obesity

Risk of Newborn Heart Defects Increases With Maternal Obesity. In an NICHD-funded and -conducted study, researchers found that, on average, obesity increases a woman's chance of having a baby with a heart defect by around 15 percent. The risk increases with rising obesity. Moderately obese women were

found to be 11 percent more likely to have a child with a heart defect, and morbidly obese women were 33 percent more likely. The current findings strongly suggest that by losing weight before they become pregnant, obese women may reduce the chance that their infants will be born with heart defects. To conduct this current study, the researchers analyzed data in the New York State Congenital Malformations Registry, a repository of case reports on children born with birth defects in New York State, excluding New York City. Using 1.53 million births that took place in the State over the course of 11 years, the researchers compared the records of mothers of 7,392 of children born with major heart defects with those of more than 56,000 mothers of infants born without birth defects. The obese mothers were 15 percent more likely than mothers with normal body mass index (BMI) to have children with heart defects. Women classified as morbidly obese—with a BMI of 40 or higher—were 33 percent more likely than women with normal BMI to have children with heart defects. On average, women who were overweight but not obese had no increased risk. However, the researchers saw the chances of having a child with a congenital heart defect increase for obese women and increase sharply for morbidly obese women (http://www.nichd.nih.gov/news/releases/040710-newborn-heart-defects.cfm?from=women).

Primary Ovarian Insufficiency

Most Young Women With Menopause-Like Condition Retain Scores of Eggs. Primary ovarian insufficiency (POI) results in a menopause-like condition years before normal menopause begins—sometimes as early as the teens and twenties. Women with POI stop producing normal amounts of reproductive hormones, develop hot flashes, and typically become infertile. POI occurs in 1 of 100 women by age 40. In addition to experiencing hot flashes, women with POI cease having regular menstrual periods. The symptoms may be lessened or relieved by therapy to replace the missing hormones. Contrary to what researchers had previously believed, most young women and girls who experience POI still have immature eggs in their ovaries, according to this study conducted by scientists at NICHD. Refinement in ultrasound technology allowed the researchers to detect ovarian follicles in three-quarters of the POI patients who took part in the study. The discovery that most women with POI have immature eggs remaining in their ovaries raises the possibility of developing treatments for the infertility that accompanies the condition. The findings were published online in *Fertility and Sterility* (http://www.nichd.nih.gov/news/releases/042610-POI.cfm).

Plan Offers Guidance for Evaluating Menopause-Like Condition in Girls and Young Women. NICHD has developed a comprehensive plan to help health care professionals diagnose and treat POI. In POI, the ovaries stop releasing eggs and producing estrogen and other reproductive hormones. The sudden cessation of ovarian function results in a condition similar to that of normal menopause: loss of menstrual periods, infertility, hot flashes and night sweats, sleep loss, and increased risk for bone fracture and heart disease. The sudden and unexpected loss of fertility frequently results in feelings of grief, anxiety, and depression. NICHD outlined a number of steps health care professionals can take to identify potential causes for the cessation of a woman's menstrual cycle. These steps include learning whether the woman has an underlying disease or condition, is exercising excessively and perhaps eating too little, or has had prior chemotherapy or radiation therapy. The diagnosis of POI is made largely by the presence of follicle-stimulating hormone (FSH) levels in the menopausal range. Once the diagnosis is made, additional tests for various chromosomal conditions and hormonal abnormalities should be performed (http://www.nichd.nih.gov/news/releases/020409-Evaluating-Menopause.cfm).

Delay in Diagnosis of Menopause-Like Condition in Young Women Linked to Low Bone Density: *Women Who Do Not Receive Treatment May Risk Osteoporosis.* According to new research by scientists at NICHD, women and young girls who experience delays in diagnosing a premature, menopause-like condition face increased risk of low bone density. The researchers concluded that a delay in diagnosing the condition, called primary

ovarian insufficiency (POI), may make women more susceptible to osteoporosis and fractures later in life. Delays in diagnosis are common because the main symptom, irregular or stopped menstrual periods, is often disregarded by women and their doctors. The researchers also found that the beginning of menstrual irregularity before age 20 was a strong risk factor for lower bone density. The teen years are a critical period for developing healthy bones. The minority patients in the study were more likely to have low bone density than were White patients in the study. African-American women were less likely to consume sufficient calcium than were White women and more likely to have low vitamin D levels. Asian women were less likely than White women to take the replacement hormones prescribed as a treatment for the condition. For years, POI has been known to put women at risk of low bone density. The new study helps explain why some women with the condition are more likely to develop low bone density. It also provides strong evidence that by having the condition diagnosed early, replacing deficient estrogen, and getting adequate calcium and vitamin D, these women can protect their bones from weakness and fractures (http://www.nichd.nih.gov/news/releases/061909-Young-Women.cfm?from=women).

Cancer and Fertility

New Technique Could Sustain Cancer Patients' Fertility: Researchers Grow Immature Egg Cells in the Laboratory for 30 Days. Researchers funded by NICHD have completed a critical first step in the eventual development of a technique to retain fertility in women with cancer who require treatments that might otherwise make them unable to have children. Men facing such treatments can freeze their sperm for use at a later date, but female cancer patients have fewer options. Unlike sperm, eggs rarely survive freezing and thawing. The researchers have developed a method to advance undeveloped human eggs to near maturity in laboratory cultures maintained outside the body. The technique focuses on the follicle, a tiny sac within the ovary that contains the immature egg. The researchers were able to grow human follicles in the laboratory for 30 days, until the eggs they contained were nearly mature. The accomplishment represents the successful completion of the first of three steps needed to preserve a woman's fertility after radiation treatments or chemotherapy. For the next step, researchers must induce the egg's final division so that it contains only half the genetic material of its precursors. Finally, the researchers will have to demonstrate that they can freeze and thaw human follicles before growing them in culture (http://www.nichd.nih.gov/news/releases/071409-fertility.cfm?from=women).

Preterm Birth

NIH Scientists Identify Maternal and Fetal Genes That Increase Preterm Birth: Findings Support the View of Preterm Labor as an Immune Response to Infection or Injury. In this study, NICHD researchers identified DNA variants in mothers and fetuses that appear to increase the risk for preterm labor and delivery. The DNA variants were in genes involved in the regulation of inflammation and of the extracellular matrix, the mesh-like material that holds cells within tissues. The current findings add evidence that individual genetic variation in that response may account for why preterm labor occurs in some pregnancies and not in others. Like sensitivity to allergens such as house dust or pollen, the severity of the immune response appears to vary from individual to individual, potentially accounting for why some pregnancies end in early labor and delivery. The findings may one day lead to new strategies to identify those at risk for preterm birth and to ways to reduce the occurrence of preterm birth among those at risk. The findings were presented at the 30th Annual Society for Maternal-Fetal Medicine meeting by Dr. Roberto Romero, M.D, chief of the Perinatology Research Branch and program head for perinatal research and obstetrics at NICHD. At the meeting, Dr. Romero and his team received the March of Dimes Excellence Award for innovative research on preterm birth for this study.

Endometriosis

Animal Study Shows Statin Drug May Help Form Basis for Endometriosis Treatment. Endometriosis is a common condition associated with infertility and pelvic pain in women. An NICHD-sponsored study evaluated the effects of simvastatin (a statin) on development of endometriosis in a mouse model. Simvastatin induced a dose-dependent decrease in the number and size of endometrial implants in mice. Mechanisms of action of simvastatin may include inhibition of MMP-3. The findings may lead to the development of novel treatments of endometriosis involving statins.

Significant Plans for Sex/Gender Analysis

Pragmatic Skills of Young Males and Females With Fragile X Syndrome. Children's pragmatic skills, including their conversation and narration skills, will be assessed annually for 4 years. Children's language content and structure (receptive vocabulary and expressive syntax), cognition (nonverbal cognitive level and attention), social-emotional behavior (anxiety and autistic characteristics), and family environment (responsiveness and support of home environment and maternal contingency) also will be examined annually. In addition, fragile X mental retardation protein (FMRP) analysis from blood samples will be completed on the girls and boys with fragile X syndrome (FXS), and activation ratios will be computed for the girls with FXS. Growth curve methods will be used to quantify patterns of change over time in the overall level and rate of growth in pragmatic development. Pragmatic skills are essential for effective communication, and pragmatic difficulties can compromise all aspects of communicative competence in daily interactions. Determining whether a unique pragmatic phenotype exists for FXS that is syndrome specific or related to gender, intellectual disability, or autism and identifying the potential mechanisms underlying pragmatic skills have critically important implications for defining treatment protocols.

Sexual Differentiation and Development of Reproductive Neural Circuits. Several facets of reproduction are sexually differentiated, including the onset of puberty and the ability to generate a preovulatory luteinizing hormone surge. A number of reproductive diseases and disorders, such as idiopathic hypogonadotropic hypogonadism (more common in men), precocious puberty (more prevalent in girls), and constitutional delayed puberty (more common in boys) also are sexually differentiated. Researchers are investigating the underlying hormonal, cellular, and molecular mechanisms contributing to the sexual differentiation of kisspeptin neurons, which have been implicated in regulating puberty and fertility and therefore may be involved in the etiology of sexually dimorphic reproductive disorders. This study will contribute to the understanding of how developmental sex steroids influence the sexual differentiation of reproductive neural circuits and will ultimately provide insight into developmental regulation of several reproductive disorders.

Gender Norms and Partner Selection: HIV/STI Risk Among Urban Youth. Researchers are examining gender role beliefs and partner selection patterns among a community-based, economic and racially diverse sample of 15- to 24-year-olds in Baltimore, MD. The study will enhance our understanding of the mechanisms of sexual risk behaviors among this population, which is at a heightened risk for HIV and sexually transmitted infections (STIs). The study will identify factors beyond socioeconomic status and individual sexual behaviors, particularly social contexts, which contribute to high rates of STIs in African-American youth.

Sleep and Metabolism in Obesity: Impact of Gender. Obesity is a major risk factor for obstructive sleep apnea (OSA), a condition characterized by repetitive respiratory disturbances, intermittent hypoxia, sleep fragmentation by frequent microarousals, and low amounts of deep slow-wave sleep (SWS). Today, more than 10 million American women suffer from OSA. OSA has been identified as an independent risk factor for the metabolic syndrome. Because OSA is more prevalent in

men than in women, a disproportionate number of studies of OSA and its consequences have been conducted in men. Recent evidence suggests that reduced amounts and intensity of SWS (i.e., slow-wave activity [SWA]) may play a pivotal role in the development of metabolic and cardiovascular disturbances in obese men and women, particularly those with OSA. Researchers will focus on sex differences in SWA and their relationship with daytime sleepiness and metabolic vulnerability in obese men and women with and without OSA. The study will provide important insights regarding the pathophysiology of OSA and its adverse consequences in obese men and women, and the basis for the development of effective sex-specific prevention and treatment strategies.

Initiatives

Requests for Applications

Pelvic Floor Disorders Network Clinical Sites (RFA-HD-10-002). NICHD, in partnership with the Office of Research on Women's Health (ORWH), solicited grant applications from institutions/organizations willing to participate with NICHD in an ongoing multicenter clinical program designed to study clinical and health aspects of pelvic floor disorders in women. For the purpose of this funding opportunity announcement (FOA), pelvic floor disorders include urinary incontinence, fecal incontinence, pelvic organ prolapse, and other sensory and emptying abnormalities of the lower urinary and gastrointestinal tracts. Clinical and health aspects of pelvic floor disorders include surgical and nonsurgical treatments, social and behavioral contributions, pharmacologic therapies, any outcomes from the broad array of treatments available, and prevention efforts, among others. Particular attention will be paid to develop innovative solutions to the challenging problems in women with pelvic floor disorders and to reduce the burden of pelvic floor disorders for women and their families (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-10-002.html).

***Eunice Kennedy Shriver* NICHD Maternal-Fetal Medicine Units Network (RFA-HD-10-008).** NICHD invited applications to participate with NICHD under a cooperative agreement in an ongoing multicenter clinical program designed to investigate problems in clinical obstetrics, particularly those related to prevention of low birth weight, prematurity, and medical problems of pregnancy (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-10-008.html).

Fertility Preservation Research: Advancing Beyond Technology (RFA-HD-09-009). NICHD, in partnership with the **National Institute for Occupational Safety and Health**, solicited grant applications that are designed to (1) characterize the risks and mechanisms of gonadal damage secondary to exposure to chemotherapy, radiation therapy, or occupational or environmental hazards, (2) elucidate more reliable biomarkers of reproductive capacity, and (3) examine the social, legal, and ethical ramifications of fertility preservation technologies (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-009.html).

Program Announcements

Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (PAR-10-190). NICHD invites applications that address basic, clinical, translational, epidemiologic, and/or behavioral research on vulvodynia and related symptom-based conditions. The goal of the initiative is to facilitate new research on diagnostic, prevention, and therapeutic approaches to vulvodynia, a chronic pelvic pain condition in women. An expected outcome will be to provide findings useful for development of future prevention or treatment strategies. It is anticipated that these studies will increase our understanding of the pathophysiology, biologic and behavioral risk factors, natural history, and genetics of vulvodynia (http://grants.nih.gov/grants/guide/pa-files/PAR-10-190.html).

Biosocial Approaches to Infertility Research (PA-09-032). NICHD encourages applications that represent exploratory/developmental collaborations between sociobehavioral and biomedical scientists in the area of infertility. Research supported through this

FOA should aim either to develop methods or theories incorporating biomedical aspects of infertility into social and behavioral science research projects or to generate methods or theories that allow biomedical researchers to address the broader social and behavioral concerns about their patient populations. Appropriate applications will include teams of investigators who span multiple disciplines in their training and methodologies and who propose innovative ways of combining aspects of their respective scientific backgrounds. Projects may focus on basic or clinical research (http://grants.nih.gov/grants/guide/pa-files/PA-09-032.html).

Contextual Approaches to Prevention of Unintended Pregnancy (PA-09-014). In an effort to strengthen and revitalize scientific research on the prevention of unintended pregnancies in the United States, NICHD invites R01 research grant applications that will inform interventions addressing the cultural and structural factors that produce high rates of unintended pregnancy across the reproductive age span, especially in low-income populations in the United States. These interventions can operate at a wide range of levels, from clinical interventions to interventions that influence cultural, economic, social, structural, and/or policy factors contributing to unintended pregnancy (http://grants.nih.gov/grants/guide/pa-files/PA-09-014.html).

Women's Mental Health in Pregnancy and the Postpartum Period (PA-09-174). In this FOA, the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), NICHD, and the Agency for Healthcare Research and Quality (AHRQ) encourage research on women's mental health in relation to pregnancy and the postpartum period. As illustrated by a few highly publicized cases, the consequences of severe untreated postpartum depression and psychosis can be devastating for individuals, families, and communities. A recent evidence-based practice report from AHRQ noted that depression is prevalent during pregnancy as well as the postpartum period; therefore, research that occurs throughout pregnancy and the postpartum period (the perinatal period) is encouraged (http://grants.nih.gov/grants/guide/pa-files/PA-09-174.html).

Program Notices

Participation of NICHD in PA-09-106 (R01) and PA-09-107 (R21) Medications Development for the Treatment of Pregnant/Postpartum Women With Substance-Related Disorders and/or In Utero Substance-Exposed Neonates (NOT-HD-09-011). NICHD is interested in research to improve the safety and efficacy of pharmacotherapeutics for pregnant/postpartum women with substance use disorders and/or in utero substance-exposed neonates. Appropriate studies include research to examine pharmacokinetics, metabolism, disposition, and pharmcodynamics of medications commonly used for the treatment of pregnant/postpartum women with substance use disorders and/or in utero substance-exposed neonates. Studies on the mechanisms of adverse drug reactions to these medications also are encouraged (http://grants.nih.gov/grants/guide/notice-files/NOT-HD-09-011.html).

Publications

NIH Research Plan on Fragile X Syndrome and Associated Disorders. This 95-page scientific plan outlines research goals and objectives on fragile X syndrome and related disorders for NIH Institutes, including NICHD, which support and conduct research related to fragile X syndrome and its associated disorders. The plan was developed by the NIH Fragile X Research Coordinating Group, which includes representatives from multiple NIH Institutes, Centers, and Offices and relevant scientific, family, and advocacy communities (http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5729).

ARRA Funds

Developing a National Standard for Normal Fetal Growth. In 2009, the National Standard of Normal Fetal Growth Study, a project of NICHD's Division of Epidemiology, Statistics, and Prevention Research, was selected as one of NIH's Signature Projects and thereby received supplemental funding under the ARRA of 2009. The division was

awarded ARRA funds in support of research on establishing a national standard for normal fetal growth. Normal fetal growth is critical to a healthy pregnancy and the long-term health of children. The proposed research will, for the first time, establish a U.S. national standard for fetal growth, which will include twins, and should have a profound impact on patient management and research for years to come.

Conferences and Workshops

Pregnancy and Contraception in Microbicide Development (March 9–10, 2009). Sponsored by several NICHD branches, the NIH OD, ORWH, and NIAID, this workshop tasked six study groups to address the issues of contraception and pregnancy on the outcome, or potential outcomes, in clinical trials. This meeting represented the first comparison of pregnancy rates across several large studies. The knowledge conveyed at this meeting and summarized in the proceedings document may assist others in planning HIV prevention-related clinical studies in women.

2009 Research Meeting of the Specialized Cooperative Centers Program in Reproduction and Infertility Research (SCCPIR) (May 11–12, 2009). Sponsored by the Reproductive Sciences Branch (RSB), Center for Population Research (CPR), NICHD, this meeting was designed to highlight significant advances in research, technology, resource development, and bioinformatics efforts supported by the SCCPIR program.

Pregnancy in Women With Physical Disabilities (January 25–26, 2010). Sponsored by OD, NICHD, this 2-day workshop was designed to review the current body of evidence on management of pregnancy in women with physical disabilities, to identify key gaps in knowledge, and to recommend priority avenues for future research.

Vulvodynia Preapplication Workshop (August 13, 2010). RSB, CPR, NICHD held a workshop to provide technical assistance to prospective applicants responding to three program announcements involving systematic epidemiologic, etiologic or therapeutic studies of vulvodynia. The workshop provided an overview of the research program, discussion of the grant mechanisms used, information on preparing an application, highlights of the review process, and opportunities to address participant questions.

NICHD Aspen Conference on Maternal-Fetal-Neonatal-Reproductive Medicine (August 25–28, 2010). Sponsored by OD, NICHD, the NICHD Aspen conference is an annual meeting held in collaboration with the University of Colorado to facilitate the interest and training of academic physician scientists. The meeting is open to fellows in neonatology, maternal fetal medicine, and reproductive endocrinology who are planning a career in academic medicine.

Workshop: Obesity and Oral Contraception: What Do We Know and Need To Know? (November 9–10, 2010). NICHD supported a workshop to bring together leaders from the United States and Europe to discuss and debate the compelling issues of the obesity epidemic and its implications for effective contraception. This workshop included presentations covering the current obesity epidemic, risks of pregnancy, endocrinology, oral contraceptive failure, obesity effects on the metabolism of oral contraceptive hormones, thromboembolic risks, combination and progestin-only hormonal contraceptives, and the difference between U.S. and European populations. Gaps in knowledge also were addressed, and the discussion helped create strategies to move forward.

Advances in Uterine Leiomyoma Research: Third NIH International Congress (November 22–23, 2010). This meeting was sponsored by RSB, CPR, Reproductive Biology and Medicine Branch, Division of Intramural Research (DIR), NICHD, along with several other Federal Agencies and NIH Institutes/Centers, including NIH's ORWH. Uterine leiomyomas (fibroids) are the most common gynecologic neoplasms in women of reproductive age. As the number one cause of hysterectomy, uterine leiomyomas (fibroids) have a profoundly negative impact on women's health. The goal of the conference was to bring together researchers working in the fields of medicine, epidemiology, basic research, and therapeutics to foster an exchange of scientific information among members of the uterine

leiomyoma research community. The congress addressed clinical management and therapeutic strategies, epidemiology, pathogenesis, environmental influences, model systems, hormonal regulation, and molecular and (epi) genetic characteristics of leiomyomas.

Health Disparities and Special Populations of Women

Recruitment Strategies to Increase Diversity in Clinical Trials (December 2, 2009). This meeting focused on Public Law 103-43, which details how women and minorities are included in phase III clinical trials. Scientists and community representatives discussed successful recruitment strategies used in NICHD intramural research.

Career Development/Training for Women in the Sciences

Women's Reproductive Health Research Career Development Program. NICHD and ORWH solicited applications to continue to support a national program of mentored institutional career development programs for junior faculty who have recently completed postgraduate clinical training in obstetrics and gynecology and are committed to an independent research career in women's reproductive health. The supervised research training will assist junior faculty in their transition into productive physician scientists in areas related to obstetrics and gynecology and its subspecialties (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-026.html).

National Institute on Deafness and Other Communication Disorders

Executive Summary

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. NIDCD also conducts and supports research and research training related to disease prevention and health promotion.

NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute also supports efforts to create devices that substitute for lost and impaired sensory and communication functions. A number of diseases, disorders, or conditions within the mission of NIDCD affect women disproportionately. Examples of significant research programs have been selected for inclusion in this report. Highlights of the latest research advances and plans for the future in these areas follow.

Accomplishments

Cytomegalovirus

Cytomegalovirus (CMV) is the leading cause of nonhereditary deafness. CMV also is recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. About 20,000 to 30,000 infants are born infected with CMV each year, 10 to 15 percent of whom are at risk for eventually developing hearing loss. NIDCD-sponsored scientists continue to make significant progress to fully characterize the effects of CMV on sensorineural hearing loss (SNHL) as well as the mechanisms and epidemiology of CMV maternal transmission. Recent results demonstrate a highly significant effect of CMV infection on the development of late onset SNHL.

NIDCD supports both basic and clinical studies to better understand the relationship between congenital CMV infection and hearing loss. NIDCD-supported investigators have developed a mouse model of congenital CMV infection and are pursuing fundamental questions concerning disease pathogenesis. Human studies are aimed at the characterization of maternal CMV status in an effort to determine the relationship between the type of maternal infection (recurrent or primary) and congenital CMV infection. This research is critical for determining the features in the natural history of maternal CMV infection and mother-to-child transmission that contribute to SNHL and late-onset SNHL. Such studies are essential

for the development of rational clinical approaches aimed at reducing CMV-induced congenital hearing loss.

In July 2005, NIDCD awarded a contract titled "The Natural History of CMV-Related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing Screening in the Newborn." The goals of the contract are to (1) correlate CMV status at birth with the presence of permanent or progressive SNHL, (2) acquire data on the incidence, time course, and audiologic outcomes of CMV-related hearing loss, and (3) determine the extent to which CMV screening can improve detection and prediction of either existing or progressive hearing loss if combined with the metrics already in use for newborn screening.

More than 80,000 newborns have been screened to date, and screening continues. CMV-positive newborns continue to be enrolled in the study and are being followed every 6 months until they are 4 years of age to determine onset of any hearing loss.

Taste Perception

Genetic and pathologic variations exist in taste quality perception and affect the intensity of bitter foods and the preference for sweet and fat foods, which are important mediators of proper nutrition, cardiovascular disease, and cancer. Oral phantoms (sensations in the absence of stimulation) and oral pain (burning mouth syndrome) often accompany pathologies associated with the taste cranial nerves. Burning mouth syndrome occurs predominantly in postmenopausal women. NIDCD-funded research is exploring the dysfunctional relationships between the taste system and oral (trigeminal) pain systems in women with burning mouth syndrome and will provide new insights into oral pain assessment and treatment.

Olfactory Loss in Multiple Sclerosis

Multiple sclerosis is the most common neurologic disability in the young adult and is characterized by a progressive demyelination of axons in the central nervous system. A greater proportion of women than men with multiple sclerosis show olfactory loss, and the loss is more profound in women. Olfactory loss has significant adverse dietary and nutritional consequences that affect overall health status. NIDCD-funded research will define the nature of the olfactory dysfunction present in multiple sclerosis in women and will determine the relationship between the degree of olfactory deficit, cognitive function, and pathologic alterations within specific central nervous system structures.

Assessment and Treatment of Voice Disorders

Voice disorders affect millions of Americans, influencing their quality of life and impairing their ability to communicate effectively and function in our society. A number of voice disorders appear to affect women more frequently than men. NIDCD currently supports a number of projects focused on normal and disordered voice processes. Of note are studies examining behavioral vocal hyperfunction, which is the result of a habitual pattern of voice use that may be traumatic to laryngeal tissue and function. A currently funded project is examining the vocal performance of teachers, a profession dominated by women.

Spasmodic dysphonia is a neurologic disorder (dystonia) affecting the voice muscles in the larynx. In spasmodic dysphonia, the muscles inside the vocal folds experience sudden involuntary movements—called spasms—that interfere with the ability of the folds to vibrate and produce voice. Spasmodic dysphonia causes voice breaks and can give the voice a tight, strained quality. People with spasmodic dysphonia may have occasional breaks in their voice that occur once every few sentences. Usually, however, the disorder is more severe and spasms may occur on every other word, making a person's speech very difficult for others to understand. At first, symptoms may be mild and occur only occasionally, but they may worsen and become more frequent over time. Spasmodic dysphonia is a chronic condition that continues throughout a person's life. It can affect anyone, although the vast majority of people affected are female, with estimates as high as 80 percent. This rare disorder occurs in roughly 1 to 4 per 100,000 people. The first signs of spasmodic dysphonia are found most often in people between 30 and 50 years of age. NIDCD has released two program

announcements (R01, R21) on spasmodic dysphonia and has received applications in response to these solicitations.

Stuttering

Stuttering is a speech disorder in which sounds, syllables, or words are repeated or prolonged, disrupting the flow of speech. These disruptions may be accompanied by struggling behaviors, such as rapid eye blinks or tremors of the lips. Stuttering can make it difficult to communicate with other people. Boys are twice as likely to stutter as girls. Although stuttering is not life-threatening, it is life-altering. A recent discovery by a team of NIDCD intramural researchers identified three different gene mutations responsible for stuttering in some adults. The genes control enzymes that help break down and recycle components in cells, and researchers believe that a group of cells in the brain that are dedicated to the fluency of speech are uniquely sensitive to the defect caused by these mutations.

NIDCD extramural researchers continue to study stuttering to increase the understanding of potential subtypes. The Institute recently awarded a grant whose objective is to identify structural and functional neural markers of stuttering close to the onset of symptoms and determine gender-specific developmental markers in the brain that serve to differentiate those children who do or do not recover from stuttering.

Initiatives

A number of funding opportunity announcements (FOAs) have been released in the areas of tinnitus, translational research, patient-oriented research, autism, and spasmodic dysphonia, among others.

National Institute of Dental and Craniofacial Research

Executive Summary

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to promote the general health of the American people by improving craniofacial, oral, and dental health through research. This work includes funding clinical and basic research to understand, prevent, and treat oral and craniofacial diseases that disproportionately or solely affect women. These diseases include orofacial pain, temporomandibular joint disorders (TMJD), osteoporosis of the craniofacial complex, salivary gland diseases, autoimmune diseases, and oral diseases of pregnant women.

NIDCR women's health clinical initiatives in FY 2009 and FY 2010 included large cohort studies designed to identify risk factors and to characterize diseases that affect women. One study is following a large group of young women to identify those who develop TMJD. Other researchers investigated the treatments for TMJD and the effect that treatment of periodontal disease during pregnancy has on the incidence of preterm birth and low birth weight. Studies of underserved populations helped define caregiver factors that make children more likely to develop dental decay (caries). Two groups supported by NIDCR continue to characterize individuals with Sjögren's syndrome, an autoimmune disease that disproportionately affects women and severely impacts oral health.

NIDCR also supports basic science studies examining the growth and development of teeth, cartilage, and bone. These studies have led to advances in biomaterials research and to the emerging field of tissue engineering and biomimetics, fields that study the use of the body's own cellular and molecular processes to repair and regenerate tissues and organs. This work includes indepth studies of the characteristics of the TMJ disk at the cellular level.

Recognizing the importance of gene-to-gene, gene-environment, and behavioral interactions, NIDCR has long emphasized

the importance of genetic, behavioral, social science, and epidemiological research. Researchers supported by NIDCR during FY 2009 and FY 2010 have continued to define genes associated with cleft lip and palate. Ongoing studies are designed to define susceptibility genes for TMJD and other genes associated with craniofacial diseases.

This report highlights accomplishments and initiatives in the areas of chronic pain and temporomandibular disorders, osteoporosis and basic bone biology, bisphosphonate-associated osteonecrosis of the jaw, oral health of pregnant women, oral health disparities, Sjögren's syndrome, human immunodeficiency virus (HIV) infection, and craniofacial anomalies related to the health of women.

Accomplishments

Pain Research

For many years, NIDCR has supported research that examines pain conditions, including those that primarily affect women. Findings from these studies continue to demonstrate that there are sex differences in responses to painful stimuli and that women are more likely to develop chronic pain conditions. Human and animal studies include research in the following areas:

Temporomandibular Joint and Muscle Disorders

The precise etiology of temporomandibular joint disorders (TMJD) is not known, but diverse mechanisms are likely to contribute to TMJD, including psychological stress and estrogen status. Previous studies have shown that persistent stress will enhance pain behaviors in male rats. A recent study in rodents showed that females with both high and low estrogen levels that were subjected to repeated psychological stress (forced swim) exhibited increased numbers of activated neurons in a brain stem region that receives sensory input from the TMJ. Interestingly, these increases were independent of the estrogen levels or a noxious treatment of the TMJ. This study also documented an increase in pain measures in the animals subjected to repeated psychological stress. The importance of this work lies in the discovery that, for female rodents, psychophysical stress alone, independent of estrogen status, was sufficient to activate a brain stem center important in integrating sensory input from the TMJ.

Another potential etiological mechanism of TMJD is heightened responsiveness to painful stimuli. An underlying controversy is whether this increased responsiveness is a peripheral phenomenon affecting just the TMJ area or part of a more widespread central nervous system hypersensitivity. A recent study showed that female myofascial TMJD patients have prolonged painful after-sensations when a repetitive, noxious thermal stimulus is applied to the skin overlying the muscle in the cheek that closes the jaws during chewing, but not when this stimulus is applied to the back of the hand. Interestingly, there were no differences among female TMJD patients and controls in their initial responses to repetitive noxious thermal stimuli to the face or hand. The significance of these studies lies in the discovery that the heightened sensitivity to noxious stimuli in myofascial TMJD patients is found only in the facial region, suggesting that the increased sensitization may not be widespread as in other comorbid pain conditions like fibromyalgia. This discovery has important implications for how chronic TMJD patients are treated. Pharmacological and other treatments focused locally might be more specific in action with fewer side effects. Experimental measures that aid in distinguishing TMJD patients with either central or localized hypersensitivity will be an important addition to a growing list of phenotypes useful for characterizing the heterogeneous nature of TMJD.

Examples of NIDCR basic and clinical research on TMJD include the following:

- NIDCR continues to fund a 7-year clinical study that will enhance our understanding of the biological and psychological risk factors for developing chronic TMJD and provide insights for its treatment. The study, named Orofacial Pain: Prospective Evaluation and Risk Assessment, or OPPERA, is the first large longitudinal prospective clinical study to identify risk factors for the onset and persistence of TMJD. Investigators are following 3,200 healthy volunteers for 3 to 5 years to see

how many develop the disorder. The multicenter research program involves investigative units at the University of Florida in Gainesville, University at Buffalo-SUNY, University of Maryland, Baltimore, and University of North Carolina Chapel Hill. The initial analysis and publication of baseline data from these subjects is in progress. Plans are underway to initiate a genome-wide association study of approximately 1,200 TMJD cases and appropriate controls in order to identify, in an unbiased way, new genetic risk factors for onset of TMJD.

- A study to test and improve the reliability and validity of the widely used Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) has been completed. This project has resulted in several publications that further validate the criteria used to diagnose individuals for clinical studies and clinical trials of TMJD. This work has led to the modification and validation of several components of RDC/TMD that may soon be used by practicing dentists to more reliably diagnose and treat these disorders.
- A recently completed randomized clinical trial assessed whether a brief cognitive-behavioral treatment (six to eight sessions) for TMJD-related pain could be efficacious in reducing pain, pain-related interference with lifestyle, and depressive symptoms. After a yearlong assessment of subjects, researchers concluded that brief cognitive-behavioral skills training can significantly reduce pain, lifestyle interference, and depressive symptoms in TMJD sufferers and that the addition of cognitive-behavioral coping skills will add to the efficacy of the treatment in selected patients.
- NIDCR is supporting a study to assess an instrument's ability to predict whether a patient with acute TMJD is likely to progress to chronic TMJD and to determine the best therapy for those most likely to develop chronic TMJD. TMJD patients at highest risk for developing chronic TMJD are randomly assigned to one of two possible treatments.
- The NIDCR-funded Dental Practice-Based Research Networks (PBRNs) conducted a trans-PBRN survey of dentists participating in the three networks. The aims of the survey were to estimate the number of PBRN dentists who provide TMJD pain treatments, to estimate the number of TMJD pain patients seen per month by these dentists, and to determine their preferred treatment options. It is anticipated that this and subsequent studies will lead to a better understanding of how TMJD is treated by practicing dentists and which treatments are most successful.
- NIDCR also is conducting research into identifying new treatments for pain. NIDCR intramural scientists and their NIH colleagues report that they have discovered an enhancer for the vanilloid receptor 1, or TRPV-1. TRPV-1 resides on the plasma membrane of certain neurons, where various chemical stimuli can activate it to open a specific ion channel and ultimately transmit the unpleasant sensations of heat and pain to the brain. The newly discovered enhancers are novel chemical derivatives of existing calcium channel blockers called 1,4-dihydropyridines, or DHP. In their studies, the researchers found that DHP derivatives greatly increased the maximum flow of ions stimulated by capsaicin, the neuroactive component of chili peppers. Interestingly, the derivatives had minimal or no agonistic or inhibitory activity of their own. These enhancers open up the much needed therapeutic possibility of selectively regulating TRPV-1 receptors in the nerve endings of skin and deep tissue and thus one day better controlling certain types of chronic pain.

Reconstruction of the TMJ

Ongoing studies are characterizing the TMJ disk at cellular and tissue levels. This knowledge could be used to engineer in vitro TMJ disc prototypes that approximate native disc structure and function for use in future clinical trials testing treatments of individuals with advanced TMJ destruction. Other studies are developing stem cell-based approaches for regeneration of the TMJ and creating optimal biomaterials, scaffolds, and bioreactors to use for TMJ bone tissue engineering and regeneration. Research in the area includes the following studies:

- Detailed studies are underway to investigate the influences of mechanical properties of the engineered scaffold on bone regeneration. The central hypothesis to be tested is that the scaffolds with the highest interconnected porosity and minimum elastic modulus will promote the greatest degree of bone regeneration. To test this hypothesis, the investigators are designing and fabricating scaffolds of the same elastic modulus but different porosity, as well as scaffolds with the same porosity but different moduli. The newly generated scaffolds are then tested in a functional minipig mandibular model. This work will help to derive tissue engineering-based bone regeneration strategies for treatment of severe TMJD with advanced disc and condylar destruction.
- The biochemical content, mechanical properties, and ultrastructural tissue organization of the porcine TMJ disc is being investigated with the goal of determining TMJ disc-specific structure/function relationships. These findings will be used to develop rational tissue engineering-based approaches for treatment of human TMJD. The investigators have already obtained sufficient information to begin optimizing their tissue-engineered constructs.
- Advanced tissue engineering bioreactors with are being developed to derive functional composite tissue-engineered bone and cartilage TMJ constructs that approximate the size and anatomy of human TMJ. The bioreactors that support cultivation of osteochondral constructs have a two-compartment design. One compartment contains chondrogenic medium and provides cartilage-enhancing mechanical loading, while another compartment is designed to optimize bone regeneration. The investigators expect that their advanced bioreactors will generate constructs for testing tissue engineering-based strategies for treatment of TMJD. Other investigators are engineering seamless constructs of bone and cartilage using a novel cell source, human umbilical cord matrix (HUCM) stem cells, in combination with a number of new technologies that should lead to constructs with superior cartilage and bony regions, and continuous transition between the cartilage and the bone that mimics the structure of native TMJ. This work may generate new paradigms for manufacturing of complex multitissue constructs for a variety of tissue engineering applications.
- Work is currently underway to investigate the mechanisms of estrogen- and estrogen receptor-mediated regulation of growth and differentiation of cartilage in the jaw, with a particular emphasis on the role of estrogen on the regulation of cartilage growth induced by mechanical loading. It is envisioned that this work will aid in the understanding of how estrogen and mechanical loading interact to influence development of TMJD.
- TMJ osteoarthritis is a degenerative disease marked by permanent cartilage destruction and loss of extracellular matrix (ECM). NIDCR intramural scientists used a genetic mouse model of TMJ osteoarthritis that is deficient in two ECM proteins, biglycan and fibromodulin, and discovered that TMJ osteoarthritis arises from abnormal and accelerated chondrogenesis, the process by which cartilage is formed. Transforming growth factor beta 1 (TGF-β1), a growth factor critical for chondrogenesis, binds to both biglycan and fibromodulin. The studies revealed that sequestration of TGF-β1 was decreased within the ECM of cells derived from this mouse model system, leading to overactive TGF-β1 signal transduction. In addition, overactive TGF-β1 signals could induce chondrogenesis and ECM turnover. This study demonstrated for the first time the importance of ECM in maintaining cartilage integrity in the jaw and identified biglycan and fibromodulin as novel key players in regulating chondrogenesis and ECM turnover during TMJ osteoarthritis.

Several investigators have studied basic biological processes involved in the development and maintenance of bone, cartilage, and/or teeth. These studies have implications beyond TMJD, including bone conditions such as osteoporosis, which researchers estimate affects as many as one of five American women older than age 50. Research in the area includes the following studies:

- The TGF-β family comprises pleiotropic growth factors that regulate a wide array of cellular processes, including those associated with bone development, differentiation, homeostasis, and apoptosis. NIDCR-supported investigators applied a small molecule-based approach to perturb the TGF-β signaling network in mice before measuring bone function. The small molecule is a compound called SD-208, which is a TGF-β receptor kinase inhibitor that functions by blocking ATP binding to the receptor kinase. Four-week old mice were treated daily for 6 weeks with one of two doses of SD-208. The investigators reported that bone mineral density and bone volume were increased in treated animals. SD-208 promoted differentiation of osteoblasts (bone-forming cells) and inhibited differentiation of osteoclasts (cells associated with resorption and removal of bone). In addition, long bones displayed an increase in bone matrix mineral, coupled with enhanced material properties and resistance to fractures. Taken together, these data suggest that manipulation of TGF-β signaling has significant effects on the adult skeleton at the cellular, matrix, and tissue levels.
- Bone growth, development, and homeostasis are orchestrated by a complex repertoire of molecular switches, and deregulation of any of the components may lead to debilitating bone disorders. Two ongoing projects are studying candidate genes and cellular pathways that are critical for the maintenance of bone cells (osteoblasts). Funds from the American Recovery and Reinvestment Act of 2009–2010 allow these projects to establish new collaborations and to extend their studies into a comprehensive genomewide approach to identify and characterize additional modes of DNA modification and protein binding to these uniquely regulated sites. These projects are generating large and rich datasets for further mining.
- Bone homeostasis is a tightly controlled biological program coupling bone formation and bone resorption. Each step of this program is regulated by a series of activators and inhibitors. MicroRNAs (miRNA; miR) are small noncoding RNAs that broadly regulate protein expression, and studies to date have demonstrated their involvement in every biological process being examined. In a previously conducted screening study, approximately 60 miRNAs involved in bone formation were identified. A study is being conducted to establish the functional significance of a specific cluster of miRNAs, called the miR-23a~27a~24-2 cluster. This study showcases the importance and value of functional studies that follow on evidence generated from high-throughput screening assays. We continue to enhance our understanding of bone homeostasis through assembling new molecular pathways and networks.
- The search for biologic proteins that can increase bone mass has begun to focus on Wnt-induced secreted protein 1 (WISP-1). Expression of WISP-1 has been observed in the developing skeleton and later in both preosteoblastic and osteoblastic cells, specifically at sites of new bone formation during development or in healing fracture calluses. To determine the function of WISP-1 during bone formation, NIDCR intramural scientists used osteogenic bone marrow stromal cells (BMSCs) and found that WISP-1 overexpression enhanced the ability of bone morphogenic protein 2 (BMP-2) to direct BMSCs toward osteogenic differentiation. Other experiments confirmed a functional interaction between WISP-1 and BMP-2. These studies show, for the first time, that WISP-1 has a positive influence on bone cell differentiation and function and may work by enhancing the effects of BMP-2 to increase osteogenesis through a mechanism potentially involving binding to integrin α(5)β(1).
- Matrix vesicles (MVs) are commonly found in cartilage, bone, and dentin at sites of mineral crystallization initiation. MVs are thought to facilitate tissue mineralization by altering the dynamic composition of the extracellular milieu and by controlling interactions between the mineral crystals and extracellular matrix proteins at the site of crystallization. Investigators working with an MV biomimetic proteoliposome system hope to advance our mechanistic understanding of the multistep process

of hard tissue mineralization, which will lead to generation of targeted strategies for bone and tooth regeneration for a variety of medical and dental applications.

- Other studies are examining the potential of muscle-derived stem cells (MDSCs) to improve bone healing. In particular, the researchers are analyzing the effect of the sex and age of donor mice on the number and osteogenic potential of MDSCs and are determining whether the size or source of muscle biopsy, time of culturing, hormonal stimulation, or ex vivo cyclic mechanical strain affects the number of MDSCs and their osteogenic potential. The results generated from these experiments are used for optimizing bone formation and healing for tissue engineering-based applications of MDCS.

Diseases that affect mineralized tissues of the craniofacial complex include periodontal disease, osteoporosis, and bisphosphonate-associated osteonecrosis. Advances in this area include clinical studies defining risk factors for osteonecrosis of the jaw.

Bisphosphonates are drugs that inhibit the activities and functions of osteoclasts (bone-resorbing cells) and perturb the differentiation of osteoblasts (bone-forming cells). Intravenous bisphosphonates are used primarily to treat bone erosion and hypercalcemia associated with bone metastasis, Paget's disease, and multiple myeloma. Oral bisphosphonates are used to prevent bone loss and are prescribed for patients with osteoporosis or osteopenia. In 2003, reports appeared in the literature that suggested use of bisphosphonates could lead to development of nonhealing, exposed necrotic bone in the maxillofacial (upper jaw) region. The clinical condition was named osteonecrosis of the jaw (ONJ). Most cases of ONJ are related to intravenous bisphosphonate use in cancer patients, but several cases are associated with oral bisphosphonates. Patients with ONJ present with painful, exposed, and necrotic bone, which may develop after invasive dental procedures or spontaneously. These lesions are nonhealing or slow to heal and can be complicated by secondary infection. For the past several years, NIDCR has funded the following studies examining the etiology and epidemiology of the problem:

- Although patients on high-dose bisphosphonate and immunosuppressive therapy have an increased risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ), its pathophysiology remains unknown, and appropriate therapy is not established. Investigators have developed a mouse model of BRONJ-like disease that recapitulates major clinical and radiographic manifestations of the human disease. Administration of zoledronate, a potent aminobisphosphonate, and dexamethasone, an immunosuppressant drug, causes BRONJ-like disease in mice in part by suppressing the adaptive regulatory T cells, Tregs, and activating the inflammatory T-helper-producing interleukin 17 cells, Th17. In their mouse model, investigators demonstrated that systemic infusion with mesenchymal stem cells (MSCs) prevents and cures BRONJ-like disease, possibly via induction of peripheral tolerance, shown as an inhibition of Th17 and increase in Tregs. The suppressed Tregs/Th17 ratio in zoledronate- and dexamethasone-treated mice is restored in mice undergoing salvage therapy with Tregs. These findings provide evidence of an immunity-based mechanism of BRONJ-like disease and support the rationale for in vivo immunomodulatory therapy using Tregs or MSCs to treat BRONJ.
- The three NIDCR-funded Dental Practice-Based Research Networks completed a study to define risk factors for ONJ in patients (primarily women) treated with bisphosphonates. This trans-PBRN study was a retrospective case-control study that gathered data from practicing dentists in the three networks over a period of several years. Published data suggest that the risk of developing ONJ is low but may be associated with particular dental procedures and aggravated by other systemic medical conditions. Specifically, the data suggest that patients who present with certain infections of the jaw or the need for tooth extraction may be at higher risk for developing ONJ, particularly if they have been on bisphosphonates for a longer period of time or if

they have been administered more potent formulations of these drugs.

- Through our solicitation for research on BRONJ, a number of projects have been added to our program portfolio. These projects include investigations into whether periodontal disease is a risk factor for ONJ, epidemiological assessment of ONJ in osteoporotic/osteopenic patients using bisphosphonates, elucidation of the pathophysiological mechanisms of ONJ presentation, and production of animal models for ONJ studies. Findings from these studies will broaden our knowledge base on this morbid oral condition and provide a basis for the design of prevention and treatment strategies.

Research in Oral Health Disparities

NIDCR's strategic plan includes as a goal the elimination of disparities in oral health. Vulnerable populations include women of racial and ethnic minority backgrounds, the poor, and those with developmental or acquired disabilities. Research in the area of oral health disparities includes the following:

- According to the 2000 U.S. Surgeon General's report on oral health, dental caries is the most common chronic childhood disease. In addition, most (75 to 80 percent) of the caries in children in this country occurs in a small segment of the population (20 to 25 percent), and this problem is particularly prevalent in minorities, immigrants, and low-income children. Recent NIDCR-supported studies have established that primary caregiver (PCG) beliefs, perceptions, and behaviors are risk factors for the development of caries in toddlers. In these studies, most of the PCGs were female. Factors associated with increased caries risk were types of snacks given to children, types of snacks consumed by PCGs, PCG fear of dentists, and PCG perceptions about tooth decay (e.g., the belief that bad teeth are inherited from parents or that most children eventually develop tooth decay). Preliminary data suggest that the risk factors are different in Hispanic, African-American, and Caucasian non-Hispanic populations. Other investigators found that lower PCG literacy is associated with worse oral health of families.
- Given the complex relationship of maternal behaviors and maternal oral health with children's oral health, three ongoing interventional studies supported by NIDCR are testing behavioral interventions directed at pregnant women or mothers of very young children to determine whether the interventions will reduce dental decay in study participants' children. Another study is testing an intervention to reduce untreated dental decay in pregnant women who are eligible for Medicaid.
- A large study of community-dwelling older U.S. adults living in two rural counties of North Carolina with large African-American and American Indian populations examined the impact of severe tooth loss on dietary quality. Those with 0 to 10 teeth were less likely to eat recommended amounts of total vegetables or dark green and orange vegetables and consumed more calories from solid fat, alcohol, and added sugar. Lack of dental insurance leading to tooth loss was identified by older low-income women as a barrier to increased fruit and vegetable consumption.

Oral Health of Pregnant Women

Previous studies suggested that the infectious organisms causing periodontal disease and the inflammation associated with untreated periodontitis could have serious deleterious effects during pregnancy. Therefore, NIDCR sponsored two large randomized trials to determine whether nonsurgical treatment of periodontal disease during pregnancy reduced the incidence of preterm birth (PTB) or low birth weight (LBW). Both the Obstetrics and Periodontal Therapy (OPT) trial and the Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) trial were designed to determine whether pregnant women having nonsurgical periodontal therapy during the second trimester of pregnancy had fewer preterm infants as compared with women having periodontal therapy delayed until after delivery. Results from both studies found that periodontal treatment during the second trimester did not reduce the incidence of PTB or

LBW. Both of these trials were included in a recent meta-analysis of five high-quality studies that concluded treatment of periodontal disease during pregnancy does not reduce PTB or LBW.

A cross-sectional study examined general dentists' attitudes about provision of dental care for pregnant patients. There was nearly universal agreement among the respondents that dental treatment should be part of prenatal care, and most respondents reported having favorable attitudes toward pregnancy-specific counseling. One-third of respondents reported receiving continuing dental education (CDE), and two-thirds reported an interest in receiving CDE about a pregnancy-related topic. Comparisons of self-reported knowledge and practice guidelines, including use of pharmaceuticals, demonstrated the need for continual CDE in this area.

Salivary Hypofunction (Dry Mouth)

The exocrine salivary glands produce saliva, a complex fluid that is central to maintenance of oral health. If insufficient quantities of saliva are made, severe impairments in oral health can develop. These impairments include sometimes dramatic increases in dental caries; difficulty in swallowing, chewing, and speaking; loss of enjoyment of food; mucosal infection with *Candida* species; and reduced quality of life. Many diseases and conditions can induce salivary gland hypofunction. Sjögren's syndrome (SS) and rheumatoid arthritis, which are autoimmune diseases with high prevalence in women, often have associated salivary dysfunction that is thought to be caused by a plasmolymphocytic infiltration of the salivary glands.

Intramural scientists continue to examine the physiology, growth, and development of salivary glands. These investigations help identify pathways that could be targeted by therapeutic medications or define how salivary glands could be reengineered to regain their function:

- A recent intramural study investigated TGF-β signaling, which is known to affect salivary gland physiology by influencing branching morphogenesis, regulating extracellular matrix deposition, and controlling immune homeostasis. To study the role of TGF-β1 in the salivary gland, the scientists created a transgenic mouse that conditionally overexpresses active TGF-β1, and clear defects in salivary gland morphogenesis, such as reduced branching and increased mesenchyme, could be seen. Those mice that survived into adulthood had abnormally reduced salivation. In particular, aberrant TGF-β1 overexpression caused salivary gland hypofunction in this mouse model because of the replacement of normal glandular parenchyma with interstitial fibrous tissue. These results further implicate TGF-β in pathological cases of salivary gland inflammation and fibrosis that occur with chronic infections in the glands, with SS, or with radiation therapy given to head-and-neck cancer patients.
- One potential way to regenerate the salivary glands is to isolate progenitor cells from a salivary gland biopsy before radiation, expand them in culture, and inject them back into the gland to regenerate functional tissue. Identifying which progenitor cells to use from the biopsy and determining which factors stimulate them to regenerate functioning salivary tissue are important steps in developing a strategy for organ regeneration. NIDCR intramural scientists have identified a progenitor cell type in the salivary glands of mice that is controlled by neurotransmitters produced by nerves as the gland develops. These findings identify how progenitor cells in the developing gland are maintained and show that these cells are present in the adult gland. These discoveries will be important for isolating and expanding progenitor cells from adult tissue to repair gland damage after radiation treatment.

The NIDCR Intramural Research Program launched a new public database, the Salivary Gland Molecular Anatomy Project (SGMAP), at http://sgmap.nidcr.nih.gov. This gene expression database for mouse salivary gland development provides profiles of mRNA expression for a wide range of embryonic developmental stages as well as for specific tissue sites within developing salivary glands. The database can be searched readily by gene name, gene description, or gene ontology term, and sets of genes can be identified that

share a common temporal and/or spatial expression pattern.

Autoimmune Diseases and Sjögren's Syndrome

Autoimmune disorders disproportionately affect women and cause an unintended destruction of the body's own tissues. Sjögren's syndrome, an autoimmune disease characterized by reduced secretions from salivary and lacrimal glands, is the second most common autoimmune disease in the United States. SS affects an estimated 1 to 4 million people, 90 percent of whom are women. Typically, patients with SS have increased numbers of lymphocytes and other immune cells residing in their salivary and lacrimal glands, a process thought to reduce ultimate saliva and tear production. The most serious complication of SS is the greatly increased risk for developing malignant lymphoma, which is estimated to occur 40 times more frequently in these patients. Research in this area includes the following studies:

- NIDCR continues to support the International Sjögren's Syndrome Registry Network for SS patients with the purpose of (1) examining the sensitivity and specificity of current diagnostic criteria for the diagnosis of SS; (2) collecting, processing, storing, shipping, and analyzing clinical and biological specimens from patients and families with SS; and (3) disseminating to researchers clinical information and biological specimens from SS patients and their families. More than 600 subjects have been enrolled, many of whom will be reexamined after 2 years to determine how quickly the disease progresses. In addition, specimens of tissues, blood, saliva, and tears are collected for future studies, including studies examining the genetics of primary SS.
- Because SS is a complex disease that presents symptoms shared by other diseases, it can go undiagnosed for several months or even years. A recent study collected saliva samples from patients with primary SS, patients with systemic lupus erythematosus (SLE, an autoimmune disease affecting many parts of the body), and healthy individuals. Three proteins and three mRNA biomarkers were differentially expressed in primary SS patients as compared with SLE patients and healthy individuals. The ability to use these biomarkers to discriminate primary SS from SLE individuals holds great promise for earlier detection and interventions to slow down primary SS disease progression. Future efforts will focus on measuring absolute levels of these protein biomarkers for diagnostic screening and miniaturizing this process on a microfluidic-based point-of-care device for fast and sensitive measurement of these primary SS biomarkers in saliva.
- In another effort to advance diagnostic technologies related to SS, NIDCR intramural researchers are developing a luciferase immunoprecipitation system (LIPS) for detection of major autoantibodies found in SS. This system detected levels of two different antibodies in both serum and saliva of SS patients and healthy controls with high specificity and sensitivity. Although additional research must be done to understand the autoantibody profile of SS patients, LIPS technology supports the promise of saliva as a diagnostic fluid for individuals with an impaired rate of salivary flow.

Animal Models in Studies of Autoimmune Diseases

Cytokines are a type of signaling molecule important in the generation of an immune response; patients who suffer from the autoimmune disease Sjögren's syndrome have elevated cytokine levels in their salivary glands. A number of projects are leveraging a mouse model of SS to investigate the role various cytokines play in the progression of this disease and to assess the various cytokine's potential as a therapeutic target:

- Interleukin-17 (IL-17) is a proinflammatory cytokine that mediates the body's response to the invasion of the immune system by extracellular pathogens. IL-17 also is thought to play a key role in inflammation and tissue injury in a number of autoimmune diseases, including SS, multiple sclerosis, psoriasis, autoimmune uveitis, juvenile diabetes, rheumatoid arthritis, and Crohn's disease. Thus, IL-17 has emerged

as an ideal therapeutic target for autoimmune disease. A recent study utilized a mouse model of SS to investigate the role of this cytokine during development and progression of Sjögren's. In a recent study, researchers sought to examine the effect(s) of inhibiting IL-17 on SS development. The study results strongly suggest that IL-17 is an important inflammatory cytokine in salivary gland dysfunction. Specifically, scientists found that inhibiting IL-17 at early disease stage can prevent the onset of SS development and that inhibiting IL-17 at a later disease stage could rescue salivary gland function and recover saliva secretion. Thus, a therapeutic approach targeting IL-17 may be effective in preventing glandular dysfunction.

- Mammalian salivary glands contain a variety of specialized cell types, and the polarization of the acinar cells allows for unidirectional saliva secretion. This polarized structure is maintained by a band of tight junctions that seal adjacent acinar cells in a narrow belt just beneath their apical surface. A three-dimensional parotid gland cell culture model (Par-C10) has been developed recently to study physiological and pathological salivary gland function. Researchers have used this cell model to investigate the role of the elevated levels of cytokines observed in the salivary glands of SS patients; these cytokines are suspected of altering the integrity of salivary gland cell tight junctions. Par-C10 cells assemble into acinar-like spheres, with tight junction proteins appropriately located at the surface of the apical membrane. However, when these cells are given a 48-hour treatment of certain cytokines, these tight junction proteins redistribute throughout the apical membrane and disorganize the acinar-like spheres, implying that elevation of these cytokines decreases saliva secretion by altering the integrity of tight junctions between acinar cells. The results of this study point to the usefulness of this three-dimensional cell culture model for examining salivary gland function and structure, including ion and fluid secretion. These results also have tissue engineering applications for building three-dimensional biopolymer scaffolds.
- The pathogenic mechanisms of SS remain largely unknown, in part a consequence of the heterogeneity of the disease. Improved animal models for this disease will enable a better understanding of SS, including potential therapeutic interventions and knowledge of how immune tolerance is lost. Interleukin-12 (IL-12) is a cytokine that is elevated in the affected organs of Sjögren's patients. A study was conducted to evaluate salivary gland function in mice overexpressing IL-12. When stimulated by medication, salivary flow was significantly lower in IL-12-transgenic mice than in wild-type controls. Furthermore, a number of additional conditions associated with SS are exhibited by IL-12-transgenic SJL mice, suggesting that this model might be useful in researching multiple aspects of the disease.
- Because B-cell lymphocytes are derived from bone marrow and develop into plasma cells that are the source of antibodies, they bear major responsibility for carrying out the activities of the immune system. B-cell depletion therapy has been examined as a potential treatment for autoimmune disorders, where lowering B-cell levels may subsequently decrease the body's autoreactive response. The cytokine BAFF (B cell activating factor belonging to the tumor necrosis factor family) promotes B-cell survival, and its overexpression is linked to high B-cell levels and autoantibody formation reported both in mouse models and in SS and SLE patients. Researchers manipulated BAFF levels in transgenic mice by expressing either BAFF or its natural inhibitor, DBAFF. Inhibition of BAFF slightly lowered B-cell autoreactivity. BAFF overexpression led to broad tolerance escape and promoted autoantibody formation. These results have implications for BAFF-depleting therapy, where modulation of BAFF levels can alter B-cell levels and the subsequent autoimmune response.
- Other autoimmune diseases significantly affect oral health. Persons with systemic sclerosis may have severe destruction of the mandibular condyles that form part of the TMJ. One study funded by NIDCR is examining the oral health of this population.

Human Immunodeficiency Virus

The study of the oral manifestations of HIV infection has been of great interest to NIDCR because oral changes in HIV-infected individuals are frequent and varied and are among the first symptoms of infection. The impact of HIV/AIDS on women has grown substantially since the beginning of the epidemic.

One component of the AIDS Clinical Trials Group (ACTG), the largest HIV clinical trials organization in the world, is the Oral HIV/AIDS Research Alliance (OHARA). Its main objective is to investigate oral complications associated with HIV/AIDS, in particular, the effects of antiretrovirals on oral mucosal lesion development and associated fungal and viral pathogens. Observational studies and clinical trials are being implemented at ACTG-affiliated sites in the United States and in resource-poor countries. These studies also will determine differences in the oral manifestations and therapeutic outcomes of infected men and women. Many studies have shared endpoints, which include oral diseases known to be associated with HIV/AIDS. Recently updated definitions for HIV-related oral diseases will be used to measure standardized clinical endpoints in OHARA studies. Implementation of these new endpoints will allow researchers to determine which HIV medications have the most significant impact on the oral sequelae of HIV.

Craniofacial Anomalies

Clefts of the lip and palate are common human birth defects of multifactorial etiology. NIDCR supports genetic and clinical studies to define the genetic pathways resulting in cleft lip/palate and to find treatments to prevent oral clefting.

About 1 in 600 babies in the United States is born with isolated cleft lip and/or palate (roof of the mouth). Though the condition usually is correctable with several surgeries, families undergo tremendous emotional and economic hardship during the process, and children often require many other services, including complex dental care and speech therapy. Recent research reported in *Nature Genetics* by NIDCR-supported scientists found that common genetic variations close to the transcription factor *MAFB* gene and the ATP-binding cassette *ABCA4* gene were associated with cleft lip with or without cleft palate. Their work also confirmed associations between cleft lip with or without cleft palate and common variations in the *IRF6* (interferon regulatory factor 6) gene, and in a segment of chromosome 8 that does not contain any known genes. These discoveries could lead to DNA tests to help couples better gauge their risk of having a child with isolated cleft lip with or without cleft palate. Gene variation discoveries also provide valuable clues to the complex developmental puzzle of cleft lip with or without cleft palate.

Initiatives

Funding Opportunity Announcements

Advancing Novel Science in Women's Health Research (ANSWHR). The purpose of this funding opportunity announcement (FOA), issued by the Office of Research on Women's Health (ORWH) and cosponsoring National Institutes of Health (NIH) Institutes and Centers (ICs), is to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences. Recent research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. ORWH is particularly interested in encouraging extramural investigators to undertake new interdisciplinary research to advance studies on how sex and gender factors affect women's health; however, applications in all areas of women's health and/or sex/gender research are invited (PAS-10-226).

Mechanisms, Models, Measurement, and Management in Pain Research. The purpose of this FOA, issued by the National Institute of Nursing Research (NINR) in conjunction with members of the NIH Pain Consortium, is to inform the scientific community of the pain research interests of the various ICs at NIH and to stimulate and foster a wide range of basic, clinical, and translational studies on pain as they relate to the missions of these ICs (R01, PA-10-006; R21, PA-10-007; R03, PA-10-008).

Pathophysiology and Clinical Studies of Osteonecrosis of the Jaw. The purpose of this FOA is to stimulate research regarding bisphosphonate-associated osteonecrosis of the jaw. This research initiative hopes to address gaps in our understanding of how bisphosphonates may interfere with oral mucosal healing and bone repair at the genetic, molecular, cellular, and tissue levels (R01, PAR-11-082; R21, PAR-11-083).

Trans-NIH Blueprint for Neuroscience Grand Challenge on Pain. Division of Extramural Research staff continue to head the Trans-NIH Blueprint for Neuroscience Grand Challenge on Pain initiative. Twenty-six applications were received in response to an FOA issued in May 2010 (RFA-DE-11-002). The FOA encouraged multiple principal investigator grant applications from pain and nonpain neuroscientists to explore mechanisms underlying the transition from acute to chronic neuropathic pain (R01, RFA-DE-11-002).

Social Network Analysis and Health. This FOA encourages research that aims to accomplish one or more specific goals: (1) generate new theories that would enhance the capabilities and value of social network analysis (SNA); (2) address fundamental questions about social interactions and processes in social networks; (3) address fundamental questions about social networks in relation to health and health-related behaviors; and (4) develop innovative methodologies and technologies to facilitate, improve, and expand the capabilities of SNA (R01, PAR-10-145; R21, PAR-10-146).

Behavioral and Social Science Research on Understanding and Reducing Health Disparities. This FOA encourages behavioral and social science research on the causes of and solutions to health and disabilities disparities in the U.S. population (R01, PAR-10-136; R21, PAR-10-137).

NIDCR Small Research Grants for Data Analysis and Statistical Methodology Applied to Genomewide Data. NIDCR and other ICs support genomewide association studies relevant to human dental or craniofacial conditions or traits (R03, PAR-10-041).

Conferences, Symposia, Workshops, Consortia, and Working Groups

2009 Gordon Research Conference on Salivary Glands and Exocrine Secretion, February 8–13, 2009. The conference brought together investigators to present and discuss the most recent progress in understanding the molecular basis of the development, function, and dysfunction of salivary and related exocrine glands. The general theme of this conference was the normal and disease states of glandular tissues.

NIDCR Seminar Series. In 2010, three of the NIDCR seminar series speakers highlighted research related to women's health. Their presentations were titled "Biomaterials and Biotechnology: From the Discovery of Angiogenesis to the Development of Drug Delivery Systems and the Foundation of Tissue Engineering," "Developmental Biology and Prevention and Treatment of Craniofacial Malformations," and "Reparative and Regenerative Medicine: A Surgeon's Perspective."

National Institutes of Health 4th Annual Research Symposium for Advances in Pain Research, May 22, 2009. The symposium highlighted advances in NIH-supported pain research focusing on genetics and pain. Topics included human genetic risk factors for chronic pain, genes relevant to treatment response and abuse potential, and genetic tools and models for pain research. The meeting promoted collaborations and also provided a forum for researchers to present their work in poster sessions.

Genetics of Temporomandibular Joint Disorder and Comorbid Chronic Pain Conditions, June 10–11, 2009, Bethesda, MD. The meeting was designed to gather input from the pain and genetic communities about the best approaches and needs of researchers to advance this field. In addition to providing a forum for addressing the etiology and phenotypes of pain, it examined how to use previous successes with genetics and genomewide association studies as a tool in the study of the

susceptibility, development, and persistence of chronic pain conditions.

International Consensus Workshop: Convergence on an Orofacial Pain Taxonomy IADR, March 30–April 1, 2009, Miami, FL. The goals of the workshop attended by two NIDCR program officials were to create clinical diagnostic criteria for temporomandibular disorders (CDC/TMD), based on revisions of the RDC/TMD, for immediate clinical implementation and to create an initial draft of RDC for selected other orofacial pain conditions (RDC/OFP) where existing data are sufficient to identify draft criteria.

National Institute of Diabetes and Digestive and Kidney Diseases

Executive Summary

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within NIDDK's research mission, diseases and health risks that disproportionately, predominantly, or solely affect women include gestational diabetes mellitus (GDM); obesity (especially in racial and ethnic minority populations); coronary artery disease; cardiovascular and end-stage renal disease associated with diabetes; eating disorders; irritable bowel syndrome (IBS) and other functional gastrointestinal disorders; osteoporosis; thyroid diseases (including Graves disease, goiter, and hypothyroidism); hyperparathyroidism; gallstones; primary biliary cirrhosis; interstitial cystitis/painful bladder syndrome (IC/PBS); urinary tract infections (UTIs); urinary incontinence; and lupus nephritis (the kidney disease of systemic lupus erythrematosus). Areas of the NIDDK mission also may have an important impact on diseases that are primarily within the mission of other Institutes and Centers, such as the importance of hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease. NIDDK supports research that directly addresses the important women's health questions regarding the diseases and conditions cited above, both through basic research directed to understanding underlying disease processes and through clinical research that translates this understanding into therapies and preventive interventions. In fiscal years 2009 and 2010, the Institute has made progress in the following areas important to women's health, which are highlighted in this report: prevention and treatment of diabetes and its complications; osteoporosis; estrogen and breast cancer; irritable bowel syndrome and other functional gastrointestinal disorders; liver disease research; obesity and nutrition; kidney disease; IC/PBS; UTIs; and urinary incontinence. Funds from the American Recovery and Reinvestment Act have helped to stimulate new and ongoing women's health-related efforts in these fiscal years. The Office of Research on Women's Health has also worked with NIDDK to foster research in many of these areas.

Accomplishments

Diabetes

An estimated 25.8 million Americans, including at least 12.6 million adult women, have diabetes, a group of diseases marked by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Diabetes is the leading cause of vision loss in working-age adults, kidney failure, and nontraumatic lower extremity amputations. It also increases the risk of stroke, heart attack, and premature death. Women in particular are at a much greater risk of heart disease and stroke due to diabetes, and certain populations of minority women are affected disproportionately by end-stage renal disease as a result of diabetes. Ninety to ninety-five percent of diabetes cases are type 2 diabetes. Women who are obese, women who have had gestational diabetes mellitus (GDM), older women, and women who are members of racial/ethnic minorities in the United States are at significantly increased risk of developing type 2 diabetes. NIDDK supports many basic and clinical research programs for extramural and intramural scientists aimed at increasing knowledge and understanding of the genetics, basic biology, and metabolic defects of

diabetes, while simultaneously developing and testing strategies to effectively prevent, treat, and manage diabetes and its complications, especially in populations at risk. Guiding research planning is *Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee*, published in early 2011. The new strategic plan, which was spearheaded by NIDDK and developed with broad external input, is serving as a guidepost to the National Institutes of Health (NIH), other Federal Agencies, and the investigative and lay communities in their pursuit of the goal of conquering diabetes. NIDDK, together with the Centers for Disease Control and Prevention (CDC), also supports the National Diabetes Education Program (NDEP). NDEP works in partnership with public and private groups on efforts to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and, ultimately, to prevent the onset of diabetes. The following highlights of NIDDK-supported diabetes research are particularly relevant to women's health.

Type 2 Diabetes—Susceptibility and Sex Differences

Understanding the biologic basis for susceptibility to type 2 diabetes includes understanding differences in risk factors and disease development in women and men. For example, insulin resistance is a sign of increased risk of type 2 diabetes, and accumulating evidence is defining the role of estrogen in modulating insulin resistance at various stages in the life cycle. NIDDK-supported research studies are examining the role of estrogen and other sex steroids in metabolic dysfunction and diabetes. For example, a recent study capitalized on two large cohort studies (the Women's Health Study [WHS] and the Physicians' Health Study II [PHS II]) to examine levels of sex-hormone binding globulin (SHBG)—once thought only to transport sex hormones through the bloodstream—in the development of type 2 diabetes in women and men. The scientists found that high levels of SHBG were associated with decreased risk of type 2 diabetes in women and men. They also discovered that variants in the *SHBG* gene that raised or lowered SHBG levels also were associated with risk of type 2 diabetes. Thus, the research suggests that SHBG levels may be a useful predictor of type 2 diabetes.

Previous research has suggested that the ratio between two types of blood fats (triglycerides and high-density lipoprotein [HDL]) is a good predictor of insulin resistance in overweight people. Researchers in the NIDDK Intramural Research Program examined whether this ratio could predict insulin resistance in African-American women and men. By analyzing participants in the Jackson Heart Study, they found that whereas it could be used as a predictor in African-American men, the ratio could not identify insulin resistance in African-American women. In other recent research, NIDDK scientists found that in premenopausal women racial differences in some measures of obesity can be used to predict risk for cardiovascular disease and type 2 diabetes. These findings are important to inform screening programs for all women so that high-risk individuals may be identified and appropriate prevention strategies can be employed.

Puberty confers insulin resistance and may precipitate type 2 diabetes in obese adolescents. NIDDK is supporting a multisite trial of treatment strategies for girls and boys already affected by type 2 diabetes. This trial, called Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY), is comparing the efficacy (in terms of successful blood glucose control) of three different treatment regimens that employ agents and approaches intended to improve insulin sensitivity. Data gathered during the trial will help researchers determine whether these treatment regimens help protect the insulin-producing pancreatic beta cells from "exhaustion" and delay progression of diabetes and the need for insulin therapy. Finding ways to effectively overcome the additional burden of insulin resistance during puberty may help to improve long-term outcomes for girls and boys affected by type 2 diabetes.

Continued Study of the Benefits of Preventing or Delaying Type 2 Diabetes

According to recent estimates, about 79 million adult Americans have "prediabetes," a condition of impaired glucose metabolism that identifies them as high risk for developing type 2 diabetes. New insights important to reversing this alarming statistic continue to be gleaned from research founded on the landmark Diabetes Prevention Program (DPP) clinical trial. This comparative effective research trial compared the effect of intensive lifestyle modification, treatment with the drug metformin, and standard medical advice on preventing the development of type 2 diabetes in adults at high risk. Published in 2002, DPP results showed that participants who received the lifestyle intervention had a dramatically reduced risk—by 58 percent—of developing type 2 diabetes. Metformin reduced diabetes risk by 31 percent. Sixty-eight percent of DPP study participants were women; the Office of Research on Women's Health (ORWH) support for DPP facilitated recruitment and retention of women with a history of GDM (16 percent of all female participants). The NDEP's "Small Steps. Big Rewards. Prevent Type 2 Diabetes" education campaign is continuing to translate the results of DPP into practical health information for the public.

With support from ORWH and other cosponsors, NIDDK continues to follow DPP participants in the Diabetes Prevention Program Outcomes Study (DPPOS). DPPOS is examining longer term effects of the trial interventions on prevention of type 2 diabetes and its cardiovascular complications. In 2009, DPPOS researchers reported that, after a 10-year period of following trial participants, long-term benefits of the interventions emerged: the lifestyle and metformin interventions reduced development of type 2 diabetes by 34 percent and 18 percent, respectively. People in the lifestyle group also had fewer heart disease risk factors, despite taking fewer medications to control their heart disease risk. Thus, even though sustaining weight loss with lifestyle changes is challenging, it produces long-term health rewards by lowering women's and men's risk for type 2 diabetes and reducing other heart disease risk factors.

Another recent analysis of DPP participants that focused on women with a history of gestational diabetes found that both metformin and lifestyle intervention were highly effective in delaying or preventing future development of diabetes.

Gestational Diabetes and Diabetes Prevention

GDM is a form of glucose intolerance diagnosed during pregnancy. GDM affects about 7 percent of U.S. pregnancies annually, increasing risk of complications during pregnancy and birth for both mother and fetus. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and supported by NIDDK, studied more than 23,000 pregnant women to determine whether even mildly elevated maternal blood glucose levels increase the risk of adverse outcomes for pregnant women and their babies. The HAPO study showed that pregnancy complications occur at glucose levels lower than those currently used for GDM diagnosis, which in turn led to recommendations to change the diagnostic criteria for GDM—a change that was recently adopted by the American Diabetes Association. This change in diagnostic criteria will increase the burden of GDM to nearly 18 percent of pregnancies in the United States.

Although elevated blood glucose levels often go back to normal following delivery, 5 to 10 percent of women with GDM (using the conventional criteria) are found to have diabetes immediately after pregnancy, usually type 2 diabetes. Women who have had GDM have a 35- to 60-percent chance of developing diabetes within the 10 to 20 years following pregnancy. GDM occurs more frequently among obese women, women with a family history of diabetes, and African-American, Hispanic/Latina, and American Indian and Alaska Native women—women in minority groups already at disproportionately high risk for type 2 diabetes. The children of women with a history of GDM are also at an increased risk for obesity and diabetes compared with other children. It is encouraging that the DPP study showed type 2 diabetes can be prevented or delayed in people at risk, including women

with a history of GDM. A more recent analysis of DPP participants found that women with a history of GDM were more likely to develop diabetes compared with women who had given birth but did not have a history of GDM, even though both groups had similar glucose levels at the study's onset. However, both metformin treatment and a lifestyle intervention effectively prevented or delayed onset of diabetes in women with a history of GDM. NIDDK recently partnered with ORWH to expand the NDEP campaign "It's Never Too Early... to Prevent Diabetes" to reach out to women and their health care providers to raise awareness that women with a history of GDM are at increased risk of diabetes and their children are at increased risk of type 2 diabetes and obesity. (See the section on Information and Education Efforts to Reduce Health Disparities.) In addition, using funds from the American Recovery and Reinvestment Act (ARRA) to translate DPP, NIDDK is testing evidence-informed, innovative interventions using NDEP materials to reach women who had GDM to increase the number of them who get tested for diabetes after pregnancy. The effort also will provide the women with information on metformin and support for lifestyle change to prevent diabetes development, as well as test uptake of those interventions.

New insights into how GDM develops also have been achieved. For example, during pregnancy, the body normally becomes less sensitive to insulin, and more insulin is needed to compensate. Studies suggest that to meet this demand, the body's insulin-producing pancreatic beta cells proliferate, but it has been unclear as to what causes that change. Using a mouse model, researchers discovered that beta cell proliferation is controlled by serotonin, a chemical typically associated with its role in modulating mood, appetite, sleep, and other processes. Serotonin is made from tryptophan, an amino acid found in foods such as milk, eggs, meat, and fish. The scientists found that serotonin levels dramatically increased during pregnancy. Inhibiting serotonin production in mice, such as through restricting dietary tryptophan, inhibited beta cell proliferation and led to GDM. This result suggests that modulating this biological pathway, such as through medication or dietary changes, could be a strategy for preventing GDM.

Preventing Type 2 Diabetes in Youth

An increasing number of girls (as well as boys) are being diagnosed with type 2 diabetes and hence are diabetic during their childbearing years. NIDDK intramural research studies of the Pima Indians of Arizona, who have the highest rates of type 2 diabetes in the world, have shown that diabetes during pregnancy increases the later risk of diabetes and obesity in offspring in this population. Results from the SEARCH for Diabetes in Youth study, a large, population-based study of diabetes in racially and ethnically diverse youth, have shown that type 2 diabetes is diagnosed at a younger age in children exposed to maternal type 2 diabetes in utero. SEARCH is supported by NIDDK and CDC.

Recent results from NIDDK's HEALTHY clinical trial showed that an intervention program in middle schools lowered the obesity rate in a group of students at particularly high risk for type 2 diabetes but did not have a greater impact on the overall rate of obesity and overweight than was observed in control schools. The HEALTHY results are important for informing future school-based efforts to reduce overweight and obesity in girls and boys.

Understanding Sex Differences in Cardiovascular Complications of Diabetes

Cardiovascular disease (CVD) is the leading cause of death in people with diabetes. The risk of death due to heart disease is increased two- to fourfold in all patients with diabetes compared with their age-matched nondiabetic counterparts. In women, the risk is even greater-four- to sixfold. Moreover, while CVD mortality in men with diabetes has decreased, it has not decreased in diabetic women; the reasons for this sex difference may be due to biological, behavioral, or health care differences or a combination of these factors. Previous research has shown that a sex disparity exists in the treatment of CVD risk factors in people with type 2 diabetes, with health care providers generally treating women less aggressively than men. Recent research has shown

a similar finding in women with type 1 diabetes. Women enrolled in the Epidemiology of Diabetes Interventions and Complications Study, the followup study to NIDDK's landmark Diabetes Control and Complications Trial, reported lower frequency than men in the use of interventions that reduce CVD risk.

An ongoing clinical trial addressing cardiovascular disease and diabetes that may prove especially beneficial for women is the Look AHEAD (Action for Health in Diabetes) clinical trial. This long-term multicenter trial involving more than 5,100 participants, nearly 60 percent of whom are women, is underway to determine whether lifestyle intervention can improve cardiovascular outcomes in obese patients with type 2 diabetes. The Look AHEAD study previously reported beneficial health effects after 1 year, and the investigators now have found that participants showed positive changes in their health over 4 years. On average, across all 4 years, participants in the lifestyle intervention group lost significantly more weight than those in the control group and also experienced improved fitness, glucose control, blood pressure, and HDL (good) cholesterol. Both groups showed reductions in LDL (bad) cholesterol, but the reductions were larger in the control group because of their greater use of cholesterol-lowering medications. Cosponsors include the National Heart, Lung, and Blood Institute (NHLBI), National Institute of Nursing Research (NINR), ORWH, National Institute on Minority Health and Health Disparities, and CDC.

Treating Type B Insulin Resistance

Type B insulin resistance is a rare autoimmune condition that occurs predominantly in African-American women and can lead to a serious form of diabetes. In the condition, the body inappropriately produces antibodies that prevent interaction of insulin with its receptor, blocking insulin's ability to communicate with target cells. The resulting insulin signal interference leads to blood glucose imbalance and numerous negative physiologic effects, such as weight loss, excess testosterone production, and unusual skin discoloration (acanthosis nigricans). Scientists in NIDDK's Intramural Research Program, in collaboration with other researchers, identified a combination of drugs that was remarkably effective in reversing the physiologic effects of insulin resistance with minimal side effects. These findings not only establish a promising new treatment strategy for those suffering from type B insulin resistance but also provide a framework for designing effective therapies for other autoimmune disorders, many of which disproportionately affect women.

Genetic Markers of Diabetes Susceptibility

Finding the genes that confer increased susceptibility to type 1 and type 2 diabetes will help researchers understand why some people develop diabetes and others do not. NIDDK is supporting a number of major genetic consortia to identify genes predisposing to type 1 and type 2 diabetes and their complications. For example, recent discoveries by these consortia have raised to 40 the known total of gene regions associated with development of type 2 diabetes, and to 50 the known gene regions associated with type 1 diabetes. NIDDK is supporting research to translate these genetic findings to the development of new therapies and improvements in health.

Endocrinology

NIDDK supports a substantial portfolio of basic and clinical research on or relevant to endocrine diseases and disorders. This research includes studies important to diseases disproportionately or predominantly affecting women, such as thyroid diseases (including Graves' disease, goiter, and hypothyroidism), hyperparathyroidism, breast cancer, and osteoporosis.

Nuclear Receptor Signaling Atlas

Many endocrine diseases evolve from disruption of normal patterns of signal transduction and control of gene expression by members of the nuclear receptor superfamily, such as sex steroid hormone receptors. Research on these diseases is benefiting from the Nuclear Receptor Signaling Atlas (NURSA), a consortium supported by NIDDK, NHLBI, and the National Institute of Environmental Health Sciences (NIEHS). Understanding the roles played by the nuclear receptor superfamily, a focused group of hormone-dependent

and hormone-independent receptors important for development, metabolism, reproduction, and diseases, is the central focus for NURSA. Using high-throughput methods of genomic and proteomic analysis, coupled with computational approaches, NURSA investigators are beginning to understand how the receptors intersect with large complexes of co-regulators at target genes to regulate expression.

Gene Regulation in Breast Cancer—Insights from NURSA and Other Studies

Much of NIDDK support related to breast cancer focuses on hormonal regulation of cellular growth and function by both steroid hormones and growth factors. Many tumors that arise in epithelial cells, including breast tumors, result from an inappropriate response of a normal cell to hormones, growth factors, or cytokines. In breast cancer, cells may be particularly responsive to the hormone estrogen. Hormone-sensitive cancers may initially respond to treatments that capitalize on this sensitivity, but in most instances, the tumor will eventually develop independence from hormone action and continue to thrive even when estrogen is removed or its action blocked. Researchers are intensively investigating both the target genes and the driver of gene expression in hormone-sensitive breast cancers—DNA binding by the estrogen receptor—in an effort to better understand these cancers.

One important advance of recent years is the realization that hormones such as estrogen require co-regulatory proteins to carry out their signaling program. One such co-regulator, steroid receptor coactivator-3, also called amplified in breast cancer-1 (SRC-3/AIB-1), has been found to act as an important stimulus to estrogen-dependent growth and, when present in inappropriate amounts or times, acts as a tumor promoter. Recent NIDDK-supported research has shown that SRC-3 not only enhances estrogen-dependent growth of cancer cells by activating certain genes but also sends a signal to the cell membrane to promote cell migration, which is an important element related to the spread of cancer cells to other parts of the body (metastasis). Thus, SRC-3 plays a role in both the growth and spread of breast cancer cells.

Other research is examining additional factors that play a role in the spread of cancer cells. For example, scientists studied a nuclear receptor called estrogen-related receptor-alpha (ERR-alpha). High levels of this protein have been associated with negative outcomes in breast and ovarian cancers, but the mechanism of how it may play a role in disease is unknown. In new research, scientists discovered that ERR-alpha physically interacts with another protein (beta-catenin), and the two proteins work together to regulate genes involved in migration of cancer cells. Therefore, identifying drugs that inhibit ERR-alpha or the ERR-alpha/beta-catenin complex may be a possible therapeutic approach for cancer.

Most estrogen-sensitive breast cancers (i.e., those that are estrogen receptor-positive) also have a receptor for another hormone—progesterone. Agents that mimic progesterone are used as a third-line endocrine therapy for breast cancer, but research also has conversely shown that agents that counteract the effect of progesterone may also improve outcomes in people with breast cancer. New research has shed light on the molecular mechanisms by which the progesterone receptor may regulate genes. By using a chemical screen, scientists identified more than 2,300 genes that are regulated by the progesterone receptor. They focused on a smaller number that are involved in inflammation and identified different mechanisms by which the receptor regulated gene expression. Understanding the molecular mechanisms by which the progesterone receptor may be involved in breast cancer can inform drug design to target this nuclear receptor.

Osteoporosis

Osteoporosis is characterized by low bone mass and deterioration of the bone architecture and occurs in people of all ethnic backgrounds. Women develop osteoporosis at a rate four times greater than men. According to the National Osteoporosis Foundation, approximately 10 million Americans have osteoporosis and about 34 million more have below normal bone mass, placing them at increased risk for developing this condition. NIDDK supports basic and clinical research on the hormonal regulation of bone and mineral metabolism in health and disease, including research on

factors such as calcium, vitamin D, parathyroid hormone (PTH), PTH-related protein (PTHrP), sex steroids, and bone-active cytokines, such as the bone morphogenetic proteins. These are just some of the molecules that play a role in bone remodeling, the active breakdown and regeneration of bone that occurs throughout life. When these processes are perturbed, osteoporosis and other bone diseases can result; thus, continued progress in understanding the roles of the different molecules can open a window onto potential new treatments.

Digestive Diseases

NIDDK supports a substantial portfolio of basic and clinical research on digestive diseases, a number of which disproportionately affect women, including functional gastrointestinal disorders such as irritable bowel syndrome (IBS) and fecal incontinence, and liver and biliary disorders such as primary biliary cirrhosis. The long-range research plan of the National Commission on Digestive Diseases (NCDD), titled *Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases*, is guiding NIDDK's research planning in these disease areas. ORWH joined NCDD as an ex officio member and is helping to coordinate NIH efforts to implement the research recommendations in the plan for IBS and other digestive diseases that disproportionately affect women. The following highlights of NIDDK-supported digestive diseases research are particularly relevant to women's health.

IBS and Other Functional Gastrointestinal Disorders

IBS causes pain and constipation or diarrhea and is especially common in women. Diet and stress contribute to this disorder, but the underlying causes are unknown. Symptoms may be influenced by abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. People with IBS have a colon that seems to respond strongly to stimuli that would not affect most individuals. A key goal for research is to understand the interplay of gut-and-brain pathways in these disorders and to build on this knowledge to design effective treatments. Helping to foster this research is a specialized center of research cofunded by NIDDK and ORWH that is studying sex-related differences in this interplay both in IBS and in another visceral pain syndrome, IC/PBS. (See the Women's Urologic Health section.) To better understand disease burden, NIDDK-supported researchers also are examining symptoms beyond abdominal pain and constipation or diarrhea, which are the most commonly used symptoms for diagnosing IBS. For example, investigators studying IBS patients found that 11 different symptom measurements were important for defining disease burden, rather than relying on only the commonly used symptoms. Improving ways to diagnose IBS could provide more accurate populationwide estimates of disease burden as well as help to identify individuals who could benefit from treatment.

Fecal incontinence, or impaired bowel control, is another bowel disorder that poses a major public health burden. More than 5.5 million Americans of all ages are affected, but the condition is more common in women and older adults. A dysfunctional internal anal sphincter (IAS)—a ring-like muscle located at the end of the rectum—is a primary cause for the uncontrolled release of stool that occurs in people with fecal incontinence. In recent research, scientists used smooth muscle cells obtained from mouse IAS to bioengineer three-dimensional IAS rings. Once an IAS was formed in the laboratory, it was implanted into a small pocket made surgically under the skin of a recipient mouse. In a subsequent study, the researchers found that the bioengineered muscles were able to contract and relax in a manner that mimicked the natural in vivo function of the IAS. This study's successful implantation in mice of bioengineered IAS that retained physiologic functionality presents an opportunity for new studies that one day may be translated into bioengineered IAS for people suffering from fecal incontinence.

Liver and Biliary Disease Research

Liver and biliary disease is an important cause of morbidity and mortality in the United States. Some liver and biliary conditions disproportionately affect members of ethnic and racial minority populations and the economically disadvantaged. Women are

disproportionately affected by certain liver diseases, such as primary biliary cirrhosis (PBC), drug-induced liver injury, and gallstones. PBC is a chronic autoimmune disease characterized by inflammation and damage to the bile ducts, which may ultimately lead to liver damage, cirrhosis, and end-stage liver disease. Like other autoimmune diseases, scientists think that the underlying cause of PBC has a strong genetic component. Researchers now have pinpointed six different genetic regions associated with PBC. The identified regions contain genes involved in mediating immune responses, and some of the gene regions also are associated with risk for other autoimmune diseases. By defining the genetic variants associated with disease, researchers may be able to gain insight into the molecular factors that trigger the onset and progression of PBC.

To further research on liver and biliary diseases, NIDDK is playing a leading role in promoting the implementation of the trans-NIH *Action Plan for Liver Disease Research*. This plan, developed in 2004 under the auspices of the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee, is based on input from a broad range of external investigators involved in liver disease research, NIH staff (including staff from ORWH), other Federal Agencies, industry, health care providers, and concerned lay persons. Implementation efforts include an ongoing review of progress made toward the research goals of the action plan and encouraging new initiatives and grant applications to align with efforts to realize the action plan's goals.

Obesity and Nutrition

Obesity is increasing dramatically in the U.S. population and is now considered an epidemic. The problem is particularly severe for African-American, Hispanic/Latino-American, and American Indian women. Using body mass index (BMI), a measure of weight relative to height, it is estimated that more than two-thirds of the U.S. adult population is overweight or obese, with approximately one-third of the population meeting criteria for obesity. It is estimated that nearly half of non-Hispanic African-American women and more than 40 percent of Mexican-American women are obese. Obesity increases risk for numerous life-threatening complications, including coronary heart disease, type 2 diabetes and its complications, stroke, and breast and colon cancer; it also causes morbidity by increasing the risks for osteoarthritis, gallstones, and urinary incontinence. NIDDK supports basic and clinical research on multiple fronts—including nutrition, physical activity, epidemiology, behavioral intervention, surgery, neuroendocrinology, and fat cell biology—to help understand the underpinnings of obesity, including basic biological differences that predispose to sex/gender differences in fat accumulation and deposition, and the role of the intrauterine environment on the development of obesity and other metabolic dysfunction in offspring, and to determine how best to prevent overweight and effectively maintain a healthy weight. Ongoing special programs include the university-based core centers, Clinical Nutrition Research Units (CNRUs), and Obesity/Nutrition Research Centers (ONRCs). NIDDK also supports the Weight-control Information Network (WIN). WIN provides health professionals and consumers with science-based information on obesity, weight control, and nutrition. (See the section on Information and Education Efforts to Reduce Health Disparities for further information on WIN efforts.)

Trans-NIH efforts in obesity research have been strengthened by the work of the NIH Obesity Research Task Force. This task force is cochaired by the NIDDK and NHLBI directors; multiple ICs and Offices, including ORWH, are members. The task force spearheaded development of a trans-NIH strategic plan for NIH obesity research (2004) and will publish an update of that plan in early 2011. NIDDK efforts to meet the goals of the plan are being coordinated through its Office of Obesity Research. The following highlights of NIDDK-supported obesity and nutrition research are particularly relevant to women's health.

Preventing Weight Gain in Women

Epidemiologic studies indicate that specific stages of life, including adolescence, marriage, postpregnancy, and menopause, confer high risk for the development of obesity in susceptible individuals. Studies also have

demonstrated a link between overweight during pregnancy and early weight gain in offspring. The importance of the effect of maternal overweight and the impact it has on mothers' children is underscored by new research showing that obesity, glucose intolerance, and elevated blood pressure during childhood and adolescence are associated with increased rates of early death.

NIDDK is supporting new and ongoing studies to devise effective strategies for obesity prevention in women and children, particularly in minority racial and ethnic groups in the United States. For example, a study is examining whether a behavioral lifestyle intervention during pregnancy could promote healthy weight gain and prevent postpregnancy weight retention. An ongoing randomized clinical trial is testing a community-based strategy to prevent transition to obesity among middle-aged overweight African-American women by emphasizing current weight maintenance rather than weight loss. Another randomized controlled trial is examining the effectiveness of an all-girls alternative to high school physical education classes at preventing obesity.

Obesity Interventions

Researchers continue to identify and test successful strategies to induce and maintain weight loss. The Look AHEAD clinical trial described previously demonstrated positive changes in the health of obese adults with type 2 diabetes who received an intervention to achieve and maintain long-term weight loss through physical activity and decreased caloric intake. Look AHEAD is cosupported by ORWH. The ongoing NIDDK-supported Longitudinal Assessment of Bariatric Surgery (LABS) consortium conducted a multicenter, observational study to evaluate 30-day safety outcomes in obese individuals who underwent an initial bariatric surgical procedure—a form of weight loss surgery. Similar to most populations undergoing bariatric surgery, the majority of the patients in the study were white and female. The results showed that, within 30 days of surgery, 4.1 percent of patients had at least one major adverse outcome, defined as development of blood clots in the deep veins of the legs or the pulmonary artery of the lungs, repeat surgeries, not being discharged from the hospital within 30 days, or death. Mortality rates were low: 0.3 percent of patients died within 30 days. LABS also showed that, after adjusting for individual patients' health characteristics, surgeons who had performed more bariatric surgeries had fewer patients with postsurgical complications. Findings from the LABS consortium are helping health care providers and patients make informed personalized decisions about the potential risks and benefits of bariatric surgery.

New research, cofunded by ORWH, is examining the biological signals of weight loss in African-American women, which can inform new strategies for weight loss interventions in this population. Another new study will examine factors that influence whether disadvantaged women enroll in a community health-based weight management program, in an effort to identify ways to reach more women. Scientists also are studying young and middle-aged adult women to identify factors (e.g., frequent exercise) that may promote maintenance of weight or weight loss, which could help women implement strategies to avoid weight gain or regain.

Biology of Overweight and Obesity

NIDDK has spearheaded basic research on the neuroendocrine pathways and metabolic factors influencing energy balance, metabolism, and weight regulation. Sex/gender differences in the molecular mechanisms underpinning obesity development also are under study, such as how sex hormones influence fat distribution. Mechanistic studies of the effects of the intrauterine environment—specifically, the effects of maternal obesity or diabetes—on the development of obesity and other metabolic dysfunction in offspring are ongoing. For example, new insights have emerged from recent research in nonhuman primates suggesting that a maternal chronic high-fat diet results in a significantly increased risk of fetal fatty liver disease that persists after birth. The finding held true whether or not the mothers were themselves obese or had diabetes. Pregnant animals fed a high-fat, high-calorie diet produced offspring that had increased levels of triglyceride fat in the liver, as well as a higher percentage of body fat as they got older, compared with offspring

of mothers who ate a standard diet. Also important is that after female animals were consistently fed a high-fat diet for 4 years, switching them to a lower calorie, low-fat diet reduced fetal liver abnormalities in their subsequent offspring, even though some of the mothers remained obese and insulin resistant. This research suggests that a maternal high-fat diet may result in increased fat transfer to the fetus and that unhealthy levels of fats in maternal blood could potentially be the predominant cause of some future metabolic disorders in offspring.

Kidney Disease and End-Stage Renal Disease

At the close of 2008, more than 550,000 persons with end-stage renal disease (ESRD) were either receiving hemodialysis or living with a kidney transplant to replace their failed kidneys. Approximately 23 million additional people in the United States have some degree of impaired kidney function. Diabetes and high blood pressure are the leading causes of kidney failure, and cardiovascular disease is a leading cause of death for ESRD patients. Prevalence of irreversible kidney failure is much higher in ethnic and racial minorities within the United States, and older American Indian and African-American women are affected disproportionately by kidney failure due to diabetes. Women also are differentially affected by certain kidney diseases, including kidney disease due to lupus and preeclampsia.

A major NIDDK educational outreach effort, the National Kidney Disease Education Program (NKDEP), is designed to raise awareness among patients and physicians about the problem of kidney disease and steps that should be taken to treat chronic kidney disease and prevent kidney failure—particularly in at-risk ethnic and racial populations. (For further information, see the section on Information and Education Efforts to Reduce Health Disparities.)

Lupus Nephritis

Kidney disease represents one of the common and often serious manifestations of systemic lupus erythematosus (SLE), an inflammatory connective tissue disease that affects different organ systems in varying combinations. The majority of patients afflicted with SLE are young women of childbearing age. Most people with SLE have some degree of renal disease, and many have kidney failure; nearly half of those with kidney failure are African American. The importance of renal involvement as a major cause of both morbidity and mortality of SLE is well established. Thus, an understanding of the causal mechanisms and treatment is of significant interest to NIDDK. New and ongoing research seeks to develop better understanding of the immunologic events leading to immune deposit formation in the glomerulus of the kidneys. For example, a newly funded study is using several mouse models of SLE to increase understanding about the mechanisms of kidney inflammation and remission in different types of kidney disease associated with SLE, with a goal of using that knowledge to gain insight about disease mechanisms and possible therapeutic targets in human SLE.

Lupus membranous nephropathy (LMN) accounts for approximately 10 to 20 percent of cases of lupus nephritis, and no consensus exists among health care providers as to the most effective treatment approaches for patients. Researchers in the NIDDK Intramural Research Program shed light on this gap in knowledge by conducting a clinical trial that directly compared immunosuppressive therapies in 42 patients with LMN—one of the largest such trials. Most of the trial participants were women. The trial had three arms: corticosteroid (prednisone) treatment alone, and corticosteroid plus one of two additional immunosuppressive agents (cyclosporine or cyclophosphamide). The researchers found that, after 1 year, the treatment regimens containing an additional immunosuppressive drug were more effective at inducing remission in patients with LMN compared with corticosteroid treatment alone. The results of the study are important for informing the decisions of health care providers about how best to treat their patients with LMN.

Sex Differences in Kidney Function

Sex-based differences in kidney function in health and disease can affect vulnerability to renal dysfunction. NIDDK is supporting studies of these differences. It has been proposed that estrogen normally confers protection against renal and cardiovascular complications in many diseases and that this protection is lost in diabetes. Ongoing studies are investigating the role of sex steroids in diabetic kidney disease and the possible mechanisms for the apparent protective effect of estrogen, including cross-talk between estrogen and the renin-angiotensin system, and the effect of sex hormones on hemodynamics, vasoactive mediators, and fibrosis mediators in the diabetic kidney. These studies may help point the way to novel, sex-specific treatment strategies for diabetic nephropathy.

Women's Urologic Health

Diseases and conditions affecting the bladder and associated structures of the lower urinary tract are a leading cause of urinary incontinence, pelvic pain, and kidney failure, and they often contribute to poor quality of life. Women are disproportionately affected by urologic diseases, especially urinary incontinence, urinary tract infections (UTIs), and interstitial cystitis/painful bladder syndrome (IC/PBS). Through its basic, clinical, and epidemiologic research programs in urology, NIDDK is continuing efforts to improve interventions and treatments for these diseases and to better understand their underlying causes. NIDDK's Urologic Diseases in America (UDA) project has closed many of the former gaps in knowledge about the prevalence, incidence, treatment, and economic impact of urologic diseases in the United States.. The Institute continues to promote the UDA findings.

Advances in Treating Urinary Incontinence

A conservative estimate is that approximately 13 million Americans, most of them women, suffer from urinary incontinence. Urinary incontinence is a problem often associated with pregnancy, childbirth, and aging. Recent research from the Look AHEAD clinical trial showed that urinary incontinence is also highly prevalent among overweight and obese women with type 2 diabetes and far exceeds the prevalence of other diabetes complications among this population. Women can develop stress urinary incontinence (SUI), in which urine leaks under physical stress (such as coughing, laughing, sneezing, or lifting heavy objects); urge urinary incontinence, in which involuntary urine leakage occurs after a sudden urge to urinate; or a mixture of both. Research is ongoing, but treatment options for urinary incontinence are currently limited to physical therapy to improve muscle tone and bladder control, medications, and surgical procedures. The Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr) found that a procedure using a "sling" made from the patient's own tissue to support the bladder neck and prevent urine leakage under stress helps more women with SUI achieve dryness than the Burch colposuspension technique. This rigorous trial also provided insights into surgical therapy outcomes, such as differences in side effects from the two procedures. Another trial for SUI, called TOMUS (Trial Of Mid-Urethral Slings), compared the outcomes of two minimally invasive surgical sling procedures that FDA approved to treat this condition in women. These procedures use a synthetic mesh sling rather than patient tissue to support the bladder neck. Both procedures have been shown to be safe and successful in treating SUI, but it was unknown whether one was better than the other. Recent results from this trial demonstrated that both procedures help women achieve similar levels of dryness. The trial also captured the risks and side effects of each type of surgery. These comparative effectiveness research studies have yielded results that are critically important for enabling women with SUI and their doctors to weigh more accurately the benefits and risks of available treatment options. This research has received support from ORWH.

New Directions in IC/PBS and Other Urologic Chronic Pain Syndromes

IC/PBS is a chronic pelvic pain disorder whose cause is not yet known. IC/PBS causes recurring discomfort or pain in the bladder and the surrounding pelvic region. IC/PBS affects both men and women, but it is

nine times more common in women. The number of American adults with IC/PBS is not known with certainty, and NIDDK is supporting epidemiologic studies to determine prevalence. NIDDK-supported research is focused on elucidating the cause(s) of IC/PBS and on improving treatment and interventions. NIDDK's ongoing multicenter Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) research network is conducting innovative, collaborative studies of chronic urologic pelvic pain disorders in women and men—focusing on IC/PBS and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and the potential relationships between these conditions and other chronic pain disorders, such as fibromyalgia. The National Institute of Neurological Disorders and Stroke (NINDS), NICHD, and ORWH are contributing scientific expertise to help shape the network's research focus. The MAPP network has initiated its major research efforts, including the highly collaborative Trans-MAPP Epidemiology/Phenotyping Study. This study will examine how and why chronic urologic pelvic pain conditions develop and change over time and whether there are differences that define unique subgroups of patients who may benefit from different treatment strategies. NIDDK also has used ARRA funds to support an ancillary study that will collect data and samples from normal individuals to greatly help biomarker efforts within the MAPP network. Fundamental questions about potential causes, risk factors, and prevalence of IC/PBS also are being addressed through several large studies, including the Rand IC Epidemiology study, which is cosupported by ORWH.

New insights about the molecular mechanisms underlying pelvic pain associated with UTIs have recently emerged. (See also the next section.) Researchers performed experiments in animal models to determine whether there are differences between the bacteria that cause acute, painful UTIs and those that are involved in asymptomatic infections. They placed the different strains of bacteria—either from patients with acute UTI or from patients with an asymptomatic infection—into mouse bladders and then monitored the pain the mice experienced over the course of an infection. They found that only infection with the acute UTI strain caused pain. Searching for bacterial factors that could contribute to this difference, researchers focused on lipopolysaccharide, or LPS, which is a large lipid-sugar molecule found on the surface of bacteria. When placed in mouse bladders, only LPS from the acute strain caused pain. Interestingly, treating mice with LPS from the asymptomatic bacteria significantly reduced the pain associated with UTI, implying a therapeutic response. The research suggests a possible infectious basis for the chronic pain experienced by people with IC/PBS and other urologic chronic pelvic pain syndromes, and it suggests that this pain persists well after the initial infection and inflammation have cleared. Research is exploring "designer bacteria" or bacterially based molecules that could alter the pain response in patients, providing hope that a better understanding of the genesis of pain in these conditions could lead to new treatments.

Mechanisms Underlying Recurrent UTIs

UTIs are among the most common infectious diseases acquired by humans; in fact, only respiratory infections occur more often. Women are especially prone to UTIs, primarily due to differences in female and male anatomy of the urinary tract. UTIs caused by the bacterium *Escherichia coli (E. coli,* normally found in the colon) accounted for nearly 7 million doctor visits by women in 2000, and many women suffer from frequent infections. Ongoing research in this area is helping to elucidate the cause(s) of and illuminate potential treatment approaches for recurrent UTIs. For example, scientists at a specialized center of research cosupported by ORWH and NIDDK are continuing to gain insights into host and bacterial factors that contribute to UTIs. Working in a mouse model, they recently observed that early, severe inflammatory responses to an initial UTI cause damage to the bladder and permit infection to persist longer. These severe responses put those animals at increased risk for developing future UTIs. The scientists also identified markers during early infection that could be used to predict whether the animals would develop chronic infection. In other studies, the center researchers also found that the presence of a particular kind

of capsule is required for infectious bacteria to grow and form large masses called intracellular bacterial communities (IBCs) within the urinary tract of mice. Prior studies in rodent models have indicated that formation of these IBCs helps promote sustained infection and may help explain at least some recurrent UTIs. By identifying the bacterial capsule as a factor that contributes to IBC formation, the researchers now have illuminated targets for potential novel therapeutic interventions to prevent or treat UTIs. Because IBCs have been observed in human bladder infections, these results likely have direct clinical implications.

Continued Progress in Studies of Vaccines To Prevent UTIs

Scientists have recently reported the successful use of a live, attenuated vaccine in mice to prevent bacterial infection in the bladder. The researchers hypothesized that use of attenuated bacteria that stimulate the host immune response without causing disease may be beneficial in preventing or ridding the body of UTIs. A mutant strain of UTI-causing *E. coli* engineered to lack a gene important to the bacteria's virulence appeared to be a strong candidate. The scientists found that mice inoculated with the mutant bacteria vaccine in their bladders were protected from subsequent infection with the normal UTI-causing *E. coli*. It is important to note that the mutant bacteria were not themselves able to effectively infect the mouse bladders. Vaccination with the mutant *E. coli* strain also not only protected against infection by the original bacterial strain from which it was derived but also protected against challenge from other, different strains of UTI-causing *E. coli*—indicating that this type of vaccine approach may provide broad clinical protection. Although the exact mechanism for this protection is still under investigation and additional studies will need to be performed to determine whether this live, attenuated vaccine also may hold promise for resolving recurrent UTIs in people, these findings are encouraging in the quest to find effective new UTI therapies.

Understanding the Contribution of Diabetes to Urologic Conditions in Women

NIDDK is supporting mechanistic studies of how diabetes—both type 1 and type 2—contributes to urinary incontinence and UTIs in women; ORWH is helping to foster these studies. New insights into prevalence and/or risk factors have emerged from studying urologic conditions in women with type 1 diabetes enrolled in the Epidemiology of Diabetes Interventions and Complications Study, the followup study of the Diabetes Control and Complications Trial cohort. Investigators have found that urinary incontinence is prevalent in these women, with the prevalence of urge incontinence far greater than that observed in women with normal glucose levels. Investigators also found that female sexual dysfunction is common in women with type 1 diabetes, with depression being the major predictor. Although more research will be needed to examine the mechanisms underlying these observations, the results indicate that health care providers should assess their female type 1 diabetes patients for the presence of sexual dysfunction and depressive symptoms.

Initiatives

Program Announcements

NIDDK Mentored Research Scientist Development Award (K01). The purpose of this initiative is to provide support and protected time for advanced postdoctoral and/or newly independent research scientists for an intensive, supervised career development experience in the biomedical, behavioral, or clinical sciences leading to research independence. PAR sponsor: NIDDK (PAR-09-060).

Pilot and Feasibility Clinical Research Grants in Kidney or Urologic Diseases (R21). This funding opportunity announcement (FOA) encourages exploratory/developmental research grants (R21) that propose small-scale or pilot and feasibility clinical and translational research studies, including epidemiologic studies or clinical trials related to kidney or urologic disease research, that address important clinical and translational questions

and are potentially of high clinical and public health impact. PAR sponsor: NIDDK (PAR-09-077).

New Technologies for Liver Disease SBIR (R43/R44) (PA-09-095) and New Technologies for Liver Disease STTR (R41/R42) (PA-09-094). The purpose of these companion FOAs is to solicit Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grant applications that propose to develop resources, research tools, instrumentations, biomarkers, devices, drugs, or new and innovative approaches to diagnosis, monitoring, management, treatment, and prevention of liver diseases. PA sponsors: NIDDK, National Institute of Alcohol Abuse and Alcoholism (NIAAA), NIEHS, Nattional Institute on Drug Abuse, National Institute of Biomedical Imaging and Bioengineering, and National Cancer Institute (NCI).

Exploratory/Developmental Clinical Research Grants in Obesity (R21). This FOA encourages research on exploratory/developmental clinical studies that will accelerate the development of effective interventions for prevention or treatment of overweight or obesity in adults and children. PA sponsors: NIDDK, NCI, National Center for Complementary and Alternative Medicine (NCCAM), NHLBI, and Office of Dietary Supplements (ODS) (PA-09-124).

Secondary Analyses in Obesity, Diabetes, and Digestive and Kidney Diseases (R21). This FOA encourages exploratory/developmental research applications that propose to support secondary analyses of data related to the epidemiology of disease areas of NIDDK; important and/or innovative hypotheses explored through analysis of existing data sets; secondary analyses designed to inform and support subsequent applications for individual research awards; rapid analyses of new databases and experimental modules to inform the design and content of future studies; and the archiving of datasets to be made publicly available for research purposes related to disease areas of NIDDK. PA sponsors: NIDDK and ODS (PA-09-131).

Pilot and Feasibility Clinical Research Grants in Diabetes and Endocrine and Metabolic Diseases (R21). This FOA encourages exploratory/developmental clinical research related to the prevention or treatment of diabetes, obesity, and endocrine and genetic metabolic diseases. PA sponsors: NIDDK and ODS PA-09-133).

Pilot and Feasibility Clinical Research Studies in Digestive Diseases and Nutrition (R21). This FOA encourages pilot and feasibility clinical and epidemiologic research studies of new therapies or means of health promotion and prevention of digestive and liver diseases and nutritional disorders associated with digestive and liver diseases, including cancer. PA sponsors: NIDDK, NCI, NINR, and ODS(PA-09-151).

Planning Grants for Translational Research for the Prevention and Control of Diabetes and Obesity (R34). This FOA encourages proposals to develop and pilot-test translational interventions for the prevention and control of diabetes and obesity that have a high potential to be adopted and sustained in applied health care settings. PAR sponsors: NIDDK, NICHD, and the Office of Behavioral and Social Sciences Research (OBSSR) (PAR-09-177).

Translational Research for the Prevention and Control of Diabetes and Obesity (R18). Research supported under this initiative will test the effectiveness of interventions for the prevention and control of diabetes and obesity that have a high potential to be adopted and sustained in applied health care settings. PA sponsors: NIDDK, NICHD, and OBSSR (PAR-09-176).

Noninvasive Methods for Diagnosis and Progression of Diabetes, Kidney, Urologic, Hematologic, and Digestive Diseases and Hypertensive Disorders (R01). This FOA is soliciting applications of imaging and other noninvasive or minimally invasive technologies to detect, characterize, diagnose, and identify persons with a predisposition to, or monitor treatment of, diseases within the mission of NIDDK and NHLBI. PA sponsors: NIDDK and NHLBI (PA-09-181).

Ancillary Studies of Acute Kidney Injury, Chronic Kidney Disease, and End-Stage Renal Disease Accessing Information From Clinical Trials, Epidemiologic Studies, and Databases (R01). This FOA is soliciting applications for ancillary studies to ongoing or completed clinical trials, existing administrative and clinical databases and epidemiologic studies of kidney disease, and clinical trials and epidemiologic studies of other diseases or populations that lend themselves to the study of acute kidney injury and chronic kidney disease. PA sponsors: NIDDK and NHLBI (PA-09-196).

Development and Validation of Disease Biomarkers (R01). This FOA is encouraging research to validate candidate biomarkers for well-defined human diseases of the liver, kidney, or urologic tract; digestive and hematologic systems; endocrine and metabolic disorders; diabetes and its complications; and obesity, for which there are no or very few biomarkers or for which standard biomarkers are currently prohibitively invasive or expensive. PA sponsors: NIDDK, NIAAA, NINR, and ODS (PA-09-204).

NIDDK Small Grants for Clinical Scientists To Promote Diversity in Health-Related Research (R03). This FOA is encouraging applications from clinical scientists from underrepresented racial, ethnic, or disadvantaged backgrounds or clinical scientists with disabilities to conduct small research projects in areas within the NIDDK mission. PA sponsors: NIDDK and ODS (PA-09-223).

Basic and Clinical Studies of Congenital Urinary Tract Obstruction (R01). This FOA is soliciting applications related to addressing the numerous scientific and clinical uncertainties related to the development, treatment, and prognosis of congenital obstructive uropathy. PA sponsors: NIDDK and NICHD (PA-09-226).

Ancillary Studies to Major Ongoing Clinical Research Studies To Advance Areas of Scientific Interest Within the Mission of NIDDK (R01). This FOA encourages research project grant applications to conduct ancillary studies to major ongoing clinical research studies, including clinical trials, epidemiologic studies, and disease databases. PAR sponsor: NIDDK (PAR-09-247).

Health Disparities in NIDDK Diseases (R01). This FOA seeks research to understand and mitigate issues of health disparities in high-priority diseases within the NIDDK mission. PA sponsors: NIDDK and NINR (PA-09-262).

Grants for Research in Glomerular Diseases (R01). The purpose of this FOA is to encourage research pursuing exploratory investigations of glomerular disease in order to foster development of new ideas enhancing the understanding of disease detection, pathogenesis, preemption, and/or treatment. PA sponsor: NIDDK (PA-10-113).

Home- and Family-Based Approaches for the Prevention or Management of Overweight or Obesity in Early Childhood (R21). This FOA invites exploratory pilot/feasibility study and small clinical trial applications that propose to test novel home- or family-based interventions for the prevention or management of overweight in infancy and early childhood. PA sponsors: NIDDK, NICHD, NHLBI, OBSSR, and Office of Disease Prevention (PA-10-128).

Home- and Family-Based Approaches for the Prevention or Management of Overweight or Obesity in Early Childhood (R01). This FOA invites research project grant applications that propose randomized clinical trials testing novel home- or family-based interventions for the prevention or management of overweight in infancy and early childhood. PA sponsors: NIDDK, NICHD, NHLBI, and OBSSR (PA-10-127).

Diet Composition and Energy Balance (R01). This FOA is soliciting research to investigate the role of diet composition in energy balance. PA sponsors: NIDDK, NICHD, NCI, NCCAM, NHLBI, National Institute on Aging, NIAAA, and ODS (PA-10-152).

NIDDK is also participating in the following:

- Advancing Novel Science in Women's Health Research (ANSWHR) (R21) (PAS-10-226).

- Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R01) (PAR-10-136).
- Obesity Policy Research: Evaluation and Measures (R01) (PA-10-027).
- Mechanisms, Models, Measurement, and Management in Pain Research (R01) (PA-10-006).
- Improving Diet and Physical Activity Assessment (R21) (PAR-09-225.
- Improving Diet and Physical Activity Assessment (R01) (PAR-09-224).
- Renal Function and Chronic Kidney Disease in Aging (R01) (PA-09-165).

Requests for Applications

Planning Grants for Translating Chronic Kidney Disease Research into Improved Clinical Outcomes (R34). This request for applications (RFA) seeks to support clinical trial planning grants to test the effectiveness of interventions for the prevention, treatment, and management of chronic kidney disease that have a high likelihood of being widely adopted and sustained in a wide range of health care settings and in individuals and communities at highest risk. RFA sponsor: NIDDK (RFA-DK-10-011).

Type 1 Diabetes Impact Award (DP3). The purpose of this RFA is to support groundbreaking original research addressing fundamental questions or major obstacles in type 1 diabetes research. RFA sponsor: NIDDK (RFA-DK-10-012).

Ancillary Studies in Immunomodulation Clinical Trials (R01). The purpose of this RFA is to support mechanistic studies in clinical trials of immunomodulatory interventions for immune system-mediated diseases. RFA sponsors: National Institute of Allergy and Infectious Diseases, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NINDS, and NIDDK (RFA-AI-10-014).

Conferences and Workshops

Network of Minority Research Investigators Workshop (April 22–23, 2010). This meeting of the Network of Minority Research Investigators focused on science, career development, and networking opportunities.

Novel Therapies to Enhance ESRD Patient Survival: Inflammation in Hemodialysis (April 21–22, 2010). This workshop brought together experts to discuss using novel therapies to enhance the survival of people with end-stage renal disease, with a focus on targeting inflammation that has been linked to increased mortality in patients receiving hemodialysis.

MYH9 and Kidney Disease: Clinical and Public Health Implications of Recent Genetic Findings in Populations (April 19–20, 2010). This workshop built on the recent discovery of variations in a single gene, *MYH9*, that are strongly associated with kidney diseases disproportionately affecting African Americans. The conference included discussion of possible further basic science and genetic studies as well as important questions regarding screening and social and ethical ramifications of the findings.

Circadian Rhythms and Metabolic Disease (April 12–13, 2010). This meeting focused on understanding the link between circadian rhythms and human health and disease. It included a particular emphasis on the influence of both central and cellular clocks on the physiology of behavior and metabolism, specifically effects on overall energy balance and obesity.

Genetics of Vesicoureteral Reflux (December 7–8, 2009). The purpose of this meeting was to convene a group of geneticists, clinicians, and developmental biologists to discuss the genetics of vesicoureteral reflux (VUR), a common pediatric congenital disorder that involves the abnormal flow of urine from the bladder back into the ureters. Although several genes that cause VUR have been identified, there are many children with VUR in whom no genetic cause has been identified. The meeting included discussion about utilizing existing cohorts of VUR patients to facilitate gene discovery.

Lymphatics in the Digestive System: Physiology, Health, and Disease (November 3–4, 2009). The workshop provided a forum to consider current research on the biology of the lymphatic system, the role of lymphatics in organ function with an emphasis on the digestive system, and future research directions.

Typology of Diabetes in Children and Young Adults (September 16–17, 2009). Although most children are accurately diagnosed with type 1 or type 2 diabetes, a subset of children may have clinical characteristics that overlap between the two major forms of diabetes, making it difficult for physicians to easily determine diabetes type. This conference focused on classification of diabetes type in youth, which is important for research and for clinical purposes to ensure that all youth are accurately diagnosed and given the proper treatment.

Inflammation, Immunity, and Metabolism at the Interface of Type 1 and Type 2 Diabetes (May 5–6, 2009). This meeting examined the role of the immune system in the pathogenesis of type 1 and type 2 diabetes, including trying to understand the differences and commonalities between the two forms of the disease. It also included discussion of research on other diseases that could provide insights into research on diabetes.

Chemical Approaches to Nuclear Receptors and Metabolism (April 16–17, 2009). The goal of this workshop was to bring together scientists from different disciplines to encourage collaboration toward developing a better understanding of chemical modulation of nuclear receptor action and to identify future research directions. The specific focus of the workshop was on diseases and disorders associated with lipid and carbohydrate metabolism, obesity, and type 2 diabetes.

Imaging the Pancreatic Beta Cell, 4th Workshop (April 6–7, 2009). The purpose of the workshop was to explore the considerable progress and foster collaborative research in the field of imaging the pancreatic islet cell mass, function, or inflammation in health and disease. The goal of the field is to develop clinically useful imaging approaches for monitoring the mass, function, and inflammation of endogenous and transplanted islets and beta cells in people with type 1 or type 2 diabetes and those at risk for these diseases to understand the natural history of disease and to monitor therapy.

Organ Smooth Muscle: Development, Physiology, and Pathology (March 24–25, 2009). This workshop addressed current research on the biology of smooth muscle in organs and organ systems as well as future directions for research on smooth muscle.

Urologic Complications of Obesity and Diabetes (March 10–11, 2009). This meeting convened an international group of clinical, translational, and basic researchers to discuss the urologic complications of obesity and diabetes. Urologic diseases that disproportionately affect women were discussed at the meeting, including urinary incontinence and UTIs.

NIDDK New Research Directions for Urinary Incontinence Symposium 2009 (January 7–9, 2009). Urinary incontinence disproportionately affects women. This symposium provided an opportunity for international experts to come together and discuss the state of the science with respect to research on urinary incontinence as well as future directions for research. Summary report.

miRNA and Epigenetic Regulations of the Immune Response (December 11–12, 2008). Autoimmune diseases place a disproportionate burden on women. This workshop convened scientific experts in epigenetic and miRNA-mediated regulation of T cell development and function. It included discussion about emerging therapies for autoimmune diseases based on recent research in this field. Summary report.

Drug-Induced Liver Injury: Standardization of Nomenclature and Causality Assessment Workshop (December 1–2, 2008). This workshop evaluated the diagnostic criteria and means of assessing causality in drug-induced liver injury, with a goal of standardizing nomenclature, clinical measurements, causality instruments, and definitions of outcomes in this form of liver disease that places a disproportionate burden on women.

Dynamic Epigenome and Homeostatic Regulations in Health and Disease (November 13–14, 2008). Epigenetics is the study of stable genetic modifications that result in changes in gene expression and function without a corresponding alteration in DNA sequence. This meeting featured presentations on how sex-related gene expression in the liver may contribute to differences in conditions such as alcoholic fibrosis, hepatitis, and hepatocellular carcinoma in men and women, as well as on sex- and diet-specific epigenetic programming in the placenta that could affect the development of adult conditions, including obesity, metabolic syndrome, and diabetes. Summary report.

Neuroimaging in Obesity Research (October 27–28, 2008). This meeting convened researchers to discuss approaches for using functional neuroimaging to study brain involvement in various aspects of obesity such as weight gain and loss, eating behavior and eating disorders, the neurotransmitters and brain structures associated with energy balance, taste and smell, hunger, emotion, and decisionmaking.

Minority Health Disparities

Research Efforts to Reduce Health Disparities in NIDDK Diseases

Several of the diseases that disproportionately affect racial and ethnic minority populations in the United States are high-priority research areas for NIDDK. These diseases include type 2 diabetes, obesity, nutrition-related disorders, hepatitis C, gallbladder disease, H. pylori infection, sickle cell disease, kidney disease, and metabolic, gastrointestinal, hepatic, and renal complications from infection with HIV. Moreover, some of these diseases affect women and men differently within these disproportionately affected groups. The NIDDK Office of Minority Health Research Coordination (OMHRC) oversees Institute efforts to address these disparities. In addition to developing and overseeing an NIDDK strategic plan on minority health disparities, OHMRC has established and supports the Network of Minority Health Research Investigators (NMRI), a communication network of biomedical research investigators and technical personnel from traditionally underserved communities: African American, Hispanic American, American Indian, Alaskan Native, Native Hawaiian, and other Pacific Islanders. Through NMRI, NIDDK elicits recommendations for strategies to enhance the opportunities and implement mechanisms for support of minority investigators in biomedical research. NMRI is helping NIDDK to advance scientific knowledge and contribute to the reduction and eventual elimination of racial and ethnic health disparities. OHMRC also encourages NIDDK and NIH research training programs that help promote diversity in the biomedical research community. In 2009 and 2010, OHMRC held the seventh and eighth annual NIDDK NMRI Workshop, respectively. (http://www2.niddk.nih.gov/Funding/FundingOpportunities/Minority_Health_Research_Coordination)

Information and Education Efforts to Reduce Health Disparities

Several NIDDK-supported informational activities also address minority health disparities:

NIDDK Web Site Features Health Information in Spanish

NIDDK has three portals to feature Spanish-language materials and resources about diabetes, digestive diseases, and kidney and urologic diseases on its Web site. People looking for information about these diseases in Spanish can go directly to the Spanish-language portal pages (see below), where they will find an A to Z list of topics and titles. Also, the online system for ordering NIDDK materials includes descriptions in Spanish of available publications to help visitors choose the resources they want. Bilingual staff at the clearinghouses also can assist with phone orders from Spanish-speaking requestors.

Diabetes:
http://www.diabetes-espanol.niddk.nih.gov

Digestive Diseases:
http://www.digestive-espanol.niddk.nih.gov

Kidney and Urologic Diseases:
http://www.kidney-espanol.niddk.nih.gov

NIDDK's Awareness and Prevention Series

NIDDK has developed a health information series to raise awareness about diabetes, digestive diseases, and kidney and urologic diseases among people not yet diagnosed with these illnesses. NIDDK developed the Awareness and Prevention Series for community health fairs, workplace health forums, family reunions, and other similar events. Publications in the series are each two-page fact sheets—one side in English, the other side in Spanish—on a wide range of health topics. Each sheet gives readers a snapshot of an illness, highlighting risk factors, symptoms, prevention tips, and where to go for more information. By raising awareness of these illnesses—many of which disproportionately affect racial and ethnic minorities—NIDDK is providing necessary information to the public to promote prevention and early diagnosis of many common conditions.

Diabetes:
http://diabetes.niddk.nih.gov/dm/ap.htm

Digestive Diseases:
http://digestive.niddk.nih.gov/ddiseases/ap.htm

Kidney and Urologic Diseases:
http://kidney.niddk.nih.gov/kudiseases/ap.htm

Diabetes

Diabetes disproportionately affects racial and ethnic minorities in the United States. The National Diabetes Education Program (NDEP), jointly sponsored by NIDDK and CDC, works in partnership with public and private groups on efforts to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and, ultimately, to prevent the onset of diabetes. NDEP runs a national multicultural type 2 diabetes prevention campaign—the first in the Nation—with tailored materials and messages for high-risk audiences. "Small Steps. Big Rewards. Prevent Type 2 Diabetes" campaign materials include motivational tip sheets as well as print and radio public service ads. The "It's Never Too Early To Prevent Diabetes" component of this campaign is tailored to women with a history of GDM and their offspring—especially women from racial and ethnic minority groups in the United States, who are at particularly high risk for GDM. NIDDK recently partnered with ORWH to expand the "It's Never Too Early To Prevent Diabetes" campaign to raise awareness that women with a history of GDM are at increased risk of diabetes and their children are at increased risk of type 2 diabetes and obesity. In addition, using funds from ARRA to translate the Diabetes Prevention Program, NIDDK is testing evidence-informed, innovative intervention using NDEP materials to reach women who had GDM, to increase the number of them who get tested for diabetes after pregnancy. (See the section on Gestational Diabetes and Diabetes Prevention.) Another key NDEP campaign, "Control Your Diabetes. For Life," emphasizes the key elements of diabetes management to help prevent heart attack, stroke, and other diabetes complications. Materials for both campaigns are available in up to 15 different languages. Materials also are available to help children with diabetes, their families, and school personnel deal with diabetes, including a new Web resource called *Transitions* to help young adults transition from pediatric to adult health care. NDEP also has developed a Web resource called the *Support for Behavior Change Resource* for people with diabetes, people at risk for diabetes, their families, and health care professionals to support behavior change with approaches and available tools and programs that can be readily disseminated. Finally, NDEP has a version of its Web-based publications catalog in Spanish (see below).

NDEP: http://www.ndep.nih.gov

NDEP Transition Resource:
http://ndep.nih.gov/transitions

NDEP Support for Behavior Change Resource:
http://www.ndep.nih.gov/sbcr/index.aspx

NDEP catalog in Spanish:
http://www.ndep.nih.gov/diabetes/pubs/spanishcatalog.htm

Another school-based effort is the Diabetes Education in Tribal Schools (DETS) Project, on which NIDDK partners with the Indian Health Service. The DETS Project is a K-12 curriculum focused on increasing American Indian/Alaska Native students' understanding of health, diabetes, and maintaining life in balance; understanding and application of scientific and community knowledge; and interest

in science and health professions. NIDDK is building on the success of the DETS Project to develop a K–12 curriculum for African-American and Hispanic students.

Obesity

It is estimated that nearly 50 percent of adult non-Hispanic Black women in the United States are obese, using the BMI measurement—placing them at risk for many serious health complications. The Weight-control Information Network (WIN) program, "Sisters Together: Move More, Eat Better," is a national initiative that encourages African-American women to maintain a healthy weight by becoming more physically active and eating more healthful foods. Among its publications are "Celebrate the Beauty of Youth!," "Fit and Fabulous as You Mature," "Energize Yourself and Your Family," and "Walking...A Step in the Right Direction." WIN also has developed the "Sisters Together Program Guide" and reached out to groups and organizations to distribute this and other WIN materials. The program guide walks community leaders through the steps of program planning, implementation, and evaluation. WIN also offers Spanish-language publications for adults and teens concerning healthy eating and physical activity, such as the newly developed "Tu Salud es Muy Importante (Being Healthy Is a Big Deal)," "Hazte cargo de tu salud! Guia para jovenes (Take Charge of Your Health! A Guide for Teenagers!)," and its four-part series, "Como Alimentarse y Mantenerse Activo Durante Toda La Vida (Healthy Eating & Physical Activity Across Your Lifespan)." WIN also launched a focused effort to educate consumers and the media in 20 counties identified as having the highest rates of obesity in the country by distributing materials and resources. WIN has continued to pursue community outreach opportunities, including through an exhibition at the Women's Heart Day Health Fair in Washington, DC, in February 2009. (http://www.win.niddk.nih.gov/index.htm)

Kidney Disease

Racial and ethnic minorities suffer a far greater incidence and prevalence of irreversible kidney failure than Caucasians. Rates of ESRD are disproportionately greater in African Americans, American Indians and Alaska Natives, Native Hawaiians and other Pacific Islanders, and Hispanic Americans. Diabetic kidney disease is the most common cause of ESRD in all of the racial/ethnic minority groups in the United States except for African Americans, in whom high blood pressure–induced kidney damage is also a major cause. To help address these issues, NIDDK runs the National Kidney Disease Education Program (NKDEP). This educational program seeks to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk—those with diabetes, high blood pressure, cardiovascular disease, or a family history of kidney disease—and the availability of treatment to prevent or slow kidney failure in people with chronic kidney disease and those at risk. Among its many efforts, NKDEP created an educational brochure tailored specifically for African Americans at risk for kidney disease. The brochure—*Kidney Disease: What African Americans Need to Know*—explains the connection between diabetes, high blood pressure, and kidney disease and encourages those at risk to talk to their health care providers about getting tested. NKDEP also has been promoting an African-American Family Reunion Initiative whose goal is to encourage African-American families to discuss the connection among diabetes, high blood pressure, and kidney disease at reunions and other family gatherings, as well as Kidney Sundays, a faith-based initiative designed to increase awareness about chronic kidney disease in this community and encourage those at risk to get tested. NKDEP's Spanish-language initiative is meant to raise awareness about risk factors for chronic kidney disease among Hispanic Americans; it includes a Web site (http://www.nkdep.nih.gov/espanol) and brochure that highlight the connection between kidney disease and its primary risk factors—diabetes and hypertension. Both resources offer additional Spanish-language resources on diabetes, hypertension, and kidney disease. To help primary care providers and other health professionals explain estimated glomerular filtration rate (GFR) results to their patients, NKDEP has adapted its *Explaining GFR: A tear-off pad for clinical use* into Spanish, Chinese,

and Vietnamese. In addition to including simple explanations of the kidneys, kidney function, and GFR results, as well as suggested actions for maintaining kidney health based on the GFR result, the tool presents key education concepts and talking points for providers in Spanish.

Sources of Statistics for the NIDDK Report on Research on Women's Health FY 2009–2010

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National Institute on Drug Abuse

Executive Summary

As the foremost authority on drug abuse and addiction, sponsoring the vast majority of the world's research on the subject, the National Institute on Drug Abuse (NIDA) addresses the most fundamental and essential questions about drug abuse. The Institute does this by monitoring emerging trends, identifying and studying underlying physiologic and social factors and consequences, and determining how best to use this knowledge to develop, test, and implement prevention and treatment programs. Within this effort is a major focus on studying issues specific to women, as well as sex/gender differences.

Research in this area underscores the complexity of the relationship between drug use and male-female differences in biological and environmental determinants of vulnerability to drug addiction and its consequences. A growing body of research shows that for females, drug abuse can begin and progress differently than for males, is characterized by different risk and protective factors and motivations, and has different consequences and that intervention outcomes may be enhanced by sex/gender-specific considerations. In recognition of the important role of sex/gender in drug abuse, NIDA has strongly supported research to identify sex/gender differences and sex/gender-specific aspects of drug abuse and addiction and apply these findings to improve outcomes for both males and females across the lifespan.

The current knowledge base for understanding drug abuse is not equal in males and

females. Historically excluded from drug abuse studies (until the 1990s) due to their childbearing potential and to methodological issues associated with the menstrual cycle, women have not realized the benefits of some research findings affecting both treatment and prevention of drug abuse and addiction. Since 1994, when the National Institutes of Health (NIH) published guidelines on including women and minorities as clinical research subjects, the number of reports being published on drug abuse treatment for women has increased steadily, but more studies are needed that include sex/gender as a fundamental consideration in their design—from basic laboratory animal model studies to interventions aimed at preventing and treating drug abuse in humans.

Women's Health and Sex/Gender Research at NIDA

NIDA's Women and Sex/Gender Differences Research Program coordinator and deputy coordinator, along with NIDA's Women and Sex/Gender Research Group (WGRG), lead the effort at NIDA to promote research on issues specific to women and sex/gender differences in drug abuse. WGRG has representation from all of NIDA's divisions and offices, including research areas that range from genetics and basic biology to risk and protective factors, prevention, consequences, and treatment and services for drug abuse. The major goal of this effort, which has been ongoing for nearly two decades, is to infuse the study of sex/gender differences and female-specific issues into all areas of drug abuse research and to disseminate resultant findings.

NIDA's Women and Sex/Gender Differences Research Program coordinator and deputy coordinator attend to NIDA's scientific research in this area and serve as liaisons with the National Institutes of Health (NIH) Institutes and Centers (ICs), the Department of Health and Human Services (HHS) Office on Women's Health and other HHS agencies, as well as scientific organizations. They also represent NIDA on the Office of Research on Women's Health (ORWH) Coordinating Committee for Research on Women's Health.

Accomplishments

Research findings summarized below and published over the past 2 years represent NIDA's research on women and sex/gender differences. These findings are presented under five major topic areas: (1) basic and clinical neuroscience, (2) risk and protective factors, (3) prenatal drug exposure and treatment for pregnant and postpartum women, (4) treatment and services, and (5) HIV/AIDS. Collectively, these findings continue to provide evidence for the importance of taking a sex/gender-based research approach and analyzing data separately for males and females. Importantly, they show that identification and understanding of sex/gender differences can ultimately have implications for tailoring prevention and treatment interventions that will optimize outcomes for both males and females.

Basic and Clinical Neuroscience

Sophisticated animal models of addiction, both behavioral and neurobiological, are helping us to better understand the nature of the addiction process, factors that affect it, and the behavioral and neurobiological consequences of drug exposure and drug addiction. Our clinical studies in the human laboratory similarly are exploring sex differences in the biological and behavioral mechanisms underlying drug effects, with respect to both etiology and consequences. In this vein, the 1,000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000), which collected resting-state functional magnetic resonance imaging (fMRI) data from 1,414 participants, has identified sex and age as significant determinants of interindividual variability in connections among brain regions, which should help shed new light on the neurobiological basis of sex differences in drug abuse.

Studies of sex differences in animal models of drug addiction over the past two decades have provided a growing body of research revealing greater responsiveness of females than males on various behavioral outcomes. In cocaine self-administration studies, for example, a greater percentage of females than males acquire intraveneous self-administration, and they acquire it more rapidly, escalate more quickly to high levels of intake, and

exhibit greater motivation as measured by the progressive ratio procedure. In the reinstatement model of relapse to drug seeking, using a priming dose of cocaine to reinstate previously extinguished cocaine responding, females show greater reinstatement responding. Informed by animal research, NIDA-supported human laboratory studies also are uncovering ways in which men and women are differentially affected by drugs and how the neurobiology of addiction may differ. Illustrative basic and clinical research findings are synthesized below.

Sex Differences in Cocaine and Nicotine Self-Administration and Reward Extended to Adolescents. Because drug use for many adult users begins in adolescence, researchers are continuing to explore animal models of adolescent drug exposure. As with adults, when both males and females are studied, sex differences are often found. For example, researchers at the University of Virginia examined cocaine self-administration in male and female adolescent rats and found that females acquired cocaine self-administration more rapidly than males and that the number of cocaine infusions varied with the estrus cycle. Researchers at the University of Miami further found that social enrichment (provided by addition of cage mates) can modulate cocaine reward, producing different effects in adolescent males and females—it decreased cocaine reward in males but had no effect in females. Similarly, findings on sex differences in nicotine self-administration in adolescent animals align with those seen in adults: a greater percentage of females acquire self-administration under low-dose conditions, and females show greater motivation to obtain nicotine, the latter in late adolescence only, suggesting that nicotine's effects may be modulated by gonadal hormones, as reported in humans.

Circulating Estrogen and Progesterone's Effects on Cocaine Self-Administration. Animal model researchers are exploring various basic mechanisms that may influence sex differences in addiction-related behavioral outcomes. Estrogen's facilitative role in these various outcomes is well established. In the past few years, an important role for another ovarian hormone, progesterone, has emerged. Whereas estrogen's role is facilitative, progesterone's is inhibitory when in comes to cocaine self-administration. Moreover, this effect seems to be estrous-cycle dependent; researchers at the Medical University of South Carolina showed that progesterone reduced cocaine-primed reinstatement of cocaine seeking in female rats during the estrus phase when progesterone is low but not during phases when progesterone is already high.

Sex Differences in Brain Dopamine Systems. Recent research has shown sex differences in brain reward systems that could contribute to sex differences in addiction. Dopamine is a major brain neurotransmitter involved in brain reward systems and drug addiction, and its actions are influenced by circulating gonadal hormones in adult females. Researchers at Duke University found that testosterone and estrogen in puberty may influence developing brain dopamine systems, and this influence may underlie sex differences in cocaine responsivity observed in puberty and in adulthood. In addition, researchers at Northwestern University found that neuronal spine density and spine head size in both the core and shell of the nucleus accumbens were greater in females than in males. This finding demonstrates sex differences in the neuroanatomy of this region, where dopaminergic and glutamatergic input plays a major role in addiction. At Wake Forest School of Medicine, researchers found greater sensitivity of male compared with female monkeys to dopamine D1 receptor and D3/D2 receptor agonists. Together these studies contribute to the nascent study of the neurobiological basis of sex differences in drug-related behaviors.

Findings in Human Laboratory Research Show Differences by Gender. Human laboratory research is revealing ways in which men and women are differentially affected by drugs, with varying impacts on sleep, decision-making, and response to stress and drug cues. Complementary to animal studies are clinical studies of progesterone showing that cocaine cue-induced craving is inversely related to circulating plasma progesterone levels in women and that experimentally administered progesterone decreases the positive subjective effects of cocaine in women

but not men. Investigators at Yale University School of Medicine found that when progesterone was administered to abstinent smokers, it improved their cognitive functioning and attenuated their smoking urges. Together, these studies suggest that progesterone could be an effective treatment for drug abuse in women.

Risk and Protective Factors Variability by Gender

Evidence from NIDA's field-based research indicates that drug use by males and females may begin and progress differently and is often characterized by different risk and protective factors. Thus NIDA supports research on environmental risk and protective factors and also devotes considerable effort to understanding the genetic basis of drug abuse. Data analyzed by gender reveal outcomes that often vary by gender. Identifying these male/female- based outcomes is important for designing tailored prevention programs for males and females. Selected advances in these lines of research are described below.

Adolescent Exposure to Intimate Partner Violence and Substance Use in Young Adulthood. University of Albany researchers investigated whether adolescent exposure to intimate partner violence increases the risk for problem substance use in early adulthood and whether this relationship differs by gender. They studied a subsample of 508 participants from the Rochester Youth Development Study, a longitudinal study of urban, largely minority adolescents that oversampled youth at high risk for antisocial behavior and drug use. Results revealed that young women exposed to severe intimate partner violence as adolescents were at five times increased risk of alcohol-use problems in early adulthood. This outcome, which did not occur in young men, suggests the need for targeted intervention for girls exposed to intimate partner violence.

Physical and Relational Aggression Differentially Predict Substance Use in Male and Female High School Students. University of Southern California researchers longitudinally investigated relationships between physical and relational aggression and drug use in a group of 2,064 high school students. At baseline, males reported engaging in more physical aggression than females; however, females and males reported engaging in similar rates of relational aggression. Physical aggression at baseline was found to predict alcohol use 1 year later for males but not for females. Relational aggression predicted cigarette use and marijuana use for females but not for males; it predicted later alcohol and drug use equally across gender. These results have implications for developing gender-based preventions targeting physical and relational aggression.

Parenting and Permissiveness and Drinking Among College Students: Gender Matters. In a sample of 500 students, researchers at Pennsylvania State University examined whether parental use of alcohol and permissibility of alcohol use in late high school students were related to alcohol use and experience of negative drinking consequences (e.g., hangover, trouble at work or school, arrests for drunkenness) when the students were college freshmen. The researchers found that parental permissibility of alcohol use was a consistent predictor of teen drinking behaviors, which then was strongly associated with experiencing negative consequences of drinking. Parental use of alcohol was also a risk factor and varied with the gender of the parents and teens: maternal drinking was a risk factor only for daughters, and the family drinking environment (e.g., alcohol-related behaviors of mothers, fathers, and parents in general) was a risk factor only for sons.

Parental Monitoring and Girls' Marijuana Use. Researchers at Claremont Graduate University conducted a meta-analysis of associations between adolescents' perceptions of parental monitoring (parental knowledge of child's whereabouts, activities, and relations) and their marijuana use. Analyses were conducted using 25 independent samples from 17 empirical studies involving 35,367 unique participants. Analyses revealed that the association between these two factors was significantly stronger in female-only samples. The results also indicate that parental monitoring of girls was associated with less drug use as well as more protection against adverse effects of drugs.

***MAOA* Methylation Related to Substance Dependence Only in Women.** NIDA-supported research is increasingly exploring how epigenetic phenomena, such as DNA methylation, reflect gene and environment interactions related to vulnerability to drug abuse. Using data from 191 participants in the Iowa Adoption Studies, University of Georgia researchers found highly significant associations between methylation changes at a certain gene locus (monoamine oxidase A) and lifetime symptom counts for both nicotine and alcohol dependence in females but not in males. Although it is not known whether the methylation changes occurred before or after the substance dependence, these findings suggest that methylation could play a role in the genesis of substance dependence and warrant further investigation.

***GABRA2* and Risk for Alcohol, Nicotine, and Cannabis Dependence Greater in Women.** Prior studies have shown that variation at a particular genetic locus known as GABRA2 alters vulnerability to alcohol dependence. University of Georgia researchers have now found that genetic variation at this locus is associated not only with alcohol dependence but also with nicotine and cannabis dependence. Furthermore, these associations were markedly stronger in females than in males.

Substance Abuse Interventions Targeting Risk and Protective Factors

Research described below is showing that interventions targeting mothers are providing promising results in reducing substance use and producing positive changes in risk and protective factors for themselves and their children.

Mother-Daughter Computer-Delivered Prevention Program. Columbia University researchers developed a computer-mediated intervention program to prevent underage drinking among early adolescent girls, enhance mother-daughter relationships, and teach girls skills for managing conflict, resisting media influences, refusing alcohol and drugs, and correcting peer norms about underage drinking, smoking, and drug use. Two months following program delivery and relative to a control group that did not receive this program, girls and mothers in the program had improved their mother-daughter communication skills and their perceptions and applications of parental monitoring and rule-setting regarding the girls' alcohol use. At 2 years followup, girls in the intervention program reported lower relevant risk factors and higher protective factors as well as less past 30-day use of alcohol, marijuana, other illicit and prescription drugs, and inhalants. Mothers in the intervention program exhibited more positive outcomes on variables linked with reduced substance use risk among their daughters; and they themselves reported lower rates of weekly alcohol consumption. These findings lend support to the potential of gender-specific, parent-involvement, and computerized approaches to preventing substance use among early adolescent girls.

Nurse-Family Partnership Program. Researchers at the University of Colorado at Denver have reported outcomes from a 12-year followup of a randomized trial of a prenatal and infancy nurse home-visiting program aimed at improving maternal and child outcomes, including substance abuse. This study was conducted with an urban, primarily African-American sample of first-time mothers and their firstborn children. The 515 mothers in the control condition were provided free transportation for scheduled prenatal care plus developmental screening and referral services for their children at ages 6, 12, and 24 months, and the 228 mothers in the nurse-visited condition were provided the same services as those in the control group, plus prenatal and infancy home visiting through their child's second birthday. The results showed that when firstborn children were 12 years old, mothers in the nurse-visited group had fewer alcohol and drug abuse problems and longer partners relationships compared with mothers in the comparison group. Children of these mothers were reported to have fewer substance use problems, higher academic achievement, and fewer internalizing problems at age 12.

A Brief Family Intervention for Maternal Depression. Researchers at the University of Pittsburgh investigated maternal depression and its association with child problem behavior, particularly in early childhood, in a sample of 731 families receiving services from the Women, Infants, and Children's

(WIC) program, a national food supplement and nutrition program. Families with toddlers between ages 2 and 3 were screened and then randomized to a brief family intervention, the Family Check-Up, which included linked interventions tailored and adapted to the families' needs. Results indicated intervention effects for early externalizing and internalizing problems from ages 2 to 4 and reductions in maternal depression from ages 2 to 3, which produced improvements in both externalizing and internalizing child problem behavior. This intervention provides a promising approach for reducing maternal depression, which may lead to greater parenting efficacy and reduced behavior problems in children and adolescents.

Drug Use in Pregnancy—Outcomes in Children and Treatment for Pregnant and Postpartum Women

All drugs of abuse cross the placenta to expose the fetus. Therefore, prenatal drug exposure is an important consequence of drug use and remains a public health concern. Despite the well-established dangers of using licit and illicit drugs during pregnancy, pregnant women continue to use these substances. The latest National Survey on Drug Use and Health (NSDUH) data, combined from the 2008 and 2009 surveys, reveal that 4.5 percent of pregnant women reported past-month use of illicit drugs. In addition, NSDUH reported alarming data concerning pregnant girls aged 15 to 17—15.8 percent reported past-month illicit use compared with 13 percent of nonpregnant girls of that age, and 20.6 percent reported past-month smoking versus 13.9 percent of nonpregnant girls of that age. Among women aged 15 to 44, 15.3 percent of pregnant women reported past-month cigarette smoking.

NIDA's longitudinal outcome studies continue to identify specific, often subtle differences in development between drug-exposed and nonexposed children. NIDA research also is continuing to strive to identify how best to provide treatment for pregnant and postpartum women, both for their drug addiction and for their psychiatric comorbidities that can affect drug addiction treatment success. NIDA also continues its long-term support of animal models of prenatal drug exposure, which is the only approach that allows for the ethical study of many of the relevant questions in this area. Outcomes serve the important function of providing guidance for the study of human cohorts. Highlights of recent results of these lines of research are described below.

Drug Use in Pregnancy—Effects on the Child

Drug use during pregnancy, including legal drugs such as nicotine and alcohol, has been associated with potentially deleterious and long-term effects. These effects may include heightened risk of drug abuse in the offspring, which is being studied in longitudinal cohorts followed since birth. There is also evidence that negative outcomes in exposed children can be ameliorated by supportive home environments and good-quality parenting. The research summarized below describes recent advances in identifying such effects, from birth well into adolescence, across several domains from brain to behavior. Some of this research has revealed that outcomes vary by gender.

Cocaine

Research on the effects of prenatal cocaine on infant outcomes and child development is finding troubling associations with physiologic, behavioral, and cognitive developmental deficits. Studies often report outcomes that differ in boys and girls. Recent findings are based on a range of ages across multiple outcomes, such as behavior problems, IQ scores, respiratory regulation, and more. Some of these findings are preliminary, and additional studies are needed before conclusions can be drawn. Select examples follow:

- Findings from the ongoing Maternal Lifestyle Study—a multisite longitudinal cohort study of development following prenatal exposure to cocaine and other substances—continue to reveal associations between maternal cocaine use and various health and behavioral outcomes in children followed since birth. These outcomes include elevated body mass index (BMI) and thus blood pressure levels in 9-year-old children, as well as blunted hormonal reactivity to stress in 11-year-olds, possibly increasing risk for later psychopathology and adult disease.

- Researchers at Drexel University College of Medicine studied IQ in a sample of 231 children at ages 4, 6, and 9 who were exposed to cocaine prenatally compared with controls. Cocaine-exposed boys had lower composite IQ scores compared with exposed girls—even after taking into account prenatal exposure to other drugs, neonatal medical risk, environmental risk, and maternal verbal intelligence. They also had lower scores in the Abstract/Visual Reasoning subscale. The observed outcomes for boys are consistent with prior research showing that the central nervous system in male fetuses may be more susceptible to the influence of intrauterine factors.
- NIDA's Intramural Research Program scientists have been examining the effect of prenatal cocaine exposure on early brain development in a rodent model. The research has shown that cocaine inhibits the generation of neural progenitor cells because cocaine is metabolized in a manner that creates cellular stress. More recently, the researchers found that cocaine interrupts radial migration of neurons in the neocortex, which may be responsible for impaired intellectual development and other adverse outcomes observed in children prenatally exposed to cocaine. The researchers are currently developing models that will allow them to determine whether the effects they have observed can be prevented by blocking oxidative cocaine metabolism with inhibitor drugs.

Methamphetamine

Research is examining the effects of prenatal exposure to methamphetamine on children's development from birth to age 15. Outcomes range from neurobiological to neurobehavioral and neurocognitive effects.

- Brown University researchers studying 559 infants from the United States and New Zealand from birth to 36 months found that those with methamphetamine exposure had poorer quality of movement and more indicators of physiologic and central nervous system stress.
- UCLA researchers investigated the independent and combined effects of prenatal methamphetamine and alcohol exposure on local brain volume using MRI among 61 children aged 5 to 15 years. Volume reductions were observed in those with combined use and with alcohol-only use relative to controls. Within the combined group, more severe striatal damage was associated with lower IQ.
- UCLA researchers also studied neurocognitive systems effects among children aged 7 to 15 years who had differing prenatal exposures (methamphetamine, alcohol, both) while they were engaged in a verbal paired-associate learning task. fMRI showed activation of more diffuse brain regions in the methamphetamine group, including structures known to be important for memory, and may reflect recruitment of compensatory systems to support performance of the verbal memory network.

Nicotine

Two recent studies have reported relationships between prenatal nicotine exposure and conduct disorders as well as hyperactivity-inattention in childhood; in both studies, the outcomes differed in boys versus girls. In the first study, University of York researchers found that boys whose mothers persistently smoked heavily throughout pregnancy were at significant risk of conduct disorders compared with sons of nonsmokers, with daughters of light or heavy smokers also at significant risk of conduct problems. However, daughters of the latter group were not at risk of hyperactivity-inattention, but boys were. In the second study, researchers at the University of Illinois at Chicago found that in adolescents prenatally exposed to nicotine, the *MAOA* genotype differentially predicted conduct disorder: in boys, the low-activity genotype was predictive, whereas in girls, the high-activity genotype was predictive.

Drug Use in Pregnancy—Treatment Needs and Approaches

The research highlighted above underscores the importance of substance use treatment for mothers before their babies are born as well as after. NIDA researchers have recently made important advances in identifying treatment needs and developing treatments for pregnant and postpartum women. Topics highlighted

below include opiate dependence treatment, psychiatric comorbidity, smoking cessation, and the benefits of treatment generally for mother and baby. Treatments may need to address a broad array of psychiatric comorbidities (e.g., substance use disorder [SUD] with posttraumatic stress disorder [PTSD] and various psychosocial impairments).

Buprenorphine Treatment for Opioid-Dependent Pregnant Women: Less Withdrawal Distress and Shorter Hospital Stay for Babies. Treatment of pregnant women addicted to opiates is critical for both mother and infant. Babies born to women addicted to opioids fare better when their mothers are treated during pregnancy with either the addiction medication buprenorphine or methadone than babies whose mothers are not treated at all. In a comparative effectiveness trial conducted by a multidisciplinary team of researchers from North America and Europe, buprenorphine was found to be superior to methadone in reducing neonatal abstinence (NAS) withdrawal symptoms, with newborns requiring less medication and less time in the hospital after birth. The research project, called Maternal Opioid Treatment: Human Experimental Research (MOTHER), will give health care providers and their opiate-dependent patients vital information to help them choose the treatment offering the greatest benefits. Results of the study are being used to support a request for a Food and Drug Administration (FDA) review of labeling changes for both medications.

Psychiatric Comorbidity Among Pregnant Women With Substance Use Disorders. Women who use drugs during pregnancy often have co-occurring psychiatric disorders. Co-occurrence of drug dependence and other psychiatric disorders is associated with poorer treatment outcomes. In a study of pregnant smokers conducted at Columbia University, researchers found that about 45 percent met the criteria for at least one psychiatric disorder. Among smokers with nicotine dependence, the comorbidity rate was 57.5 percent. Nicotine dependence during pregnancy significantly predicted any psychiatric disorder, any mood disorder, major depression, dysthymia (i.e., mild, chronic depression), and panic disorder. In non-nicotine-addicted smokers, however, no significant associations between cigarette use and other psychiatric disorders were found.

Voucher-Based Incentives for Smoking Cessation Treatment Also Improve Fetal and Infant Outcomes. A University of Vermont clinical trial showed that a smoking cessation treatment providing opportunities to earn vouchers exchangeable for retail items by abstaining from smoking improved quit rates among low-income pregnant and postpartum women. At the end of pregnancy, the abstinence rate was 41 percent compared with 10 percent in the control group, and at the 12-week postpartum assessment, the prevalence of smoking abstinence was 24 percent compared with 3 percent in the control group. Greater fetal growth also was associated with the incentive-based treatment, along with increased breastfeeding duration in postpartum women. This research indicates that voucher-based incentives can decrease maternal smoking and have positive effects on fetal and infant health outcomes.

Substance Abuse Treatment and Services: Gender Matters

NIDA's treatment and services research is increasingly adopting a gender-based approach and addressing special issues in women. This research has shown that women are underrepresented among individuals seeking drug abuse treatment, even when their lower drug abuse prevalence rates are taken into account. Women also enter treatment with different treatment and services needs (e.g., medical, psychiatric, educational, employment, child care).

The research described below highlights recent advances in our understanding of gender differences in severity and vulnerability to substance dependence, gender differences in psychiatric comorbidity, progress in women-specific treatments, benefits of service interventions, and progress in addressing smoking cessation in women.

Male Versus Female Rates of Substance Dependence—A Closer Look

The 2009 National Survey on Drug Use and Health (NSDUH) reported that the rates of past-year substance dependence or abuse

are more than twice as high in males (3.8 percent) as females (1.6 percent). However, these data do not account for the fact that more males use drugs than females. A recent NIDA study analyzed data aggregated from the 2002–2005 NSDUH to determine whether rates of substance use disorders among drug users differed between men and women. The study found that girls aged 12 to 17 years exceeded boys in their use of alcohol and their nonmedical use of psychotherapeutics and among users were significantly more likely to be dependent on psychotherapeutics than boys. Among young adults, the proportion of female users reporting dependence on cocaine or psychotherapeutics was significantly higher than for male users, who nonetheless reported significantly greater use of these drugs. Understanding the reasons for these differences and continuing to evaluate these patterns over time could help in the development of targeted and more effective prevention and treatment interventions.

A close look at data from individuals in treatment reveals a clinical picture that differs for male versus female drug-dependent patients. For example, women typically enter treatment with more psychiatric comorbidities and a greater need for treatment services. Two recent studies from NIDA's Clinical Trials Network (CTN) illustrate the need to look beyond population-based differences in dependence/abuse rates between men and women. The first shows that females are more severely dependent on illicit stimulant drugs than males; the second, that female cocaine users are more likely than male users to be cocaine dependent.

- In the first study, researchers identified the presence of DSM-IV (Diagnostic and Statistical Manual-IV) subtypes for dependence on cocaine and amphetamines among 415 outpatient stimulant users at 8 geographically diverse community treatment programs in the United States. Among the four subtypes of primary cocaine users identified, 67 percent of the women were in the most severe subtype versus 45 percent of the men. Among the three subtypes of primary amphetamine users identified, 71 percent of the women were in the most severe subtype versus 44 percent of the men.
- The second, and related, CTN study examined rates of cocaine dependence among 682 patients across 14 community treatment sites and found that, among cocaine users, women were more likely than men to meet the diagnostic criteria for dependence independent of age, race/ethnicity, years of cocaine use, addiction treatment history, comorbid drug dependence diagnoses, and treatment setting.

Substance Use Disorders and Psychiatric Comorbidity

A high prevalence of co-occurring psychiatric disorders exists among individuals with SUDs. This co-occurrence is higher among women than men and has been shown to negatively affect the substance abuse treatment outcomes. A history of trauma is also highly prevalent among women with SUDs as are trauma-related disorders such as PTSD and other co-occurring employment, family/social, and psychiatric problems. As the studies described below show, there is growing evidence that trauma-related histories and co-occurring psychiatric pathology play a role in substance abuse and treatment outcomes.

Childhood Trauma and Cocaine Relapse. A Yale University School of Medicine study highlights the need for women in substance abuse treatment to receive comprehensive assessment for trauma-related history and pathology. Researchers found that childhood trauma differentially affected cocaine relapse among women and men receiving inpatient treatment: for women, greater severity of childhood emotional abuse was associated with an increased risk of relapse within 90 days after discharge, with number of use days during the followup associated with the severity of emotional abuse, sexual abuse, and overall childhood trauma. In men, there were no associations between childhood trauma and cocaine relapse outcomes.

Treatment for Women With Co-Occurring SUDs and PTSD. The NIDA CTN conducted the largest randomized clinical trial to date of a trauma-focused behavioral therapy for women with co-occurring SUDs and PTSD. In the trial, 353 women from 7 community-based

intensive outpatient substance abuse treatment programs throughout the United States were randomized to receive either a women's health psychoeducational intervention or Seeking Safety treatment, a trauma-focused, short-term manualized therapy using cognitive-behavioral strategies. The trial yielded several important findings regarding treatment of women with co-occurring SUDs and PTSD. One finding was that implementing trauma-focused treatment within a substance abuse program did not adversely affect substance use outcomes, which contradicted conventional wisdom suggesting that the two should be addressed separately and sequentially. Seeking Safety produced greater PTSD symptom reduction than the control condition in women with alcohol misuse and more severe PTSD symptoms, suggesting a particular benefit for this subgroup of women. A followup secondary analysis found that Seeking Safety also produced better drug abuse outcomes than the control condition among women who had more severe substance use at the start of treatment and who had reductions in their PTSD symptoms during treatment.

Added Benefits of Women-Focused Group Therapy for Substance-Abusing Women. A pilot clinical trial conducted at Harvard University not only holds promise as a new substance abuse treatment for women, it also demonstrates that group substance abuse therapy can have the added benefit of improving psychiatric symptoms. The randomized study compared the newly developed 12-session women-focused women's recovery group (WRG) treatment with a mixed-gender group drug counseling (GDC) group. At treatment end, both interventions were equally effective in reducing substance use. However, at a 6-month followup, the WRG demonstrated significantly greater reductions in drug and alcohol use compared with the GDC. And within the WRG, women with high psychiatric severity had greater reductions in substance use than those assigned to the mixed-gender GDC group. Finally, improvement in depression, anxiety, and general psychiatric symptoms remained durable through the 6-month followup for both treatment groups.

Improving Smoking Cessation Outcomes in Women

Cigarette smoking and nicotine addiction is one of the most common, and most difficult, substance abuse problems to treat. Although there has been a decline in smoking in the United States in recent years, the decline is greater in males than in females and studies have shown that women have more difficulty quitting than men. Nicotine replacement therapies are effective for both men and women but are less effective for women. Thus, NIDA supports a program of behavioral and combined behavioral and pharmacologic research that includes a focus on women. In addition, research is examining the role that the menstrual cycle plays in smoking and how that knowledge may lead to better treatment outcomes. Other research is using brain imaging to predict treatment outcomes, with the hope that this knowledge could lead to individually tailored interventions. Some highlights of these recent advances are described below.

Smoking and the Menstrual Cycle. For several years, NIDA researchers have been reporting that the menstrual cycle plays a role in various aspects of smoking. For example, a recent study of heart rate and skin conductance reactivity to smoking cues and stressful imagery cues conducted at the Medical University of South Carolina found that reactivity varied with the menstrual cycle, with both measures highest in follicular phase. This finding suggests that women who smoke in response to stress and/or cigarette cues may have greater difficulty trying to quit in the follicular phase than in the luteal phase. Similarly, University of Minnesota researchers recently found that on the quit day, craving at wake-up was significantly greater in the follicular phase than the luteal phase and that craving at wake-up was a significant predictor of time to relapse. Researchers are continuing to explore how consideration of the menstrual cycle plus associated factors such as craving and withdrawal can together optimize outcomes in smoking cessation attempts in women.

Using Brain Imaging To Predict Smoking Cessation Success. A new line of investigation that holds promise for identifying nicotine-dependent women at high risk for

relapse is using brain imaging technology. In a study of women smokers, researchers at Harvard University found that when assessed before a quit attempt, fMRI brain reactivity to smoking-related images and brain reactivity to an Emotional Stroop test, which involved smoking-related words, predicted the ability to maintain tobacco abstinence. Women who "slipped" (smoked one or more cigarettes after abstinence) had heightened fMRI reactivity to smoking-related images in brain regions implicated in emotion, introspective awareness, and motor planning and execution. Findings suggest that relapse-vulnerable women smokers can be identified before quit attempts, with implications for individually tailored interventions.

Smoking Cessation for Weight-Concerned Women. Women smokers who are concerned about postcessation weight gain have poorer cessation outcomes than women without this concern. Adding weight-control interventions to standard cessation counseling does not improve outcomes in weight-concerned female smokers; neither does adding buproprion (e.g., Wellbutrin). A cognitive behavior therapy developed by University of Pittsburgh investigators to address weight concerns (versus trying to control weight) does improve cessation outcomes over standard cessation counseling, and in this case the addition of bupropion further improves outcomes.

HIV/AIDS—Risks and Intervention

Among both males and females, few drug abuse consequences are more severe than HIV infection. Drug abuse heightens the risk of contracting HIV through shared injection equipment and altered decisionmaking, resulting in increased sexual risk-taking behaviors. However, although all groups are affected by HIV/AIDS, not all are affected equally, with drug-involved women among the fastest growing groups with AIDS. Recent data show that among persons living with an HIV diagnosis, 73 percent of females contracted HIV via heterosexual contact compared with 12 percent of males; among persons living with an AIDS diagnosis, 65 percent of females contracted HIV via heterosexual contact compared with 11 percent of males. Indeed, along with injection drug use (IDU), heterosexual contact is a larger factor in both HIV and AIDS in females than in males.

To address these HIV/AIDS issues in women, NIDA's HIV/AIDS research portfolio includes studies of gender-related differences in factors that contribute to and protect from HIV risk. Other studies are pursuing gender-specific strategies to decrease IDU and high-risk sexual behaviors among women and men. Highlights of selected research findings summarized below demonstrate the importance of assessing HIV risk factors and prevention and treatment interventions separately by gender.

HIV Risk Factors for Women

The representative studies described below highlight the need for integration of HIV sexual risk reduction interventions into substance abuse treatment programs, with attention to gender-specific risk factors.

Adolescent Girls and HIV. In a sample of 409 HIV-infected youth 13 to 24 years of age, Johns Hopkins University researchers found that young women who have sex with men (WSM) reported significantly lower rates of condom use at last sex with their male partner compared with men who have sex with men (MSM). In general, sexual risk behaviors for HIV were high among both WSM (68.1 percent) and MSM (74.7 percent). These high rates underscore the need for targeted interventions with HIV-infected youth.

Gender Differences in the Rates and Correlates of HIV Risk Behaviors Among Drug Abusers. In a secondary data analysis, researchers in NIDA's CTN identified gender differences in the rates and correlates of HIV risk behaviors among 1,429 individuals participating in multisite trials throughout the United States between 2001 and 2005. Women had overall higher sexual risk than men due to multiple partners and unprotected sex, whereas men were more likely to inject drugs than women. Greater alcohol use and psychiatric severity were associated with higher risk behaviors for women, whereas impaired social relations were associated with decreased risk for men. Identification of specific risk factors that are differentially predictive of HIV risk behaviors for women and men

underscores the need for gender-specific risk-reduction interventions.

HIV Prevention and Treatment Efforts

Because drug-involved women are among the fastest growing group with AIDS, sexual risk reduction interventions for them are a public health imperative. The following studies highlight promising intervention efforts, as well as NIDA research on HIV treatment.

Drug Treatment Is Associated With Better HIV Treatment Adherence. Using longitudinal data from the Women's Interagency HIV Study to evaluate the relationship between drug abuse treatment modality and adherence to antiretroviral therapies, researchers found that women who reported accessing a drug abuse treatment program, irrespective of modality, were significantly more likely to report adherence to their antiretroviral regimens. Involvement in either a medication-based or medication-free drug treatment program was similarly associated with improved adherence. These data point to the need for coordinated efforts to enroll HIV-positive drug-using women into treatment programs to improve HIV disease outcomes.

Interventions Named by the Centers for Disease Control and Prevention as Providing "Best or Promising Evidence" in 2009. Aimed at reducing HIV risk behaviors in men and women by targeting high-risk populations, the interventions summarized below produced positive outcomes with sustained benefits:

- *Motivational Interviewing–Based HIV Risk Reduction.* Women with incarceration histories show high risk for HIV and intimate partner violence (IPV). Researchers in Portland, OR, conducted a randomized controlled trial with more than 500 women who had recent criminal justice system involvement and were at risk for HIV and IPV. The Portland Women's Health Study evaluated two motivational interviewing–based interventions to reduce either HIV or HIV and IPV risk. At followup, the intervention groups had significant decreases in unprotected intercourse and needle sharing compared with controls, and IPV decreased over time in all three groups, although not differentially.
- *Real Men Are Safe.* In this NIDA CTN study, 288 men in methadone maintenance and 301 men in outpatient psychosocial treatment were randomly assigned to attend either Real Men Are Safe (REMAS) or HIV education. REMAS participants engaged in significantly less unprotected sex than the education participants. Completers reduced unprotected sex 21 percent from baseline to 6-month followup compared with just a 2-percent reduction among the education group.

Initiatives

NIDA seeks to promote and facilitate research on sex/gender differences and issues specific to women by using a variety of strategies, some of which are listed below. These strategies include the issuance of funding opportunity announcements, travel awards, development and sponsorship of symposia and meetings, scientific presentations, and publications.

Multisite Initiatives—"Pooling Our Efforts"

NIDA's Clinical Trials Network (CTN). NIDA's CTN, (http://www.nida.nih.gov/CTN) is a national consortium of drug abuse investigators and community treatment providers (CTPs) who cooperatively develop, validate, refine, and deliver new treatment options to patients in community-level clinical practice. Currently, CTN comprises 13 regional centers at academic medical centers, affiliated with 57 academic institutions and more than 240 CTPs throughout the United States and Puerto Rico. CTN has conducted 6 multisite studies specifically targeting gender differences, publishing 25 manuscripts from this work. These studies focused on (1) treatment outcomes or services for special populations of women with SUDs, including pregnant women and women with co-occurring disorders (e.g., PTSD and eating disorders); and (2) gender differences in HIV risk behaviors and outcomes of gender-specific protocols for HIV risk reduction. In addition, CTN has conducted three secondary analyses

across multiple studies examining specific gender differences. CTN established a Gender Special Interest Group, which has played a key role in the overall gender research across the CTN studies and identified substance abuse research areas that could benefit from additional attention to gender-related outcomes. Currently, data for 23 multisite studies are available for secondary analyses at http://www.ctndatashare.org. NIDA encourages investigators to take advantage of these data for addressing gender-specific questions. In addition, as new trials are planned, NIDA invites scientists to work with the trial investigators to plan ancillary or platform studies to provide needed information on issues that can affect women in drug abuse treatment.

The 1,000 Functional Connectomes Project. The 1,000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000) is a paradigm-shifting grassroots effort that has successfully aggregated resting-state fMRI-based brain connectivity data from more than 1,000 healthy control subjects; data were freely donated from 35 different neuroimaging laboratories. The robust and relatively consistent nature of the resting-state signal across individuals and labs enables pooling of data despite differences in image data acquisition from site to site. This capability has enabled tremendous statistical power to examine effects such as age and gender. An initial analysis of the pooled data indicates significant gender differences in connectivity of brain regions when the brain is at rest. Future efforts may disentangle relationships between these differences and emotion-processing, personality, and other traits and provide a platform for further understanding of male-female differences in drug addiction. The 1,000 Functional Connectomes Project is supported by grants from NIDA, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and NIH's Blueprint for Neurosciences Research (http://neuroscience-blueprint.nih.gov; Contract N02-EB-6-4281, to TCG, Inc.).

NIDA-Issued Funding Opportunity Announcements (FOAs)

The following are NIDA-issued funding opportunity announcements, including requests for applications (RFAs), program announcements (PAs), and notices (NOT) in effect during 2009 and 2010 that seek to promote research on sex/gender differences and issues specific to females:

NIDA-Issued FOAs Specific to Women and Sex/Gender Differences

- PAR-10-020, Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Sex/Gender Differences (R36), re-released January 16, 2010.
- PA-11-047, PA-11-048, PA-11-049, Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence, re-released November 5, 2011: R01 (047), R21 (048), R03 (049).

Other NIDA-Issued FOAs with an Emphasis on Women and Sex/Gender Differences

- PA-09-106, PA-09-107,. Medications Development for the Treatment of Pregnant/Postpartum Women With Substance-Related Disorders and/or In Utero Substance-Exposed Neonates, released March 3, 2009: R01(106), R21(107).
- RFA-DA-10-001, RFA-DA-10-002, Substance Use and Abuse Among U.S. Military Personnel, Veterans, and Their Families, released July 29, 2009: R01 (001) and R21 (002).
- PAR-10-018, Accelerating the Pace of Drug Abuse Research Using Existing Epidemiology, Prevention, and Treatment Research Data (R01), released October 2009.
- RFA-DA-10-017, Seek, Test, and Treat: Addressing HIV in the Criminal Justice System (R01), released November 24, 2009.

Other FOAs in Which NIDA Participates

In addition to the above NIDA-issued FOAs, NIDA participates with other ICs in the following announcements that seek to promote

research on sex/gender differences and issues specific to females:

- PAS-10-226 (R21), ORWH-led, Advancing Novel Science in Women's Health Research (ANSWHR), released July 1, 2010.
- PA-09-175, NIMH-led, Women's Mental Health in Pregnancy and the Postpartum Period (R21), released April 25, 2009.
- PA-08-191, ORWH-led, Research Supplements To Promote Reentry into Biomedical and Behavioral Research Careers, released July 1, 2008, expiration date September 30, 2011.
- NOT-Al-10-023, NIAID-led, Limited Competition: Administrative Supplements for HIV/AIDS Implementation Science in PEPFAR Settings, released April 5, 2010.

Nurturing the Next Generation of Researchers: NIDA-Sponsored Travel Awards on Women and Sex/Gender Differences

Women and Gender Junior Investigator Travel Award Program for the Annual Meeting of the College on Problems of Drug Dependence. These $750 travel awards (approximately 30 per year) have been made annually beginning in 2000 and are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. At the 2009 meeting, June 20–25 in Reno/Sparks, NV, there were 28 awardees. At the 2010 meeting, June 12–17 in Scottsdale, AZ, there were 27 awardees.

NIDA Staff Presentations

- Invited co-host of American Psychological Association Division 50 (Addictions) Conversation Hour, "Addiction, Men and Women," American Psychological Association, Toronto, ON, Canada, August 6–9, 2009.
- Invited talk, "Evidence for Gender-Specific Addiction Risk," American Society for Addiction Medicine's Course on the State of the Art in Addiction Medicine. Washington, DC, October 22–24, 2009.
- Invited talk, "Gender Differences in Tobacco Addiction," Division of Basic Neuroscience and Behavioral Research, NIDA, February 19, 2010.
- Invited talk, "Gender Differences in Tobacco Addiction," International Women's Medicine and Mental Health International Congress, Medelin, Colombia, March 2–7, 2010.
- Psychiatry ground rounds invited talk, "Gender Differences in Drug Abuse," University of Miami Miller School of Medicine, March 26, 2010..
- Invited talk, "Observations from the IOM Workshop: Sex Differences and Implications for Translational Neuroscience Research," Organization for the Study of Sex Differences, Ann Arbor, MI, June 3–5, 2010.

NIDA-Organized Sessions at Scientific Conferences

- Symposium, "Biobehavioral Mechanisms of Sex Differences in Nicotine Addiction: A Translational Perspective," Joint Meeting of the Society for Research on Nicotine and Tobacco (SRNT) and SRNT-Europe, April 27–30, 2009, Dublin, Ireland.
- Symposium, "Biological Basis of Sex Differences in Drug Abuse: A Translational Perspective," American Psychiatric Association, May 16–21, 2009, San Francisco, CA.
- Symposium, "Problematic Relationships as Shared Risk Factors for Adolescent Dating Violence," Society for Prevention Research Annual Meeting, May 26–29, 2009, Washington, DC.
- Symposium, "Preclinical Studies of Sex Differences in Response to Cocaine in Adolescents: Are They Different From Adults?" College on Problems of Drug Dependence, June 20–25, 2009, Reno/Sparks, NV.
- Symposium, "Role of Sex and Stress in Smoking Maintenance and Relapse," American Psychological Association, August 6–9, 2009, Toronto, ON, Canada.
- Symposium, "Making Health Care and Treatment Services Work for Abused Women," American Psychological Association, August 6–9, 2009, Toronto, Canada.

- Roundtable Discussion, "Women Leading Health Disparities Research for Women—Career Development Moves," American Psychological Association, August 6–9, 2009, Toronto, ON, Canada.
- Conversation Hour, "Addiction, Men and Women," American Psychological Association, August 6–9, 2009, Toronto, ON, Canada.
- Symposium, "New Directions in Research on Prenatal Nicotine Exposure: Early Neurobehavioral Outcomes, Genetic Influences, and Treatment for Pregnant Women Who Smoke," American Academy of Child and Adolescent Psychiatry, October 27–November 1, 2009, Honolulu, HI.
- Invited Panel, "Intersecting Problems of HIV, Partner Abuse, and Trauma Among Drug-Involved Women: Implications for Prevention and Treatment," National Summit on Interpersonal Violence and Abuse Across the Lifespan: Forging a Shared Agenda," February 24–26, 2010, Dallas, TX.
- Symposium, "Sex/Gender Differences and Women-Specific Issues in Drug Abuse: Predicting and Improving Treatment Outcomes," American Psychiatric Association Annual Meeting, May 22–27, 2010, New Orleans, LA.
- Symposium, "Gender Differences in Response to Social Stress: Parallels From Cocaine and Alcohol Research in Human and Nonhuman Primates," College on Problems of Drug Dependence, June 12–17, 2010, Scottsdale, AZ.
- Symposium, "Bridging Gaps in Current Medication Treatment Research for Pregnant Women and In Utero Substance-Exposed Neonates: Ethics, Advances, and Future Directions," Substance-Exposed Newborns: Collaborative Approaches to a Complex Issue, June 23–24, 2010, Alexandria, VA.
- Symposium, "Gender Sensitive Health Care/Treatment Services for a Vulnerable Population: Transgenders," American Psychological Association Annual Meeting, August 12–15, 2010, San Diego, CA.
- Symposium, "Social Stress and Drug Addiction—Sex and Gender Matter," American Psychological Association, August 12–15, 2010, San Diego, CA.
- Symposium, "Sex and Gender Considerations in Laboratory and Treatment Outcome Studies in Addiction," American Psychological Association, August 12–15, 2010, San Diego, CA.
- Symposium, "Valuing Gender-Sensitive Health Care and Treatment Services for Abused Women," American Psychological Association, August 12–15, 2010, San Diego, CA.
- Symposium, "Adolescent Substance Abuse and Its Consequences," International Conference on Violence Abuse and Trauma, September 12–15, 2010, San Diego, CA.
- Symposium, "Gender Differences in ADHD, Substance Use, and Other Comorbid Psychiatric Disorders: Implications for Treatment of Adolescent and Young Adult Females," 57th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October 26–31, 2010, New York, NY.
- Symposium, "Sex/Gender Differences and Women-Specific Issues in Drug Abuse," American Academy of Addiction Psychiatry, December 2–5, 2010, Boca Raton, FL.
- Symposium, "Drugs of Abuse and Postpartum Depression," American College of Neuropsychopharmacology, December 5–9, 2010, Miami Beach, FL.
- Symposium, "Girls in the Juvenile Justice System: Substance Abuse, Mental Health, and HIV/Sexually Transmitted Infection Risk," Joint Meeting on Adolescent Treatment Effectiveness, December 14–16, 2010, Baltimore, MD.

Events at NIDA

- Webinar, "Postpartum Smoking Relapse: Women's Weight and Worries," May 1, 2009.
- Seminar, "Sex Differences in the Human Brain and Implications for Addiction," May 14, 2009.

- Symposium, "Maternal-Fetal HIV Transmission: The Role of Drugs of Abuse," October 26–27, 2009.
- Seminar, "Effects of Contingency Management on Cigarette Smoking and Birth Outcomes Among Pregnant Women," April 7, 2010.
- Seminar, "Women-Focused HIV Prevention for Women Who Use Drugs: Domestic and Global Perspectives," April 20, 2010.
- Seminar, "Women and Addiction Treatment: New Findings," May 4, 2010.
- Symposium, "Sex Differences in Pain and Opioid Analgesia," October 13, 2010.

NIDA Publications

- ***Mini-Program: Focus on Women and Sex/Gender Differences (2009) (2010).*** This publication has been prepared for the College on Problems of Drug Dependence (CPDD) annual conference since 1999. Excerpted from the CPPD program book, this miniprogram contains only those program listings related to women and sex/gender differences. It also contains the CPDD abstracts on women and sex/gender differences, information about the Women and Gender Junior Investigator Travel Awardees, announcement of the travel award program for the following-year CPDD meeting, and information on current NIDA funding opportunities relative to women and sex/gender differences.
- ***Monitoring the Future: National Results on Adolescent Drug Use*** (http://www.monitoringthefuture.org). Published yearly, this report provides a summary of drug use trends from a survey of 8th, 10th, and 12th grade students nationwide, including analysis by gender. It also includes perceived risk, personal disapproval, and perceived availability of each drug by this group.
- In 1998, NIDA created the Web site ***Women and Sex/Gender Differences Research Program*** (http://www.nida.nih.gov/WHGD/WHGDHome.html).
- In May 2009, NIDA developed a ***Topic in Brief on Prenatal Exposure to Drugs of Abuse*** for the NIDA Web site (http://www.nida.nih.gov/tib/prenatal.html).
- Cotto JH, Davis E, Dowling GJ, Elcano JC, Staton AB, Weiss SR. Gender effects on drug use, abuse, and dependence: A special analysis of results from the National Survey on Drug Use and Health. Gend Med 2010 Oct;7(5):402-13.

Efforts for Special Populations

NIDA-supported research has shown that the causes and consequences of drug abuse and addiction, as well as prevention and treatment needs, often vary among female population groups. Thus, NIDA research is exploring new approaches to address special populations of women, such as those with children or who are pregnant or postpartum, women with drug-using partners, and women experiencing current and past violence and trauma. Other special populations of female drug abusers include criminal offenders, the homeless, those living with or at risk for HIV/AIDS, members of particular ethnic or minority groups, and more. Ongoing NIDA-supported research targets these and other groups, reflecting NIDA's belief that ongoing research into population-specific needs related to preventing and treating drug abuse and addiction will help keep more people from abusing drugs in the first place, and for those who do, it will lead to better treatments for them. Findings described throughout this report highlight the need for continuing research focused on special populations at increased or unique risk.

Sex/Gender Analysis––Plans and Implications

For nearly two decades, NIDA has emphasized sex/gender analysis in all areas of drug abuse research. From basic research on animal models to prevention and treatment, the resultant findings reveal that outcomes are not always the same in males and females. Failing to detect these sex/gender-specific outcomes because of failure to perform a sex/gender analysis of data will lead to scientific conclusions that are wrong—wrong for females, wrong for males, or wrong for both. These sex/gender-specific research findings and

their scientific and translational implications highlight the need for a widespread scientific recognition that sex/gender should be an integral consideration in the design of all drug addiction research in order to achieve optimal value from it—for both males and females.

To continue to urge researchers in the field of drug abuse to design research with sex/gender-based hypotheses, in 2010, NIDA partnered with the National Institute on Alcohol Abuse and Alcoholism and reissued its program announcement titled Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (http://grants.nih.gov/grants/guide/pa-files/PA-11-033.html; http://grants.nih.gov/grants/guide/pa-files/PA-11-049.html; http://grants.nih.gov/grants/guide/pa-files/PA-11-048.html).

National Institute of Environmental Health Sciences

Executive Summary

Certain health conditions and diseases, including menopause, pregnancy, ovarian cancer, cervical cancer, breast cancer, certain autoimmune diseases, endometriosis, and osteoporosis, occur only in women. A number of these conditions and diseases may be environmentally mediated. Other cancers, cardiovascular diseases, pulmonary diseases, and neurological diseases are among the diseases that occur in both males and females. Gender may influence differences in susceptibility and outcome of these diseases. For example, data from recent studies on urban air pollution indicate that women have a greater risk of developing fatal coronary heart disease from long-term exposure to airborne particles than men. The National Institute of Environmental Health Sciences (NIEHS) supports research investigating women's susceptibilities to these diseases, environmental factors involved in disease etiology or exacerbation, and identification of important factors that can reduce risk. NIEHS also is investigating gender differences in susceptibility and clinical presentation to identify and correct gender differentials and inequities in health. As results of these studies become available, women can better determine how to alter lifestyle factors leading to these diseases, and environmental health policymakers can better define standards that protect women from environmental triggers of these diseases and develop better gender-specific interventions and therapies.

Working Groups Focused on Women's Health

NIEHS includes several groups focused entirely or in part on women's health. The work of the Women's Health Group focuses on fertility, early pregnancy, and the epidemiology of uterine fibroids and uses the tools of reproductive epidemiology to address women's reproductive health issues. The Laboratory of Reproductive and Developmental Toxicology conducts basic research on reproductive and developmental health, including developmental biology, gene regulation, pharmacogenetics, and receptor biology. The Reproductive Endocrinology Group focuses on the role of environmental chemicals in breast developmental timing as it relates to puberty, increased susceptibility to breast cancer, and altered lactational ability. The Reproductive Epidemiology Group investigates environmental substances that affect fertility, conception, and early pregnancy; low birth weight; and teratogensis. The Reproductive Medicine Group focuses on the basic reproductive biology of early mammalian embryogenesis, including gametes, fertilization, preimplantation embryo development, and implantation; this group studies specific areas with direct relevance to human reproduction and human infertility and considers how the environment influences these areas. NIEHS also supports women's health research through the Division of Extramural Research and Training (DERT). Many of the projects funded by DERT investigate gender differences in response to exposure to environmental substances. In 2009–2010, NIEHS initiated several new projects, primarily at institutions of higher learning, to investigate women's health and gender differences and to educate/train researchers in this field.

Accomplishments

Immunogenetic Risk and Protective Factors for the Development of Eosinophilia-Myalgia Syndrome. In 1989, an epidemic outbreak occurred characterized by acute onset of incapacitating myalgia and peripheral eosinophilia. This outbreak came to be called eosinophilia-myalgia syndrome (EMS). Scientists evaluated L-tryptophan (LT) dose, age, gender, and immunogenetic markers as possible risk or protective factors for the development of LT-associated EMS and related clinical findings. Multivariate analyses compared LT dose, age, gender, and alleles among groups of subjects who ingested LT and subsequently developed surveillance criteria for EMS, developed EMS or characteristic features of EMS (EMS spectrum disorder), or developed no features of EMS (unaffected). Considering all sources of LT, researchers found that higher LT dose, age greater than 45 years, and *HLA-DRB1*03*, *DRB1*04*, and *DQA1**0601 were risk factors for the development of EMS, whereas *DRB1**07 and *DQA1**0501 were protective. Analysis showed similar risk and protective factors for developing EMS following ingestion of implicated LT, except that *DRB1**03 was not a risk factor and *DQA1**0201 was an additional protective factor. EMS spectrum disorder also demonstrated similar findings, but with *DRB1**04 being a risk factor and *DRB1**07 and *DQA1**0201 being protective. There were no differences in gender distribution, Gm/Km allotypes, or Gm/Km phenotypes among any groups. In addition to the xenobiotic dose and subject age, polymorphisms in immune response genes may underlie the development of certain xenobiotic-induced immune-mediated disorders, and these findings may have implications for future related epidemics.

African-American Genetic Obesity Susceptibility. Obesity is approximately 1.5-fold more prevalent in African Americans than European Americans. To determine whether genetic background may contribute to this observed disparity, researchers scanned the genomes of African Americans, searching for genomic regions where obese individuals display a difference from the average proportion of African ancestry. By examining genetic data from more than 15,000 African Americans, they showed that the proportion of European ancestry is inversely correlated with body mass index (BMI). In obese individuals, the researchers detected two loci with increased African ancestry on chromosome X (Xq13.1 and Xq25) and one locus with increased European ancestry on chromosome 5 (5q13.3). The 5q13.3 and Xq25 regions both contain genes that are known to be involved in appetite regulation. Because the identified admixture peaks were located on chromosome X, which has a different copy number in men and women, the scientists also performed analyses for each gender separately to explore whether the strength of association differed significantly between males and females. They found that the evidence of association at Xq25 was stronger in females than in males and that the association signal at Xq13.1 in males grew stronger, with the local LOD score rising to 4.40. In the more comprehensive linear regression analysis of local ancestry, there was a significant gender difference at Xq13.1. For the two peaks on chromosome X, the researchers further examined whether the effects of local ancestry on BMI were modified by gender. The local ancestry at Xq13.1 tended to be more strongly associated with BMI in males than in females. After adjusting for genomewide European ancestry, the gender difference at Xq13.1 was significant, which was in line with the results of dichotomous admixture scans. At Xq25, the effects of local ancestry did not show significant heterogeneity between the two gender groups, either before or after adjusting for genomewide European ancestry. A potential mechanism for the difference in the strength of association in men and women at the Xq13.1 locus is that women carry two copies of chromosome X whereas men carry only one; therefore, this stronger association in women may simply reflect a difference in the genetics of the two genders on chromosome X. The results suggest that genetic factors may contribute to the difference in obesity prevalence between African Americans and European Americans. Further studies of the regions may identify the causative variants affecting susceptibility to obesity.

Differences in Gender Susceptibility to Glass Wool Fibers. Among female workers in the U.S. cohort, no increase in respiratory cancer (trachea, bronchus, and lung)

was observed in the whole cohort compared with national or local mortality rates, but in an internal analysis of glass wool-only versus filament-only exposed workers, a threefold increase in these cancers was observed. A significant trend between increasing asbestos body count and increasing number of methylated cell-cycle pathway genes remained after controlling for age, gender, and tumor histology, consistent with the hypothesis that asbestos body burden contributes to epigenetic dysregulation of cell-cycle genes. Gender was associated with asbestos body count, with significantly higher asbestos body count in males compared with females.

Sex Differences in Chromatin Structure Associated With Sex-Specific Liver Gene Expression. Sexual dimorphism in gene expression is common in mammalian tissues and has broad implications for human health. Sex differences in gene expression may contribute to differences between men and women in the prevalence, extent, and progression of disease, including autoimmune diseases, kidney disease, cardiovascular diseases, and liver diseases, such as hepatocellular carcinoma. In addition, sex-related differences in pharmacokinetics and pharmacodynamics are common and may affect drug response. To identify sex-related differences in mouse liver chromatin structure on a global scale, scientists combined a DHS analysis with ultrahigh-throughput sequencing (DNase-seq) to probe the open chromatin structure at single-base-pair resolution. The study identified 71,264 hypersensitive sites, with 1,284 showing robust sex-related differences. Continuous GH infusion suppressed the vast majority of male-specific sites and induced a subset of female-specific sites in male livers. In addition, the researchers identified broad genomic regions (up to ~100 kb) showing sex-dependent hypersensitivity and similar patterns of GH responses. A strong association of sex-specific sites with sex-specific transcription; however, the study revealed a majority of sex-specific sites with more than 100 kb from sex-specific genes. By analyzing sequence motifs within regulatory regions, the researchers identified two known regulators of liver sexual dimorphism and several new candidates for further investigation. This approach can readily be applied to mapping condition-specific regulatory sites in mammalian tissues under a wide variety of physiological conditions.

Gender Differences in Response to Cadmium Exposure. Researchers evaluated gender differences in the association of blood and urine cadmium concentrations with peripheral arterial disease (PAD) by using data from 6,456 U.S. adults aged 40 years or older who participated in the 1999–2004 National Health and Nutrition Examination Survey. For men, the adjusted odds ratios for PAD comparing the highest with the lowest quintiles of blood and urine cadmium concentrations were 1.82 and 4.90, respectively, with a progressive dose-response relation and no difference by smoking status. For women, the corresponding odds ratios were 1.19 and 0.56, but there was evidence of effect modification by smoking: among women who had ever smoked, there was a positive, progressive dose-response relation; among women who had never smoked, there was a U-shaped dose-response relation. Higher blood and urine cadmium levels were associated with increased prevalence of PAD, but women who had never smoked showed a U-shaped relation with increased prevalence of PAD at very low cadmium levels. These findings add to the concern about increased cadmium exposure as a cardiovascular risk factor in the general population.

Calcitriol's Effects on Inflammatory Airway Diseases. An in vitro investigation was conducted to assess whether calcitriol, a secosteroidal vitamin D receptor modulator, inhibited human airway smooth muscle (ASM) cell growth derived from subjects who are normal or those with asthma. In all cases of comparisons between normal and asthma ASM, the researchers used five distinct cell lines from each cohort. Overall, the subject characterization regarding age and gender showed no statistical differences between those with fatal asthma compared with normal subjects. This study demonstrated that calcitriol inhibited ASM cell proliferation by preventing progression of the cell cycle and not by inducing apoptosis. These data suggest that calcitriol may be a useful therapeutic agent in the prevention of increases in ASM mass described

in patients with inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (COPD).

A Reduced Folate Carrier Polymorphism Associated With Red Cell Folate Concentrations. The SLC19A1 c.80G>A polymorphism was not strongly associated with either serum folate or homocysteine concentrations in either men or women. However, in women, but not in men, this polymorphism explained 5 percent of the variation in red blood cell (RBC) folate levels. Relative to women with the SLC19A1 c.80GG genotype, women with the GA and AA genotypes had higher RBC folate concentrations. Consequently, compared with women with the SLC19A1 c.80GA and AA genotypes, women who are homozygous for the 80G allele may be at increased risk of having a child affected with a neural tube defect (NTD) and of developing pathologies associated with folate insufficiency, such as cardiovascular disease. The SLC19A1 c.80GG genotype is associated with relatively low folate concentrations in Northern Irish women. Because a maternal low-folate/high-homocysteine phenotype is associated with increased risk of NTDs in offspring, women with the SLC19A1 c.80GG genotype may have an increased risk of having a child affected by an NTD relative to those with the GA and AA genotypes. In addition, SLC19A1 c.80GG homozygous women may be at increased risk of a range of other major pathologies, including cardiovascular disease, in which a low-folate/high-homocysteine phenotype is a predisposing feature.

Sex/Gender Analysis

The general toxicology assessments conducted by the National Toxicology Program (NTP) usually involve exposures of rats and mice of both sexes to test articles for periods of 14 days or 13 weeks. Assessments almost always performed include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The NTP long-term toxicology and carcinogenesis studies (bioassays) in rodents generally employ both sexes of rats (Harlan Sprague Dawley) and mice (B6C3F1 hybrid) with three exposure concentrations, plus untreated controls in groups of 50 animals for 2 years. Both sexes are evaluated to determine whether differences in outcome are caused by gender differences.

Initiatives

Advancing Novel Science in Women's Health Research (ANSWHR) (R21) PAS-10-226. The purpose of this funding opportunity announcement (FOA), issued by the Office of Research on Women's Health (ORWH) and cosponsoring NIH Institutes and Centers, is to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences. Recent research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. ORWH is particularly interested in encouraging extramural investigators to undertake new interdisciplinary research to advance studies on how sex and gender factors affect women's health; however, applications in all areas of women's health and/or sex/gender research are invited.

Research Consortium for 2-Year Bisphenol A (BPA) Toxicity Study (U01) RFA-ES-10-009. The objective of this research program is to take advantage of scientific expertise in the extramural community to develop a consortium of investigators who will propose hypothesis-driven mechanistic studies focusing on disease/dysfunction endpoints that can be added to the chronic study design. The independent scientific ideas and approaches will either use animals generated from the core study or, if needed, add additional animals to the core study to assess the effects of BPA on specific diseases/dysfunctions over a lifetime.

Breast Cancer and the Environment Research Centers (BCERCs) are part of a program studying the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer. The program supports transdisciplinary research during windows of susceptibility throughout a woman's lifespan. It studies the interactions of environmental factors (including chemical, physical, and social environmental) with genetic factors that potentially influence breast

cancer risk. Each research project is required to partner with a local community-based or advocate organization with a focus on breast cancer. This program is conducted jointly by NIEHS and the National Cancer Institute (NCI). The following FOAs are coordinated parts of the overall BCERC program:

- **Continuation of Studies on Early Environmental Exposures and Human Puberty (U01) RFA-ES-09-008.** The purpose of this FOA is to continue support of the centers' ongoing longitudinal studies examining how environmental, genetic, biologic, lifestyle, and socioeconomic factors influence female pubertal development and subsequent breast cancer risk, with a continued emphasis on the essential role of collaboration between researchers and breast cancer advocates in attaining research goals. Continued followup of girls enrolled in BCERC epidemiologic studies will maximize the investment made in establishing these unique cohorts and increase power to draw significant conclusions regarding the impact of early environmental determinants on puberty.
- **Environmental Influences During Windows of Susceptibility in Breast Cancer Risk (U01) RFA-ES-09-009.** This program includes cooperative agreement grants to institutions to conduct (1) basic laboratory or ancillary research projects involving existing populations or (2) clinical studies focused on gene-environment interactions and the molecular mechanisms engaged, during specific windows of susceptibility, that have the potential of modifying a woman's lifetime risk for developing breast cancer.
- **Coordinating Center for the Breast Cancer and the Environment Research Program (BCERP) (U01) RFA-ES-09-010.** The main focuses of the coordinating center are to (1) act as a central repository and clearinghouse for cross-site data from an ongoing study of environmental influences in puberty in young girls, (2) organize annual meetings and regular conference calls for the BCERP Steering Committee and its subcommittees, BCERP supported investigators, and the public, (3) facilitate the BCERP Steering Committee and the Breast Cancer and the Environment Working Group,, and (4) provide progress reports and updates as requested by NIH staff.

Workshops and Conferences

Researching Women's Environmental Health Workshop, 2009. The Researching Women's Environmental Health (RWEH) workshop was designed to achieve three goals: (1) to provide examples of environmental impacts on women's health in a manner that is clear and compelling to users of this information (health practitioners and the interested public), (2) to evaluate these research presentations as to their success in communicating to interest groups and health care providers, and (3) to enable the investigators to produce an RWEH publication that provides consumers of research findings with a successful translation of research results.

Researching Women's Environmental Health Workshop, 2010. The second RWEH workshop was held on September 15, 2010, in Rochester, New York, at the University of Rochester School of Medicine and Dentistry. This workshop had four goals: (1) to present cutting-edge scientific findings that show how environmental exposures can alter food safety, nutritional content, and ability to promote obesity, (2) to present a case study that illustrates a successful translation from science to policy in the area of food, nutrition, and the environment, (3) to learn what information policymakers, the media, and community leaders need to take appropriate action on scientific findings in the area of food, nutrition, and the environment, and (4) to identify barriers that prevent the translation of environmental health research in these areas to actionable policy and understand how to overcome these obstacles.

Health Disparities Among Special Populations of Women

Racial Differences in Circulating Insulin-Like Growth Factor-I and IGF-Binding Protein-3 Levels. Circulating insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) levels are associated with common diseases. Although family-based studies suggest that genetic variation contributes to

circulating IGF-I and IGFBP-3 levels, analyses of associations with multiple IGF-I and IGFBP-3 single nucleotide polymorphisms (SNPs) have been limited, especially among African Americans. Scientists evaluated 30 IGF-I and 15 IGFBP-3 SNPs and estimated diplotypes in association with plasma IGF-I and IGFBP-3 among premenopausal African American and White women. Evidence of a causal association was strongest for the nonsynonymous IGFBP-3 SNP, rs2854746, with plasma IGFBP-3 levels. In both races, the rs2854746 CC genotype was associated with higher mean IGFBP-3 levels than were estimated for the GG genotype, whereas mean levels for the CG genotype were intermediate. In addition, IGFBP-3 diplotypes with the rs2854746 GG genotype had consistently lower mean IGFBP-3 levels than those estimated for referent diplotypes with the CG genotype in both races, whereas IGFBP-3 diplotypes with the CC genotype had higher mean IGFBP-3 levels. Because African Americans have more genetic heterogeneity than Whites, the frequency of etiologically relevant SNPs may differ and may at least partly explain racial disparities in the burden of cancer and cardiovascular disease. Therefore, assessing IGF-I and IGFBP-3 SNPs that predict circulating IGF-I and IGFBP-3 levels will improve the understanding of the biological role of IGF-I and IGFBP-3 in the etiology of common diseases.

Social Isolation and Breast Cancer. Clinical studies have revealed that social support improves the outcome of cancer patients, whereas epidemiologic studies suggest that social isolation increases the risk of death associated with several chronic diseases. However, the precise molecular consequences of an unfavorable social environment have not been defined. Female C3(1)/SV40 T-antigen mice deprived of social interaction from weaning exhibited increased expression of genes encoding key metabolic pathway enzymes in the premalignant mammary gland. Chronic social isolation was associated with up-regulated lipid synthesis and glycolytic pathway gene expression. Both pathways are known to contribute to increased breast cancer growth. Consistent with the expression of metabolic genes in premalignant mammary tissue, isolated mice subsequently developed a significantly larger mammary gland tumors burden compared with group-housed mice. Endocrine evaluation confirmed that isolated mice developed a heightened corticosterone stress response compared with group-housed mice. A chronically isolated social environment correlates with specifically altered mammary gland gene expression. Furthermore, the complement of differentially expressed mammary gland genes associated with social isolation suggests activation of key cancer-linked metabolic pathways. Understanding the specific molecular networks connecting an individual's environment with his or her physiologic stress response and, ultimately, with tissue gene expression favoring tumor growth is expected to uncover novel mechanisms promoting tumor growth in the context of specific environmental stressors. It is possible that the metabolic gene expression pathways identified in this study also may contribute to the mechanisms underlying the observation that patients with self-reported social isolation are at higher risk for diabetes (51) and hypertension (1) as well as cancer (2).

Disparities in Biological "Wear and Tear" Measured by Allostatic Load in a Nationally Representative Sample of U.S. Adults. Despite decades of research on socioeconomic status (SES) gradients in health, the underlying causes remain only partially understood. No studies have examined the independent contribution of neighborhood SES (NSES) to allostatic load (AL) in a nationally representative sample. This study assessed whether NSES is associated with cumulative biological wear and tear, or dysregulation (measured by AL), in a nationally representative sample of U.S. adults after adjusting for individual level demographic and SES characteristics. Being male, older, having lower income, less education, being Mexican-American, and being both female and Black or African American were all independently associated with a worse AL. After adjusting for these characteristics, living in a lower NSES was associated with a worse AL. The relationship between NSES and AL did not vary significantly by gender or race/ethnicity. Living in a lower NSES in the United States is associated with significantly greater biological wear and tear as measured by AL, and this relationship is independent of individual SES characteristics. The findings show that where one lives is independently associated with AL,

thereby suggesting that policies that improve NSES may also yield health returns.

Career Development Initiatives

Women's Health and the Environment Over the Entire Lifespan. Public and scientific concerns about the potential impacts of environmental chemicals on human and environmental health have increased greatly in the past 10 years. The Women's Health and Environment over the Entire Lifespan (WHEEL) program at the University of Rochester Medical Center (URMC) addresses the concern that, through their effects on hormonal pathways, environmental chemicals can differentially affect females, particularly at critical and sensitive periods across the lifespan. These critical periods include stages of particular vulnerability (such as during fetal development and among the elderly), major life transitions (such as during midlife and into late life), and stages of rapid cell proliferation and growth (such as during fetal development, puberty, and lactation). The WHEEL program trains junior faculty to conduct outstanding interdisciplinary research to help identify environmental agents that can adversely affect women's health at all stages of life. Results of this research will provide a strong foundation for risk assessment and regulation, when appropriate, thus decreasing risks to public health.

The Commitment of the Environmental Mutagen Society to Women Scientists and Gender-Associated Disease Topics. The 2009 Women in the Environmental Mutagen Society (WEMS)-sponsored symposium at the annual Environmental Mutagen Society (EMS) meeting served to introduce the audience to the many roles and promises of new genomic and genetic technologies in diagnosis, treatment, and prognosis of diseases in women that have strong genetic components or critical gene-environment interactions. Ovarian cancer, breast cancer, cardiovascular disease, diabetes, and obesity all fall into this disease category, and all are important public health issues that affect women disproportionately or exclusively. As the role of WEMS within the EMS matures over the Society's next 40 years, an important facet of its mission will be the encouragement and support of women scientists and scientists who are exploring gene-environment interactions associated with diseases and conditions that affect women's health. The rapid evolution in genomic technologies should provide new tools to explore some of the critical questions raised by the research projects described in this article. In the future, EMS will continue to provide a forum for the presentation and discussion of the science that affects women's health. EMS activities and members are supported by NIEHS and other sponsors.

National Institute of General Medical Sciences

Executive Summary

The National Institute of General Medical Sciences (NIGMS) supports research and research training for the basic biomedical sciences. Studies supported by NIGMS do not necessarily target any particular disease or condition but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, genetics, developmental biology, drug discovery, pharmacology, physiology, bioinformatics, computational biology, and selected areas of behavioral sciences. NIGMS-supported research often is applicable to a wide variety of diseases or organ systems, including those specific to, or disproportionately affecting, women.

Interindividual drug responses depend on genetic variation as well as modifying factors such as environment, diet, other medications, age, and gender. NIGMS supports investigations of critical candidate proteins and genes that may contribute to pharmacogenetic and pharmacogenomic variations in drug metabolism and clearance. Advances in understanding the genetic basis of individual drug responses come from the National Institutes of Health (NIH) Pharmacogenomics Research Network. Scientists in this nationwide collaboration have studied genes and medications relevant to a wide range of diseases, including breast cancer. For example, key findings reveal that women with a specific genetic variation do not respond as well to the widely prescribed

breast cancer drug tamoxifen and that certain antidepressants can hinder the drug's effectiveness. Discoveries like these have already led to changes in prescribing some medications.

The water content of bone tissue decreases with age and is associated with a reduction in biomechanical properties that are critical to the function of bone. The underlying structural changes in the matrix protein and mineral of water brought about by dehydration are unclear. Understanding the structural changes in bone at the molecular level could provide insights into the susceptibility of bone to fracture, especially in the osteoporotic tissue of women. Researchers led by chemist Ayyalusamy Ramamoorthy of the University of Michigan performed nuclear magnetic resonance (NMR) experiments to study the water-dependent structural and dynamic changes in the intact bone by slowly dehydrating a cylindrical specimen of bovine cortical bone in an NMR rotor. They found that the characteristic triple helix structure of the main protein collagen was not completely damaged, but its mobility was altered, in addition to a disorder in the structure. These researchers plan to continue to use solid-state NMR to understand the roles that water molecules play in bone structure, toughness, and mechanical strength.

The BRCA2 gene is often linked to inherited cases of breast and ovarian cancers, but efforts to understand its exact role have been hampered because the gene's protein has been difficult to purify. The protein is large, does not express well, and degrades easily. Two groups at University of California, Davis, now have overcome this challenge. Dr. Stephen Kowalczykowski's group purified the protein from human cells; another group, led by Professor Wolf-Dietrich Heyer, used genetic engineering techniques to manufacture the human protein in yeast. Experiments with the BRCA2 protein confirm that it plays a role in repairing damaged DNA. It acts as a mediator, helping another protein, RAD51, to associate with a single strand of DNA and stimulating its activity. One BRCA2 molecule can bind up to six molecules of RAD51. One application of the purified protein could be to make antibodies to BRCA2 that could be used in test kits as a supplement to existing genetic tests. Purified proteins also could be used to screen for drugs that activate or inhibit the interaction between BRCA2, RAD51, and DNA.

Taxol, also known as paclitaxel, is a powerful cell-division inhibitor commonly used to treat ovarian, lung, and breast cancers. Two to four Pacific yew trees are required to obtain enough Taxol to treat one patient. In the 1990s, bioengineers came up with a way to produce it in the lab from cultured plant cells or by extracting key intermediates from plant material like the needles of the decorative yew. Even produced in this way, Taxol is very expensive. MIT researchers and collaborators from Tufts University have now engineered E. coli bacteria to produce large quantities of a critical compound that is a precursor, the first committed intermediate, to Taxol. The engineered bacteria can produce 1,000 times more of the precursor, taxadiene, than any other engineered microbial strain. Now that researchers have achieved taxadiene synthesis, there are still another 15 to 20 steps to go before they can generate Taxol. Nonetheless, this study shows potential by providing the basis for the functional expression of two key steps in Taxol biosynthesis.

NIGMS funds research on a variety of model organisms, such as the fruit fly *Drosophila*. Like most animals, fruit flies behave differently toward males and females. *Drosophila* males fight with other males and do not attack females. By manipulating a gene called *transformer*, researchers have uncovered the triggers for these sex-specific responses. Masculinization of female pheromones is sufficient to trigger aggression from wild type males towards females. In addition to the expected role played by pheromones, behavioral patterns associated with each sex are important. By simultaneously manipulating pheromones and behavioral patterns of opponents, the behavioral response of males towards females and males could be switched completely. Unraveling this decision-making process in flies could help reveal how other animals, including humans, make complex decisions governing behavior.

NIGMS supports interdisciplinary research training of predoctoral and postdoctoral scientists in basic medical sciences relevant to the mission of NIGMS. Twelve predoctoral student training program areas span the research interests of the Institute. For example, the NIGMS

training program aimed at the chemistry/biology interface has the goal of preparing more chemists with knowledge and understanding of biological systems, which is an area of study critical to the design of new drugs and diagnostic and preventive approaches. This program complements the NIGMS training program in the pharmacologic sciences that prepares young scientists to investigate the biochemical systems that are amenable to pharmacologic intervention and to investigate the pharmacology of drug action and drug toxicity. The NIGMS training programs aimed at the behavior/biomedical science interface integrate training in basic behavioral research with similar rigorous training in the biological and biomedical sciences. These programs train students in basic behavioral science that is not targeted to a specific developmental stage or disease but which is fundamental to a range of diseases and health conditions. The institutional postdoctoral research training grants support the training of outstanding clinician-scientists in the four clinically relevant research areas within the mission of NIGMS: anesthesiology, clinical pharmacology, medical genetics and trauma, and burn and perioperative injury. NIGMS supports the training of dual-degree candidates through the Medical Scientist Training Program (MSTP). The postdoctoral research training programs and the MSTP program graduate doctors who can address basic research problems and relate their findings to clinical areas.

Office of Research on Women's Health Report

NIGMS is actively involved in the National Institutes of Health (NIH) Working Group on Women in Biomedical Careers, a trans-NIH committee established and co-chaired by the NIH director and the ORWH director and comprising a number of working group committees.

NIGMS is taking part in the funding opportunity developed and implemented by ORWH in partnership with many NIH Institutes and Centers., "Advancing Novel Science in Women's Health Research (ANSWHR)," http://grants.nih.gov/grants/guide/pa-files/PAS-10-226.html, seeks to promote innovative, interdisciplinary research to advance new concepts in women's health research and the study of sex/gender differences.

As part of its efforts to promote diversity in the scientific workforce, NIGMS held a workshop titled "Advancing Biomedical Research Workforce Diversity: NIGMS Workshop for Postdocs Transitioning to Independent Positions," on March 11–12, 2010, on the NIH campus. Although the transition to independence is a challenge for all postdoctoral researchers, NIGMS recognizes that young investigators who are members of groups that are underrepresented in the biomedical or behavioral sciences may have an especially difficult time finding and establishing themselves in their first independent positions. For this reason, this workshop emphasized issues specific to members of these groups, including women. The workshop agenda covered a broad range of topics that are key to making a successful transition to independence, including making the right career choice, finding the right institutional fit, applying for a position, succeeding in the job interview and seminar, negotiating a startup package, establishing a lab, finding a mentor, networking and forming collaborations, applying for and getting a grant, undergoing the tenure process, teaching, and balancing research with many other commitments. Approximately 150 postdoctoral researchers were brought to NIH for an exciting, successful program.

National Institute of Mental Health

Executive Summary

The epidemiology and disability burden of mental disorders provide clear evidence of the value of a focus on both sex differences and women's mental health. There are differences in both the prevalence and clinical course of mental disorders between men and women. Starting in childhood, girls have higher rates of anxiety disorders and eating disorders than boys, whereas boys are more likely to suffer from autism spectrum disorder and attention deficit disorder. After puberty, women have higher rates than men of depression, eating disorders,

and anxiety disorders, including posttraumatic stress disorder. There are also differences in the course and severity of mental disorders between men and women. In addition, some women are at increased risk of depression during certain times of reproductive change, such as in the perinatal period and perimenopause.

Through its research programs and related programmatic activities, the National Institute of Mental Health (NIMH) has increased scientific understanding of the effects of sex and gender differences in mental health and mental illness. NIMH also has advanced knowledge in the area of specific mental disorders that affect women either exclusively (e.g., perinatal depression) or predominantly (e.g., eating disorders). Through crosscutting programs such as the Women's Mental Health Team, NIMH has fostered interdisciplinary collaboration and research to improve diagnosis, treatment, services, and prevention of mental disorders in women. This 2009–2010 NIMH report highlights offices and groups designated to focus on women's mental health, papers on sex differences and women's mental health research, specific initiatives to promote research in this area, efforts on behalf of special populations of women, and specific initiatives in the area of sex/gender differences research and research during pregnancy and the perinatal period. Research highlights are grouped by three major subheadings: (1) Research on Sex Differences in Brain and Behavior, (2) Research on Specific Mental Disorders, and (3) Research on Women With HIV, followed by Workshops and Initiatives. Findings regarding adolescents, low-income women, rural women, and mental health disparities are featured throughout the research highlights.

Office and Groups Designated To Focus on Women's Mental Health

The Women's Mental Health Program is located organizationally in the Office for Research on Disparities and Global Mental Health within the Office of the NIMH Director. The women's mental health program was established to ensure coordination of NIMH-funded research on women's mental health and on sex and gender differences. Other functions include serving as an organizational focal point for women's mental health science communication and liaising with the NIH Office of Research on Women's Health and other government and nongovernment organizations interested in women's issues. The office coordinates NIMH activities that serve to fulfill the congressional mandate for tracking the inclusion of women and minorities in clinical research.

The Women's Mental Health Team serves as the focal point for coordination of NIMH scientific activities related to women's health and sex/gender differences research. Members of the team include representatives from all five extramural research divisions and the Office of Science Policy, Planning and Communications, Office of Constituency Relations and Public Liaison, and Executive Office. Team members work together across disciplinary boundaries to plan workshops, prepare/review science reports, and create funding opportunities related to women's mental health.

Accomplishments/Research Highlights

Research on Sex Differences in Brain and Behavior

Many mental disorders have striking gender disparities in prevalence, as shown in population-based epidemiology studies of U.S. adults. For example, adult women experience major depression at almost twice the rate of adult men. Sex differences can be due to a variety of factors, including the effects of sex-linked genes, sex hormones, and differences in environmental stressors that affect brain structure and function. Understanding the mechanisms underlying these sex differences may provide clues as to why men and women are differentially vulnerable to certain mental illnesses. The following examples of NIMH-supported studies illustrate the Institute's efforts in this area.

Epigenetics and Sexual Differentiation. It is well established that pre- and perinatal sexual differentiation of the brain depends on relative levels of gonadal hormones in males and females. Hormonal effects within specific brain regions are mediated by hormone receptors and downstream changes in gene

transcription. Transcriptional regulation can be modified by epigenetic changes, specifically histone modifications. In the past 2 years, there has been a marked and exciting increase in the number of studies investigating the epigenetics of sexual differentiation in the brain. Two such studies are summarized below.

Emilie Rissman's group has shown that histone acetylation and methylation levels are higher in the brains of male mice during pre- and perinatal development. These differences were found specifically within the cortex and hippocampus. The differences emerged during different developmental periods. Sex differences in acetylation were found at embryonic day 18 and on the day of birth (postnatal day 0, PN0); sex differences in methylation were seen later, at PN0 and PN6. The investigators then demonstrated that acetylation (but not methylation) could be masculinized by prenatal treatment with testosterone. The investigators propose that sex differences in histone modifications during early development may be related to the sexually dimorphic incidence rates of several childhood mental illnesses (Tsai HW, Grant PA, Rissman EF. Sex differences in histone modifications in the neonatal mouse brain. *Epigenetics* 4(1):47-53, 2009).

NIMH-supported investigators Geert de Vries and Nancy Forger tested the hypothesis that histone acetylation levels play a role in the sexual differentiation of the bed nucleus of the stria terminalis (BNST)). Normally, BNST of males is larger than that of females. These investigators transiently inhibited deacetylation in mice at birth. They observed a decrease in volume and cell number in BNST of male mice and of masculinized female mice, without any effect on BNST of control female mice. These data establish a causal relationship between histone acetylation and sexual differentiation of BNST. Because BNST reduces stress responsivity, these results may be directly relevant to sex differences in the incidence of major depressive disorder (Murray EK, Hien A, de Vries GJ, Forger NG. Epigenetic control of sexual differentiation of the bed nucleus of the stria terminalis. *Endocrinology* 150(9):4241-7, 2009).

Effects of the Menstrual Cycle on Brain Activity and Processing of Negative Emotions. Levels of the hormones estrogen and progesterone change significantly during different phases of the menstrual cycle. Neuroimaging studies have previously demonstrated estrogen-related changes in regional brain activity when women were presented with negative emotional stimuli. In a new functional magnetic resonance imaging (fMRI) study, Andreano and Cahill (2010) have used a similar behavioral paradigm to examine the effects of endogenous progesterone on activity in amygdala and hippocampus. Women were studied at two time points—during the early follicular phase when progesterone levels were low and during the midluteal phase when progesterone levels peaked. At each time point, women viewed a series of emotional images; investigators then compared regional blood-oxygenation level dependent (BOLD) responses to negative versus neutral images. They found higher activity in amygdala and hippocampus in response to negative images. They also demonstrated that these differences in activity were much greater during the midluteal, high-progesterone phase. The results suggest that progesterone levels can significantly affect brain activity in regions related to emotional responses, stress reactivity, and emotional memory formation. The results highlight the need for careful consideration of menstrual phase in future neuroimaging studies (Andreano JM, Cahill L. Menstrual cycle modulation of medial temporal activity evoked by negative emotion. *Neuroimage* 53(4):1286-93, 2010).

Sex Differences in Vulnerability to Stress. A major response to stress in the brain is the release of a hypothalamic hormone called corticotrophin-releasing factor (CRF). The released CRF binds to a cell membrane receptor found on multiple target neurons, and this occurrence activates a cascade of events that may change cell metabolism, activity, and gene expression. Bangasser and colleagues found that that the levels of functioning CRF receptors are higher in the brains of unstressed female rats compared with unstressed males. Exposure to stress deactivates CRF receptors by causing them to be transported inside the cell, thereby desensitizing the cell to further exposure to the CRF stress hormone. But this effect was observed only in male rats. The findings show that sex differences in responsiveness to

stress may be mediated, at least in part, by regulation of the number of functional CRF receptors available on the cell membrane because of differential cellular trafficking. The inability to reduce the number of CRF receptors in response to stress may make the CRF-receptive neurons in females more responsive to high levels of CRF. This responsiveness may contribute to the higher susceptibility of women to stress-related psychiatric disorders (Bangasser DA et al. Sex differences in corticotrophin-releasing factor receptor inactivation may contribute to vulnerability to stress in females. *Mol Psychiatry* 15, 896-904, Epub 2010 June 15).

Stress Remodels Neural Circuit- and Sex-Specific Neurons. In laboratory animals, chronic stress can result in changes in the connectivity among brain areas that integrate cognitive functioning and emotions. In female rats receiving estrogen-replacement treatment, chronic stress increases synaptic spine density and dendritic complexity in neurons in the prefrontal cortex that project to the basolateral nucleus of the amygdala. However, in the same female rats, with or without estrogen replacement, no stress-induced remodeling was found in prefrontal cortex neurons that project to brain regions other than the amygdala. These prefrontal cortex neurons do undergo remodeling in male rats in response to stress. The results suggest that stress produces circuit- and sex-specific neuronal remodeling and that estrogens modulate the effect of stress in a circuit-specific fashion, conferring sex-specific resistance in some circuits and an increased sensitivity in others. These results may help explain the role of ovarian hormones in the differential sensitivity of males and females to stress (Shansky RM, Neural circuit- and sex-specific neuronal remodeling in response to stress. *Cereb Cortex* 20:2560-2567, Epub 2010 Feb 5).

Cycle Phase and Hormone Levels Linked to Fear Extinction. The processing of fearful experiences is likely to be a fundamental factor in the pathogenesis of psychiatric disorders such as anxiety and posttraumatic stress disorder, and gonadal hormones have been shown to modulate acquisition of fear memories in laboratory animals. The ability to extinguish, or unlearn, a fearful memory in female rats varies across the reproductive cycle. The process of learning that a stimulus is no longer linked to an aversive response (fear extinction) is more efficient when the circulating levels of estrogen and progesterone are higher or when the hormones are administered exogenously. Lower extinction of fear occurs in female rats compared with male rats, but only when the females are in the low estrogen/low progesterone phase of the cycle. The sex differences in the capacity to forget fearful experiences and the modulatory role of ovarian hormones may help explain the increased susceptibility of women to anxiety disorders (Milad, M. et al., Estrous cycle phase and gonadal hormone levels linked to the ability to forget fearful experiences. *Neuroscience* 164 (3):887-895, 2009).

Estrogen and Progesterone Regulate the Corticotrophin-Releasing Factor and Urocortin Systems in the Midbrain of Nonhuman Primates: Implications for Regulation of Mood and Anxiety. It is believed that CRF, serotonin, and ovarian hormones interact synergistically in the brain and thus influence mood and anxiety in females. In this study, the ovarian hormones estrogen and progesterone were chronically given to adult monkeys whose ovaries had been removed surgically to determine how this treatment changes the expression of specific stress-related genes and their resulting protein products in the midbrain. Treatment with an estrogen with or without progesterone decreased expression of the CRF-receptor 1 gene and protein in the raphe nucleus. Treatment with an estrogen increased expression of the CRF-receptor 2 gene in the raphe nucleus, and the stimulatory effect of an estrogen was blocked by administration of progesterone. Because these results suggest that ovarian steroid hormones regulate the expression of CRF receptors in neurons involved in stress circuits, changing levels of ovarian steroid hormones across the lifespan may alter the risk for anxiety and stress-related disorders in women (Sanchez RL, Reddy AP, Bethea CL. Ovarian steroid regulation of the midbrain corticotrophin releasing factor and urocortin systems in macaques. *Neuroscience* 171:893-909, Epub 2010 Sep 15, 2010).

Towards Understanding the Mechanism of Sex Differences in Incidence of Depression: Loss of a Brain-Derived Neurotrophic Factor

in the Hippocampus Differentially Increases Stress-Related Behaviors in Females. Major depressive disorder occurs twice as often in females as it does in males. The basis of this sex difference is unknown but is suspected to include both experiential and biological factors. Recent work has strongly implicated brain-derived neurotrophic factor (BDNF), the most prevalent growth factor in the brain, in depression-related behavior and as a possible mediator of the therapeutic action of antidepressants. In support of the BDNF hypothesis of depression, animals with decreased expression of BDNF in hippocampus have attenuated response to antidepressant drugs. However, increases in baseline depressive-related measures have not been observed in BDNF-deficient models. The current report examined the combined effects of decreasing BDNF in hippocampus and chronic stress exposure in male and female mice. Results demonstrated much greater sensitivity of the females to combined effects of stress and decreased BDNF across several behavioral paradigms indicative of anxiety and depression. In contrast, loss of BDNF in males failed to increase most measures of anxiety, anhedonia, and depression-like behavior following stress. The vast majority of previous work on stress or genetic susceptibility to depression and antidepressant research has been done exclusively in male systems. The data reported in this study, in combination with previous work by the group, highlights the need for inclusion of females in research aimed at elucidating risk factors and treatment paradigms for sex-biased disorders such as major depressive disorder (Autry AE, Adachi M, Cheng P, and Monteggia LM. Gender specific impact of BDNF signaling on stress-induced depression-like behavior. *Biol Psychiatry* 66:84-90, 2009).

Effects of Female Hormonal Cycle on Stress Response. Findings suggest that sex differences in stress response circuitry are hormonally regulated via the impact of subcortical brain activity on the cortical control of arousal. These findings demonstrate that females have been endowed with a natural hormonal capacity to regulate the stress response that differs from males (Goldstein JM, Jerram M, Abbs B, et al. Sex differences in stress response circuitry activation dependent on female hormonal cycle. *J Neurosci* 1330(2):431-8, 2010).

Hormones, Aging, and Sexual Function. Studies fail to find uniform effects of age-related or -induced hypogonadism on human sexual function. A study carried out in the Intramural Research Program of NIMH examined the effects of induced hypogonadism on sexual function in healthy men and women and attempted to identify predictors of the sexual response to induced hypogonadism or hormone "add-back." Participants in the study received depot leuprolide acetate (Lupron) every 4 weeks for 3 months (men) or 5 months (women). After the first month of Lupron alone, men also received testosterone enanthate or placebo every 2 weeks for 1 month each. Women received Lupron alone for 2 months, and then, in addition, they received estradiol and progesterone for 5 weeks each. In women, hypogonadism resulted in a significant decrease in global measures of sexual functioning, principally reflecting a significant decrease in the reported quality of orgasm. In men, hypogonadism resulted in significant reductions in all measured domains of sexual function. Testosterone restored sexual functioning scores in men to those seen at baseline, whereas neither estradiol nor progesterone significantly improved the reduced sexual functioning associated with hypogonadism in women. Induced hypogonadism decreased sexual function in a similar number of men and women. No predictors of response were identified except for levels of sexual function at baseline. In conclusion, our data do not support a simple deficiency model for the role of gonadal steroids in human sexual function; moreover, while variable, the role of testosterone in sexual function in men is more apparent than that of estradiol or progesterone in women (Schmidt PJ, Steinberg EM, Negro PP, et al. Pharmacologically induced hypogonadism and sexual function in healthy young women and men. *Neuropsychopharmacology* 34(3):565-76, 2009).

Treatment Utilization Differences in Borderline Personality Disorder. Minimal data exist on treatment utilization by gender in borderline personality disorder (BPD). This study used an online questionnaire to

investigate initial and lifetime patterns of utilization of multiple treatment modalities by patients with BPD and parental satisfaction with treatment. Respondents were parents of probands diagnosed with BPD who completed a 100-question anonymous Internet survey. Of the 495 surveys analyzed, 409 pertained to female subjects with BPD and 86 to male subjects with BPD. Results for probands with BPD across gender were notable for similar high lifetime levels of use of care, including hospitalization, day programs, and halfway houses, but not similar levels of use of drug/alcohol rehabilitation services, which were greater among the male subjects with BPD. The male subjects with BPD received significantly less lifetime psychotherapy and pharmacotherapy than the female subjects with BPD, although the duration of medication and psychotherapy treatment did not differ by gender. These results highlight the need for more research to better understand what might account for these gender differences in treatment and improve strategies to provide appropriate care for male patients with BPD (Goodman M, Patil U, Avedon J et al. Treatment utilization by gender in patients with borderline personality disorder *J Psychiatr Pract* 16(3):155-63, 2010).

Research on Specific Mental Disorders. According to the National Comorbidity Replication Study, approximately 24.9 percent of women will experience a mood disorder and 36.3 percent will experience an anxiety disorder at some time during their lives. Research continues to link depression with other medical disorders. Some women appear to be vulnerable to mood disorders during pregnancy and the postpartum period, or during menopause or perimenopause. Eating disorders, while less common than mood and anxiety disorders, are associated with severe metabolic consequences that can be life threatening. Genetic and hormonal factors, sex differences in stress response, and risk factor exposures have all been implicated in gender disparities in these disorders. The following examples of NIMH-supported studies illustrate the Institute's research efforts on specific mental disorders. Studies are grouped in categories of Depression and Other Mood Disorders, Postpartum Depression and Perinatal Mental Health Disorders, and Eating Disorders.

Depression and Other Mood Disorders

Factors Other Than Vasomotor Symptoms Appear To Account for Perimenopausal Depression. In a study of risk factors for depression during the menopausal transition, Bromberger and colleagues followed 256 middle-aged, premenopausal, or early perimenopausal women with no prior history of depression over a 7-year period and found that 15.8 percent of them experienced a first lifetime episode of major depressive disorder during that time. Though the frequency of vasomotor symptoms such as hot flashes and/or night sweats was significantly associated with major depression, multivariate analyses showed that these symptoms did not add significantly to predicting depression onset when other relevant factors were taken into account, such as lifetime histories of anxiety disorder, physical health-related role limitations at study baseline, and recent experience of stressful life events. These findings are significant in indicating that other long- and short-term circumstances may be more important than the physiologic symptoms associated with menopause in accounting for new-onset depressive episodes among women going through this period of their lives (Bromberger JT, Kravitz HM, Matthews K, et al. Predictors of first lifetime episodes of major depression in midlife women. *Psychol Med* 39:55-64, 2009).

Onset of Depression in Perimenopause. This review focuses on the relationship between the onset of depression in women and the reproductive events of the menopause transition. Epidemiologic studies have documented that the majority of women do not become depressed during the menopause transition. However, recent longitudinal studies suggest that in some women, the reproductive events related to the menopause transition could play a role in the onset of depression. No abnormality of ovarian hormones has been identified that distinguishes women with depression from those who remain asymptomatic during the menopause transition. Nonetheless, several findings suggest a role of ovarian hormones in the onset of these depressions. First, episodes of depression cluster during the stage of the menopause transition

that is accompanied by estradiol withdrawal. Second, randomized controlled trials have documented the short-term (3 to 6 weeks) antidepressant efficacy of estradiol in women who are depressed during the perimenopausal period. Third, experimentally induced estradiol withdrawal triggers mood symptoms in some women. Thus, although depression is not a uniform accompaniment of the menopause transition, in some women, age-related changes in ovarian estrogen production may alter central nervous system function and predispose them to develop depression (Schmidt PJ, Rubinow DR. Sex hormones and mood in the perimenopause. *Ann N Y Acad Sci.*1179:70-85, 2009).

Relationship Between Menopause Transition and Depression. Epidemiologic studies have documented that the majority of women do not become depressed during the menopause transition. However, recent longitudinal studies suggest that in some women, the physiological events related to the menopause transition could play a role in the onset of depression. This article reviews evidence suggesting a relationship between the menopause transition and depression. In addition, several findings are described that suggest a role of ovarian hormones in the onset of these depressions, including the clustering of episodes of depression during the stage of the menopause transition that is accompanied by estradiol withdrawal and the therapeutic effects of short-term estradiol in women who are depressed during the perimenopausal period. Possible causes of affective disturbances during the menopause transition are discussed (Harsh V, Meltzer-Brody S, Rubinow DR, Schmidt PJ. Reproductive aging, sex steroids, and mood disorders. *Harv Rev Psychiatry* 17(2):87-102, 2009).

Premenstrual Dysphoric Disorder, Estrogen, and Psychological Traits. Premenstrual dysphoric disorder (PMDD) is a mood disorder affecting about 5 percent of women and is associated with substantial morbidity. PMDD is described as being characterized by heritable personality traits, albeit inconsistently so. Although PMDD is a heritable disorder, it is unclear whether any of the heritable susceptibility to PMDD resides in heritable personality traits. In groups of carefully characterized women with PMDD (n=68) and controls (n=56), researchers attempted to determine whether diagnosis-related traits could be confirmed and whether such traits were associated with previously demonstrated findings in estrogen receptor alpha genes associated with PMDD. Researchers found a number of traits to be significantly different in patients and controls and further showed that 11/12 significant associations involved the single-nucleotide polymorphisms previously shown to be the locus of the association with PMDD. Although several interactions between genotype and diagnosis were observed, the effect of genotype in most instances was in the same direction in patients and controls. These data demonstrate affective state-independent personality traits that distinguish patients with PMDD from controls and further support the relevance of ESR-1 polymorphic variants in the regulation of nonreproductive behaviors (Miller A, Vo H, Huo L, Roca C et al. Estrogen receptor alpha (ESR-1) associations with psychological traits in women with PMDD and controls. *J Psychiatr Res* 44(12):788-94, 2009).

Depression Associated With Metabolic Syndrome and a Risk Factor for Coronary Artery Calcification. In other reports from this same research project, the investigators have examined depression and other mental health issues as risk factors for the development of other adverse health outcomes for women in middle age. Goldbacher and colleagues found that major depression was significantly associated with onset of metabolic syndrome among 429 middle-aged women who were free of the syndrome at study baseline. Although a history of alcohol abuse or dependence also was associated with metabolic syndrome and, when taken into account, somewhat attenuated the association of depression with metabolic syndrome, depression remained a significant independent predictor over and above this. Furthermore, Matthews and colleagues examined whether depression, a known risk factor for coronary heart disease, was related to progression of atherosclerosis in middle-aged women before the onset of obvious heart disease. Among 149 women who reported no heart disease, stroke, or diabetes at study baseline, they found that recurrent major depression in particular was

a risk factor for coronary artery calcification, especially in those women who manifested at least some initial calcification. Both analyses are significant in pointing to interventions to prevent and/or treat depression as likely to be useful in alleviating other health conditions that women may experience in midlife (Goldbacher EM, Bromberger J, Matthews KA. Lifetime history of major depression predicts the development of the metabolic syndrome in middle-aged women. *Psychosom Med*, 71:266-72, 2009; Matthews KA, Chang Y-F, Sutton-Tyrell K, Edmundowicz D, Bromberger JT. Recurrent major depression predicts progression of coronary calcification in healthy women: Study of Women's Health Across the Nation. *Psychosom Med* 72:742-7, 2010).

Depression, Neuroinflammation, Gender and Racial/Ethnic Patterns, and Personality Factors. Growing evidence links both allostatic load (wear and tear on the body as it tries to adapt to chronic exposure to stress) and neuroinflammation to risk for depression, particularly in older adults. In a study of demographic and individual differences in allostatic load and inflammatory processes among 103 middle-aged and elderly primary care patients, Chapman and colleagues found that both women and minorities tended to have elevated circulating levels of the pro-inflammatory cytokine interleukin-6 (IL-6). However, in addition, significant individual differences were apparent within the gender and racial/ethnic patterns, whereby the risk of inflammation also was related to the personality factors of higher neuroticism and lower extraversion (particularly reductions in the extraversion facets of dispositional vigor and energy as opposed to those of sociability and positive emotionality). Although further research is needed to confirm these findings, if substantiated, the personality patterns detected may point toward potential avenues of intervening with women and minorities to reduce their susceptibility to inflammation (e.g., via methods for increasing regular activity levels) (Chapman BP, Khan A, Harper M et al. Gender, race/ethnicity, personality, and interleukin-6 in urban primary care patients. *Brain Behav Immun* 23(5):636-42, 2009).

Postpartum Depression and Perinatal Mental Health Disorders

Accuracy of Depression Screening Tools and Rates of Postpartum Depression Among Low-Income Urban Mothers. This is the first study to describe the high prevalence of depression, determined with a diagnostic interview, among low-income, young African-American mothers attending well-child care visits in the first year postpartum, and the first to describe the accuracy of three depression screening tools in this understudied population. The striking findings among 198 mothers revealed that, at some point between 2 weeks and 14 weeks after delivery, 56 percent of mothers met criteria for either major depressive disorder (37 percent) or minor depressive disorder. Although the screening tools showed high accuracy in identifying depression, cut-off scores may need to be altered to identify depression more accurately among urban low-income mothers (Chaudron, LH, Szilagyi PG, Tang W et al., Accuracy of depression screening tools for identifying postpartum depression among urban mothers, *Pediatrics* 125(3):e609-17, 2010).

Review of Nonmedication Interventions To Prevent Depression During Pregnancy and Postpartum. Perinatal depression is a serious and disabling disorder that has enduring consequences for both women and their children. Although efficacious pharmacologic strategies are available, many perinatal women are reluctant to continue or start antidepressant medications because of the concern about impact on the fetus or, later, the nursing infant. Weighing the costs and benefits of pharmacologic strategies often requires complex decisionmaking on the part of obstetric providers and patients. Nonpharmacologic intervention and prevention strategies offer the potential of beneficial outcomes without substantial risk profiles. This paper reviews the evidence base for nonpharmacologic intervention and prevention strategies for depression during pregnancy and postpartum. The evidence base suggests that efficacious nonpharmacologic options are available for women during pregnancy and postpartum; however, important research questions remain (Dimidjian S, Goodman S. Nonpharmacologic intervention

and prevention strategies for depression during pregnancy and the postpartum, *Clin Obstet Gynecol* 52(3):498-515, 2009).

Impact of Depression Treatment on Pregnancy and Neonatal Outcomes. An ongoing NIMH study has shown that untreated major depression, as well as the use of antidepressant medications, may increase the risk for premature (preterm) birth, but the risk of other problems in fetuses, such as breathing, gastrointestinal, or motor problems, may not be increased. More research is needed to better determine whether women with major depression who are treated with the class of antidepressant medications of SSRIs and experience remission during pregnancy have more favorable outcomes compared with nonmedicated women with depression. NIMH is currently funding other research on exercise intervention, Internet interventions, mindfulness-based cognitive therapy, and supportive listening and preventative psychoeducation to reduce postpartum depression symptoms (Wisner KL, Sit DKY, Hanusa BH, et al. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. *Am J Psychiatry* 166(5):557-66, 2009).

Identifying Risk for Postpartum Mental Illness and Its Effects on Children. Two recent significant publications on the effects of perinatal stress (depression/anxiety), antidepressant treatment, and genetic influences on infant and maternal outcomes include an effort to determine genetic susceptibility and a study that shows perinatal depression associated with increased stress reactivity (cortisol) in infants (Mahon PB, Payne JL, MacKinnon et al. Genome-wide linkage and follow-up association study of postpartum mood symptoms, *Am J Psychiatry* 166(11):1229-37, 2009; Brand SR, Brennan PA. Impact of antenatal and postpartum maternal mental illness: How are the children? *Clin Obstet Gynecol* 52(3):441-55, 2009).

Obsessive-Compulsive Disorder and Symptoms May Appear More Frequently in Pregnancy Than Previously Recognized. This study described the phenomenology of obsessive-compulsive symptoms (OCS) and disorders (OCD) in perinatal women and explored the relationship of OCS/OCD to postpartum depression. A prospective longitudinal study of 44 women screened with the Obsessive-Compulsive Inventory-Revised (OCI-R) and Edinburgh Postnatal Depression Scale (EPDS) between 30 and 37 weeks of pregnancy. Twenty-four women completed a diagnostic interview and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) before delivery and were contacted postpartum to repeat the EPDS and Y-BOCS. In the third trimester, 32 percent reported high levels of anxiety and/or depressive symptoms (EPDS ≥ 10 and/or OCI-R ≥ 15), and 29 percent of those who completed the diagnostic interview met criteria for OCD. At 1 month postpartum, 12.5 percent had new OCS (Y-BOCS ≥ 8) and 25 percent had new high levels of depressive symptoms (EPDS ≥ 10). OCS increased in intensity postpartum but did not change in character. OCD and OCS may be more prevalent during the perinatal period than previously recognized. The high rates provide new information and require replication in larger, more diverse populations. Research in the perinatal period must expand beyond the exploration of depression to include anxiety disorders and specifically OCD. (Chaudron LH, Nirodi N. The obsessive-compulsive spectrum in the perinatal period: a prospective pilot study. *Arch Womens Ment Health* 13(5):403-10, 2010).

Eating Disorders

Preventive Intervention for Eating Disorders. Researchers had previously developed a brief (4-hour) school-based program that takes a dissonance-based approach to eating disorder prevention. More than 300 adolescent girls who expressed body image concerns were randomly assigned to a dissonance-based intervention or a psychoeducational brochure control condition. In the dissonance intervention, girls voluntarily engaged in verbal, written, and behavioral exercises in which they critiqued the internalized thin ideal. Theoretically, these activities produce psychological discomfort, which motivates the young women to reduce their pursuit of the thin ideal, thereby decreasing body dissatisfaction, dieting attempts, and eating disorder symptoms. The current study was an effectiveness trial—an evaluation to determine whether this efficacious intervention would produce similar effects when delivered by endogenous

providers (e.g., high school counselors, nurses, and teachers) under real-world conditions, in natural settings, with heterogeneous populations. Compared with the psychoeducational control condition, adolescent girls who participated in the dissonance-based program showed significantly greater decreases in thin-ideal internalization, body dissatisfaction, dieting attempts, and eating disorder symptoms from pretest to posttest. Although the intervention effects persisted at 1-year followup, the effects were slightly smaller than those previously found in the efficacy research trial, suggesting that additional booster sessions may be needed when the intervention is delivered in ecologically valid settings (Stice E, Rohde P, Gau J, Shaw H. An effectiveness trial of a dissonance-based eating disorder prevention program for high-risk adolescent girls. *J Consult Clin Psychol*. 77(5):825-34, 2009).

Impaired Brain Activity Underlies Impulsive Behaviors in Women With Bulimia. Women with bulimia nervosa (BN), when compared with healthy women, showed different patterns of brain activity while doing a task that required self-regulation. This abnormality may underlie binge eating and other impulsive behaviors that occur with the eating disorder. In the first study of its kind, Marsh and colleagues assessed self-regulatory brain processes in women with BN without using disorder-specific cues, such as pictures of food. Instead, subjects viewed a series of arrows on a computer screen and identified the direction in which the arrows were pointing while the researchers observed their brain activity using fMRI. Women with BN tended to be more impulsive during the task, responding faster and making more mistakes when presented with conflicting information, compared with healthy controls. Patterns in brain activity also differed between the two groups. Even when they answered correctly to conflicting information, women with BN generally did not show as much activity in brain areas involved in self-regulation as healthy controls did. Women with the most severe cases of the disorder showed the least amount of self-regulatory brain activity and made the most errors on the task. Altered patterns of brain activity may underlie impaired self-regulation and impulse control problems in women with BN. These findings increase the understanding of causes of binge eating and other impulsive behaviors associated with BN and may help researchers to develop better targeted treatments (Marsh R, Steinglass JE, Gerber AJ et al. Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. *Arch Gen Psychiatry:* 66(1):51–63, 2009).

Purging Disorder Associated More With Anxiety Disorders Than Mood Disorders. Recent studies suggest that purging disorder (PD) may be a common eating disorder associated with clinically significant levels of distress and high levels of psychiatric comorbidity. However, no study has established evidence of disorder-related impairment or whether distress is specifically related to PD rather than to comorbid disorders. Three groups of normal-weight women [non-eating-disorder controls (n=38), with PD (n=24), and with BN-purging subtype (n=57)] completed structured clinical interviews and self-report assessments. Both PD and BN were associated with significant comorbidity and elevations on indicators of distress and impairment compared with controls. Compared with BN, PD was associated with lower rates of current and lifetime mood disorders but higher rates of current anxiety disorders. Elevated distress and impairment were maintained in PD and BN after controlling for axis I and axis II disorders. Researchers concluded that PD is associated with elevated distress and impairment and should be considered for inclusion as a provisional disorder in nosological schemes such as the *Diagnostic and Statistical Manual* to facilitate much-needed research on this clinically significant syndrome (Keel PK, Wolfe BE, Gravener JA, Jimerson DC. Co-morbidity and disorder-related distress and impairment in purging disorder. Psychol Med 38:1435-42, 2008).

Effects of Estradiol on How Much Genes Influence Disordered Eating. Puberty moderates genetic influences on disordered eating attitudes and behaviors, with little genetic influence before puberty but large (50 percent) genetic effects during and after puberty. To date, however, nothing is known about the mechanisms that underlie these effects. Estradiol is a particularly promising candidate because estrogens become elevated at puberty

and regulate gene transcription within neurotransmitter systems important for eating-related phenotypes. The aim of this pilot study was to examine whether estradiol levels moderate genetic influences on disordered eating during puberty. Participants included 198 female twins (ages 10 to 15 years) from the Michigan State University Twin Registry. Disordered eating attitudes and behaviors were assessed with the total score, weight preoccupation, body dissatisfaction, and binge eating/compensatory behavior subscales of the Minnesota Eating Behavior Survey (MEBS). Afternoon saliva samples were assayed for estradiol levels. Moderation of genetic effects was examined by comparing twin correlations in low- versus high-estradiol groups. Results showed that in the low-estradiol group, monozygotic (MZ) and dizygotic (DZ) twin correlations for all MEBS scales were similar, suggesting little genetic influence. In the high-estradiol group, the MZ twin correlation was more than double the DZ twin correlation, indicating the presence of genetic effects. Findings could not be accounted for by age, body mass index, or the physical changes of puberty. Researchers concluded that estradiol may be one important moderator of genetic effects on disordered eating during puberty. Larger twin studies are needed to replicate this pilot work and quantify the extent of genetic moderation (Klump KL, Keel PK, Sisk C, Burt SA. Preliminary evidence that estradiol moderates genetic influences on disordered eating attitudes and behaviors during puberty. *Psychol Med* (10):1745-53. Epub 2010 Jan 11).

Research on Women With HIV

Women at risk for or diagnosed with HIV/AIDs often live with other factors, such as violence and poverty, that affect health, present obstacles to health care, and lead to mental health sequelae. Research on health behaviors related to HIV/AIDS is increasingly important to the reduction of health disparities in minority populations, for example, the disproportionate increase in HIV infection experienced by African-American women. Intervention and services research in this area often targets adolescents and underrepresented minorities and can dovetail with other areas of high research significance to NIMH, including perinatal mental health. The following examples of NIMH-supported studies illustrate the Institute's research efforts on HIV/AIDS.

Intimate Partner Violence: A Risk for HIV Infection Among Young Women Around the World. Young women represent one of the highest risk groups for HIV infection around the world. A greater understanding of the factors related to increased risk of infection is needed to better target those at increased risk and address the factors that place women at risk. Two sets of NIMH-funded researchers examined the impact of intimate partner violence on the risk of HIV infection—one group in Capetown, South Africa, and another in Atlanta, GA. It is noteworthy that the South African study undertook nationwide efforts to include migrant youth in the study and the Atlanta study focused on urban African-American women. Women who reported having experienced intimate partner violence in South Africa were more likely to become HIV positive over the course of the study, whereas women in Atlanta who reported intimate partner violence were more likely to report having risky partners, use condoms inconsistently, and test positive for a sexually transmitted infection. Future HIV-prevention interventions need to address the role that intimate partner violence plays in HIV infection among young women (Jewkes, RK, Dunkle, K, Nduna, M, Shai, N. Intimate partner violence, relationship power inequity, and incidence of HIV infection in young women in South Africa: a cohort study. *Lancet,* 376(9734), 41-8, 2010; Seth, P, Raiford, JL, Robinson, LS, et al. Intimate partner violence and other partner-related factors: correlates of sexually transmissible infections and risky sexual behaviours among young adult African American women. *Sex Health* 7(1),25-30, 2010).

Bundling HIV Prevention With Prenatal Care Reduces Risky Sex Behaviors Among At-Risk Mothers. An HIV prevention program targeted at women receiving prenatal care may effectively reduce risks for HIV, sexually transmitted infections, and unplanned future pregnancies, according to NIMH-funded researchers. Bundling such interventions into existing health care models, like prenatal care, also may be more accessible to those who may

not have the time, interest, or resources to attend a stand-alone HIV prevention program. Changing the way prenatal care is provided may create sustainable advantages in reproductive health for all at-risk women (Kershaw TS, Magriples U, Westdahl C, et al. Pregnancy as a window of opportunity for HIV prevention: effects of an HIV intervention delivered within prenatal care. *Am J Public Health* 99(11):2079-86, 2009).

Structural Ecosystems Therapy Helps Women Living With HIV Adhere to Life-Saving Medications. With the availability of highly active antiretroviral therapy (HAART), HIV has become a chronic condition that can be managed with antiretroviral medications. However, taking medications on a consistent basis is challenging, prompting the need for interventions to assist those living with HIV to adhere to their drug regimens. NIMH-funded researchers compared structural ecosystems therapy (SET) with person-centered therapy among HIV-positive women and found that SET helped more women reach high levels of adherence, levels necessary to prevent the development of resistance to antiretroviral medications. SET promotes social support among family members and helps women become empowered to address the challenges associated with living with HIV. SET is another approach that health care providers can turn to in their work with HIV-positive women (Feaster, DJ, Brincks, AM, Mitrani, VB, The efficacy of structural ecosystems therapy for HIV medication adherence with African American women. *J Fam Psychol* 24(1):51-9, 2010).

Stigma Prevents HIV-Positive Pregnant Women From Accessing Prevention of Mother-to-Child Transmission Services in India. Only a third of HIV-positive pregnant women in India receive the medications they need during delivery to prevent the transmission of HIV to their babies. NIMH-funded researchers interviewed women who had received services through programs targeting the prevention of mother-to-child transmission (PMTCT) as well as family members and HIV service providers. Stigma played a large part in women's fear to access services. Future interventions to address the low levels of uptake of PMTCT services among HIV-positive pregnant women should address institutional and interpersonal HIV-associated stigma (Rahangdale, L, Banandur, P, Sreenivas, A, et al. Stigma as experienced by women accessing prevention of parent-to-child transmission of HIV services in Karnataka, India. *AIDS Care* 22(7), 836-42, 2010).

Reduced Levels of Monocytes in HIV-Associated Dementia. The severity of cognitive impairments in HIV-1 infection parallels monocyte entry into the brain through the blood-brain barrier; however, the functional correlates of the monocytes remain unresolved. Five Hispanic women with HIV-associated dementia (HAD) and four patients without cognitive impairment donated blood. Monocytes were isolated from the donated blood and subjected to proteomic analysis. In monocytes from patients with HAD, six proteins were expressed at a lower level compared with control patients. An additional cohort of 30 patients donated their blood for analysis by flow cytometry and validated the proteomic results for three of the six proteins: myeloperoxidase, thioredoxin, and peroxiredoxin 3. These proteins are involved with hydrogen peroxide scavenging, and lower protein expression indicates that deficits in monocyte antioxidants may contribute to the development and progression of HIV-associated cognitive impairment (Kraft-Terry S, Gerena Y, Wojna V, et al. Proteomic analyses of monocytes obtained from Hispanic women with HIV-associated dementia show depressed antioxidants. *Proteomics Clin Appl* 4(8-9):706-14, 2010).

Tools To Evaluate Progression of HIV-Associated Cognitive Impairment. A subset of HIV-infected people on antiretroviral therapy still exhibit neurocognitive impairment; therefore, a revised classification of clinical assessments was agreed upon in Frascati, Italy, in 2007. The Frascati scale was in concordance with the previous 1991 scale in assessment of the study cohort of patients and was able to distinguish between asymptomatic neurocognitive impairment and mild neurocognitive disorder. Though the cohort was small, 14 subjects (31 percent) progressed to a higher level of neurocognitive impairment within 12 months of the initial clinical assessment. Predictors of progression toward HIV-associated neurocognitive

disorders in this cohort of patients were people older than age 50 years and women Gandi, NS, Moxley, RT, Creighton, J. Comparison of scales to evaluate the progression of HIV-associated neurocognitive disorders. *HIV Therapy* 4(3):371-379, 2010.

Workshops and Initiatives

Postpartum Depression and Perinatal Mental Health

NIMH sponsored the following workshops on postpartum depression and perinatal mental health during FY 2009–10:

Fresh Perspectives in Perinatal Depression Research: Psychosocial Interventions and Mental Health Services. On October 5–6, 2010, the NIMH Division of Services and Intervention Research convened a workshop to provide the growing number of early-stage perinatal depression psychosocial intervention and services investigators with the opportunity to discuss research strategies consistent with public health needs and NIMH priorities. NIMH priorities for perinatal depression align with current developments in Federal health care legislation concerning the mental health of pregnant and postpartum women. Research priorities also address calls for comparative effectiveness research and personalized intervention approaches; emerging developments in novel research diagnostic criteria; and, implementation of the NIMH Strategic Plan and the National Advisory Mental Health Council Work Group Report, "From Discovery to Cure: Accelerating the Development of New and Personalized Interventions." The workshop provided a forum for perinatal depression investigators, along with NIMH and NIH staff, to review and discuss current psychosocial services and intervention research. With input from the Centers for Disease Control and Prevention and experts from the broader field of depression research, the workshop incorporated informative viewpoints from outside the immediate field of perinatal mental health. Plenary presentations, large group discussions, and smaller breakout group sessions facilitated the exchange of ideas about findings from current research, challenges and limitations of current work, and fresh perspectives to bring to bear on next steps in perinatal depression research.

NIMH Director Thomas Insel, M.D., discussed NIMH interest in better understanding the pathophysiology of mental illness to support the development of interventions that are both preemptive and personalized. He also spoke about the importance of investigators working more collaboratively by utilizing standardized measures and sharing data. Attendees were encouraged to consider mental health in global terms, to see linkages between research conducted in low- and middle-income countries and research conducted in the United States, and to consider learning opportunities arising from a bidirectional exchange of knowledge and ideas.

The meeting included talks on epidemiology, genetics and biomarkers, and child mental health outcomes and a presentation on issues to consider regarding the adaptation of existing interventions to specific populations or health care settings. The second day of the workshop involved presentations and plenary discussion oriented toward identifying fresh perspectives with regard to research questions, research design and methodology, and the provision of mental health interventions in communities with limited resources. The discussion from the plenary sessions and breakout groups yielded numerous themes of interest to investigators in the field and to NIMH. For more information, see the meeting summary Web page.

Perinatal Mood Disorders: Components of Care. A 2-day meeting convened May 7–8, 2009, educated participants on essential components of care for women with perinatal mood disorders. The event brought together 100 mental health providers, including psychiatrists, psychologists, social workers, and nurses from the Washington metropolitan area and beyond. Peter Schmidt, M.D., of the NIMH Intramural Research Program, presented the results of ongoing research focusing on the role of sex steroids in the onset of perinatal mood disorders. He emphasized the need for developing new, effective therapies for these conditions. Postpartum Support International, an advocacy organization with independent branches across the country, presented training material covering standard-of-care drug and

psychotherapy treatments, the role of social support systems, and professional resources for mental health providers working with this population. Participants discussed the suggestion to replace the term "postpartum depression" with the more inclusive diagnostic label "perinatal mood and anxiety disorders" to reflect the variable timing of onset and the prominence of anxiety in this condition.

In addition to these workshops and the ongoing program announcements listed below, NIMH provided funding for the Marce Society's annual meeting in 2010, "Perinatal Mental Health Research: Harvesting the Potential," at which a number of NIMH-funded researchers made presentations. NIMH also initiated Web-based dissemination efforts to further educate researchers and consumers about postpartum depression and perinatal mental health. For more information, please see

- Director's Blog, *Spotlight on Postpartum Depression*
- Video: http://www.nimh.nih.gov/media/video/postpartum-depression.shtml

HIV Workshop

2010 Joint Center for AIDS Research Symposium on HIV Research in Women. On Oct 27–28, 2010, NIMH cosponsored, with other NIH Institutes, the 2010 Joint Center for AIDS Research (CFAR) Symposium on HIV Research in Women. The 2-day meeting in Chicago focused exclusively on research pertaining to HIV among women. The goals of this meeting were to review the current research on how to prevent new infections among women most effectively—including talks on female physiology and fertility desires among women in sero-discordant couples—as well as how to best treat HIV and subsequent comorbidities among women living with HIV. Research highlighted the need to continue to examine sex and gender differences as well as the unique biological, social, and psychological factors that must be taken into account when working with women.

Program Announcements and Requests for Applications

The program announcements and requests for applications listed below were active in FY 2009–2010 and had a significant focus on women's mental health and/or sex differences research.

Requests for Applications

- Epigenomic Modifications in Neurodevelopment (R01) http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-11-030.html
- Epigenomic Modifications in Neurodevelopment (R21) http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-11-031.html

Program Announcements

- Women's Mental Health and Sex/Gender Differences Research (R01) http://grants.nih.gov/grants/guide/pa-files/PA-09-108.html
- Women's Mental Health and Sex/Gender Differences Research (R21) http://grants1.nih.gov/grants/guide/pa-files/PA-06-334.html
- Women's Mental Health in Pregnancy and the Postpartum Period (R01) http://grants.nih.gov/grants/guide/pa-files/PA-09-174.html
- Women's Mental Health in Pregnancy and the Postpartum Period (R21) http://grants.nih.gov/grants/guide/pa-files/PA-06-377.html

In FY 2009–2010, NIMH also participated in the following ORWH program announcements:

- Supplements To Promote Reentry Into Biomedical and Behavioral Research Careers http://grants1.nih.gov/grants/guide/pa-files/PA-08-191.html
- Advancing Novel Science in Women's Health Research (ANSWHR) (R21) http://grants.nih.gov/grants/guide/pa-files/PAS-10-226.html

National Institute on Minority Health and Health Disparities

Executive Summary

The National Institute on Minority Health and Health Disparities (NIMHD) promotes minority health and conducts and supports research aimed at eliminating health disparities. It also plans, leads, coordinates, and assesses the efforts of the National Institutes of Health (NIH) to reduce and eliminate health disparities. To achieve its mission, the NIMHD employs a multifaceted strategy to conduct and support research in basic, clinical, social, and behavioral sciences, bioethics, and on the social determinants of health; disseminate information; promote research infrastructure and training; foster emerging programs; and extend its reach to minority and other health disparity communities. Congress mandated the development of three principal programs within the NIMHD aimed at addressing health disparities—the Loan Repayment Program (LRP), the Centers of Excellence (COE) program, and the Research Endowment program. Additionally, the NIMHD supports the Community Based Participatory Research (CBPR) initiative, the Building Research Infrastructure and Capacity (BRIC) program, the Minority Health and Health Disparities International Research Training (MHIRT) program, and the Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) programs. Since 2009, NIMHD has launched three new research project programs: the Advances in Health Disparities Research on the Social Determinants of Health program, the Health Disparities Research program, and the Innovative Faith-Based Approaches to Health Disparities Research program. Additionally, the NIMHD has a long history of collaborating with other NIH Institutes and Centers (ICs) and Federal agencies. In 2010, the NIMHD in collaboration with the Office of Minority Health, Office of Public Health and Science, Department of Health and Human Services (HHS), launched the Comparative Effective Research for Eliminating Health Disparities (CERED) at the NIMHD COE program.

Recent accomplishments in women's health resulting from NIMHD programs and collaborations during Fiscal Years (FY) 2009–2010 are summarized below. Because NIMHD-supported research is focused on the health of racial and ethnic minorities and other health disparity populations, the range of diseases and conditions under investigation by NIMHD researchers is broad. It includes, for example, cardiovascular disease (CVD), obesity, metabolic syndrome, diabetes, cancer, HIV/AIDS and substance abuse. Some of these projects involve research on women only. However, several of these projects include both men and women in the study population. Within these diseases and conditions, researchers conduct research on both biological and nonbiological factors using various study types and interventions, such as prevention studies, comparative effectiveness studies, and community-based participatory research studies; as well as behavioral and educational interventions. NIMHD investigators also provide training to new investigators and engage communities in innovative efforts to improve minority health and to reduce and eliminate health disparities. Central concepts found in many of the NIMHD-supported studies include cultural competency and culturally tailored interventions.

NIMHD Organizational Components

While there is no office specifically designated to address research on women's health issues, women's health is an integral part of the NIMHD health disparities research portfolio which is administered through NIMHD extramural grants, cofunding with other ICs, and collaborations with other Federal agencies.

Accomplishments of the NIMHD

Consistent with its mission to improve minority health and to eliminate health disparities, the NIMHD supports research on the broad range of diseases and conditions experienced by racial and ethnic minorities and other health disparity populations. Guided by the NIMHD Health Disparities Strategic Plan, the NIMHD supports research on CVD,

obesity, metabolic syndrome, diabetes, cancer, HIV/AIDS, substance abuse, bioethics, and on the social determinants of health, for example. Thus, NIMHD-supported research is not limited to combating a specific disease or condition or to a specific organ or body system, but embraces the entire range of biological and nonbiological areas and factors contributing to the existence and persistence of health disparities experienced by racial/ and ethnic populations. Priority is given to research on those diseases, conditions and risk factors most likely to aid in eliminating the excess burden of mortality and comorbidity experienced by health disparity populations. Health disparity populations include African Americans, Hispanics, American Indians and Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islander populations and subpopulations, as well as low socioeconomic status populations and those residing in rural and underserved communities. The NIMHD also works in partnerships with other NIH ICs and other Federal agencies in these efforts.

Research and research training advancing women's health and career development of women researchers is conducted under several NIMHD initiatives, including for example the congressionally mandated COE, LRP, and Endowment programs. Additionally, the CBPR initiative, the MHIRT program, and the SBIR/STTR programs also contribute to advancing women's health research. During the period 2009–2010, the NIMHD launched the Advances in Health Disparities Research on the Social Determinants of Health program, the Health Disparities Research program, and the Innovative Faith-Based Approaches to Health Disparities Research program. These three programs utilize the R01 and R21 mechanisms, two of the most widely used extramural grant mechanisms at NIH, and these three programs have expanded NIMHD's capacity to support and conduct research projects for advancing women's health, especially the health of racial and ethnic minorities and other health disparity populations. The Disparities Research and Education Advancing Mission (DREAM) Career Transition Award (K22), launched in December 2008, is expanding NIMHD's capacity to both conduct research and train women researchers; the first eight DREAM awards have been made to women. This innovative NIH intramural research training program provides a mentored research experience at the NIH for former or current NIMHD LRP recipients and others. Applicants are highly qualified postdoctoral fellows that have no more than 10 years of postdoctoral research training at the time of application submission. Descriptions of all NIMHD programs can be found at the NIMHD website, http://www.nimhd.nih.gov. Brief descriptions of initiatives launched in 2009 and 2010 are provided in Section D of this report. The NIMHD does not currently support any Phase III clinical trials. NIMHD also supports projects through cofunding with other ICs and collaborations with Federal agencies.

Research Addressing Women's Health

NIMHD researchers are engaging in a broad range of research and research-related activities addressing women's health, especially racial and ethnic minority women and women from health disparity populations. Much research is being conducted on the behavioral risk factors for CVD, cancer, stroke, and diabetes, four of the top five leading causes of death for racial and ethnic minority females based on 2006 Centers for Disease Control and Prevention (CDC) data. Several studies addressing the excess burden of HIV/AIDS among racial/ethnic minorities are also being conducted by NIMHD researchers.

Obesity and Diabetes

The growing epidemic of obesity and the impact of other associated and prevalent health concerns, including diabetes, high blood pressure, high cholesterol, metabolic syndrome (MetS), and CVD are affecting all populations, especially racial/ethnic minorities and other health disparity populations. Comparatively, in the general population, women are slightly more obese than men. However, according to CDC data, over half of American Indian/Alaska Native women are overweight, and American Indian/Alaska Native women are 40 percent more likely than white women to be obese. Fifty-two percent of African-American women and 44 percent of Mexican women are obese compared to 33.2 percent of white women (not Hispanic or Latino). Persons are considered overweight if they have a Body Mass Index

(BMI) of 25 or greater, and obese if they have a BMI of 30 or greater.

In the examples that follow, NIMHD researchers are investigating strategies for decreasing obesity, diabetes, or both among the American Indians/Alaska Natives; Native Hawaiians and other Pacific Peoples, including Filipinos, Samoans, and Tongans; and among Latino women residing in East Harlem. The intervention and prevention strategies being utilized include faith-based, culturally appropriate, and community-based participatory research methodologies, some of which include the randomization of subjects to control or intervention groups, and that couple, in at least one case, the use of innovative approaches for recruiting and retaining minority and health disparities population in studies. Collectively, these studies are addressing the well-known disparities in overweight and obesity among minority women compared to white women.

The Native Proverbs 31 Health Project. This project will develop, implement, and evaluate a CVD prevention program among Lumbee Indian women in Robeson County, NC, focusing on the biblical messages in Proverbs 31. The Lumbee Indian tribe is the largest American Indian tribe east of the Mississippi River. This non-reservation tribe with a population of about 50,000 is largely concentrated in Robeson County, in southeastern North Carolina. This county is largely rural, has a high poverty rate, and is almost equally divided among American Indians, African Americans and non-Hispanic whites. Designed to be culturally appropriate, the expected primary outcomes for this study are changes in health behaviors (diet, physical activity) and movement along the transtheoretical model stages of change for tobacco use. Secondary outcomes will include changes in BMI and changes in self-efficacy and self-esteem. This study is being conducted by researchers at the Wake Forest University Health Sciences.

Reducing Metabolic Syndrome among Filipino, Native Hawaiian and Samoan Youth and the Partnerships for Improving Lifestyle Interventions (PILI). According to reports by the Hawai'i Department of Health, CVD has been the leading cause of death in Hawai'i since 2005, and in 2008 there were 3106 deaths resulting from CVD (diseases of the heart, cerebrovascular disease, atherosclerosis, and other circulatory diseases). Overweight and obesity are two known risk factors for CVD, and the prevalence of overweight/obesity is 82 percent for Native Hawaiians, which is considerably higher than the national prevalence of 53 percent. The Partnerships for Cardiometabolic Disparities in Native and Pacific Peoples is the NIMHD Center of Excellence at the University of Hawaii. This Center provides a regional focal point for research, research training and community engagement aimed at improving cardiometabolic health and eliminating health disparities among Alaska Natives, Native Hawaiians, and other Pacific Islanders (NHOPI), including Filipinos, Samoans, and Tongans. To address NHOPI health needs, the Center conducts a Metabolic Syndrome study, an epidemiological study involving Filipino, Native Hawaiian and Samoan Youth.

Additionally, a novel CBPR project, PILI, has been formed between five community groups, the medical school and the state department of health to focus on reducing and eliminating obesity health disparities. A recent report of the findings from the pilot CBPR project shows that the CBPR approach was successful in translating the Diabetes Prevention Program-Lifestyle Intervention into a culturally relevant intervention and successful weight loss program for NHOPI communities. Nearly 240 NHOPIs, 83 percent female, were enrolled, and after 12 weeks the mean weight loss was –1.5 kg, with 26 percent of the participants losing greater than 3 percent of their baseline weight. Weight loss was significantly higher for those completing the eight lessons (12 weeks) compared to those that completed less than eight lessons.

Vitamin D Status, Cardiovascular Health and Diabetes in American Indians. Our understanding of the role of vitamin D in skeletal and non-skeletal health and its possible contribution to adverse health outcomes experienced by racial/ethnic minorities and other heath disparity populations continues to expand. More specifically, a low level of vitamin D may be a risk factor for cancer and

site specific neoplasms, CVD, hypertension, type 2 diabetes, metabolic syndrome, obesity, overweight, infectious diseases, autoimmune disorders, and chronic kidney disease. Research being conducted by the NIMHD COE established at the University of Wisconsin will aid in advancing our knowledge of vitamin D and its diverse effects, especially regarding its contribution to CVD and type 2 diabetes. These diseases/conditions account for two of the four top causes of death among American Indians (AI). The specific aims of this study are: to evaluate the relationships between vitamin D status and heart function, specifically endothelial function; and to explore relationships of vitamin D status with glucose control parameters. In this study, 100 postmenopausal AI women up to age 70 years without diabetes mellitus (type 2 diabetes) or known CVD will be randomly assigned to receive vitamin D3 at either the current standard intake of 400 International Units (IU) or a dose estimated to achieve optimal status, 2,500 IU, daily for 6 months. The researchers will define the effects of vitamin D status and subsequent response to supplementation on heart functioning, arterial stiffness, inflammation, and glucose control. They propose that vitamin D supplementation should reduce inflammation, lead to better glucose control and thereby reduce CVD and type 2 diabetes risk.

Effective recruitment of minority populations through community-led strategies. This recently published study conducted by researchers and service providers from Mount Sinai School of Medicine, Cornell University Medical College, Little Sisters of the Assumption Family Health Service, and the Department of Community Outreach and Health Education, North General Hospital, New York, used a CBPR approach to compare the effectiveness of various strategies in recruiting and enrolling adults with prediabetes into a peer-led, diabetes prevention intervention. The Community Action Board, consisting of 20 East Harlem residents, leaders, and advocates, created 5 recruitment strategies: (1) recruiting through clinicians; (2) recruiting at large public events such as farmers markets; (3) organizing special local recruitment events; (4) recruiting at local organizations; and (5) recruiting through a partner-led approach in which community partners developed and managed the recruitment efforts at their sites. In a 3-month period, 555 local adults were approached and 249 were appropriate candidates for further evaluation (i.e., overweight, nonpregnant, East Harlem residents without known diabetes). Approximately 179 consented and 99 revealed indications of prediabetes and enrolled in a pilot randomized trial. The partner-led approach was highly successful, recruiting 68 percent of those enrolled. This strategy was also the most efficient; 34 percent of those approached through partners were ultimately enrolled versus 0 percent–17 percent enrolled through the other four strategies. Participants were predominantly low-income, uninsured, and undereducated Spanish-speaking women.

Social Determinants of Health

There is increasing appreciation for the influence of social determinants on minority health and health disparities, and several continuing, and new NIMHD studies launched in 2009 and 2010, promise to expand our understanding of how social determinants contribute to the persistence of health disparity experienced by women. The social determinants of health are the conditions in which people are born, grow, live, work, and age, including the health system. These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels, which are themselves influenced by policy choices. The following examples of NIMHD supported studies will advance our understanding of:

(1) how social processes generate and sustain health disparities;

(2) health disparities within integrated and between segregated but matched social environments;

(3) how to recruit and retain racial/ethnic minorities and other health disparity populations for cancer research studies;

(4) the contribution of interpersonal violence against women to the existence and persistence of cancer health disparities;

(5) how to detect intimate partner violence and effectively link victims to counseling and other resources;

(6) the role of economic stability/empowerment in improving the health of women in the Democratic Republic of the Congo;

(7) how adverse maternal childhood experiences may contribute to overweight at midlife and obesity of offspring; and

(8) the effectiveness of HIV risk reduction interventions that

(9) are designed for Latino women communities and delivered by Latino researchers;

» use targeted mass media messages and strategies to decrease HIV transmission among 18–34-year-olds;

» are designed to increase public awareness of HIV among women over 50; and

» are conducted within a communal living setting supportive of abstinence compared to a usual care condition.

A Social Demography of Racial Health Disparities. The purpose of this project being conducted at San Diego State University is to understand which social processes generate health disparities and how these disparities persist amidst declining morbidity and mortality rates. Because genetics does not offer a complete answer to the question of persistent disparities, investigations into possible social, economic, and structural explanations are necessary in order to better understand the origin and cause of modern health disparities. This research project will utilize a demographic approach by looking at age, period, and cohort effects; and how they change to produce health disparities; and how health disparities change over time. The researchers will stratify their results by sex/gender to appropriately interpret patterns and to account for social forces and processes regarding males and females.

The Johns Hopkins Center for Health Disparities Solutions. Exploring Health Disparities in Integrated Communities Study—Researchers at this NIMHD COE at Johns Hopkins University are conducting research that is advancing our knowledge of the biological, behavioral and socioenvironmental etiology of race disparities in health status and of the determinants of race disparities in healthcare access, utilization through epidemiological studies of adult residents of segregated and integrated urban communities having no race differences in income or education.

Recent findings from a study investigating whether race disparities in obesity among women persist in communities of black people and white people living in the same social context in southwest Baltimore (SWB) and with similar incomes show that in contrast to the findings of a national sample where black women exhibited greater odds (approximately 2:1) of being obese than white women, black women in the SWB study had similar odds of being obese as compared to white women. These conclusions were reached after adjusting for covariates in each study. The researchers conclude that there are no race disparities in obesity among poor, urban women sharing the same social context. They advance that developing policies focused on modifying social aspects of the environment may reduce disparities in obesity among low-income women living in urban communities.

African-American Nutrition for Life (A NULIFE) Study. Strategies needed to recruit younger African-American women for clinical trials have not been well defined. This recent study by researchers at the Center for Minority Health, University of Texas M.D. Anderson Cancer Center, assessed different methods used for recruiting and retaining healthy premenopausal African-American women. The number of women contacted, enrolled and retained, and the efficiency of individual recruitment strategies were calculated. Social networking was most effective in contacting large numbers of healthy premenopausal African-American women. The interpersonal relationships recruitment approach proved most efficient in retaining participants who completed the year-long study. The worksite recruitment method was the most efficient recruitment strategy employed. The findings from this study add to the evolving body of literature on minority recruitment strategies for research studies but specifically address effective recruitment of healthy young premenopausal African-American women. The results demonstrate the need to use multiple recruitment strategies when recruiting this subgroup of African-American women.

Does Violence Against Women Result in Disparities in Cancer Care for Women with Breast, Colorectal or Cervical Cancer? This cohort study of 9,600 women being conducted at the University of Kentucky examines whether women who experience interpersonal violence have more negative cancer care outcomes than women who do not. Recruitment of the sample and data collection are under way. Up to 25 percent of women nationally experience interpersonal violence. In Kentucky, where this study is being conducted, nearly 40 percent of women experience interpersonal violence. Determining whether violence against women influences the life course of cancer prevention and control for women with breast, cervical or colorectal cancer can result in an important opportunity to understand and address cancer care disparities. If violence against women does influence cancer care, interventions can be developed to provide appropriate support to ensure receipt of recommended care among women experiencing violence.

Community Health Center Intervention for Intimate Partner Violence. This study being conducted at the University of Pennsylvania proposes a large-scale demonstration project using a quasi-experimental design to evaluate the impact of a multilevel intervention on intimate partner violence (IPV) detection and social work counseling. The four intervention components are: (1) an effective social health screening procedure; (2) provider training and social marketing to increase IPV awareness and elevate clinician confidence in their ability to address and refer IPV; (3) IPV-focused motivational counseling for male and female patients by specially trained social workers; and (4) community-based family advocates providing social support and help linking abused women to resources.

A microfinance intervention to improve the health of rape survivors in the Democratic Republic of the Congo. The study, led by a researcher at Johns Hopkins University, will examine the effectiveness of a village-led microfinance program in villages of the Democratic Republic of the Congo, involving women survivors of sexual and gender-based violence. The success of the program will be evaluated by the economic stability of the household and the women's reintegration to their families and villages.

Intergenerational Obesity: Do Early Adversity and Pregnancy Explain Disparities? The purpose of this longitudinal secondary data analysis study is to investigate racial/ethnic differences in the impact and interactions between several factors that may increase maternal BMI at midlife as well as obesity in offspring. These factors include: early maternal social environment (e.g., socioeconomic status and family structure), pregnancy-related weight (e.g., excessive gestational weight gain and postpartum weight retention), and adverse maternal childhood experiences (e.g., physical abuse, substance abuse or mental illness in the home). This project will analyze data from the National Longitudinal Survey of Youth (NLSY) 1979, and the NLSY 1979 Children and Young Adults. New data on the history of maternal adverse childhood experiences will be collected in the 2012 wave of the NLSY. The researchers will collaborate with investigators having expertise within the fields of perinatal epidemiology, nutrition and obesity, neurobiology, health disparities, psychology, social epidemiology and biostatistics. The ultimate goal is a new understanding of obesity and the development of new interventions for the prevention of obesity health disparities. This study is being conducted by researchers at the University of California, Berkeley.

HIV/AIDS

NIMHD Center for Culturally Tailored Hispanic Health Disparities. This NIMHD COE established at the University of Miami addresses the disproportionate burden and impact of HIV/AIDS on women of color and is evaluating the efficacy of an HIV risk reduction intervention delivered by Hispanic women. The intervention is culturally tailored to meet the needs of Hispanic women, who are disproportionally affected by HIV/AIDS. The intervention is designed to increase HIV prevention behaviors in inner-city Hispanic women. This Center is also exploring the role of acculturation, family, stress, and family functioning as risk factors, protective factors, or both in the prevention of HIV/AIDS among

Hispanic women. Recent findings from a study of the predictive factors for perceiving susceptibility for acquiring HIV (SAHIV) among Hispanic women show that 88.5 percent of the participants reported not feeling SAHIV. Women who felt SAHIV had a significant probability of reporting a higher chance for acquiring HIV from their partner's actions and a higher probability of not being tested for HIV. The researchers suggest that: (1) educational strategies to increase the perception of SAHIV among Hispanic women would be beneficial in decreasing the burden and impact of HIV/AIDS within this population and (2) Hispanic women who do not perceive to be at risk from their partner's actions might benefit the most from strategies to increase their knowledge of HIV testing.

HIV Prevention among African Americans: A Media Campaign. The goal of this research project being conducted by researchers at the University of North Carolina at Chapel Hill is to develop effective mass media messages and strategies to decrease HIV transmission among African Americans by reducing concurrent sexual partnerships. The researchers will conduct qualitative and quantitative research among African American men and women, ages 18–34, in seven eastern North Carolina counties to: (1) construct prevention messages and communication strategies that target participation in concurrent partnerships; (2) work with an established communications firm to design and implement a culturally competent 8-month mass communication campaign that informs African Americans about the relationship between concurrency and HIV dissemination and decreases their willingness to participate in this network pattern; and (3) evaluate the campaign's effects on African Americans' attitudes, beliefs, and norms about concurrency, reported participation in concurrent partnerships, and reported condom use through the conduct of phone surveys among 600 men and women before and after the campaign. This research represents a critical first step in the development of a mass media campaign that will play a key role in a multi-component HIV prevention program for African Americans in the rural Southeastern United States and throughout the nation.

HIV Prevention PROWESS (Program Regarding Older Women's Education for Sexual Safety). This SBIR Phase I proposal will develop a targeted intervention addressing the need for HIV education, awareness, and prevention among English and Spanish-speaking women age 50 and older. Because substance abuse and HIV/AIDS are increasingly common among older adult women in the United States and because research shows that many healthcare providers do not routinely screen older patients for substance abuse and HIV, this prevention-focused intervention aims to increase public awareness of HIV among women over 50 and to educate older women and their healthcare providers about HIV risk among this same population. This program will develop a variety of written and print materials, including but not limited to patient education brochures, provider training materials, provider talking points, formatted provider contact note, provider "prescription pads," follow-up reminders for providers, and awareness posters. It will also conduct focus groups, assess needs, and convene an expert panel. The development of a smartphone/personal digital assistant (PDA) application along with CD-ROM and Web site materials is proposed. This project is being conducted by Social Solutions International, Silver Spring, Maryland.

Community Participatory Intervention with High-Risk African-American Women. This project uses CBPR methodology and a randomized pretest and posttest experimental design to compare communal-living settings supportive of abstinence to a usual care condition. The researchers hypothesize that women—African-American women who are exiting the criminal justice system—assigned to the communal living condition will report reduced HIV risk behaviors and better health outcomes (i.e., increased health services utilization), decreased recidivism, increased abstinence from substance use, improved psychological functioning, and higher levels of support than women assigned to the usual care condition at all follow-up intervals. All steps in this project will be guided by active involvement of the community advisory board and lead to more rapid translation of research findings into community practice. This study is being conducted by researchers at De Paul University.

Collaborations Supporting Research on Women's Health

The Jackson Heart Study. This population-based, longitudinal cohort study is the largest single-site, prospective, epidemiologic investigation of CVD among African Americans ever undertaken. The study site is located in Jackson, Mississippi. The Jackson Heart Study exemplifies a unique collaborative model among Jackson State University, Tougaloo College and University of Mississippi Medical Center, the Jackson community and NIH to discover and test best practices for eliminating health disparities. Since 1998, NIMHD has worked with the National Heart, Lung, and Blood Institute to initiate the study and more recently to assess success in meeting milestones, including ensuring adequate participation by key stakeholders and advice on scientific direction, and including the identification of genetic, biological, and environmental risk factors in African American women and men. In FY 2009 and FY 2010, NIMHD contributed over $6.5 million to the Jackson Heart Study.

The Sister Study. This study, a unique public-private partnership, seeks to identify some of the genetic and environmental causes of breast cancer. The Sister Study is the only long-term study in the United States and Puerto Rico of women from age 35 to 74 whose sisters had breast cancer. Begun in 2003, the study prospectively examines the environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The Sister Study is cofunded by NIMHD and led by the National Institute of Environmental Health Sciences. In FY 2009 and FY 2010, NIMHD contributed a total of $2.45 million over the 2-year period to the study to assist in the recruitment and retention of a diverse cohort of women—African Americans, Asians, American Indians/Alaska Natives, Hispanics, and seniors (ages 65 and older).

Racial and Ethnic Approaches to Community Health across the United States (REACH US), Centers for Disease Control and Prevention. In addition, the NIMHD provides supplemental funding for 2 of the 40 CDC REACH US projects: one at the Morehouse School of Medicine in Georgia and the second at Virginia Commonwealth University (VCU). REACH US projects work with communities to plan and develop strategies for the dissemination of lessons learned in order to increase the effectiveness of future programs aimed at eliminating health disparities across the country. The CDC and REACH US also continue to assist local communities in the collection of data, which aids in the evaluation of community specific strategies designed to reduce or eliminate health disparities. At the Morehouse School of Medicine, its Prevention Research Center has established the Southeastern U.S. Collaborative Coalition to provide training and technical assistance to community-based organizations in strategies to increase breast and cervical cancer screenings among African-American women. The Promoting Healthy Pregnancies Coalition at VCU aims to improve patient compliance with prenatal care for African Americans through a health navigation system.

Women in Biomedical Science Careers

In addition to the NIMHD supported training and career development projects discussed below, the LRP, the NIMHD COE, the CBPR initiative, and the SBIR/STTR programs are also assisting in advancing women's careers in the biomedical and behavioral sciences. Based on a recent analysis, women constitute 47 percent of the 154 principal investigators/program directors supported by the CBPR, NIMHD COE, and SBIR/STTR programs. The LRP for Health Disparities Research is designed to increase the number of highly qualified health professionals in research careers focused on health disparities. The Extramural Clinical Research LRP for Individuals from Disadvantaged Backgrounds seeks to increase the participation of highly qualified professionals from disadvantaged backgrounds in clinical research careers. In FY 2009 and FY 2010, approximately 75 percent of all NIMHD LRP awards were made to women.

NIMHD Intramural Research Program

In 2008, the NIH launched the NIMHD Health Disparities Intramural Research Program. It consists of a health disparities

career development component and a health disparities research intervention component. A key focus of the career development phase of the program is the Disparities Research and Education Advancing Mission (DREAM) Career Transition program. The purpose of this Career Transition Award is to facilitate the transition from mentored health disparities researcher to an independent health disparities researcher. The program provides an opportunity for investigators to develop solid research skills during the initial period of up to 2 years of study and research. DREAM participants are placed in the intramural research program of NIH ICs based on their research interests. The award may also include a follow-on period of up to 3 years' salary and mentored research support at the candidate's current institution or an organization or an academic or research grantee institution of the candidate's choice. The first cohort of DREAM recipients commenced their initial assignment in 2010. To date a total of eight individuals have received the DREAM award and all eight are women. NIMHD anticipates that the DREAM program will enhance collaborations and training of health professionals and will lead to expanded opportunities to partner with other ICs in addressing health disparities.

NIMHD FY 2009 and FY 2010 Initiatives

Establishing Exploratory Centers of Excellence (P20). Two RFAs, MD09-005 and MD09-007, were released for establishing Exploratory COE with support years of up to 5 or 2, respectively. NIMHD Exploratory COE contribute either to the improvement of minority health, the elimination of health disparities, or both.

Research Endowment Program (S21). The purpose of this program is to build capacity and research infrastructure and to facilitate minority health research and research regarding other health disparity populations at eligible institutions, but not to directly support the research itself. RFA-MD-09-002, a reissue of RFA-MD-08-001, was released in 2009.

Loan Repayment Program

Extramural Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds (L32) (NOT-OD-09-112 and NOT-OD-10-110). The objective of the LRP-ECR is the recruitment and retention of highly qualified health professionals from disadvantaged backgrounds to clinical research careers. The emphasis on clinical research and individuals from disadvantaged backgrounds highlights the need for the involvement of a cadre of competent health professionals in clinical research.

Extramural Loan Repayment Program for Health Disparities Research (L60) (NOT-OD-09-110 and NOT-OD-10-108). The objective of the LRP-HDR is the recruitment and retention of highly qualified health professionals to research careers that focus on minority health or other health disparity issues.

NIMHD Health Disparities Research (R01) (RFAs MD09-004 and MD10-003). The overarching goal of this FOA is to solicit innovative research addressing elements that eliminate health disparities. Research focused on disease and/or conditions that disproportionately affect racial/ethnic minorities is a growing field and has been employed lately in understanding dynamics contributing to health disparities. Funding for this FOA will support investigators who propose to conduct health disparities research using its principles to improve health inequities.

NIMHD Building Research Infrastructure and Capacity Program (P20) (RFAs MD09-003 and 10-002). The goal of this program is to build, strengthen or enhance the research infrastructure and research training capacity of non-research intensive institutions that educate students from health disparity populations. The BRIC grant award provides a means for an institution to: (1) strengthen its basic research infrastructure and capacity in basic, natural, social or biomedical science, mathematics and/or allied health degree programs; (2) institute a comprehensive research faculty development training program with measurable training outcomes; (3) establish an academic research enrichment training program for students'

pursuit of research career path(s) in basic, biomedical, social and/or behavioral science; and (4) support individual junior faculty-initiated research subprojects that may ultimately lead to successful independent research in minority health and/or the elimination of health disparities under traditional entry-level or advanced research grant funding mechanisms.

NIMHD Community-Based Participatory Research Initiative (R24). The ultimate goal of this America Recovery and Reinvestment Act (ARRA) FOA, RFA-MD09-006, is to support disease intervention research in reducing and eliminating health disparities using CBPR that is jointly conducted by health disparity communities and researchers. These awards provided two years support. CBPR can be defined as a participatory, collaborative, scientific process in which community organizations and members of the research community are full and equal partners in all stages of the research process; from conception of a research question to design, conduct, analysis, interpretation, conclusion and communication of research results.

NIH Conference and Scientific Meetings (R13) (PA-10-071). The purpose of the NIH Research Conference Grant Program (R13 and U13) is to support high quality conferences/scientific meetings that are relevant to the scientific mission of the NIH and to the public health. A conference/scientific meeting is defined as a gathering, symposium, seminar, scientific meeting, workshop or any other organized, formal meeting where persons assemble to coordinate, exchange, and disseminate information or to explore or clarify a defined subject, problem, or area of knowledge.

Disparities Research and Education Advancing Mission Career Transition Award (K22) (RFAs MD09-002 and 10-001). The purpose of this award is to facilitate the transition of early-stage investigators working in health disparities or areas that address health disparity conditions and populations from the mentored stage of career development to the independent stage of investigator-initiated health disparities research. The program will provide an opportunity for investigators to develop solid research skills during the initial period of up to 2 years of study and research within the environment of the NIH Intramural Research Programs located at the NIH. The award may also include a follow-on period of up to 3 years of salary and mentored research support at the candidate's current institution or organization or an academic or research grantee institution of the candidate's choice. This period of extramural support will facilitate the transition to independence as a researcher in health disparities research.

Advances in Health Disparities Research on the Social Determinants of Health (R01) (RFA-MD-10-005). The overarching goal of this FOA is to encourage groundbreaking research addressing the social determinants of health and health disparities. The intent of this FOA is to intensify investigator-initiated research in an understudied area, to attract new investigators to the field, and to encourage translational and transdisciplinary research that will advance health disparities science through interventions and information dissemination.

Innovative Faith-Based Approaches to Health Disparities Research (R21) (RFA-MD-10-004). The purpose of this program is to solicit applications that propose translational and transdisciplinary interventions on health disparities, social determinants of health, health behavior and promotion and disease prevention, especially those jointly conducted with faith-based organizations or faith-motivated programs and the research community. The ultimate goal is to foster empirical, formative, evaluative and intervention research on effective faith-motivated initiatives, concepts and theories that have played an important role in addressing health disparities. Funding is also intended to provide support for early and conceptual stages of exploratory and developmental research projects. These studies may involve considerable risk but may lead to a breakthrough in addressing health disparities or the development of a model or application that could have a major impact on the field of health disparities research.

NIMHD and Other IC Joint Programs

Development and Translation of Medical Technologies that Reduce Health Disparities (RFA-ED-10-002). This FOA encourages SBIR grant applications from small business concerns (SBCs) that propose to develop and translate medical technologies aimed at

reducing disparities in health care access and health outcomes. Appropriate medical technologies should be effective, affordable, culturally acceptable, and deliverable to those who need them. Responsive grant applications must involve a formal collaboration with a health-care provider or other health care organization serving a health disparity population.

Small Business Research Programs - Small Business Innovation Research / Technology Transfer (SBIR/STTR) (R41/R4: PA-10-051; R43/R44: PA-10-050). This FOA issued by NIH, CDC, the Food and Drug Administration (FDA), and the Administration for Children and Families (ACF) invites eligible U.S. SBCs to submit SBIR grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH, CDC, FDA and ACF awarding components identified in this FOA are encouraged to submit SBIR grant applications in response to identified topics. It also invites eligible U.S. SBCs to submit STTR grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH awarding components identified in this FOA are encouraged to submit STTR grant applications in response to identified topics.

ARRA-Funded Programs

In addition to the previously mentioned ARRA FOAs, NIMHD also supported the following:

Recovery Act Limited Competition: NCMHD Dissertation Research Award to Increase Diversity (R36) (RFA-MD-09-008)

Recovery Act Limited Competition: NIH Challenge Grants in Health and Science Research (RC1) (RFA-OD-09-003):

- Bioethics. 02-OD (OSP)-102 *Ethical Issues in Health Disparities and Access to Participation in Research*
- Clinical Research. 04-MD-101 *Development of effective approaches to increase minority recruitment and retention into clinical trials*
- Comparative Effectiveness Research
  - » 05-MD-101—Social Determinants of Health
  - » 05-MD-102—Prevention of Chronic Diseases in Disparity Populations
  - » 05-MD-104—Screening of Health Disparity Conditions
  - » 05-MD-105—Health Literacy
- Enabling Technologies. 06-MD-101—*Development of Telehealth Tools to Promote Health and Connect At-Risk Youth to the Health System via Low-Cost, Mobile, and Wireless Technologies*
- Health Disparities
  - » 09-MD-101—Creating Transformational Approaches to Address Rural Health Disparities
  - » 09-MD-102—Trans-disciplinary Research to Integrate the Biological and Non-biological Determinants of Health to Address Health Disparities
  - » 09-MD-10—Initiating Innovative Interventions to Prevent Family Violence

Recovery Act Limited Competition for NIH Grants: Research and Research Infrastructure "Grand Opportunities" (RC2) (RFA-OD-09-004):

- Bioethics Research Infrastructure Initiative (RC2)
- Transdisciplinary Research Recovery Centers (RC2)
- Enhancing Information Dissemination on Health Disparities Research (RC2)
- Social Determinants Initiative (SDH) (RC2)

Biomedical Research, Development, Growth to Spur Acceleration of New Technology BRDG-SPAN (RC3) (RFA-OD-09-008)

Building Sustainable Community-Linked Infrastructure to Enable Health Science Research (RC4) (RFA-OD-09-010)

Comparative Effectiveness Research for Eliminating Disparities for NIMHD Centers of Excellence Program NIMHD/ Office of Minority Health ARRA Program RFA-MD-10-500/NOT-MD-10-002. The purpose of this RFA, funded by the NIMHD in partnership with the Office of Minority Health,

Office of Public Health and Science, HHS is to solicit revision applications (formerly termed competitive supplements) from institutions/organizations with active NIMHD-supported Exploratory Centers of Excellence (P20) and Comprehensive Centers of Excellence (P60) grants to support the establishment of Centers of Excellence for conducting CERED. This funding opportunity for revisions is one part of the overall HHS Recovery Act investment strategy, as described at http://www.hhs.gov/recovery and will be funded from the $400 million allocated to the Secretary.

Health Disparities and Special Populations

All NIMHD-supported research is categorized as minority health or health disparities research and contributes to the promotion of minority health, the reduction and elimination of health disparities or both. The target populations and communities include racial/ethnic populations and subpopulations and other health disparity populations.

National Institute of Neurological Disorders and Stroke

Executive Summary

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurologic disease, a burden borne by every age group, every segment of society, and people all over the world. Most nervous system disorders affect men and women equally, but certain disorders, such as chronic pain, epilepsy, multiple sclerosis, Rett syndrome, and stroke, disproportionately affect or are of special interest to women. NINDS supports basic, translational, and clinical research on these disorders as well as targeted research to understand sex-based differences in normal behavior, development, cognition, and perception.

Chronic pain is caused by the improper functioning of neuronal pain circuits and results in abnormal pain that persists for weeks, months, or even years. Certain chronic pain conditions like migraine headaches, temporomandibular joint disorders, endometriosis, or fibromyalgia are diagnosed more often or exclusively in women and are often comorbid in nature, with more than one condition present at the same time. It is now widely believed that men and women experience and respond to pain differently due to the influence of sex hormones estrogen and testosterone.

Epilepsy is characterized by chronic, recurring seizures caused by abnormal electrical activity in the brain. Although antiepileptic drugs (AEDs), brain stimulation, or surgery can help many patients control the disorder, for others treatments are ineffective or cause unacceptable side effects. Women with epilepsy can face special problems such as catemenial epilepsy in which increased seizure frequency occurs during phases of the menstrual cycle or higher-than-normal rates of birth defects occur while pregnant and taking selected AEDs.

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that causes inflammation and the loss of myelin, a protective covering around nerve fibers. The disorder, which can present in progressive or relapsing-remitting form, is characterized by attacks of muscle weakness, trouble with coordination, vision problems, abnormal sensations, and sometimes cognitive impairments. Hormonal factors may influence some forms of MS, making them more common in women.

Rett syndrome is a childhood neurologic impairment that causes severe cognitive impairment, autistic behavior, stereotypic movements, and seizures. The disease, which is considered an autism spectrum disorder, is associated with mutations in a gene located on the X chromosome. These mutations lead to an insufficient amount or abnormal function of the methyl-CpG-binding protein 2 (MeCP2). The disease is almost exclusively seen in females because male fetuses carrying the mutation are unviable.

Stroke is the third leading cause of death in the United States and a major cause of disability in both women and men. It is caused by a rapid disruption in the blood supply to part

of the brain as a result of either blood vessel blockage (ischemic stroke) or blood vessel rupture (hemorrhagic stroke). A stroke can result in sudden numbness or weakness; confusion; trouble with vision, speech, or coordination; or sudden severe headache. Although women in general have a lower risk of stroke than men, because of their longer life expectancy, they account for 60 percent of stroke fatalities.

Women's Health Research Coordination at NINDS

Women's health research at NINDS is covered across a number of extramural research "clusters" or teams of program directors organized around scientific and disease areas. The Office of Clinical Research, in collaboration with the Office of Minority Health Research, oversees and tracks recruitment of women and minorities in clinical trials. In addition, NINDS actively participates in NIH women's health research initiatives by designating a program director as the Institute's primary representative and a staff member from the Office of Science Policy and Planning as a secondary representative to the NIH Coordinating Committee for Research on Women's Health.

Accomplishments

Chronic Pain

Migraine sufferers sensitive to thermal pain in between migraine attacks. Migraines consist of moderate to severe headaches often accompanied by increased sensitivity to light and sound, nausea, vomiting, and an inability to carry out daily activities. Migraines have been found to be three times more common in women than in men. Studies have observed that migraine sufferers often maintain a sensitized state even during an intermigraine or interictal period, which possibly predisposes them to future attacks. NINDS-funded researchers recently showed that sufferers of chronic migraine and episodic migraine have lower thermal pain thresholds and thermal pain tolerance during interictal periods compared with people not suffering from migraine. Understanding these sensitization mechanisms during interictal periods may lead to new markers for migraine activity or new targets for therapy (Schwedt et al., 2011, Cephalalgia, 31(1):6-12).

Finding the correct dosage of metoclopramide for treating acute migraine. Intravenous metoclopramide is effective as a primary therapy for acute migraine, but the optimal dose of this medication is not yet known. In a NINDS-funded clinical trial involving 356 subjects, researchers tested 3 doses of intravenous metoclopramide (10, 20, and 40 mg) for safety and efficacy in treating acute migraine. Improvement in pain after 1 hour and 48 hours was comparable across the three doses, and the researchers concluded that the 20 and 40 mg doses were no better than 10 mg of metoclopramide in treating acute migraine (Friedman et al., 2011, Ann Emer Med, Epub).

Epilepsy

Cogntive outcomes in children with in utero exposure to antiepileptic drugs. Epilepsy is one of the most common neurologic disorders affecting women of childbearing age, and poor pregnancy outcomes are increased in these women and their children. Researchers from the NINDS-funded Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) prospective cohort study investigated the relationship between AED exposure and outcomes in mothers and their children to improve care and reduce adverse outcomes. They compared neurodevelopmental outcomes among children born to women taking a single AED (carbamazepine, lamotrigine, phenytoin, or valproate) while pregnant. At 3 to 4 years of age, the children exposed to valproate in utero had significantly lower IQ scores as well as impaired fluency and originality than those who had been exposed to other antiepileptic drugs. This finding supports a recommendation that valproate not be used as a first-choice drug in women of childbearing age (McVearry et al., 2009, Epilepsy Behav. 16(4):609-16; Meador et al., 2009, N Engl J Med, 360(16):1597-605). In a preliminary analysis, the researchers also found that cognitive outcomes in children with in utero AED exposure were not influenced by breastfeeding during AED therapy (Meador et al., 2009, Neurology 75(22):1954-60).

Multiple Sclerosis

Estrogen-based therapy for multiple sclerosis. MS is characterized by inflammatory demyelination and neurodegeneration of the central nervous system. In recent years, researchers have focused on estrogen as a potential therapy after observing that the disease goes into remission during pregnancy. In a NINDS-funded study, researchers investigated a treatment strategy using estrogen to induce neuronal self-myelination in experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis. Results showed that estrogen-treated mice had fewer demyelinated and damaged nerves, accompanied by thicker myelin sheath thickness and faster nerve conduction. The findings demonstrated that estrogen-based therapies may be promising treatments to prevent MS-induced neurodegeneration (Crawford et al., 2010, Brain, 133(10): 2999–3016). An ongoing NINDS-funded double-blind, placebo-controlled phase II clinical trial is now testing whether oral estrogen combined with Copaxone, an anti-inflammatory drug, can reduce the number of relapses in relapse-remitting multiple sclerosis (ClinicalTrials.gov Identifier: NCT00451204).

Rett Syndrome

Loss of MeCP2 function in Rett syndrome causes learning disability in mice by reducing synaptic connectivity. Rett syndrome in humans is caused by mutations in the *MeCP2* gene and is characterized by severe learning and cognitive disabilities. *MeCP2*-null mice also exhibit similar symptoms including learning deficits. NINDS-funded researchers studied learning mechanisms in *MeCP2*-null as well as wild mice and found that synaptic connections were fewer and weaker in *MeCP2*-null mice, suggesting that *MeCP2* loss may lead to reduced synaptic connectivity and learning deficits (Dani et al, 2009, J Neurosci. 29(36):11263-70).

Abnormal MeCP2-dependent neurotransmitter composition causes specific behavioral deficits in Rett syndrome. Rett syndrome in humans is caused by mutations in the *MeCP2* gene and is characterized by severe learning and cognitive disabilities. Several of these cognitive deficits observed in Rett syndrome occur in other disease states associated with alterations in neurotransmitters containing amines. Based on these reports, researchers investigated the contribution of neurotransmitter changes toward Rett syndrome deficits and found that both humans with Rett syndrome and *MeCP2*-null mice had lower than normal levels of amine content in their neurotransmitters. Moreover, deleting MeCP2 from certain neuronal populations caused specific behavioral deficits, likely due to MeCP2 regulation of enzymes involved in aminergic neurotransmitter production. MeCP2-dependent regulation of aminergic neurotransmitters levels suggests that therapies that target these specific systems may lessen specific deficits in people with Rett syndrome (Samaco et al., 2009, Proc Natl Acad Sci USA., 106(51):21966-71).

Stroke

Gender differences in acute stroke symptoms. Motivated by reports that women with stroke had a 30-percent lower chance of receiving rt-PA treatment and greater in-hospital delays than men, NINDS-funded researchers tested whether these discrepancies could be due to differential stroke symptom presentation between men and women. Prevalence of nontraditional and traditional stroke symptoms was calculated by gender for 461 ischemic stroke patients. The researchers found a high prevalence of nontraditional symptoms among both genders, but women were more likely to report nontraditional symptoms and, in particular, altered mental status, compared with men. This study demonstrated the clinical consequences of gender differences in stroke symptoms (Lisabeth et al., 2009, Stroke, 40:2031-2036).

Public outreach and the Know Stroke campaign. For over a decade, NINDS has conducted "Know Stroke: Know the Signs. Act in Time," a public awareness campaign to disseminate knowledge of the warning symptoms of stroke and the importance of seeking urgent treatment. NINDS partners with a number of government and nongovernment organizations such as the Centers for Disease Control and Prevention (CDC), National Council

of La Raza (NCLR), National Alliance for Hispanic Health (NAHH), General Federation of Women's Clubs (GFWC), American Stroke Association (ASA), and National Stroke Association (NSA) in its efforts to provide information on stroke prevention and treatment to the public.

Sex/Gender Studies, Analyses, and/or Plans

All NIH-funded phase III clinical trials are required to include sufficient numbers of males and females to perform an analysis of sex differences in treatment outcomes, when appropriate to the condition under study. NINDS also supports targeted research to understand sex-based differences in neurologic disorders and normal behavior, cognition, and perception. Special advances resulting from sex/gender analyses or plans for upcoming studies are highlighted below:

Stroke

Gender differences in stroke incidence and poststroke disability. Studies on gender differences in stroke incidence, stroke severity, and poststroke disability have largely been inconclusive to date. To address these questions, NINDS-supported researchers monitored participants in the Framingham Heart Study (FHS) when they experienced their first stroke and measured gender-specific outcomes. Results showed that women had significantly poorer outcomes than men when considering stroke incidence at older ages, lifetime risk of stroke, age at first stroke, poststroke disability, and institutionalization rates, but not when comparing stroke severity. Prestroke disability and sociodemographic factors were thought to contribute towards differences in institutionalization rates and poorer outcomes in general (Petrea et al., 2009, Stroke, 40:032-1037).

Women undergoing carotid artery stenting not at higher stroke risk rate compared with men. The NINDS-funded Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) tested whether carotid endarterectomy, "cleaning" a clogged blood vessel, or carotid artery stenting, widening the vessel by inserting a device, is more effective in reducing the risk of subsequent stroke. Results showed that both methods were equally successful in preventing future strokes, irrespective of gender (Brott et al., 2010, N Engl J Med, 363(1):11-23). An additional gender analysis of the CREST results showed that women did not have a higher 30-day stroke or death rate than men after undergoing carotid artery stenting (Howard et al., 2009, Stroke, 40(4):1140-7).

Clinical study to investigate sex differences in stroke risk factors. Men and women with stroke have different risk factor profiles; specifically, women tend to develop stroke risk factors and subclinical disease and experience strokes postmenopause, whereas men tend to develop vascular disease at younger ages. Despite these observations, sex differences in subclinical disease are poorly understood. NINDS is currently funding a prospective cohort study titled Sex Differences in Vascular Markers of Stroke Risk (SAVVY) to investigate gender differences in vascular functions and stroke risk factors in 150 women and 100 men. Results from this study will be used to develop a comprehensive gender-specific model of subclinical disease, discover novel biological and vascular markers for stroke, and inform stroke prevention efforts (ClinicalTrials.gov Identifier: NCT00681681).

Initiatives

RFAs and PAs

Mechanisms, Models, Measurement, and Management in Pain Research (R01, R03, R21), PA-10-006 ,PA-10-007, PA-10-008. Seeks proposals to investigate the causes, costs, and societal effects of both acute and chronic pain and the relationships between the two, as well as proposals that link such understandings to the development of better approaches to therapeutic interventions. Interdisciplinary and multidisciplinary scientific teams are strongly encouraged, as is research from underrepresented, minority, disabled, or women investigators. Cofunded by 11 other ICs in the Pain Consortium.

Neurobiology of Migraine (R01, R21), PA-10-258, PA-10-259. Encourages innovative research to expand our current knowledge

of neurobiologic mechanisms underlying migraines, examine the role of neuromodulators, study genetic and environmental influences in migraine susceptibility, and explore new targets for therapy development. Cofunded by NIDCD, NIDCR, and NIEHS.

Chronic Fatigue Syndrome: Pathophysiology and Treatment (R01, R21), PA-08-246, PA-08-247. Encourages investigator-initiated proposals to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME/CFS), in diverse groups and across the lifespan. Issued by ORWH. Cofunded by 11 other ICs.

Advancing Novel Science in Women's Health Research (ANSWHR) (R21), PAS-10-226. Promotes innovative, interdisciplinary research to advance new concepts in women's health research and the study of sex/gender differences. Issued by ORWH. Cofunded by 22 other ICs.

Research on Causal Factors and Interventions That Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (R01), RFA-GM-09-012. Supports research on causal factors explaining the patterns observed in the careers of women in biomedical and behavioral science and engineering, variation across different subgroups, and the efficacy of programs designed to support the careers of women in these disciplines. Research on variation among underrepresented minority women and socioeconomically disadvantaged women is encouraged. Cofunded by 18 ICs, including ORWH.

Recent Workshops:

The Headache Research Planning Meeting, May 16–17, 2010, Bethesda, MD. This NIH-sponsored workshop was held to develop the second phase of a strategic planning effort for headache research. NIH is working to develop and coordinate a long-term strategy to support and promote headache research. This strategy will include the efforts of the ICs with interests in headache research, private and public organizations, health care providers, headache researchers, and patient advocates.

Fourth Annual Research Symposium for Advances in Pain Research: Generalized Pain Conditions, May 22, 2009, Bethesda, MD. Sponsored by the NIH Pain Consortium, the symposium focused on the genetics of pain. The three major areas covered were genetic risk factors for chronic pain, genetics of analgesic drug responsiveness and addiction, and genetic tools and models for studying and treating pain.

Fifth Annual Research Symposium for Advances in Pain Research: Generalized Pain Conditions, May 5, 2010, Bethesda, MD. The symposium focused on personalized pain management and emerging therapies in pain with discussion of new therapeutic targets, novel compounds in development, and animal models for pain management.

Health Disparities

Strategic Plan

NINDS Strategic Planning Advisory Panel on Health Disparities. In 2010, NINDS convened an advisory panel to provide recommendations to the Institute for ways to maximize the impact of its efforts to reduce or eliminate neurologic health disparities in underrepresented populations, including women. The Health Disparities Advisory Panel Report noted that, although there have been improvements in the enrollment of African Americans and women in NINDS-funded clinical trials, the Institute could benefit from a consolidation of its health disparities research. The advisory panel recommended the creation of an office or position for driving and coordinating all health disparities research at NINDS and accommodating all forms of health disparities research, including women, rural populations, individuals with disabilities, and the very elderly.

Studies

Ethnicity- and gender-based differences in health services to acute ischemic stroke patients. As part of the NINDS-funded Brain Attack Surveillance in Corpus Christi (BASIC) project, researchers compared time to hospital arrival and emergency medical services use

for stroke care based on ethnicity and gender among Mexican-American and non-Hispanic white ischemic stroke patients in southern Texas. Results showed that sex and ethnic differences in hospital presentation existed among the community. Non-Hispanic whites arrived via emergency medical services more often than Mexican Americans, and men were more likely than women to be present at a hospital within 3 hours of a stroke. The results highlighted the need to address ethnic and gender differences in medical responses to stroke, especially in groups who experience high stroke burden (Smith et al., 2010, Stroke; 41:905-909).

Career Development Initiatives for Women

NINDS Diversity Research Education Grants in Neuroscience (R25), PAR-11-010. Seeks to support the development and implementation of programs to increase the number of graduate, postdoctoral, and junior-faculty career level research scientists from diverse backgrounds in the neuroscience workforce.

Research Supplements To Promote Reentry Into Biomedical and Behavioral Research Careers (R01), PA-08-191. Encourages individuals with high potential to reenter an active research career after a qualifying interruption for family or other responsibilities. Issued by ORWH and cofunded by 23 other ICs.

National Institute of Nursing Research

Executive Summary

The National Institute of Nursing Research (NINR) supports clinical and basic research to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, and enhance end-of-life and palliative care. Confronting these issues requires a shift to a patient-provider partnership paradigm that is increasingly person-centered rather than disease-oriented, that focuses on preventing the development of chronic illness rather than treating it, and that features the person as an active participant in his or her own health. The Institute's multi- and interdisciplinary scientific approach unites the biological and behavioral sciences to better understand the complex interactions between the physiologic factors of health and disease and the knowledge, beliefs, and behavior of the individual, family, and community. Across all scientific programs, NINR's research addresses the special needs of at-risk, vulnerable, and underserved populations with particular emphasis on eliminating health disparities and promoting health equity.

The research goals of NINR's strategic plan, *Changing Practice, Changing Lives*, emphasize areas of public health in which NINR can have the greatest impact. Developed in 2006 in close consultation with representatives of the research community, this plan details NINR's scientific priorities for research in health promotion and disease prevention; improving quality of life through self-management, symptom management, and caregiving; eliminating health disparities; and leading critical research on the end of life. The plan emphasizes four cross-cutting strategies to advance science: (1) integrating biological and behavioral science, (2) adopting and adapting new technologies, (3) improving methods for future scientific discovery, and (4) developing the next generation of research investigators. The full text of the strategic plan can be found on NINR's Web site at http://www.ninr.nih.gov.

The breadth and depth of NINR's research portfolio is ideally suited to explore some of the most important challenges affecting the health of women, including the following:

- Growth of an aging female population faced with chronic diseases requiring complex management
- Growth of diverse racial and cultural populations of women and the associated issues of health disparities in these at-risk, underserved populations
- Predominance of women as care coordinators, nurses, and caregivers adding to their own health burden throughout the lifespan and at the end of life

- The need to build a cadre of next generation scientists and practitioners in women's health

In advancing the science of women's health, NINR funds and cofunds meritorious initiatives with specific attention to research that focuses on unique issues surrounding pain, aging, pregnancy, childcare, health disparities, and the participation and promotion of women in research. Central to the themes of its strategic plan, NINR seeks to strengthen and enhance research dedicated to the study of diseases and disorders specific to women, whether as patients, caregivers, or communities. The Institute actively ensures that diverse populations of women are represented in its studies and that disparities experienced by women in minority, rural, immigrant, and other underserved populations are addressed. NINR-supported investigators have contributed to new knowledge by addressing women's health across the lifespan. Numerous findings during fiscal years 2009 and 2010 have furthered understanding of issues uniquely relevant to women's health, including the following:

- Pregnancy, preterm birth, lactation, postpartum depression, infertility, and childrearing
- Aging and menopause
- Chronic and life-limiting disease investigation for heart disease, stroke, and breast cancer
- Symptom management for conditions such as pain, incontinence, osteoporosis, and irritable bowel syndrome
- Caregiving
- Promotion of healthy physical and dietary lifestyles to prevent obesity, diabetes, heart disease, osteoporosis, and depression

In 2009 and 2010, NINR investigators made significant contributions to these research areas, including designing new ways to improve health services among minority and underserved women, promoting cost-effective interventions for mothers and their premature infants, increasing understanding of menopause and aging effects, and developing new methods to assist women with breast cancer, heart disease, and diabetes. In addition, NINR remained committed to improving the science of women's health through the development of leaders in nursing science and the promotion of careers for women in biomedical science and clinical research. Today's challenges in the field of women's health present unprecedented opportunities for the Institute to further expand its impact on the health of the Nation. NINR will continue to support innovative studies in research areas highlighted in its strategic plan, and results from these studies are informing future strategies that will be reflected in the next NINR strategic plan.

Introduction

The National Institute of Nursing Research (NINR) is committed to the development of science that addresses women's health. For example, through its funding of the University of Washington's Center on Women's Health and Gender Research (P30), NINR has expanded the cadre of collaborations among interdisciplinary investigators in basic and clinical research related to women's health across the lifespan. The program is a focused effort to enhance an understanding of the biobehavioral and sociocultural dimensions of women's health, advance knowledge of genetics and gender differences, expand understanding of health disparities, and close the gap among vulnerable subpopulations of women. Through additional support to the center's training program under a T32 award, NINR continues to build research capacity to enable the study of diverse populations of women in culturally competent ways and to promote the development of research skills and opportunities for scholarship in women's health.

In addition, NINR remains active in supporting National Institute of Health (NIH) programs that promote research on women's health. Dr. Patricia Grady, director of NINR, is a member of the NIH Working Group on Women in Biomedical Careers and participates in a number of internal NIH subcommittees within this program.

In 2009 and 2010, NINR participated in several workshops on topics related to women's health:

(1) Bridging Preeclampsia and Future Cardiovascular Diseases, September 16–17, 2010

(2) SWAN Person-to-Person meetings: November, 2009; May, 2010; November, 2010

(3) NIH Consensus Development Conference: Vaginal Birth After Cesarean—New Insights, March 8–10, 2010

(4) Contextual Influences on Breastfeeding Decisionmaking Processes, July 27, 2010

Accomplishments

Pregnancy, Childbirth, and Perinatal Health

A significant part of NINR's overall research portfolio in women's health comprises health issues surrounding pregnancy and the perinatal period. NINR investigators continue to make important contributions to improving pregnancy outcomes and ensuring the health of mothers and their infants. For example, pregnancy is a time when many women who smoke give up cigarettes, at least temporarily. A survey of a racially diverse group of low-income new mothers who stopped smoking during pregnancy found that most quit to protect the health of their infants. However, although almost two-thirds said they planned to remain nonsmokers after delivery, by the end of the second postpartum week, 69 percent returned to prepregnancy habits. Infant irritability, parenting uncertainty, and not knowing where to seek help contributed to both thoughts of and a return to previous smoking behaviors. These findings are being applied to educate mothers about the adverse health effects of smoking on their children and provide training on healthful coping skills.

According to the National Center for Health Statistics, in 2007 nearly one-third (32 percent) of all births were cesarean deliveries. Although there are often clear clinical indications for a cesarean delivery, the short- and long-term benefits and risks for both mother and infant have been the subject of intense debate for many years. Cesarean delivery involves major abdominal surgery and is associated with higher rates of surgical complications and maternal rehospitalization. In addition, hospital charges for a cesarean delivery are almost double those for a vaginal delivery. In 2010, NINR cosponsored with the National Institute of Child Health and Human Development (NICHD) the NIH consensus development conference titled Vaginal Birth After Cesarean: New Insights. At this conference, experts presented and discussed the evidence regarding short- and long-term risks to mothers and babies. The panel recommended that women who have had one previous, low transverse incision and whose current pregnancy is low to moderate risk should be supported for a trial of labor and be assisted in informed decisionmaking. More information is available at http://consensus.nih.gov/2010/images/vbac/vbac_statement.pdf.

NINR supports research that seeks to understand maternal stress, psychological well-being, self-help, and caretaker support. Almost half a million premature infants are born in the United States each year, and most require hospitalization in a neonatal intensive care unit (NICU). The ongoing physical and developmental problems of many premature infants contribute to high levels of parental stress, anxiety, and depression. To identify and manage the needs of these parents, NINR-supported researchers developed a parental education program, Creating Opportunities for Parental Empowerment (COPE), for mothers and fathers of premature infants. Compared with parents in a control group, COPE parents reported higher beliefs in their parenting role, exhibited more positive interactions with their babies, and had a better understanding of expected characteristics and behaviors of premature infants. A critical predictor of successful COPE implementation and translation was the presence of an evidence-based nurse mentor in the NICU unit. Compared with standard care, this intervention decreased the length of NICU hospitalization for infants by about 4 days, which reduced associated hospital costs by about $4,800 per infant. In infants weighing less than 1,500 grams at birth, the net savings was $9,864 and 8 fewer days in the NICU per infant. These findings could translate to nationwide cost savings of $2.4 to $4.9 billion dollars annually in direct medical costs while enhancing the health of parents and their children. These results have sparked interest among hospitals and insurers across the United States.

Although the American Academy of Pediatrics recommends breastfeeding for all

newborns, mothers of premature, low birth weight (LBW) infants face numerous obstacles in starting and maintaining such practices. The challenges faced with these infants may contribute to only one-third of mothers with LBW infants initiating breastfeeding and fewer than half continuing breastfeeding efforts after their infants are discharged from the hospital. However, researchers have found that supporting and encouraging mothers to begin and maintain breastfeeding may be an important intervention that makes a difference in the long-term developmental outcomes of the children. Infants who received some form of breast milk until 6 months corrected age scored approximately 10 points higher in mental development and nearly 15 points higher in motor development than those who did not receive human milk over the same period of time.

In 2010, an NINR-funded analysis of 111 mothers providing pumped human breast milk for their very low birthweight babies demonstrated favorable cost results These analyses demonstrated costs ranging from $0.95–$1.55/100 ml of human milk without opportunity costs to $2.60–$6.18/100 ml when the maternal opportunity costs were included. The researchers indicated that pumped human breastmilk is reasonably inexpensive to provide.

Another 2010 study from an NINR-supported randomized controlled trial reported on the success of an intervention to improve breastfeeding practices in urban mothers. Breastfeeding mothers (328) of full-term infants who were eligible for the Special Supplemental Nutrition Program for Women, Infants, and Children were recruited for participation in either the intervention or usual-care group. The 24-week intervention included hospital visits by a breastfeeding support team, home visits, telephone support, and 24-hour pager access. The study found that the intervention group was more likely to be breastfeeding at 6 weeks postpartum compared with the usual-care group, a time that coincided with the most intensive part of the intervention.

Postpartum depression (PPD) is a potentially debilitating disorder that occurs in a significant percentage of women during the first year after giving birth. Characterized by sadness, guilt, and despair, PPD can be a devastating disorder that may carry long-term consequences for these women and their families. Although several psychosocial risks for PPD have been identified, its biological precursors are unclear. A group of researchers focused on the role of elevated inflammatory cytokines (IL-6 and IL-1β) in women with PPD recruited after delivery and followed for several postpartum days. Early increases in IL-1β levels occurred on day 14 in women who later experienced depressive symptoms on day 28. These elevated inflammatory cytokine levels early in the postpartum period may serve as a measurable, identifiable biomarker of women at risk for later PPD.

Aging and Menopause

NINR maintains a diverse research portfolio that focuses on multiple health issues surrounding women and aging, including issues associated with menopause. The NINR-cofunded (with the National Institute on Aging) multisite research project titled Study of Women's Health Across the Nation (SWAN) continued during 2009–2010 and published several important findings. SWAN examines women between 40 and 60 years of age during the period of the menopausal transition. In one SWAN report, NINR-supported researchers examined the association between body fat and vasomotor symptoms using a multiethnic sample of more than 1,700 women transitioning through menopause. Vasomotor symptoms such as hot flashes and night sweats are reported by 70 to 80 percent of women during the menopausal transition and often result in impaired sleep, mood, and quality of life. In this study, a greater percentage of total body fat was associated with an increased chance of vasomotor symptoms. These results are particularly relevant given current interest in developing nonhormonal methods, including behavioral approaches, to manage symptoms of menopause such as weight loss. Using statistical analysis and available data from SWAN, scientists found that bioavailable testosterone is significantly associated with increased visceral fat in menopause. This relationship exists independent of age, race, percentage of total body fat, and other cardiovascular risk factors. In addition, testosterone appears to be a stronger predictor of visceral fat than estradiol, even

after adjusting for insulin resistance, suggesting that it plays an important role in regional fat distribution. These findings may have direct implications for explaining the effect of menopause-related testosterone predominance on visceral fat accumulation and subsequent elevated cardiovascular risk.

The Seattle Midlife Women's Health Study continues to define the stages and symptoms of the menopausal transition. This longitudinal study produced a number of important findings regarding the changes that midlife women encounter as they progress through the menopausal transition, including changes in symptoms, hormone levels, stress and use of health services. Findings included the identification of three predictable stages in reproductive aging: an early, middle, and late stage of the menopausal transition. In addition, the study defined clusters of symptoms that occurred during the transition. The symptoms, including hot flashes, sleep disruptions, and depressed mood, appeared to be interrelated and suggest that clinicians should use caution in designing treatment approaches to avoid exacerbating one symptom when treating another.

NINR science also addresses the impact of aging and cognition on women's health. Approximately 50 percent of the more than 1.5 million Americans residing in nursing homes have significant cognitive impairment. The majority of these residents are women. Researchers have developed simple screening tools available to nurses and other health care providers to detect early warning signs of cognitive decline. In a sample of elderly residents (81 percent female) in nursing homes, assisted living facilities, and senior housing, a team approach to detect and classify early signs of cognitive impairment correctly classified the memory skills of 95 percent of elderly participants. In another NINR-supported study, the multisite Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) program looked at the risks for loss of independence in more than 2,800 older adults of whom more than three-quarters were women. All participants received one of three cognitive training programs: (1) memory, (2) reasoning, or (3) speed of processing. The speed-of-processing group participants experienced significantly fewer increases in depressive symptoms. No differences were observed among the control, memory, or reasoning groups. Although many studies of cognitive and behavioral interventions for depression have been undertaken in recent years, this study was the first to include the speed-of-processing intervention. These results indicate that a speed-of-processing intervention could provide a plausible, readily available, and non-pharmacologic strategy for reducing the risk of depressive symptoms in the elderly.

With a growing population of aging women, developing programs to maintain not only cognitive skills but also physical skills is important for functional independence. As women age, falls become a leading cause of injury and hospitalization. Previous NINR research demonstrated that 14 percent of reported falls resulted in injury, at an average health care cost of $6,600. However, about 4 percent of fall-related injuries resulted in fractures which, in the case of hip fractures alone, averaged more than $35,000 in health care costs. The risk of trips and falls is one of the major challenges facing older persons in community or assisted living environments. NINR-supported researchers are developing and assessing the effectiveness of a lighting solution that can potentially reduce the risk of falls among older adults. This research investigates a novel lighting solution designed to provide illumination, as well as vertical and horizontal cues to help with perception of lines, along the desired pathway. Evaluating such interventions, health care use, and costs related to falls helps build a repository of cost-effective, individualized prevention programs for the growing population of elderly women.

Osteoporosis compounds the potential for injury with falls. NINR research has demonstrated that the addition of aerobic exercise to a weight loss program improves bone density and inflammatory markers in overweight postmenopausal women. Although obesity is a significant risk factor for the development of many chronic diseases, researchers also have linked it to a possible protective effect in maintaining bone mineral density (BMD). Furthermore, in the absence of exercise training, postmenopausal weight loss has been linked with a reduction of BMD. A group of NINR-funded researchers hypothesized that

weight loss through aerobic exercise, rather than through diet alone, may both minimize the loss of bone and contribute to a decrease in inflammation (another BMD-loss risk factor). These researchers analyzed 86 overweight and obese postmenopausal women (50–70 years of age; body mass index [BMI], 25–40 kg/m[2]) who participated in a 6-month weight loss (WL) (n = 40) or weight-loss-plus-walking (n = 46) program. Outcome measures included BMD, bone mineral content, inflammatory cytokines, maximal aerobic capacity, and fat and lean mass. The study results indicated that weight decreased by about 8 percent in both groups and fat decreased by 15 percent in the WL group and 12.5 percent in the walking group. However, in contrast to the WL group, the walking group experienced significant increases in aerobic capacity along with a 2 percent increase in BMD. In addition, while the walking group experienced significant decreases in inflammatory markers, those in the WL group experienced significant increases in one marker. These findings suggest that the addition of aerobic exercise to weight loss interventions for overweight, postmenopausal women may protect against loss of BMD and decrease inflammation.

Cardiovascular Health

NINR supports a number of studies related to the cardiovascular health of women, including research that examines the prevention, early detection, and prompt treatment of coronary heart disease (CHD). CHD is the leading cause of death and disability for women in the United States. For example, despite evidence of positive outcomes associated with cardiac rehabilitation (CR), little is known about rehabilitation risk factors in females with CHD. Researchers in the NINR-supported Women-Only Cardiac Rehabilitation Study found that a woman's age was a significant factor in identifying success in CHD management programs. Younger women demonstrated significantly worse psychosocial profiles than older women, were considerably more obese and inactive, and were more likely to be active smokers. The research team then developed and tested a tailored CR program for its effects on perceptions of health in women with CHD. Preliminary results demonstrated that a modified, gender-tailored CR program reduced depressive symptoms in women compared with a traditional program..

Recognition of symptoms and the expedient receipt of treatment within 1 hour of heart attack onset greatly increase the chance of survival. However, in an NINR-funded analysis of survey data from 1,009 women who had recently suffered a heart attack, only 17 percent of all women, both Black and White, attributed their initial symptoms to a possible heart attack. The average time of delay in seeking treatment was 13 hours. White women were more likely than Blacks to correctly identify symptoms of a heart attack, with the correct identification of these symptoms and the woman's eligibility for public insurance as the most significant factors associated with their actively seeking treatment. These results highlight the continued need for improved strategies to educate all women on early recognition of heart attack symptoms.

Breast Cancer

Breast cancer affects older postmenopausal women at a rate nearly twice that of young women. In keeping with NINR's focus on improving quality of life through symptom management, a number of NINR-supported studies have focused on the unique challenges faced by women with breast cancer. For example, fatigue, sleep disturbances, and depressive symptoms frequently occur in women with breast cancer during and following their treatment; however, these symptoms have not been well-studied in older, postmenopausal women with breast cancer receiving hormonal therapy. In one NINR-supported study, the effectiveness of a home-based walking exercise intervention was compared with a more traditional program of usual care provided in older women receiving hormone treatment for breast cancer. The research team looked at the relationships among a selection of biomarkers important in regulating sleep, fatigue, and depression. Sleep quality (longer periods of sleep, less movement during sleep) significantly improved in the exercise group whereas no changes were noted in the usual care group. These preliminary data may contribute to the development of a better understanding of common physiologic links

surrounding clusters of symptoms experienced by breast cancer patients.

Researchers also explored the long-term effects of psychoeducational support interventions on quality-of-life (QOL) outcomes for rural breast cancer survivors. Results of a preliminary evaluation demonstrated that an intervention group showed improvement in overall QOL and that significant differences existed in overall QOL between the experimental and wait-control groups at 3 and 6 months after the intervention.

Caregiving

Demographic shifts, health service developments, workforce issues, and even cultural differences in preferences for care all contribute to numerous significant challenges facing those potentially in need of care and those providing it. Women are much more likely than men to be caregivers, and evidence shows that the burden on women's health is significant. The NINR research portfolio contains multiple examples of projects that span the full spectrum of caregiving research, from informal caregiving in the home, to professional clinicians in institutional settings. For example, NINR investigators are involved in the following projects:

- Developing interventions to promote physical activity in informal caregivers of Alzheimer's disease patients
- Testing associations between caregiver communication and symptom management for critically ill patients who cannot speak for themselves
- Exploring the natural course of caregiving, caregiving burden, and admission to nursing homes among Mexican-American families
- Building community-based preventive interventions to address maternal depressive symptoms among mothers of young children with developmental delays
- Evaluating the quality-of-care impact of caregiving burdens for cancer patients

Incontinence

For women with mild to moderate urinary incontinence (UI), simple self-management techniques may help decrease the frequency and amount of urine leakage. These techniques are generally safe, inexpensive, and easy to teach, but they have not received sufficient study to recommend as a first step in UI treatment programs. NINR-sponsored researchers conducted a clinical trial of a self-monitoring intervention with 224 women with self-reported UI. The women were divided into two groups—one group participated in the self-monitoring intervention, which consisted of individualized counseling about the timing and adequacy of fluid intake, maintaining frequent voiding, limiting caffeine consumption, and doing simple pelvic floor muscle (Kegel) exercises. The control group continued in their usual care. At 3 weeks, the women who completed the intervention program had a greater average decrease in urine loss than women in the control group. In addition, women in the intervention reported a greater improvement in quality of life. This intervention was particularly effective in decreasing urine loss among women who reported nine or more episodes of UI a day, who were older than 65 years of age, and who were premenopausal or on hormone replacement therapy. These findings indicate that teaching simple self-monitoring practices can help improve urine control and quality of life and could be considered as a treatment option for women experiencing mild to moderate UI.

Sex/Gender Analysis

Many NINR-supported clinical studies are specifically designed to analyze gender differences or compare the effectiveness of novel interventions in women versus men. For example, NINR supports research initiatives that explore gender as a risk factor for pain and effectiveness of pain treatments through program announcements issued under the auspices of the NIH Pain Consortium, titled Mechanisms, Models, Measurement, and Management in Pain Research (R01, R21, and R03; PA-10-006, -007, and -008, respectively). An important component of studies supported by NINR is the examination of gender differences with respect to diseases or conditions or

with respect to the effectiveness or efficacy of clinical interventions.

For example, NINR researchers investigated gender differences in responses to stress. Researchers found that 30 minutes after experiencing a stressful event, production of proinflammatory cytokines was elevated in both men and women. However, from before to immediately after stress, men demonstrated a significant drop in cytokine production compared with women. Furthermore, postmenopausal women demonstrated greater subsequent increases in the production of certain cytokines compared with men. These data bolster existing evidence that stress causes the immune system in postmenopausal women to produce larger inflammatory responses than either premenopausal women or men. The results also demonstrate gender differences in stress-related cytokine activity and suggest a possible reason for an observed increased susceptibility of postmenopausal women for developing inflammatory disease.

Occurring in an estimated 10 to 20 percent of the U.S. population, irritable bowel syndrome (IBS) is the most common chronic health disorder in the United States, affecting more people than asthma, diabetes, and depression combined. At least 75 percent of IBS sufferers are female. Although it is commonly believed that IBS has psychological causes, IBS is a physical disorder that affects mainly the bowel (large intestine) with potentially life-limiting symptoms and consequences, such as lower abdominal pain or discomfort, diarrhea, constipation, gas, bloating, and nausea. At present, there is no cure for IBS, but researchers in NINR's Intramural Research Program have been investigating the underlying dysfunction mechanisms and possible effective ways of controlling and even eliminating IBS symptoms. One published study described research on inflammatory dysregulation in overweight and obese women. It is believed that this gut-to-brain malfunction results in hypersecretion of proinflammatory cytokines after sugar consumption. A number of extramurally funded NINR studies also have examined how IBS interferes with functional activities and health care utilization. Special attention has been given to identifying patterns within subgroups of women with IBS and underlying polymorphisms. These studies have found that women with moderate to severe IBS and GI symptoms report more severe levels of depression and anxiety. Researchers have noted that women with specific IBS symptoms demonstrate significant changes in autonomic nervous system functions during sleep. Understanding these and other factors that contribute to IBS in women is important to advance new therapies for managing the complex symptoms of IBS.

Initiatives

Funding Opportunity Announcements

Advancing Novel Science in Women's Health Research (ANSWHR). NINR cosponsors this initiative, which is administered by the Office of Research on Women's Health (ORWH). ANSWHR is devised to promote innovative interdisciplinary research to advance new concepts in women's health research and the interdisciplinary study of sex/gender differences. [PAS-07-381]

Transdisciplinary Research on Fatigue and Fatigability in Aging. This initiative, cosponsored by NINR in collaboration with other Institutes and Centers (ICs) and ORWH, seeks to encourage submission of exploratory developmental research applications on fatigue and fatigability in older persons. Women are particularly affected by fatigue, whether related to physical, mental, emotional, and/or social aspects of aging. Understanding the phenomenology of and mechanisms underlying these relationships may lead to improved methods for symptom management and intervention. [PA-08-162]

Mechanisms, Models, Measurement, and Management in Pain Research. This initiative, sponsored by NINR in collaboration with the other ICs of the NIH Pain Consortium, seeks to stimulate a wide range of basic, clinical, and translational research studies on acute and chronic pain across all disciplines, including biobehavioral, genetics, and pain management research. Women are particularly affected by several of the conditions of special interest in this initiative, such as osteoporotic pain,

fibromyalgia, and temporomandibular joint and muscle disorders. [PA-10-007, PA-10-008]

Chronic Fatigue Syndrome—Pathophysiology and Treatment. NINR is a cosponsor of this ORWH-led initiative. The initiative seeks to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome (CFS) in diverse groups across the lifespan. Of particular relevance to the strategic goals of NINR, the initiative calls for research into behavioral factors that influence CFS and ways to manage symptoms and improve quality of life. [PA-08-246, PA-08-247]

Research on Causal Factors and Interventions That Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (R01). NINR participated as a cosponsor with other ICs and ORWH in this funding opportunity to support research on (1) causal factors explaining the current patterns observed in the careers of women in biomedical and behavioral science and engineering and variation across different subgroups and (2) the efficacy of programs designed to support the careers of women in these disciplines. [RFA-GM-09-012]

NINR Mentored Research Scientist Development Award for Underrepresented or Disadvantaged Investigators; Research Supplements To Promote Reentry Into Biomedical and Behavioral Research Careers. As part of NINR's focus on developing today's and tomorrow's nurse scientists, this NINR initiative encourages development of underrepresented or disadvantaged nurse scientists to become independent investigators in research settings. Through these and other awards, NINR promotes diversity among investigators in women's health and supports the training of women in scientific careers. [PAR-09-074]

Ruth L. Kirschstein National Research Service Award (NRSA). This individual predoctoral fellowship (F31) is intended to provide biomedical and/or behavioral research training experiences to individuals committed to pursuing a career in research within the scientific mission of NINR. Although nurses of both genders are equally likely to pursue advanced degrees, 95 percent of all registered nurses are women. The research training experience must enhance the applicant's conceptualization of research problems and research skills under the guidance and supervision of a committed mentor who is an active and established investigator in the area of the applicant's proposed research. In addition, the training must be conducted in a research environment that includes appropriate human and technical resources and is demonstrably committed to the research training of the applicant in the program she proposes in the application. [PAR-09-227 and PAR-05-091]

Health Disparities Among Special Populations of Women

NINR's strategic plan, *Changing Practice, Changing Lives*, highlights the elimination of health disparities as an area of research emphasis throughout the Institute's entire research portfolio, and NINR's grants related to women's health are no exception. The special populations of women encompassed by NINR health disparities research include adolescents, racial and ethnic minorities, sexual minorities, rural women, and women living in poverty.

Adolescents

Many adolescents in the United States engage in sexual risk behaviors that can result in unintended health outcomes, including sexually transmitted diseases, HIV/AIDS, or pregnancy. Despite declining birth rates over the past few decades, the United States continues to have the highest teenage pregnancy rate of all industrialized nations. Although the proportion of high school students reporting sexual intercourse declined from 54 percent in 1991 to 46 percent in 2009, only 61 percent of those sexually active teenagers used condoms to reduce disease transmission or pregnancy. In fiscal year 2010, Congress provided funding for the President's new Teen Pregnancy Prevention Initiative. Under this Initiative, the Department of Health and Human Services (HHS) is charged with supporting the replication of prevention programs determined to be effective through rigorous evaluation criteria for the evidence-based prevention of teen pregnancy. To develop a list of programs eligible for funding under this initiative, HHS contracted with an outside organization to

conduct an independent review of the current evidence base for programs to prevent teen pregnancy. The review established a set of criteria that programs had to meet to be deemed effective and, therefore, eligible for funding and dissemination.

The HHS review identified 28 programs as effective at preventing teen pregnancy according to these strict criteria. Of these 28 programs, several were developed and tested by NINR-supported investigators, including Be Proud! Be Responsible!; Cuidate!; and Be Proud! Be Responsible! Be Protective! These program were found to effectively reduce teen pregnancy and HIV/AIDS risk behaviors in diverse groups of adolescents. For more information on the President's Teen Pregnancy Prevention Initiative and the HHS review, and to view the full list of selected programs, please see http://www.hhs.gov/ophs/oah/prevention/research/programs/index.html.

Racial and Ethnic Minorities

Among older Hispanic women, the prevalence of obesity is 47.9 percent compared with 21.5 percent among non-Hispanics. Despite the known benefits of physical activity in reducing obesity and other cardiovascular risks, 46 percent of older Mexican-American women report that they do not engage in physical activity. An NINR-supported study evaluated groups of postmenopausal, obese, and sedentary Hispanic women between 45 and 70 years of age in a physical activity intervention designed to reduce coronary heart disease. For 36 weeks, one group of women walked for 3 days a week while a second group walked for 5 days a week. The primary factor that encouraged the women to begin and sustain their walking program was the development of a "gran amiga," or special friend. These women became comrades, providing each other with consistent encouragement to care for themselves and promote better health through a planned walking program. Further research should focus on encouraging women to set aside time for formal walking and on examining strategies to encourage shorter and more frequent walks.

African-American women suffer disproportionately high infection rates of several sexually transmitted infections (STIs), including HIV/AIDS. According to the the Centers for Disease Control and Prevention (CDC), African-American women experience a rate of gonorrhea 20 times higher, and chlamydia 8 times higher, than White women. Health clinics and other primary care settings offer opportunities to teach sexually active African-American women protective behaviors to reduce their risk of STI exposure. The Well Woman Program (WWP), a community-based randomized trial to prevent STIs in low-income African-American women, tested a nurse practitioner-delivered, intensive tailored intervention compared with usual care. The results indicated that the WWP intervention resulted in a 20 percent lower rate of long-term clinically verified STIs.

The 2009 Compendium of Evidence-Based HIV Prevention Interventions included a previously concluded NINR study, the Sister-to-Sister program. The original study evaluated four separate, nurse-led, preventive, culturally sensitive behavioral interventions among a group of 564 sexually experienced Black women from an inner-city women's health clinic. NINR-supported researchers tested this brief, behavioral skill-building program in sessions lasting as little as 20 minutes. Less intensive, information-only interventions also were evaluated. Participants in the skill-building program reported improved protective behaviors for up to 1 year after receiving the program. Another NINR-supported investigator adapted this intervention into practice for Latina youths. Since the 2009 Compendium of Evidence was released, CDC has adopted the most rigorously evaluated evidence-based interventions for distribution to improve HIV/AIDS awareness and protective behaviors. More information is available at http://www.cdc.gov/hiv/topics/research/prs/best-evidence-intervention.htm.

Sexual Minorities

A dearth of research exists regarding the unique barriers to cancer screening experienced by lesbian women. As with other marginalized populations, research is needed to establish best practices for cancer prevention and treatment. An NINR-funded study is developing a culturally focused, patient navigation

training curriculum aimed at increasing breast, cervical, and colorectal cancer screening behaviors in lesbian, gay, bisexual, and transgender (LGBT) persons. This information will serve as a basis for adapting and culturally targeting an existing health system navigation curriculum that will assist patient navigators in helping to reduce barriers to appropriate cancer screening and followup care among nonadherent LGBT individuals. This study is among the first to attempt to systematically develop a targeted patient navigation training curriculum aimed at reducing cancer screening disparities. The study aims to provide an improved understanding of LGBT-specific barriers to cancer screening and the preliminary data necessary to conduct a full randomized trial testing the cancer screening patient navigation program.

Rural Women

As women age, their risks for chronic illness increase, along with the likelihood that they will endure more years of disability and functional impairment than men. Rural older women, in particular, experience poorer health status and have higher obesity prevalence than urban women. The NINR-sponsored Wellness for Women Project compared a generic health newsletter with an individually-tailored newsletter to determine which is more effective in increasing healthy eating and physical activity in older rural women. After the 12-month randomized controlled intervention, improvements in healthy behaviors (e.g., increased physical activity, fruit and vegetable intake) and physical outcomes (e.g., increased cardiovascular fitness) were assessed at 12 (baseline), 18, and 24 months. Over time, both groups maintained some healthy behaviors gained in the initial intervention. However, the tailored newsletter group had achieved and maintained (at 18 and 24 months) a higher proportion of Healthy People 2010 goals in healthy eating and physical activity after the initial intervention. Individually tailored interventions that can be delivered by mail have the potential to reach rural women with relatively low cost and may have long-lasting impacts on their healthy behaviors and health outcomes. Continued efforts to examine the long-term benefits of such interventions will be important for improving healthy living in older rural women and other groups.

Women Living in Poverty

Over the past 15 years, policy initiatives at the Federal and State levels have increased access to prenatal care, especially among minorities and women living in poverty. One NINR-supported study examined the pregnancy experiences of low-income, primiparous African-American, Mexican-American, Puerto Rican, and White women participating in focus groups. The research suggested that, despite dissatisfaction with their prenatal care, these low-income new mothers demonstrated a concerted interest in enhancing their health literacy through requests for information and clarification from their health care providers. Trust in provider relationships—as indicated by effective communication—creates opportunities in which women living in poverty can ask for and receive information about their health, pregnancies, and postpartum issues. Developing personal relationships with providers is critical in an increasingly diverse population and constrained health care system.

Researchers in the NINR Intramural Research Program have identified that low-income urban women with posttraumatic stress disorder (PTSD) experience more adverse medical conditions than either higher income or suburban women with PTSD. Women with PTSD seeking health care report significantly lower health status, suffer more medical impairments, and visit health care providers at a much higher rate. Such health disparity findings could assist health care providers considering the broad ramifications of PTSD.

Career Development

Because women comprise such a large percentage of the nursing workforce (about 95 percent according to some estimates), NINR is in a unique position to increase the representation of women in the scientific workforce through training opportunities and enhance the scientific base of women's health research. For example NINR supports many awards each year under the Ruth L. Kirschstein NRSA program for individual predoctoral fellowships. This program is intended to provide

biomedical and/or behavioral research training experiences to individuals committed to pursuing a career in research within the scientific mission of NINR. This research training experience seeks to enhance a trainee's conceptualization of research problems and research skills under the guidance and supervision of a committed mentor who is an active and established investigator in the area of the trainee's proposed research.

In addition, NINR actively promotes efforts to enhance the scientific workforce by encouraging the career development of nurse scientists from underrepresented and disadvantaged backgrounds. NINR initiatives seek to expand women's health research and provide opportunities to underrepresented and disadvantaged women by: recruiting the most talented researchers from all groups; improving the quality of the educational and training environments; balancing and broadening perspectives in setting research priorities; improving the ability to recruit subjects from diverse backgrounds into clinical research protocols; and improving the Nation's capacity to address and eliminate health disparities. NINR's research supplements to promote diversity in health-related research are examples of these efforts at the predoctoral and postdoctoral levels.

In 2010, NINR participated in multiagency collaboration with schools of nursing in Pakistan to assist in building and strengthening Pakistan's nursing faculty to conduct research and to mentor and train nurses.

NINR also has continued a longstanding research effort to explore nursing workforce shortages and their effect on health outcomes. Building on previous research demonstrating a positive link between nurse-staffing levels and measures of patient outcomes, as well as nurse job satisfaction and retention, an NINR-sponsored project published results in 2009 showing that better nurse-staff organizational support services and work engagement are associated with greater patient satisfaction and symptom management. Another NINR-funded study examined the impact that California's mandatory nurse-staffing levels would have had on two other States' patient outcomes. The authors estimated that, had patient-to-nurse ratios in Pennsylvania and New Jersey been consistent with those in California during the period of the study, 486 fewer surgical deaths would have occurred in those two States combined. Also reported were that nurses in California reported higher job satisfaction, less burnout, and better ability to care for patients. This study is particularly relevant to women's health because of the exceptionally high proportion of female nurses, and it presents important policy implications for policymakers in other States currently considering health care workforce legislation.

Fogarty International Center

Executive Summary

The Fogarty International Center (FIC) supports a range of research and research training programs focused on the needs of low- and middle-income countries. These programs cover both communicable diseases (e.g., HIV/AIDS, TB, malaria); chronic, noncommunicable diseases (e.g., tobacco addiction, brain disorders); and crosscutting areas such as population health, environmental health, and research ethics. The Office of Research on Women's Health (ORWH) supports many of these efforts, along with several other National Institutes of Health (NIH) Institutes. Although these programs were not designed to specifically address women's health, they do support important projects related to women's health. Significant research or research training programs related to women's health include the following:

Global Research Initiative Program, Basic/Biomedical Sciences and Social Science. The Global Research Initiative Program (GRIP) promotes reentry of NIH-trained low and middle income country (LMIC) investigators into their home countries as part of a broader program to enhance the scientific research infrastructure in LMICs and to stimulate research on a wide variety of high-priority health-related issues. Examples of GRIP-supported research topics relevant to women's health include the effects of genetic predisposition and modifiable factors on the risks of hypertension and diabetes, the association

between mortality and outdoor air pollution, risk factors for preterm birth, and gender differences of HIV risks among injecting drug users in China.

International Tobacco and Health Research and Capacity Building Program. The International Tobacco and Health Research and Capacity Building Program (Tobacco) supports transdisciplinary research and capacity-building projects that address the burden of tobacco consumption in low- and/or middle-income nations by (1) pursuing observational, intervention, and policy research of local importance and (2) building capacity in these regions in epidemiologic and behavioral research, prevention, treatment, communications, health services, and policy research. This program is supporting the development of a network for tobacco control among women in Parana, Brazil, to establish community and institutional capacity to promote gender-relevant tobacco control efforts among Brazilian women through community-based participatory research and training.

AIDS International Training and Research Program. The AIDS International Training and Research Program (AITRP) supports HIV/AIDS-related research to strengthen the capacity of institutions in LMICs to conduct multidisciplinary biomedical and behavioral research to address the AIDS epidemic in the collaborating country. AITRP supports epidemiologic studies on attitudes of women to highly active antiretroviral therapy (HAART), AIDS-related mortality and long-term survival rates, and other factors that may have a differential impact on HIV-infected women.

International Training and Research in Environmental and Occupational Health. The International Training and Research in Environmental and Occupational Health (ITREOH) program provides training for health scientists, clinicians, epidemiologists, toxicologists, engineers, industrial hygienists, chemists, and allied health workers in LMICs and emerging democracies in both general environmental and occupational health research. An example of a project supported by ITREOH is a study on the association between arsenic and/or water pollution in various diseases, such as chronic obstructive pulmonary disease in women.

Millennium Promise: Noncommunicable Chronic Diseases Research Training Program. The Noncommunicable Chronic Diseases Research Training Program (NCoD) is designed to build research capacity in LMICs in fields related to cancer; cerebrovascular disease, including stroke; and lung disease, including chronic obstructive pulmonary disease. NCoD also builds research capacity regarding environmental factors, including indoor air pollution; obesity and lifestyle factors related to these conditions; and the genetics of noncommunicable diseases. A current award supported by NCoD investigates the occupational conditions in Mongolian mines, especially those that affect women. According to a 2006 study by Navch et al., Mongolia is a region with over 100,000 persons, including women and children, working in mine excavation and processing. These activities create health and safety risks, sometimes violent, for workers. A pilot feasibility study, conducted by the PI, investigated the risk factors for mercury exposure among women involved in small scale gold mining in Gobisumbar and central Mongolia. The current NCoD will draw upon the previous study and continue to look at the impact mining has on women's health.

Global Infectious Disease Research Training Program. The Global Infectious Disease Research Training Program (GID) addresses research training needs related to infectious diseases that are predominantly endemic in or affect people living in LMICs. The ultimate goal is to build a critical mass of researchers and support staff to conduct independent infectious disease research in LMIC institutions. Examples of GID-supported research include understanding the impact of P. vivax infection in pregnant women and establishing a center of excellence in Tanzania to focus on malaria in pregnant women and children, with an emphasis on research and intervention.

Global Research Training in Population Health. The Global Research Training in Population Health (POP) program supports research training of low- and middle-income country scientists with the long-term objective

of strengthening low- and middle-income country research programs and institutions related to population health, including the study of demographic processes such as aging, fertility, sex and gender, and other social, behavioral, and economic factors that influence population dynamics. The POP program also studies reproductive processes (including biology, immunology, genetics, endocrinology), fertility and infertility, contraceptive development, contraceptive clinical trials, and contraceptive and reproductive health evaluation. Many of the fertility and reproductive studies pertain to women's health issues.

International Research Scientist Development Award. The International Research Scientist Development Award (IRSDA) program supports U.S. postdoctoral biomedical, epidemiologic, clinical, social, and behavioral scientists in the formative stages of their careers to pursue careers in research on global health and to prepare for independent research careers. These awards support 3- to 5 years of "protected time" for mentored research and career development experiences, leading to an independent research career focused on global health. A current award supported by the IRSDA program examines family planning and maternal health in Afghani women.

Significantly, FIC incorporates language in all of its research training announcements to encourage the recruitment and retention of women as faculty and trainees. An example of such language follows: "The ICOHRTA-AIDS/TB program strongly encourages PIs to include women and individuals from underrepresented racial, ethnic, or socially disadvantaged groups in the country as trainees and faculty at all sites. Applicants should describe strategies for recruiting and retaining women and socially and economically disadvantaged persons as trainees."

Accomplishments

The following are examples of selected projects supported by FIC that focus on women's health:

Genomewide Association Study of Anthropometric Traits and Evidence of Interactions With Age and Study Year in Filipino Women. Over the past few decades, the adoption in Asian populations of western-style diets of increased fats and carbohydrates and of more sedentary habits has led to a marked increase in obesity. In particular, a cohort of women from the ongoing Cebu Longitudinal Health and Nutrition Survey (CLHNS) based in the Philippines showed a sixfold increase in prevalence of overweight and obesity associated with nearly two decades of substantial and continuing socioeconomic modernization. The portion of increased prevalence due to the changes in environment versus increased age of these women is unclear. This study performed a genomewide association study to test for main effect single-nucleotide polymorphism (SNP) associations with measures of body mass index (BMI), weight, waist circumference, and height in 1,792 Filipino women. The longitudinal nature of this cohort allowed researchers to examine the interactive effect of age and genotype on BMI over a 22-year period from 1983 to 2005. The findings replicated several previously reported SNP associations with variation in BMI, weight, and height. They also further characterized in a longitudinal setting the *MC4R*, *BDNF*, and *FTO* loci associated with BMI. Together, these results show that multiple genetic risk factors identified in other populations are also associated with anthropometric traits in Filipinos despite a transitioning nutritional environment (Croteau-Chonka DC et al. *Obesity*, 2010).

Circumcision in HIV-Infected Men Does Not Reduce Risk of HIV Infection in Female Partners. Recent clinical studies conducted in sub-Saharan Africa demonstrated that circumcision reduced risk of HIV infection in men by 50 to 60 percent; however the impact it has on their female partners has yet to be thoroughly explored. This study in Rakai, Uganda, is the first randomized controlled trial to assess whether circumcision in HIV-infected men reduces transmission of the virus to uninfected female sexual partners. Recruitment into the trial was stopped at interim analysis because fewer serodiscordant couples enrolled concurrently than anticipated, decreasing the

power of the study to detect a protective effect. Couples were followed for up to 24 months. Researchers found that circumcision of HIV-infected men did not reduce transmission of HIV to uninfected female partners over a 24-month study period. The results also did not exclude the possibility that couples who resumed intercourse before complete surgical healing from circumcision were at higher risk of HIV transmission. Despite the findings of this study, the authors recommend that male circumcision be offered in conjunction with HIV counseling services, condoms, and HIV prevention education for HIV-infected circumcised men and their partners. The authors believe that denying HIV-infected men from circumcision procedures will result in stigmatization and a false belief that circumcised men do not have HIV. (Wawer MJ et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: A randomised controlled trial). *Lancet* July 18;374(9685):229-37, 2009).

Simple and Inexpensive Point-of-Care Tests Improve Diagnosis of Vaginal Infections in Resource-Constrained Settings. Bacterial vaginosis (BV) and trichomonas vaginalis (TV) infections have been associated with adverse birth outcomes and increased risk for HIV. This study compares the performance of simple inexpensive point-of-care (POC) tests with laboratory diagnosis and syndromic management of BV and TV in poor settings. Between 2005 and 2006, 898 sexually active women attending two reproductive health clinics in Mysore, India, were recruited into a cohort study investigating the relationship between vaginal flora and HSV-2 infection. Participants were interviewed and screened for reproductive tract infections. Among the entire study population, POC correctly detected 82 percent of laboratory-diagnosed BV cases and 83 percent of laboratory-diagnosed TV infections. These findings suggest that during the absence of laboratory diagnostics, POC is an inexpensive and practical alternative. In addition, POC is significantly more sensitive than the syndromic management approach, resulting in less overtreatment (Madhivanan P et al. *Tropical Medicine & International Health* 14(6):703-8, 2009).

Metformin in the Treatment of Infertility in PCOS: An Alternative Perspective. Polycystic ovary syndrome (PCOS) is a clinical diagnosis characterized by the presence of two or more of the following features: chronic oligo-ovulation or anovulation, androgen excess, and polycystic ovaries. It affects 5 to 10 percent of women of childbearing age and is the most common cause of anovulatory infertility in LMICs. The majority of women with PCOS, regardless of weight, have a form of insulin resistance that is intrinsic to the syndrome and is poorly understood. This study discusses the use of metformin, a drug that improves insulin sensitivity and is shown to retard or prevent progression to type 2 diabetes. However, most of the randomized, controlled trials on metformin are conducted in populations without PCOS. The author recommends that additional trials specifically involve patients with PCOS and those patients looking at long-term treatment use with metformin to determine whether it should it be used as monotherapy or in combination with antiandrogens or hormonal therapies (Nestler JE. *Fertility and Sterility* 90(1):14-16, 2008).

Smokeless Tobacco Use and Reproductive Health Among Married Women. Smokeless tobacco use is increasing dramatically among women in India and has been shown to contribute to reproductive health problems, including premature birth, low birth weight, still birth, and maternal morbidity among low-income Indian women. The current research project in Mumbai will contribute to culturally and contextually appropriate interventions focused on smokeless tobacco prevention and cessation among women in low-income communities. Significance lies in the study's capacity to address a critical public health problem in India—the apparent increase in risky and addictive new forms of smokeless tobacco with potentially serious implications for pregnancy and morbidity and mortality of women—and to provide the basis for educational and other forms of appropriate intervention to reduce smokeless tobacco use, a practice intertwined with other aspects of their lives, among women of reproductive age. This study plans to contribute to the development of situational and culturally appropriate interventions in the India context and to multilevel approaches

that can be applied to diverse communities of smokeless tobacco users in the United States. (Fogarty International Research Collaboration, Behavioral and Social Sciences/Currently funded study).

Effectiveness and safety of tenofovir gel, an antitretroviral microbicide for prevention of HIV infection in women. Scientists trained through FIC's AIDS International Training and Research Program have been instrumental in a microbicide effectiveness and safety trial in 900 South African women. Led by the Center for the AIDS Program of Research in South Africa (CAPRISA) and funded by the United States Agency for International Development, this study evaluated tenofovir gel, an antiretroviral microbicide gel that has been linked to prevention of HIV infection in women. Women who received the vaginal gel containing the anti-HIV drug had a 39 percent lower chance of infection compared with women who used a placebo gel. In the 444 women receiving placebo, 60 became infected with HIV versus 38 infections in the 445 women who received the microbicide. Serious side effects were not reported, and the results were statistically significant (Karim A et al. Effectiveness and safety of tenofovir gel, an antitretroviral microbicide for prevention of HIV infection in women. *Science* 329(5996):1168-74, 2010).

Risk Factors for Cervical Precancer and Cancer in HIV-Infected, HPV-Positive Rwandan Women. Although cervical cancer is an AIDS-defining condition, infection with human immunodeficiency virus (HIV) may only modestly increase the risk of cervical cancer. There is a paucity of information regarding factors that influence the natural history of human papillomavirus (HPV) in HIV-infected women. A Fogarty-sponsored study examined factors associated with cervical intraepithelial neoplasia grade 3 or cancer (CIN3+) in Rwandan women infected with both HIV and HPV. The findings showed that in this HIV+/HPV+ population, lower CD4 blood count was significantly associated with CIN3+ (cancer) only in women infected with carcinogenic non-HPV16. There was a trend for higher risk of CIN3+ in HIV+ women reporting recent malarial infection; this association should be investigated in a larger group of HIV+/HPV+ women (Anastos D et al. PLoS One 5(10):e13525, 2010).

Understanding Barriers and Facilitators for Mammography Screening Among Chilean Women. Breast cancer is the leading cause of cancer among women in Chile and in many Latin American countries. Breast cancer screening is an effective strategy to reduce mortality, but it has a very low compliance among Chilean women. This study sought to understand barriers and facilitators for breast cancer screening in a group of Chilean women aged 50 to 70. Forty-eight women with diverse experiences with breast cancer and screening practices provided information that was later coded following the grounded theory model. The findings suggest that the presence of symptoms and/or the finding of lumps through breast self-examination were the main predisposing factors for getting a mammogram. Secrecy, embarrassment, and fatalism about breast cancer were significant cultural factors that influenced the decision to seek mammogram screening. The study highlights the importance of using culturally appropriate strategies to better inform women about the importance of mammography screening and the limitations of breast self-examination for preventing advanced breast cancer (Gaziano TA et al. If I feel something wrong, then I will get a mammogram: Understanding barriers and facilitators for mammography screening among Chilean women. *Current Problems in Cardiology* 35 (2):72-115, 2010).

Risk Factors for Postpartum Hemorrhage in Vaginal Deliveries in a Latin-American Population. In economically developed and developing countries, postpartum hemorrhage is a leading cause of severe maternal morbidity and mortality. Approximately 14 million women suffer postpartum hemorrhage annually. Worldwide, 529,000 pregnancy-related deaths occur every year. Several articles have cited determinants of postpartum hemorrhage; however, the majority of the published studies rely on visual estimation of blood loss, which is an inaccurate methodology. This study used a calibrate receptacle to measure the blood loss for all vaginal deliveries among the study participants. The findings confirmed the risk

factors identified in previous studies, such as retained placenta, multiple pregnancy, macrosomia, episiotomy, and suture. However, other risk factors, such as maternal age, nulliparity, augmentation and/or induction with oxytocin during the first or second stage of labor, and preterm birth, were not associated with increased risk of postpartum hemorrhage. The findings show that active management of the third stage of labor, low birth weight, and multiparity (more than three deliveries) are protective factors against developing moderate postpartum hemorrhage (Sosa CG et al. *Obstetrics and Gynecology 113(6):1313-9, 2009)*.

Family Planning and Maternal Health in Afghanistan. This study investigated whether immediate postpartum provision of a long-acting family planning method would be feasible and acceptable to both men and women in Kabul, Afghanistan. An additional goal was to determine whether the retraining and assignment of health care providers dedicated to intrapartum rapid testing and postpartum counseling will positively affect maternal and neonatal health indicators compared with existing providers of these services among a randomized sample of women delivering in four public maternity hospitals in Kabul sampled over a 12-month period. At baseline, 6 months, and 12 months, patients randomized to the intervention were assessed as to whether they perceived a value in postpartum counseling. Results showed that the postpartum intervention was successful in improving breastfeeding, contraceptive use, and vaccination completion at the appropriate times, particularly in the first 6 months (International Research Science and Development Award/ Grantee Progress Report).

Domestic Violence and Forced Sex Among the Urban Poor in South India: Implications for HIV Prevention. This study examined the prevalence of physical and sexual violence among 1,974 married women from low-income communities in Chennai, India. The authors found a 99 percent and 75 percent lifetime prevalence of physical abuse and forced sex, respectively, whereas 65 percent of women experienced more than five episodes of physical abuse in the 3 months preceding the survey. Factors associated with violence after multivariate adjustment included elementary/ middle school education and variables suggesting economic insecurity. These domestic violence rates exceed those in prior Indian reports, suggesting that women in slums may be at increased risk for HIV and other sexually transmitted infections (Solomon S et al. *Violence Against Women* 15(7):753-73, Date?).

Sex/Gender Analysis

FIC has incorporated language in all of its research training announcements that encourages research training activities related to sex and gender differences: "Where appropriate, the design of training-related research projects should take into account potential sex and gender differences that may affect the questions asked and the analyses performed. These might include different responses to and impacts of health interventions, differences in physiology, and different behavioral bases for disease prevention strategies."

Initiative

Fogarty International Clinical Research Scholars Program (R24 mechanism). The Fogarty International Clinical Research Scholars Program (FICRS) responds to the acute need for future clinical investigators who can help translate basic research advances into clinical practice on a global scale. This next generation of clinical researchers will require hands-on experience in conducting clinical research in countries where the disease burdens are highest, typically in low- and middle-income countries (LMICs). FICRS provides highly motivated U.S. medical and graduate students in the health sciences the opportunity to experience 1 year of mentored clinical research training at distinguished LMIC research institutions. Each U.S. student is paired with a foreign student, who also receives training as an equal partner. In 2008, this program was expanded to include a postdoctoral program for medical residents and fellows, as well as scientists with PhDs engaged in health-related postdoctoral programs. In 2008, the majority of scholars and fellows in this program were women (65 percent). In the summer of 2008, Dr. Vivian Pinn participated in the scholars/fellows orientation, and

ORWH contributed $150,000 to the program for FY 2008. In FY 2010, ORWH contributed $240,000.

National Center for Complementary and Alternative Medicine

Executive Summary

The National Center for Complementary and Alternative Medicine (NCCAM) is the Federal Government's lead agency for scientific research on complementary and alternative medicine (CAM). NCCAM's mission is to define, through rigorous scientific investigation, the usefulness and safety of complementary and alternative medicine interventions and their roles in improving health and health care.

NCCAM defines CAM as a group of diverse medical and health care interventions, practices, products, or disciplines that are not generally considered part of conventional medicine. The boundaries between CAM and conventional medicine (also called Western or allopathic medicine) are not absolute and are constantly evolving. For example, interventions such as hospice care or relaxation and breathing techniques in childbirth that were once considered unconventional are now widely accepted.

The most current and comprehensive picture of Americans' use of CAM has been developed under NCCAM leadership through the National Health Interview Surveys (NHIS), conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention in 2007. The survey showed that nearly 40 percent of adults and 12 percent of children reported using some form of CAM.

NHIS data show that CAM therapies are used for a variety of diseases and conditions, most frequently for back pain, neck pain, anxiety, arthritis, and headaches. The CAM therapies used most often are natural products, deep breathing, meditation, and chiropractic and osteopathic manipulations. These findings have led NCCAM to emphasize research on pain management, which is the most common reason for CAM use, and natural products, which are the most commonly used CAM treatment.

NCCAM's goals, as articulated in its new strategic plan (http://nccam.nih.gov/about/plans/2011), are to (1) advance the science and practice of symptom management, (2) develop effective, practical, personalized strategies for promoting health and well-being, and (3) enable better evidence-based decisionmaking regarding CAM use and its integration into health care and health promotion. NCCAM aims to achieve these goals by maintaining its focus on basic research while increasing its emphasis on translational, efficacy, and outcomes research.

NCCAM-sponsored research has yielded important findings that advance symptom management in women's health issues such as fibromyalgia, menopause, pregnancy, irritable bowel syndrome, and urinary tract infections. NCCAM-sponsored research also has yielded results that promote health and well-being in women's health issues such as stress management and osteoporosis.

NCCAM also funds five centers for research into botanical dietary supplements, two of which are focused on women's health. The University of Illinois at Chicago/NIH Center for Botanical Dietary Supplement Research in Women's Health focuses on the safety of botanical dietary supplements and their impact on women's estrogenic hormones. The Botanical Research Center at the University of Illinois at Urbana-Champaign is addressing the safety, efficacy, and mechanism of action of botanical estrogens consumed by women.

Accomplishments

Fibromyalgia

Tai Chi Benefits Patients With Fibromyalgia. Fibromyalgia is a disorder characterized by chronic widespread muscle pain, fatigue, and the presence of "tender points," which are painful when slight pressure is applied. Fibromyalgia disproportionately affects women, who make up 80 to 90 percent of those with fibromyalgia. Researchers evaluated the physical and psychological benefits

of tai chi (a mind-body practice that combines meditation, slow movements, deep breathing, and relaxation) in 66 people with fibromyalgia. The participants were assigned to one of two groups: an attention control group that received wellness education and practiced stretching exercises or a tai chi group that received instruction in tai chi principles and techniques. Both groups met twice a week for 12 weeks and also practiced daily at home. The tai chi group had a significant improvement in fibromyalgia-related symptoms, sleep quality, mood, and quality of life. The researchers concluded that these findings support previous research indicating benefits of tai chi for musculoskeletal pain, depression, and quality of life.

Menopause

Black Cohosh, Red Clover No Better Than Placebo in Treating Menopause Symptoms. Researchers tested the herbs black cohosh and red clover in women experiencing at least 35 episodes of hot flashes and night sweats per week. During the yearlong investigation, 89 women were randomly assigned to take daily doses of black cohosh, red clover, placebo, or hormone therapy. As researchers expected, the most significant effects were seen in the women who took hormone therapy. They had a 94-percent decrease in the average number of symptoms they experienced per week. Women given placebo experienced a symptom decline of 63 percent. Those who took red clover showed a 57-percent decline in symptoms, while women who took black cohosh had only a 34-percent decline in symptoms. These findings suggest that the herbs black cohosh and red clover are no better than placebo in treating the hot flashes and night sweats that often accompany menopause.

Pregnancy

Exploratory Trial Finds Possible Benefits of Osteopathic Treatment for Back Pain During the Third Trimester of Pregnancy. Most pregnant women experience low-back pain, which often is associated with sleep disturbance and can affect daily activities. Researchers investigated the effects of osteopathic manipulative treatment on back pain during the third trimester of pregnancy. In this exploratory trial, 144 women in weeks 28 to 30 of pregnancy received usual obstetrical care only, usual care plus a systematic osteopathic manipulative treatment protocol provided by an osteopathic specialist, or usual care plus a sham treatment in which the specialist applied pressure with a nonfunctional ultrasound instrument. At the end of 7 weeks, those in the osteopathic manipulative treatment group were less limited by their back pain and maintained a more normal daily routine than those in the other two groups. The results of this preliminary study suggest that osteopathic manipulation in the third trimester of pregnancy may have benefits for maintaining normal functioning in those with back pain but may not do much to relieve the pain itself. Larger trials are needed before definitive conclusions can be drawn.

Irritable Bowel Syndrome

Supportive Patient-Practitioner Relationships May Benefit Patients With Irritable Bowel Syndrome. Irritable bowel syndrome (IBS) is a gastrointestinal syndrome consisting of abdominal pain and altered bowel habits without a clear organic cause. It affects women twice as often as men and is the second most common cause for missing work. Researchers randomly assigned participants with IBS to one of three groups: wait list, placebo acupuncture with minimal practitioner interaction, or placebo acupuncture plus supportive practitioner interaction. Simulated acupuncture with minimal interaction yielded modest improvement of IBS symptoms, whereas simulated acupuncture with supportive interaction brought significant improvement. Upon further analysis of participant characteristics, people who were reclusive (avoided contact with other people) or had previously been enrolled in any clinical trial benefited more than others from the supportive interaction. In light of these findings, the authors recommended additional research to explore the role of patient-practitioner interactions and other social factors in healing, both for IBS and for other conditions.

Benefits of a Placebo in Adults With IBS Do Not Depend on Deception. Researchers followed 80 adults with IBS over the course of 3 weeks. Participants were randomly assigned to receive either placebo pills or no treatment. The participants in the placebo group were informed that "placebo pills, made of an inert substance, like sugar pills, have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body healing processes." The quality of the practitioner-patient interaction was similar in both groups. The researchers found that the participants in the placebo group had significant improvement of overall symptoms, severity of symptoms, and adequate relief compared with those in the group that did not receive treatment. In addition, the placebo group had a trend toward improvement in quality of life. Based on these findings, the researchers suggest that placebos given without deception improved symptoms of irritable bowel syndrome. Researchers note that more studies are needed on IBS, as well as other conditions, to confirm that placebos can be beneficial when used openly and to determine the best methods for administering such treatments.

Stress

Long-Term Yoga Practice May Decrease Women's Stress. Recent research has shown that women who practice hatha yoga (a type of yoga involving body postures, breath control, and meditation) regularly recover from stress faster than women who are considered yoga "novices." Building on this, researchers enrolled 25 women identified as yoga "experts" (those who practiced yoga at least weekly for 2 years) and 25 novices (those who participated in yoga classes or home practice for 6 to 12 sessions). The researchers assessed participants before and after they took part in three activities: yoga practice, slow walking on a treadmill, and passively watching a video. They also measured participants' physiologic responses before and after certain stressful events by measuring particular molecular markers in the blood. Although differences were not unique to the yoga sessions, the researchers found that the novices' blood had 41 percent higher levels of the stress-related marker interleukin-6 than those of the experts. In addition, the novices' levels of C-reactive protein, a marker for inflammation, were nearly five times that of the experts. Experts had lower heart rates in response to stressful events than novices. Yoga also boosted mood in both groups, whereas the other two interventions did not. The researchers suggested that this study shows that regularly performing yoga could have health benefits that may only become evident after years of practice.

Urinary Tract Infections

Study Indicates Cranberry Juice Does Not Interfere With Two Antibiotics Women Take for Recurrent Urinary Tract Infections. About 50 to 60 percent of women are diagnosed with a urinary tract infection (UTI) at least once during their lifetime with many experiencing multiple recurrences. Cranberry juice, a popular home remedy for UTI, is often taken along with low-dose antibiotics as a preventive measure. Researchers studied the effect of cranberry juice on two antibiotics frequently prescribed for UTI. Two parallel studies were conducted, one for amoxicillin and one for cefaclor. In each study, 18 healthy women took a single oral dose of the antibiotic with either water or cranberry juice cocktail and a week later took the same antibiotic with the other liquid. Those who drank juice also drank it for 2 days before the treatment to approximate real-life consumption. The data showed that cranberry juice did not significantly affect either antibiotic's oral absorption or renal clearance (how completely the body processed the drugs in the kidneys). Based on these results, the researchers concluded that cranberry juice cocktail, consumed in usual quantities, is unlikely to change the effects of these two antibiotics on UTIs.

Osteoporosis

Laboratory Study Shows Turmeric May Have Bone-Protective Effects. Osteoporosis is a bone disease, common in postmenopausal women, which can lead to an increased risk of fractures. Researchers studied the effects of turmeric—an herb commonly used in curry powders, mustards, and cheeses—in an animal model of postmenopausal osteoporosis. This study tested two turmeric extracts containing

different amounts of curcuminoids (active components of the herb) in female rats whose ovaries had been surgically removed to mimic menopause. Researchers injected rats with curcuminoid-enriched turmeric extract or non-enriched turmeric extract. As controls, other rats received placebo injections after either ovary removal or sham surgery. Enriched turmeric extract prevented up to 50 percent of bone loss and preserved bone structure and connectivity, whereas nonenriched turmeric extract did not have bone-protective effects. Other physiologic changes associated with ovary removal were unaffected—an indication that the bone-protective effects did not involve an estrogen-based chemical pathway. This preliminary animal study shows that turmeric may protect bones but that the effect depends on the amount of curcuminoids present. Researchers emphasized that the next step is clinical research in humans to evaluate the use of turmeric-derived curcuminoid products to guard against osteoporosis.

Quality of Life and Safety of Tai Chi and Green Tea Extracts in Postmenopausal Women. Osteopenia is a thinning of the bones that precedes osteoporosis. Previous clinical studies have suggested that tai chi has beneficial effects on bone health. Likewise, animal research has indicated that green tea polyphenols (substances rich in antioxidants) also may have bone-protective effects. Researchers randomly assigned 171 postmenopausal women with osteopenia to receive green tea polyphenols, green tea polyphenols plus tai chi training, placebo pills, or placebo pills plus tai chi training over a 24-week period. Researchers measured participants' depression (mood), general health status, and liver and kidney function throughout the study. Participants in the tai chi groups reported significant beneficial effects in quality of life in terms of improving their emotional and mental health. The researchers found that green tea supplements did not significantly affect participants' liver enzymes or kidney serum levels and had no effect on quality of life. Based on these findings, the researchers concluded that green tea polyphenols at a dose of 500 mg daily for 24 weeks, alone or in combination with tai chi, appears to be safe in postmenopausal women with low bone mineral density. In addition, the study confirmed previous findings that tai chi has a positive effect on emotional and mental health.

Initiatives

Dietary Supplement Research Centers: Botanicals (RFA-OD-09-001). Through this research program, the NIH Office of Dietary Supplements (ODS), NCCAM, and the National Cancer Institute support research centers that (1) promote collaborative integrated interdisciplinary study of botanicals, particularly those found as ingredients in dietary supplements and (2) conduct research of high potential for being translated into practical benefits for human health. This initiative is intended to advance the spectrum of botanical research activities, ranging from plant identification and characterization to early-phase clinical studies. Of the five centers that NCCAM funds, the two below focus on women's health.

Center for Botanical Dietary Supplement Research in Women's Health. This center at the University of Illinois at Chicago was established in 1999 to focus on botanical dietary supplement research on women's health. The center's mission is to focus on the safety of botanical dietary supplements, such as black cohosh and licorice, which are widely available. Investigators are studying how multicomponent mixtures work together; how they are absorbed, distributed, and eliminated by the body; how they affect chemical and physical processes within the body; how they interact with drugs; and how they affect women's own estrogenic hormones.

Botanical Research Center at the University of Illinois at Urbana-Champaign. This newly created center at the University of Illinois at Urbana-Champaign was established in fiscal year 2010. It is examining the safety, efficacy, and mechanism of action of botanical estrogens such as wild yam, soy, and dong quai. The center's projects are looking at the biological effects of botanical estrogens on molecular mechanisms and cellular pathways as well as their actions on bone, uterus, breast tissue, breast cancer metastasis, and cognition.

Advancing Novel Science in Women's Health Research (PAS-10-226). This funding opportunity announcement, issued by the Office of Research on Women's Health, NCCAM, and other cosponsoring NIH Institutes and Centers, promotes innovative interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences.

National Center for Research Resources

Executive Summary

The National Center for Research Resources (NCRR) provides basic scientists and clinical researchers with the resources and environment to pursue research on a wide range of diseases. This support enables discoveries that begin at a molecular and cellular level to move to animal-based in vitro studies and on to patient-oriented clinical research, resulting in cures and treatments for both common and rare diseases. NCRR connects researchers with one another as well as with patients and communities across the Nation to harness the power of shared resources and research. NCRR develops and supports biomedical resources that include sophisticated instrumentation, specialized animal models for human diseases, flexible support mechanisms to invest in emerging research opportunities, a cost-saving nationwide network of clinical research centers, state-of-the-art equipment available on a shared basis, strong research infrastructure for predominantly minority institutions; infrastructure enhancement and mentorship at institutions in States with historically low funding from the National Institutes of Health (NIH), and alterations and renovations to research facilities and animal care facilities. Through its support of multidisciplinary research, NCRR is uniquely positioned to provide funds directly for research or to act in partnership with other NIH components to address emerging clinical and basic research needs. NCRR is leading a national consortium—funded through Clinical and Translational Science Awards—that will transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients.

NCRR did not specifically develop dedicated initiatives in the area of women's health in fiscal years 2009 or 2010. However, through its support of unique resources, NCRR contributes a significant portion of its budget to women's health research and continues to support initiatives developed by other components of NIH for such efforts. In addition, NCRR supports research on the prevention and treatment of various diseases, disorders, or conditions that are unique to women or may have a significant impact on women. The recent accomplishments in women's health research described below exemplify the breadth of science and technology supported by NCRR.

Accomplishments

Potential New Markers for Regulating Breast Cancer Development. At Meharry Medical College, Dr. James Hildreth and colleagues have been studying how BRCA2 levels go up in many aggressively growing breast cancer cells. About 25 percent of autosomal-dominant familial breast cancers are proposed to be caused by mutations in the BRCA2 gene (germ-line mutations). Another potential mechanism of BRCA2 involvement in breast cancer may be through deregulation of the BRCA2 gene expression. The investigators discovered that a novel protein called C4-type zinc finger protein (ZAR2), transcribed by the bidirectional activity of the BRCA2 gene promoter, regulates the expression of the BRCA2 gene. ZAR2 over-expression in human breast cells will inhibit the tumor suppressor protein BRCA2. These findings provide new insights into another potential mechanism of BRCA2 involvement in breast cancer progression. BRCA2 and ZAR2 could potentially serve as biomarkers for aggressive breast cancer. The NCRR grant for the Meharry Clinical and Translational Research Center provided support for pilot studies and core facilities.

Endometrial Profile of Tamoxifen and Low-Dose Estradiol Combination Therapy. Through an NCRR-supported Special Emphasis Research Career Award, Dr. Wood

and his colleagues at Wake Forest University in North Carolina investigated the endometrial safety of estrogen + SERM co-therapy in treating breast cancer. This first preclinical study utilizing female cynomolgus macaques addresses the endometrial profile of an estrogen (E2) + selective estrogen receptor modulators (SERM-[tamoxifen]) co-therapy. The results indicate a dominant effect of tamoxifen over E2 on measures of endometrial morphology, proliferation, and transcriptional profiles. These results suggest that the endometrial risks for E2 + tamoxifen may be similar to the effects of tamoxifen alone. Results from this study should be considered for postmenopausal women who are taking or considering estrogen + progestin therapy for menopausal symptoms or for future trials of estrogen + SERM co-therapies.

Multiple Sclerosis in Only One Identical Twin: Nature vs. Nurture. Investigators at the National Center for Genome Resources, supported partially by NCRR's IDeA Networks of Biomedical Research Excellence, integrated state-of-the-art, next-generation DNA sequencing and analysis technologies to compare genes (genome), gene activity, and methylation gene controls in female twins where one twin has multiple sclerosis (MS). In the first systematic effort to estimate the extent to which twins are identical on a genetic level, the researchers did not find evidence that explained why one twin had MS and the other did not, in spite of looking at the genetic, gene expression, infectious, and epigenetic (environmentally induced methylation) causes of the disease. This study further validates the utility of twins for the assessment of nature versus nurture in complex disorders.

A Laser Microbeam Biotechnology Resource—Monitoring and Predicting the Response to Neoadjuvant Chemotherapy by Diffuse Optical Spectroscopy/Imaging. At the University of California, Irvine, Dr. Tromberg and colleagues developed an optical-based laser breast scanner and used it to evaluate the effectiveness of chemotherapy treatments. The scanner provides detailed information on changes in breast tumor metabolism during chemotherapy. This information, which can be accessed quickly at the bedside, can allow oncologists to target chemotherapy treatments more effectively and safely, tailoring them to the patient's response. Owing to the initial promising results, the technology will be deployed in a National Cancer Institute (NCI)-sponsored five-center clinical study, coordinated by NCI and the American College of Radiology Imaging Networks. The use of chemotherapy for tumor reduction before surgery is an important approach for certain types of breast cancer. The metabolic fingerprint the laser breast scanner provides gives detailed clues on how the chemotherapy is working and allows doctors to adjust treatments. Optical technologies employed by the scanner were developed by the NCRR-funded Laser Microbeam and Medical Program Biomedical Technology Research Center.

Emergence of a Prediabetic State in Juvenile Baboon Offspring of Mothers Exposed to Moderate Maternal Nutrient Reduction. At the University of Texas at San Antonio, Dr. Nathanzelisz and colleagues are studying developmental programming (DP) as a response to a specific challenge to the mammalian organism during a critical developmental time window (pregnancy) that alters the trajectory of development with persistent effects on the offspring phenotype. Compelling evidence from human epidemiologic studies and controlled animal (e.g., rodents, sheep) investigations indicate that maternal nutrient reduction (MNR) in pregnancy and during lactation may result in dysfunction of β-cell secretion and peripheral insulin sensitivity leading to type 2 diabetes in offspring. This effort is the first attempt in nonhuman primates to determine the emergence of DP of β-cell function and peripheral insulin resistance as a result of poor maternal nutrition. This study demonstrates, for the first time, that exposure of the developing primate fetus and newborn to moderately reduced nutrient availability during pregnancy and lactation results in DP of both β-cell function and peripheral insulin sensitivity before puberty. These animals are available to other investigators under the NIH resource sharing policy. Human MNR occurs in developed countries in many situations, not just countries affected by famine and food shortage. In 2002, 34.9 million people in the United States lived in households experiencing

food insecurity, compared with 33.6 million in 2001 and 31 million in 1999.

Injectable Candidate Sealants for Fetal Membrane Repair: Bonding and Toxicity in Vitro. At Northwestern University, Dr. Messersmith and colleagues tested injectable surgical sealants that are biocompatible with fetal membranes and that are to be used eventually for the closure of iatrogenic membrane defects. Dermabond (Ethicon Inc, Norderstedt, Germany), Histoacryl (B. Braun GmbH, Tuttlingen, Germany), and Tissucol (Baxter AG, Volketwil, Switzerland) fibrin glue and three types of in situ forming poly(ethylene glycol)-based polymer hydrogels were tested for acute toxicity on direct contact with fetal membranes for 24 hours. For the determination of elution toxicity, extracts of sealants were incubated on amnion cell cultures for 72 hours. Bonding and toxicity were assessed through morphologic and/or biochemical analysis. Extracts of all adhesives were nontoxic for cultured cells. However, only Tissucol and one type of poly(ethylene glycol)-based hydrogel, which is a mussel-mimetic tissue adhesive, showed efficient, nondisruptive, nontoxic bonding to fetal membranes. Mussel-mimetic tissue adhesive applied over membrane defects created with a 3.5-mm trocar accomplished leak-proof closure that withstood membrane stretch in an in vitro model. A synthetic hydrogel-type tissue adhesive that merits further evaluation in vivo emerged as a potential sealing modality for iatrogenic membrane defects. Investigators are currently testing the mechanical qualities of the mussel-inspired sealant and plan to conduct in vivo experiments in animal models. Results from this study will be used to prevent ruptures in the fetal membrane leading to leakage of amniotic fluid and resulting in premature labor or termination of pregnancy. This research is based on pilot funding from the Clinical and Translational Science Award at Northwestern University, which targets new high-risk/high-reward projects that address significant unmet needs with a direct bearing on clinical problems.

Office of Behavioral and Social Sciences Research

Executive Summary

In 1993, the United States Congress established the Office of Behavioral and Social Sciences Research (OBSSR) at the National Institutes of Health (NIH). The office opened in July 1995. NIH already had a long history of supporting health-related behavioral and social sciences research, and the results of this work have contributed significantly to our understanding of the basic underlying mechanisms and treatment of mental and physical health and illness. Establishing an office focused specifically on the behavioral and social contributions to health and well-being enables NIH to leverage existing efforts and develop synergy across multiple Institutes, Centers, and disciplines.

Situated within the Office of the Director's Division of Program Coordination, Planning, and Strategic Initiatives, OBSSR furthers the mission of NIH by emphasizing the critical role that behavioral and social factors play in health, health care, and well-being. With a budget of approximately $27 million, OBSSR serves as the focal point for the coordination and development of policies, goals, and objectives in the behavioral and social sciences at NIH. OBSSR's mission is to (1) integrate a behavioral and social sciences perspective across NIH; (2) disseminate behavioral and social sciences research findings; and (3) provide advice to and communicate with the NIH director, Congress, other Government Agencies, the research community, and the general public on matters regarding behavioral and social sciences research.

OBSSR's leadership is crucial at a time when exciting scientific opportunities, persistent public health needs, and emergent public health challenges face our Nation. The vision of the office is to bring together the biomedical, behavioral, and social science communities to work more collaboratively to solve complex pressing health challenges. Notable areas of research in which OBSSR has led efforts include behavior change, adherence, social and cultural dimensions of health,

community-based participatory research, health literacy, mind-body, mobile and wireless health, and systems science approaches to health. The four core elements of OBSSR's vision for the future are as follows:

(1) *"Next-generation" basic science:* OBSSR supports and facilitates the next generation of basic behavioral and social science research informed by breakthroughs in complementary areas such as genetics, informatics, computer science, measurement, methods, and multilevel analyses.

(2) *Interdisciplinary research:* OBSSR facilitates collaborative research across the full range of disciplines and stakeholders necessary to elucidate the complex determinants of health and health systems challenges. Such collaborations yield new conceptual frameworks, methods, measures, and technologies that speed the improvement of population health.

(3) *Systems-thinking approaches to health:* OBSSR stimulates systems thinking and modeling approaches to research that integrates multiple levels of analysis—from cells to society—required to understand the ways in which individual, contextual, and organizational factors interact over time to determine health status.

(4) *Population impact:* OBSSR works with its NIH partners to identify key problems in population health on which scientists, practitioners, and decisionmakers can work together to accelerate the translation, implementation, dissemination, and adoption of behavioral and social sciences research findings.

Initiatives

Since opening its doors, OBSSR has worked to achieve the goals of its authorizing legislation by effectively highlighting and supporting the scientific opportunities that exist in basic and applied behavioral and social sciences research. OBSSR has been actively addressing its congressional mandate and has encouraged research in the behavioral and social sciences by developing ideas for initiatives and gaining support for them within the NIH community. Although OBSSR does not have grant-making authority, it has been active in organizing and funding (through transfers to NIH Institutes and Centers) a variety of trans-NIH research programs. Therefore, the majority of our contributions to women's health research are in the form of cofunding grants administered by NIH Institutes and Centers.

In 2009, OBSSR cofunded the following 10 grants with a women's health component:

Achieving Energy Balance in Overweight Postpartum Teens (R01-CA121534; PI: Debra Haire-Joshu). The purpose of this research project is to test an intervention designed to reduce overweight in postpartum teens.

Genes, Prenatal Drug Exposure, and Postnatal Environment: An Adoption Study—Bench to Bedside (R01-DA020585; PI: Jenae M. Neiderhiser and Y1OD-9487-01; PI: Brenda LaRochelle). This research project explores how prenatal drug exposure affects early child development.

Preventing Excessive Weight Gain in Adolescent Girls at High Risk for Adult Obesity—Bench to Bedside (R01-DK080906; PI: Debra Tanofsky-Kraff and Y3-CL-9018-01; PI: Jack Yanovski). The purpose of this research project is to test an intervention designed to reduce loss-of-control eating in adolescent girls as a way to prevent obesity in adulthood.

Translating an Evidence-Based Group-Delivered HIV/STD Risk-Reduction Intervention for African-American Adolescent Females (R01-MH070537-S; PI: Ralph J. DiClemente). This project will provide information about the factors influencing translation, adoption, usability, and maintenance of an evidence-based HIV/STD risk-reduction intervention for African-American adolescent females seeking sexual health care via DVD in county health departments.

Trajectories of Drug Abuse in High-Risk Youth (R01-DA019380; PI: Linda A. Teplin). This project aims to examine the dynamic relationship between risk and protective factors for drug use and abuse in youth entering young adulthood from the juvenile justice system.

The Aftermath of Rape on Mental Health (R03-TW007964; PI: Gail Wyatt). The purpose of this study is to explore the short- and

long-term mental health consequences of women in South Africa.

Parental Knowledge and Attitudes of Confidential Sexually Transmitted Infection (STI) Services for Teens (R01-HD053408; PI: Mary Ann Shafer). This multimethod project works with parents to assess their knowledge of STI prevention and treatment in youth to effectively develop tools for programs to increase parental involvement in youth sexual health.

Advancement of Women in Science, Technology, Engineering, Math, and Medicine (STEMM): A Multilevel Research and Action Project (R01-GM088477; PI: Mary L. Carnes). This project aims to assess the role of departmental climate in the rate of women attaining senior levels in the STEMM fields.

In 2009, OBSSR also cofunded a National Academy of Sciences workshop on the science of research with families (N01-OD-4-2139). This workshop was designed to bring together leaders in family research to explore how this science could be strengthened and better integrated.

In 2010, OBSSR cofunded the following eight grants with a women's health component:

Genes, Prenatal Drug Exposure, and Postnatal Environment: An Adoption Study (R01-DA020585; PI: Jenae M. Neiderhiser). This research project explores how prenatal drug exposure affects early child development.

The Aftermath of Rape on Mental Health (R03-TW007964; PI: Gail Wyatt). The purpose of this study is to explore the short- and long-term mental health consequences of women in South Africa.

Neurobiological and Behavioral Consequences of Cocaine Use in Mother/Infant Dyads (P01-DA022446; PI: Josephine Johns). This research project seeks to elucidate neurobiological and biobehavioral consequences of cocaine use (by mothers) and prenatal exposure (in infants) that may underlie poor mother-infant interactions.

Preventing Excessive Weight Gain in Adolescent Girls at High Risk for Adult Obesity—Bench to Bedside (R01-DK080906; PI: Debra Tanofsky-Kraff and Y3-CL-9018-01; PI: Jack Yanovski). The purpose of this research project is to test an intervention designed to reduce loss-of-control eating in adolescent girls as a way to prevent obesity in adulthood.

Advancement of Women in Science, Technology, Engineering, Math, and Medicine (STEMM): A Multilevel Research and Action Project (R01-GM088477; PI: Mary L. Carnes). This project aims to assess the role of departmental climate in the rate of women attaining senior levels in the STEMM fields.

Assessing and Improving Cognitive Measures in the Health and Retirement Study (R43-AG0087137; PI: John J. McArdle). This study will build on a growing evidence base of ways to better assess cognitive abilities and age-related changes (e.g., intelligence) to be used in large-scale population studies.

Developing an Intervention To Prevent Visceral Fat in Premenopausal Women (U01-HL097894; PI: Linda Powell). The purpose of this study is to develop and test an intervention to reduce stress and increase activity in premenopausal women to reduce early cardiovascular risk that has been found to be linked to changes in body composition during the menopause period.

Reading Disabilities in Zambian Children (R01-TW008274; PI: Elena L. Grigorenko). This study examines the development etiology of specific reading disabilities in Zambian children and their siblings.

Flexible Work and Well-Being Center at the University of Minnesota (U01-HD051256; Erin L. Kelly). The purpose of this project is to design, implement, and examine the feasibility of a workplace intervention to improve the health of employees and their families.

Treating Children With Trauma: An Evidence-Based Curriculum (R25-MH084786; PI: M. Katherine Shear). To promote evidenced-based treatment of youth exposed to trauma, this study will explore the effectiveness of teaching empirically validated

methods to graduate students in clinical social work as a part of a standardized curriculum.

Oncofertility Consortium Annual Conference (R13-HD063248; PI: Teresa K. Woodruff). This grant funds a multidisciplinary conference of experts in fertility and cancer. The meeting brings together leading scientists with families facing fertility issues associated with cancer treatment.

Creating a Virtual Clinician Research Tool (R21-DA024262; PI: Geoffrey C. Williams). This project funds the development of an interactive computer program for assessing and intervening with research participants on common health concerns (e.g., high cholesterol) and behaviors (e.g., smoking).

Neighborhood and Family Effects on Disparities in Chronic Diseases (R01-HD058514; PI: Anne R. Pebley). The goal of this study is to significantly advance knowledge about the role of specific family and neighborhood characteristics for observed disparities in the development of chronic diseases, such as asthma and hypertension, and metabolic syndrome.

Examining Human Behavior in Dengue Prevention Efforts in Iquitos, Peru (K01-TW008414; PI: Valerie A. Paz-Soldan). This career development award examines human movement and activity in the transmission and prevention of dengue virus.

In 2010, OBSSR also cofunded the Childhood Community Obesity Study with the National Heart, Lung, and Blood Institute. The study evaluates existing community efforts to reduce local childhood obesity rates in 300 demographically diverse communities across the Nation.

In 2010, OBSSR also cofunded an Institute of Medicine report titled *Lesbian, Gay, Bisexual, and Transgender Health Issues: Research Gaps and Opportunities* (OD-4-2139). The report will investigate the state of the science in the health of lesbian, gay, bisexual, and transgender individuals, including health risks and protective factors, developmental processes (including sexual development), and interactions between the social determinants of health and sexual orientation.

In 2010, OBSSR cofunded a teen dating violence project (OD-0619-01) with the National Institute of Justice to use concept mapping to understand youth conceptualizations of dating relationship characteristics. Hearing the voices of youth is an essential component to developing effective prevention efforts and responses to teen victims of abuse as well as generating meaningful research agendas.

Office of Disease Prevention—Office of Dietary Supplements

Executive Summary

The Office of Dietary Supplements (ODS) was created in 1995 in the Office of Disease Prevention, Office of the Director, National Institutes of Health (NIH), to meet the requirements of the Dietary Supplement Health and Education Act (DSHEA) of 1994. DSHEA defined the purposes and responsibilities of ODS as follows:

Purposes

- To explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care
- To promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions

Responsibilities

- To conduct and coordinate scientific research within NIH relating to dietary supplements and the extent to which the use of dietary supplements can limit or reduce the risk of diseases
- To collect and compile the results of scientific research relating to dietary supplements, including scientific data from foreign sources
- To serve as the principal advisor to the Secretary and to the Assistant Secretary for Health and provide advice to the Director

of NIH, the Director of the Centers for Disease Control and Prevention (CDC), and the Commissioner of the Food and Drug Administration (FDA) on issues relating to dietary supplements. These issues include dietary intake regulations, the safety of dietary supplements, the claims characterizing the relationship between the use of dietary supplements and the prevention of disease or other health conditions and the maintenance of health, and scientific issues arising in connection with the labeling and composition of dietary supplements

- To compile a database of scientific research on dietary supplements and individual nutrients
- To coordinate funding relating to dietary supplements for NIH

Subsequent congressional mandates directed ODS to develop a botanical research center initiative (1999), conduct evidence-based reviews of the efficacy and safety of dietary supplements (2001), and accelerate the validation of analytic methods and reference materials for dietary supplements (2004). ODS developed its mission statement as part of its first strategic planning process in 1998. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

Initiatives

ODS Extramural Investments

ODS's guidelines and criteria for initiating, expanding, or otherwise modifying its extramural investments have reflected DSHEA and congressional mandates. These guidelines are a response to gaps in scientific knowledge, requests for research support from investigators, requests for information, and available resources. ODS extramural investments are categorized into four broad areas: (1) research support, (2) research tools, (3) communications, and (4) science-policy interactions. The Office's key activities are grouped into 15 programs under these 4 areas (see below); these 15 programs capture most of ODS's activities.

The budget allocation for each of the four areas is included in the description of the areas. These budget figures are based on an FT 2008 extramural budget of $22.3 million for grants, contracts, interagency agreements, and workshops. Another $5.2 million covers staff salaries and other expenses associated with ODS administration. Ninety-seven percent of the Office's extramural budget supports research grants and research tools. Communication and science policy efforts rely heavily on investments of ODS staff time and expertise rather than direct funding.

An ODS staff member is responsible for overseeing each of the 15 ODS programs that supports extramural research, and most ODS staff members are active in more than one program. Each program interacts with one or more stakeholder communities, including research investigators; educators and teachers; health practitioners; research and educational institutions; agencies of the Federal Government; dietary supplement, food, and related industries; media; consumer, and public interest groups; and members of the public. The 4r areas and 15 programs are described briefly below.

Area 1: Research Support

Research Grant Portfolio. This portfolio consists of grants administered by NIH Institutes and Centers that receive funding from ODS for research components related to dietary supplements. This investment supports the development of new knowledge on the health effects of dietary supplements.

Botanical Research Centers (BRCs). ODS established six centers in response to a congressional mandate. The Office administers the centers in partnership with the National Center for Complementary and Alternative Medicine. These centers expand the scientific base for botanicals used as dietary supplements.

Training and Career Development. These extramural investments consist primarily of cofunding for selected NIH research training and career grants. These grants enable junior

scientists to develop research programs related to dietary supplements.

Conferences and Workshops. ODS funds research conferences and workshops primarily through NIH grant mechanisms, although it also supports conferences and workshops initiated by NIH. These conferences and workshops bring together key scientists to discuss and define the research needs for various dietary supplements.

Area 2: Research Tools

Analytical Methods and Reference Materials. ODS established this program in response to a congressional mandate and administers it primarily through contracts originated by ODS. Supporting the development of analytic methods and reference materials for dietary supplements has been key to making informative studies of dietary supplements possible.

Population Studies Program. The Population Studies Program focuses on the evaluation of dietary supplement use, including the assessment of biological measures of supplement exposure and associated health effects in nationally representative populations, in order to evaluate nutrients of concern for inadequacy or excess. In collaboration with other Government agencies and academia, the efforts of this program are building our capacity to analyze population data (including economic cost), such as those from the National Health and Nutrition Examination Survey, and will serve as a training environment for postdoctoral fellows.

Surveys of Dietary Supplement Use. ODS provides intellectual and financial support to Federal agencies conducting national nutritional surveys that include use of dietary supplements.

Dietary Supplement Databases. ODS provides intellectual and financial support and leadership to Federal agencies that are establishing databases to enable the interpretation of survey data on public nutrition habits and use of dietary supplements. ODS and its Federal partners at the United States Department of Agriculture , CDC, National Library of Medicine, and FDA have created a dataset of dietary supplement ingredients and are developing a comprehensive database of information on supplement labels.

Evidence-Based Reviews. In response to encouragement from Congress, ODS provides intellectual and financial support, primarily to the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, to conduct reviews that are critical to determining the research needs for selected dietary supplements. These reviews are published on the AHRQ Web site and in peer-reviewed journals. Evidence-based reviews are key to identifying the status of scientifically validated knowledge about dietary supplements and the important gaps in research.

Area 3: Communications

Communications. ODS's communication activities include a broad spectrum of outreach activities, such as the ODS Web site, exhibits, and public information pieces related to dietary supplements.

Computer Access to Research on Dietary Supplements (CARDS). ODS developed this consumer-friendly, Internet-based database in response to the DSHEA mandate to compile a database of scientific research on dietary supplements. CARDS contains information on federally funded research projects pertaining to dietary supplements.

International Bibliographic Information on Dietary Supplements (IBIDS). ODS developed this consumer-friendly, Internet-based database in response to the DSHEA mandate to collect and compile the results of scientific research related to dietary supplements. IBIDS provides access to bibliographic citations and abstracts from published, international, and scientific literature on dietary supplements.

Federal Dietary Supplement Working Group. ODS established the Federal Dietary Supplement Working Group in 2005 to share information and discuss issues related to dietary supplements among Federal agencies.

Area 4: Science-Policy Interactions

These programs reflect the philosophy that good policy is founded on good science. ODS furnishes expertise in nutritional sciences to address public health issues related to dietary supplements.

Vitamin D Initiative. This initiative is an evolving partnership with NIH Institutes and Centers and other Federal agencies through the Vitamin D Federal Working Group to address the research gaps related to vitamin D.

Folate Initiative. Through this initiative, ODS and other Federal partners are examining the efficacy and safety of the folic acid fortification program in the United States.

Dietary Supplement Use in the Military. This partnership with the Department of Defense is evaluating the impact of dietary supplement use by military personnel.

Dietary Reference Intakes. ODS supports Federal programs to evaluate the reference standards for intakes of nutrients, including vitamins and minerals.

ODS Strategic Plan

Goal 1: Provide intellectual leadership by fostering research to analyze and evaluate the role of dietary supplements in promoting health and reducing the risk of disease.

Goal 2: Expand the general scientific knowledge base on dietary supplements by funding new research and training.

Goal 3: Support the development of research tools for the study of dietary supplements.

Goal 4: Make the most up-to-date scientific knowledge about dietary supplements publicly available.

Grant Funding—Research on Women's Health

Fiscal Year 2009: $3,117,721

- Botanical Dietary Supplements for Women's Health
- Prevention of Postprandial Hypoglycemia Using n-3/n-6 PUFA in PCOS
- Ginkgo Biloba Prevention Trial in Older Individuals
- Does EPA or DHA Prevent Depressive Symptoms in Pregnancy and Postpartum?
- Training in Maternal and Child Nutrition
- VITamin D and omega-3 triaL (VITAL)
- DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women
- In Utero Smoke, Vitamin C, and Newborn Lung Function
- Determination of RDA for Vitamin D in Caucasian and African-American Women
- Dietary and Serum Phytoestrogens and Women's Health Conditions in Midlife
- Nutritional Regulation of Bone
- Building Interdisciplinary Research Careers in Women's Health (BIRCWH)
- BIRCWH Program at the University of California, Davis
- Folic Acid and B Vitamins To Prevent Fracture in Women
- Impact of a Protein Supplement on Bone Mass in Older Women DHA Supplementation and Pregnancy Outcome
- Prenatal Iron Supplements: Safety and Efficacy in Tanzania
- BIRCWH Program at Tulane University

Fiscal Year 2010: $2,791,333

- Botanical Dietary Supplements for Women's Health
- Identification of Natural Product Inhibitors of Breast Cancer Bone Metastasis
- Botanical Estrogens: Mechanisms, Dose, and Target Tissues
- Probiotics and Bone Health: Role of Gender and Intestinal Health
- Does EPA or DHA Prevent Depressive Symptoms in Pregnancy and Postpartum?
- VITamin D and omega-3 triaL (VITAL)
- Dietary and Serum Phytoestrogens and Women's Health Conditions in Midlife

- DHA Supplementation and Pregnancy Outcomes
- Prenatal Iron Supplements: Safety and Efficacy in Tanzania
- BIRCWH Program at Tulane University. The BIRCWH program is an ORWH-funded innovative interdisciplinary career and research development initiative.
- BIRCWH Training Grant at Duke/North Carolina Central University
- BIRCWH Training Grant at University of California, Davis
- Training in Maternal and Child Nutrition/ Cornell University

Office of Strategic Coordination

Executive Summary

The Common Fund supports a series of exceptionally high-impact trans-National Institutes of Health (NIH) programs. These programs are designed to pursue major opportunities and gaps in biomedical research that no single NIH Institute or Center could tackle alone but that the agency as a whole can address to make the biggest impact possible on the progress of medical research. The Common Fund is managed by the Office of Strategic Coordination, part of the Division of Program Coordination, Planning, and Strategic Initiatives in the Office of the Director. In 2010, the Common Fund launched a new global health program. As part of this program, it funded eight awards in the Medical Education Partnership Initiative (MEPI).

The intent of MEPI is to develop and strengthen models of medical education and build research and clinical capacity in countries of sub-Saharan Africa that are part of the President's Emergency Plan for AIDS Relief (PEPFAR). MEPI will receive $130 million over 5 years awarded directly to African institutions in a dozen countries, working in partnership with U.S. medical schools and universities. The Office of the U.S. Global AIDS Coordinator at the Department of State has provided the majority of funds in support of PEPFAR's goals to train and retain new health care workers and improve the capacity of partner countries to deliver primary health care. The Common Fund projects totaling $15 million leverage PEPFAR resources and provide support for research and education in noncommunicable diseases, including three awards on maternal-child health.

There are 20 MEPI awards in total. One award is to a coordinating center to provide a platform for networking, technical assistance, and evaluation of the overall initiative. Eleven awards support PEPFAR goals and are funded by PEPFAR and the NIH Office of AIDS Research with additional support provided by NIH's National Human Genome Research Institute, National Institute of Nursing Research, and Office of Research on Women's Health (ORWH), which has contributed funds to six awards. These awards are being managed either by the John E. Fogarty International Center or by the Health Resources and Services Administration. The eight Common Fund awards in noncommunicable diseases received additional support from NIH's National Heart, Lung and Blood Institute, National Institute of Mental Health, and National Institute of Neurological Disorders and Stroke. The Common Fund awards are being managed by FIC. A total of 45 percent of all awards propose strategies to increase the number of women clinicians and researchers.

Accomplishments

The goal of MEPI is to develop and strengthen models of medical education and build research and clinical capacity in countries of sub-Saharan Africa that are part of PEPFAR. MEPI was just funded at the end of fiscal year 2010. The Common Fund awards in maternal and child health were given to (1) the University of Nairobi to establish a center of excellence in maternal, newborn, and child health; (2) the University of Zambia to enhance obstetric and neonatal care specialty training at a tertiary care facility in Zambia, which has one of the highest infant mortality rates in the world, and to determine the impact on population outcomes; and (3) the Eduardo Mondlane University to develop strategies for building sustainable surgical capacity in the

rural areas of Mozambique and to address surgical interventions required for safe deliveries and other emergency medical needs. It is significant that the MEPI awards were given directly to African institutions instead of to their U.S. collaborators. MEPI constitutes an extensive network of African institutions plus collaborators from the United States and other countries, and it is likely that future NIH global health initiatives will be able to leverage resources established through this initiative.

Initiative

Medical Education Partnership Initiative (MEPI) RFA. RFA-TW-10-008. The strategy of this initiative is to build human capacity for health in Africa by strengthening the medical education system in an environment that values and nurtures research and that will contribute to the sustainability and quality of the overall effort. This initiative was cofunded by ORWH.

Career Development

Though there were not any specific initiatives on women's career development, a total of 45 percent of all MEPI awards propose strategies to increase the number of women clinicians and researchers.

APPENDIX A

Ad Hoc Research Subcommittee of the NIH Coordinating Committee on Research on Women's Health

Elaine Collier, M.D., FACP, *Chair*
Assistant Director for Clinical Research
National Center for Research Resources

Subcommittee Members

Carolyn Deal, Ph.D.
Chief, Sexually Transmitted Diseases Branch
National Institute of Allergy and Infectious Diseases

Patrice Desvigne-Nickens, M.D.
Medical Officer
National Heart, Lung, and Blood Institute

Eleanor F. Hoff, Ph.D.
Science Policy Analyst
National Institute of Diabetes and Digestive and Kidney Diseases

Karen A. Johnson, M.D., Ph.D., M.P.H.
Program Director
National Cancer Institute
(Deceased August 2010)

Sooja Kim, Ph.D.
Chief, Endocrinology, Metabolism, Nutrition and Reproductive Sciences Integrated Review Group
Center for Scientific Review

Patricia L. Mabry, Ph.D.
Senior Advisor
Office of Behavioral and Social Sciences Research

Pamela Marino, Ph.D.
Program Director
National Institute of General Medical Sciences

Mary Frances Picciano, Ph.D.
Senior Nutrition Research Scientist
Office of Dietary Supplements
(Deceased August 2010)

Cora Lee Wetherington, Ph.D.
Women and Gender Research Coordinator
National Institute of Drug Abuse

ORWH Liaisons

Lisa Begg, Dr.P.H., RN
Director of Research Programs

Indira Jevaji, M.D.
Medical Officer

APPENDIX B

ORWH-Cofunded Research Summaries, FY 2009

Adolescent Health

Title: **The National Longitudinal Study of Adolescent Health (Add Health)**
P.I.: **Kathleen Mullan Harris**
Institution: **University of North Carolina, Chapel Hill**
Grant No.: **5P01HD031921-14**
Award: **$200,000**

Add Health is currently funded for Wave IV data collection. At the time the project began in 1994-1995, investigators selected a nationally representative sample of adolescents in grades 7 through 12. Participants have been followed through adolescence and the transition to adulthood with three in-home interviews. Wave IV will include additional information that encompasses social, behavioral, and biological data. In addition to data contributed in earlier surveys, these subjects, who are now between the ages of 23 and 31 years, will provide biological data to capture the prevailing health concerns as well as biological markers of future chronic health conditions.

Aging

Title: **National Social Life, Health, and Aging Project**
P.I.: **Linda J. Waite**
Institution: **National Opinion Research Center, Chicago, IL**
Grant No.: **5R37AG030481-02**
Award: **$200,000**

The National Social Life, Health and Aging Project (NSHAP) was established as an innovative, high-quality dataset for use by researchers studying the relationships between social processes and health among older adults. Wave I obtained questionnaire and biomeasure data on a nationally representative sample of 3,005 community-dwelling adults ages 57–85 in 2005–2006. The second wave in NSHAP is designed to obtain data on social networks and social support, marital and co-habitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. They propose to revisit respondents four years after their initial interview. Using these data, they can describe and model the distribution of changes in health, well-being, social networks, social participation and social context. In each case, they shall examine the distributions both for the entire sample and within subgroups defined by key sociodemographic characteristics such as gender, race/ethnicity, and socioeconomic status. They also propose to augment the sample by interviewing the spouse/cohabitating romantic partner. These data will allow us to characterize the impact of marital and romantic relationships on health by examining the effects of one person's characteristics and behaviors on the health of the other. They will also analyze the partnerships themselves, and assess the relationship between characteristics of the partnership, such as support, closeness and mistreatment, and the health of each of the partners. In sum, they will explore their overarching hypothesis that older adults with strong functioning intimate relationships

will show more positive (or less negative) health trajectories than those who have weaker relationships or lack such relationships altogether. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age.

Title: **Teaching Resourcefulness to Women Caregivers of Elders with Dementia**
P.I.: **Jaclene Zauszniewski**
Institution: **Case Western Reserve University, Cleveland, OH**
Grant No.: **1R21NR010368-01A2**
Award: **$200,000**

Dementia is one of the greatest challenges facing elders in the United States and the public health significance of dementia caregiving has permeated the scientific and lay literature for decades. Despite the number of clinical trials testing interventions for reducing caregiver stress, none have tested methods of teaching them resourcefulness skills and none have allowed caregivers (CGs) to choose a preferred intervention. Resourcefulness Training (RT), the intervention to be tested in this study, is a cost-effective, easy-to-use method for reducing caregiver stress and promoting their optimal mental health. The RT intervention has strong theoretical grounding and there is beginning empirical evidence for its effectiveness in reducing stress, minimizing depressive symptoms, and promoting optimal quality of life for populations other than women dementia CGs. The proposed 2-year pilot study will provide qualitative and quantitative data for determining the necessity, acceptability, feasibility, fidelity, safety, and effectiveness of two innovatively designed methods of RT within the context of a small partially randomized preference trial with 120 women dementia CGs. In RT, the two methods to be tested, expressive writing (EW) and verbal disclosure (VD), are used for practicing and reinforcing resourcefulness skills. However, because research has shown that both EW and VD may be effective stress-reducing techniques, they will also examine those effects without RT. They propose that RT reinforced by EW or VD will provide CGs with essential skills for managing stress and preserving mental and physical health while providing care for their elderly care recipients (CRs). Quantitative data on measures of stress, cognitions, emotions, resourcefulness, and mental and physical health will be collected at baseline (T1) and at 1 week (T2) and 6 weeks (T3) post-intervention. Qualitative data will be obtained from CG journal (EW) and recordings (VD), data collector's field notes, followup logs, etc. Baseline Resourcefulness Scale (RS) scores and qualitative data from journals and recordings will be used to examine the necessity of the RT. CGs will be randomized into "random" or "choice" conditions and their data (i.e., journals, recordings, field notes, followup logs, participation and retention logs) will be examined to determine acceptability, feasibility, and fidelity of RT. Safety of RT will be monitored for adverse events and reports of psychological distress or elder abuse. Effectiveness of RT-EW and RT-VD (compared to EW and VD without RT) will be examined in relation to specific outcomes at time intervals suggested by resourcefulness theory and in relation to factors within the CG, CR, and CG situation. Most importantly, they will learn whether giving CGs a choice of EW or VD with or without RT improves their outcomes. Conclusions drawn from the critical examination of the six intervention parameters will inform further refinement and testing of RT for dementia CGs in a full-scale randomized, controlled trial. Once established, such interventions will be useful in promoting optimal, healthy functioning among dementia CGs so that they can continue to provide adequate care for their CRs without sacrificing their own health and while avoiding placement of the elder in a long-term care facility.

Alcohol and Other Substance Abuse

Title: **Sex Differences in Vulnerability to Cocaine Addiction**
P.I.: **Therese A. Kosten**
Institution: **Baylor College of Medicine, Houston, TX**
Grant No.: **5R21DA020117-02**
Award: **$20,000**

Understanding sex differences in the initiation to addiction is an important goal that needs to be addressed. The study proposes a novel yet hypothesis-based approach to examine sex differences in stress responsivity and addiction using established animal procedures. Stress responsivity relates to acquisition of cocaine self-administration, an animal model of vulnerability to addiction. Stress responsivity shows sex differences but reports on self-administration are conflicting. Links between maternal care and stress responsivity of offspring are proposed; greater care relates to lower stress responsivity of adults. Maternal care differs by pup sex; male pups receive more care than female pups. Adult males show lower stress responsivity than females consistent with the link of maternal care with stress responsivity. The proposal hypothesizes that sex-dependent maternal care influences sex differences in stress responsivity and cocaine self-administration in the adult. The investigators will test this by manipulating maternal care via altering litter gender composition (LGC; single- vs mixed-sex litters) because pups of single-sex litters receive more care than pups of mixed-sex litters. LGC influences stress responsivity in infant mice and juvenile and maternal behaviors in rats and mice. They predict both male and female adult rats of single-sex litters will show lower stress responsivity than offspring of mixed-sex litters.

Title: **Interactive Effects of Ethanol and Estrogen on Brain Vasopressin during Puberty**
P.I.: **Toni R. Pak**
Institution: **Loyola University Chicago, IL**
Grant No.: **1R21AA018398-01**
Award: **$224,250**

Women who abuse alcohol are twice as likely to develop anxiety disorders compared with men, a phenomenon in which the underlying biological mechanisms are unknown. Their overall objective is to identify the interactive effects of alcohol and estrogen on arginine vasopressin (AVP), a well-established key molecular mediator of anxiety, in order to elucidate the molecular mechanisms predisposing women to increased risk of anxiety disorders. Adolescent binge drinking is a potential risk factor for the development of adult anxiety disorders due to the heightened stress reactivity that occurs as a direct result of increased circulating estrogens during pubertal development. Little is known about the long-term neurobiological consequences of alcohol consumption during puberty, which is a dynamic and important period of brain development that involves changes in cortical gray matter, synaptic connectivity, and increased neurogenesis. Exposure of alcohol during this critical period of extensive brain remodeling may result in permanent neuronal damage or disruptions in the formation of new neuronal connections, which might manifest as adult behavioral psychoses, including anxiety disorder. Their preliminary data show that (1) alcohol exposure during puberty increased AVP gene expression in specific regions of the brain. Therefore, the experiments proposed in Specific Aim 1 will directly test the hypotheses that there is a critical window of time during pubertal development when the AVP system is most vulnerable to the effects of alcohol and (2) that estrogen exacerbates the effects of alcohol on AVP gene expression. Also, their preliminary data demonstrates that alcohol treatment and estrogen receptor ligands increased AVP gene expression in neuronal cells derived from the hypothalamus, and gene expression is closely correlated with the activity of the gene promoter. Alcohol also activates estrogen-signaling

pathways in the brain, which suggests that the underlying mechanisms for alcohol-induced changes in AVP may be mediated by estrogen signaling pathways. Therefore, the experiments proposed in Specific Aim 2 will directly test the hypotheses that (1) acute alcohol exposure increases AVP promoter activity in neuronal cells, (2) that there are specific regulatory regions of the AVP promoter that interact with alcohol, and (3) that estrogen and alcohol interact synergistically to increase AVP promoter activity. To date, specific molecular and neuroendocrine markers that are activated by alcohol during puberty have not been identified. This proposal is focused on a specific candidate gene (AVP) and its downstream signaling pathways that are developmentally shaped during puberty. They expect these studies to show that AVP is permanently altered, either as a direct target for alcohol or indirectly through steroid hormone receptor signaling pathways. Thus, the value of this research lies in the potential for therapeutic approaches that would target specific genes and perhaps reverse brain damage caused by alcohol consumption during pubertal development as well as strengthen reasons for abstaining from alcohol during that time.

Title: **An Ethnographic and Economic Investigation of the Fresh Start Program (Detroit)**
P.I.: **Juliette Kathryn Roddy**
Institution: **University of Michigan at Dearborn**
Grant No.: **1R21DA027145-01**
Award: **$270,375**

Aside from journalistic accounts detailing the pitfalls of drug treatment, little research has been done on the recovery process as it actually proceeds within particular programs. Research is not always well incorporated into treatment settings, which may resist innovations due to internal organizational factors. Conducting research in criminal justice settings, including drug courts or programs administered through drug courts, is also problematic. Nonetheless, more such research is needed as treatment and recovery services become central features of the national response to substance abuse, especially in an era of prison downsizing. This will also require research that actively engages with communities and institutions. The proposed research will work collaboratively with multiple agencies to investigate the process of treatment and recovery as it occurs in women who participate in Fresh Start. Fresh Start is a substance abuse intervention program for female street sex workers who have come into repeated contact with law enforcement. Fresh Start is a coercive recovery-based program that serves as a direct contrast to voluntary, traditional, treatment-based programs. The program serves as an alternative to jail time for these women, who are arrested in periodic sweeps of neighborhoods where street prostitution is common. Using interdisciplinary methods, they will seek evidence of desired change in social networks, sociospatial contexts, and economic behaviors, resources and outcomes. Treatment professionals and substance abuse researchers agree that both successful drug abuse recovery and exiting street prostitution require changes in social networks and accompanying economic independence. The significance of the application is that these changes can be both quantitatively and qualitatively described by studying street prostitutes who are engaged in the treatment and recovery process through the application of ethnographic and economic instruments and an accompanying mapping of changing social networks. The proposed work has implications for women's health and welfare and the prevention and treatment of sexually transmitted disease.

Cancer

Title: Pharmacogenetics Research Network and Knowledge Base
P.I.: David Alastair Flockhart
Institution: Indiana University-Purdue; University at Indianapolis
Grant No.: 5U01GM061373-10
Award: $230,171

Drugs that interfere with the actions of estrogen represent a cornerstone in the treatment of breast cancer, and are important tools with which to study the actions of estrogen in women. These drugs are increasingly effective in breast cancer, but which drug is best for each woman remains unclear. Their work in the first cycle of the Pharmacogenetics Research Network identified, through a series of laboratory and clinical studies, new genetic patterns that predict effects of the estrogen receptor modulator tamoxifen. They will build on these data to examine the influence of an extended series of candidate genes on the effects of the aromatase inhibitor class of drugs and to refine the genetic signatures that predict tamoxifen effects. This will involve the following broad Specific Aims: (1) to identify common genetic variants of the human estrogen receptors and important nuclear coactivators and repressors of these receptors using a combined bioinformatic and direct sequencing approach; (2) to test the hypothesis that these variants alter gene expression or function using in vitro assays; (3) to test the contribution of variants identified during Specific Aim 1 and 2 to tamoxifen response in the clinical trial of tamoxifen pharmacogenetics already conducted. (4) to characterize the involvement of genetically polymorphic drug metabolizing enzymes in the human metabolism of the available aromatase inhibitors: letrozole, exemestane and anastrozole in vitro. (5) to test the hypothesis that variants in candidate genes identified in aims 1–4 are associated with well curated phenotypic outcomes, including estrogen metabolite concentrations, pharmacokinetics, hot flashes, breast density, bone metabolism and serum lipid subfractions in breast cancer patients receiving anastrozole, exemestane and letrozole. The results of this proposal will generate new information that, linked with their novel tamoxifen pharmacogenetics findings, will generate a series of genetic tools key to optimizing drug selection for women with breast cancer and to their understanding of the mechanisms of estrogen action.

Title: Novel Ovarian Cancer Detection Agents from Phage Display
P.I.: Susan L. Deutscher
Institution: University of Missouri-Columbia
Grant No.: 5R21CA134960-02
Award: $20,000

Ovarian adenocarcinomas are the largest class of gynecologic malignancies in the United States with respect to incidence and mortality. While treatable in their earliest stage, advanced or metastatic forms of ovarian cancer are usually deadly. Because ovarian cancer is often asymptomatic in its early stages, ~70 percent of patients have advanced or metastatic disease at time of diagnosis. Current screening methods include ultrasonography, pelvic exam, and serum screening for CA125. Unfortunately, these tests are not specific for ovarian cancer and invasive surgical biopsy is required for proper diagnosis. Improved early diagnosis and therapy will result from a more directed approach in which antigens specific to or overexpressed on ovarian tumor cells are targeted. New peptide-based molecular probes to facilitate cancer detection and imaging are rapidly evolving due to implementation of bacteriophage (phage) display approaches. Here, it is hypothesized that phage selected in vivo, in human ovarian tumor-bearing mice, once fluorescently labeled, can be easily re-screened in vivo for tumor-homing propensity, thus streamlining the process of development of peptide-based ovarian cancer imaging and therapeutic agents. Radiolabeled versions of the identified peptides will be examined for their ability to image ovarian tumors in mice using Single Photon Emission

Computed Tomography (SPECT). A long-term goal of this work is to translate the radiolabeled peptides into the clinic for the non-invasive screening and detection of ovarian cancer. Specifically, the study proposes to obtain new classes of ovarian cancer targeting peptides by performing in vivo phage display selections in human ovarian carcinoma-bearing mice. Second, phage selected from the screens will be fluorescently labeled and employed in in vivo optical imaging screens to expedite discovery of new ovarian tumor imaging agents. Last, peptides corresponding to phage with optimal in vivo imaging properties will be synthesized and radiolabeled with 111In and 99mTc and examined for their SPECT imaging efficacy in vivo. Novel phage display and peptide radiochemistry approaches are described to advance the detection of ovarian cancer, a cancer that deserves much more research and attention.

Title: **Exploratory Studies on the Anti-Breast Cancer Function of Bamboo Extract**
P.I.: **Jun Panee**
Institution: **University of Hawaii**
Grant No.: **1R21AT005139-01**
Award: **$191,874**

Breast cancer is the most common cancer among American women, and existing treatments are expensive, debilitating, and extremely arduous for its victims, and often have long-lasting adverse effects. This project aims to explore the anti-breast cancer function of an ethanol/water extract from bamboo, *Phyllostachys edulis*, one of the most widely distributed and fastest growing plants in the world. The long-term goal of this study is to develop this bamboo extract into a safe, efficient, low cost, and easily accessible dietary supplement for chemoprevention of breast cancer in high-risk populations, such as people carrying mutations of breast cancer susceptibility gene 1 (BRCA1). DNA damage induced by chemical exposure and oxidative stress, as well as estrogenic regulation of mammary gland differentiation and tumor growth are among the critical factors affecting the incidence and development of breast cancer. Research carried out in the laboratory of the principal investigator focused on the anti-breast cancer function of an ethanol/water extract from bamboo *Phyllostachys edulis*. The preliminary studies revealed that bamboo extract (BEX) contained a high level of flavonoids, and significantly enhanced the resistance of mammalian cells to varied oxidative stresses. BEX as a dietary supplement (0.5 percent, w/w) delayed the onset of palpable mammary tumors induced by 7,12-dimethylbenz[a]anthracene (DMBA) in female Sprague-Dawley (SD) rats, decreased the tumor incidence by 44 percent, and dramatically reduced tumor multiplicity. BEX supplementation also enhanced the activity of sulfotransferases (SULT) in the liver, an enzyme family that conjugates estrogens. The preliminary results indicate that BEX may affect the functions of multiple tissues that synergistically lead to the anti-breast cancer effect. This project will examine the hypothesis under two Specific Aims. Aim 1: To investigate BEX-induced changes in mammary tumors. Magnetic Resonance Imaging (MRI) techniques will be employed in this study to closely monitor the starting time and accurately measure the growth rate of the micro-tumors in the mammary glands before they would be perceptible by the regular palpation method; thereby efficiently evaluating the inhibitory effects of BEX on the initiation and early-stage promotion of the mammary tumor. The gene expression of key factors in cellular senescence, proliferation and apoptosis pathways, and oxidative stress damage on DNA and proteins in the tumor tissues will be assessed at different developmental stages to reveal BEX-induced changes on the molecular levels. Aim 2: To investigate BEX-induced changes in both mammary glands and the liver that favor breast cancer prevention. These include: (i) inhibition on the carcinogenic effects of DMBA through: (a) regulation of the metabolism of DMBA in the liver and mammary tissues and (b) amelioration of DMBA-induced oxidative stress in the mammary glands; (ii) enhancement of estrogen metabolism through up-regulation of SULT activity in the liver; and (iii) acceleration of mammary gland

differentiation through its potential phytoestrogenic activity. Successful performance of this project will direct more focused research into the cellular and molecular pathways, the major target tissues, and the critical time periods through which BEX exerts the anti-breast cancer function. This will lay a firm basis for the principal investigator to achieve the long-term goal of characterizing the potentially novel anti-breast cancer compound(s) in BEX, improving the efficiency of the product, and eventually applying this abundant, easily available and sustainable natural resource in the chemoprevention of breast cancer in human subjects.

Title: **Mitochondrial Catalase as a Treatment for Metastatic Breast Cancer**
P.I.: **Warren C. Ladiges**
Institution: **University of Washington, Seattle**
Grant No.: **1R21CA140916-01**
Award: **$171,600**

The chance of developing invasive breast cancer during a woman's lifetime is approximately one in eight and more than 40,000 women die of metastatic disease each year. Inherent or acquired tumor drug resistance and dose-limiting toxicity limit many agents used in the treatment of invasive breast cancer. Therefore, an important goal is the development of novel nontoxic therapeutic agents that are active against this deadly disease. Based on preliminary data that showed mitochondrial catalase (mCAT) reduces metastatic progression of primary breast cancer in mice, suggesting that targeting mitochondria with catalase could be a potential strategy to treat or prevent metastatic breast cancer in women. The data generated in this proposal would confirm their preliminary observations and provide the rationale for developing and/or testing clinically relevant mitochondrial-specific drug delivery systems for treating metastatic breast cancer. The significance of this project is that it is designed to determine the ability of mitochondrially targeted catalase to suppress metastatic breast cancer in mice.

Title: **Gender Selectivity to Colon Cancer Chemoprevention by NSAIDs**
P.I.: **Hemant K. Roy, Ramesh K. Wali**
Institution: **Evanston Northwestern Healthcare, Evanston, IL**
Grant No.: **1R21CA141112-01**
Award: **$201,300**

Colorectal cancer (CRC) is the second leading cause of cancer deaths among Americans. With proper screening and removal of adenomatous polyps, CRC risk reduction has been very promising. However, only ~50 percent of the at-risk population (age >50) receives any sort of screening and many undergo tests with suboptimal sensitivity. This underscores the need for developing alternate cancer prevention strategies such as chemoprevention. Of the myriad of purported agents, nonsteroidal anti-inflammatory drugs (NSAIDs) have reliably shown a positive outcome. Indeed, epidemiological, experimental, and clinical trials unequivocally point to the CRC preventive benefits of NSAIDs. However, the efficacy is relatively modest (30–50 percent risk reduction) and requires more than a decade to show significant benefits. In addition, the use of NSAIDs has been shown linked to severe side-effects including ulcers, gastrointestinal bleeding, hemorrhagic strokes etc., thereby cautioning that the risks may outweigh the benefits of aspirin and NSAIDs in preventing CRC for average risk use. To improve the risk-benefit analysis, it is therefore critical to selectively target subjects that can efficiently respond to chemopreventive efficacy of NSAIDs and at the same time leave out the population least likely to benefit. It is conceivable that responsive patients could be targeted with lower efficacious doses to avoid associated toxicity. Gender is an important risk factor for CRC with women frequently having biological differences (higher prevalence of proximal lesions, DNA mismatch repair deficient tumors etc.). Estrogen is a well-accepted chemopreventive agent

against CRC. Moreover, the investigators reported that women have altered susceptibility to both genetic and environmental CRC risk factors. The epidemiological data has some studies suggesting an improved chemopreventive response to NSAIDs although there are discordant reports in the literature. Thus, the issue of whether women are more sensitive to NSAID chemoprevention is unresolved with the possibility that NSAID type, dose, etc. may play a role. The investigators recently conducted a chemoprevention trial using the NSAID celecoxib in a well-validated model of intestinal tumorigenesis, the MIN mouse and noted that in this model, females were more responsive to the chemopreventive effects of celecoxib. The chemopreventive response was found to have regional propensity with stronger efficacy in the proximal intestine. Furthermore, celecoxib treated female mice had higher levels of mucosal estrogen receptor-2 (ER2) levels. The significance of the application is that the proposed studies will address the role of estrogen in gender selective chemopreventive efficacy of NSAIDs. These findings will have an important bearing on the healthcare recommendations for colon cancer chemoprevention which have to be cognizant of this gender selective efficacy for maximum cost-benefit potential of NSAIDs.

Title: **Antagonism of the Ah Receptor in Controlling Breast Cancer Growth and Invasion**
P.I.: **Jennifer J. Schlezinger**
Institution: **Boston University Medical Campus, MA**
Grant No.: **1R21CA134882-01A1**
Award: **$214,500**

Historically, the aryl hydrocarbon receptor (AhR) has been studied for its transcriptional regulation of genes encoding cytochrome P450 enzymes, which metabolize environmental and endogenous substrates into toxic and mutagenic intermediates. Accumulating studies support the hypothesis that the AhR also plays an important role in malignant epithelial cell growth and invasion apart from its role in formation of mutagens and in the absence of environmental chemicals. This new paradigm is based on several key observations: (1) AhR expression is increased dramatically in carcinogen-induced rat and mouse mammary tumors and in "spontaneous" human mammary tumor lines; (2) constitutive AhR activation is indicated by nuclear AhR localization in rat, mouse, and human mammary tumors and by AhR binding to gene promoters in the absence of environmental chemicals; (3) Constitutively active AhR regulates the expression of multiple genes, including CYP1B1, CK21, and Slug, a master regulator of tumor invasion; (4) Recent studies suggest that increased AhR activity in mammary tumors also contributes to cell migration and invasiveness; (5) Molecular downregulation of the AhR suppresses breast cancer cell proliferation and reverts cells to a non-aggressive phenotype. Molecular and biologic strategies have provided significant evidence that the AhR participates, beyond mutagenesis, in multiple mechanisms that contribute to tumor formation, growth, and invasion. Therefore, the proposal has the ability to examine effects of constitutively active AhR to determine how chemical antagonism of the AhR may translate into breast cancer prevention or a therapeutic approach to suppress tumor progression. The translational impact of these studies lies in the ability of known and newly identified antagonists to suppress tumor growth and invasion. Here, potentially therapeutic AhR antagonists will be evaluated for their ability to block the biological outcomes of constitutive AhR activity in human mammary tumor cell lines. Collectively, these studies will provide the foundation for preclinical studies on the potential for potent AhR antagonists to prevent and/or treat breast cancer in vivo. The significance of the application is that the study hypothesizes that the hyper-expression of a protein, called the aryl hydrocarbon receptor, and its binding to DNA contributes to the growth and progression of breast tumors. The applicants propose that chemicals that impede the function of this receptor (i.e., antagonists) will be effective at downregulating this protein's activity and therefore will suppress breast tumor growth and metastasis. Screening of plant and

marine natural product libraries will provide a source of novel antagonists that can be tested for their interaction with this receptor and their mechanism of interference with tumor growth, ultimately resulting in the development of therapeutic agents for the treatment of breast cancer.

Title: **Costa Rica HPV-16/18 Vaccine Trial**
P.I.: **Allan Hildesheim**
Institution: **National Cancer Institute, Bethesda, MD**
Grant No.: **N01CP11005**
Award: **$400,000**

The ORWH has supported infrastructure costs associated with the Costa Rica HPV Vaccine Trial (CVT) since its inception. In FY09, support in the amount of $400,000 was provided. These funds were utilized to support continued followup and clinical management of the 7,466 women enrolled in this community-based, randomized, phase III clinical trial and for the enrollment of participants into the extended followup phase of the trial (planned for an additional 6 years beyond the initial, 4-year blinded phase). More specifically, funds provided by ORWH in FY09 supported the following activities: (1) continued blinded followup screening of trial participants; (2) referral of participants with evidence of high-grade disease to colposcopy and treatment; (3) initiation of 4-year study visits (final visit under the blinded design—approximately 2,000 such visits of expected total of 7,000 were performed in FY09); (4) consenting of women into their long-term followup study (approximately 2,000 women of expected total of 7,000) were consented in FY09; (5) initiation of recruitment of new control group for the long-term followup study (approximately 700 women of expected total of 3,000) were recruited in FY09; and (6) additional collection of specimens from the vulva, anus, and oral cavity to allow for the evaluation of vaccine efficacy at sites other than the cervix. The activities funded by ORWH in FY09 and preceding years have resulted in several important publications in the peer-reviewed literature. These are included in the attached reference list.

Title: **Evaluation of Vaccine Efficacy at Extracervical Sites in the Costa Rica HPV-16/18 Vaccine Trial**
P.I.: **Aimee Kreimer, Allan Hildesheim**
Institution: **National Cancer Institute, Bethesda, MD**
Grant No.: **N02CP31003**
Award: **$700,000**

The ORWH has supported infrastructure costs associated with the Costa Rica HPV Vaccine Trial (CVT) since its inception. In FY09, additional one-shot funds in the amount of $700,000 were provided to this project to allow for the evaluation of the efficacy of the bivalent HPV-16/18 vaccine to protect against HPV-16/18 infection at cutaneous and mucosal sites other than the cervix. Since the HPV-16/18 vaccine has shown near complete protection against HPV-16/18 infection at the cervix, it has been suggested that HPV-16/18 vaccination might also protect against infections at other body sites. In specific, the present effort in Costa Rica will evaluate efficacy of the HPV-16/18 to protect against infections at the anus, vulva and oral cavity. It should be noted that this evaluation is of clinical relevance because infection with oncogenic HPV types, particularly HPV-16, have been linked to the development of cancers at all three of these extra-cervical sites. The funds provided by ORWH in FY09 are being used to support costs associated with high-sensitivity, PCR-based testing of anal, vulvar, and oral specimens collected from participants in CVT at their 4-year study visit, the last blinded visit as part of the trial.

Title: **Chemoprevention of Tamoxifen-Induced Endometrial Cancer by Black Cohosh and Red Clover**
P.I.: **Birgit Maria Dietz**
Institution: **University of Illinois at Chicago**
Grant No.: **1R21CA135237-01A2**
Award: **$198,211**

Breast cancer is the most common cancer in women. The selective estrogen receptor modulator tamoxifen, which antagonizes estrogen in breast tissue, is efficacious in the treatment and prevention of breast cancer. In tamoxifen treated patients, botanical dietary supplements such as red clover and black cohosh extracts are frequently used for the alleviation of tamoxifen related menopausal symptoms. Very few studies about the modifying effects of these botanicals on tamoxifen's safety and efficacy have been reported. Tamoxifen's major side effect is an enhanced endometrial cancer risk. Tamoxifen's ER1 mediated uterotrophic activity and its reactive metabolites are believed to be responsible for this effect. Black cohosh and red clover contain anti-oxidative, anti-proliferative, anti-inflammatory, and detoxification enzyme inducing compounds, which could inhibit the initiation or retard the promotion and progression of cancerous cells. The central hypothesis of this project is that black cohosh and red clover reduce the carcinogenic effects of tamoxifen on the endometrium by inhibition of cell proliferation and through enhancing detoxification pathways. Recent data suggest that black cohosh and red clover can attenuate tamoxifen-stimulated endometrial cancer growth by inhibiting cell proliferation. They will measure the influence of these botanicals on tamoxifen stimulated endometrial tumor growth in ovariectomized athymic nude mice, an established endometrial cancer model for studying estrogenic influences. The mechanism of interaction will be examined by analyzing the expression of pro-proliferative genes and proteins important for tamoxifen mediated tumor promotion in vivo and in vitro. To further identify active compounds, they will examine the anti-proliferative effect of isolated compounds in endometrial cancer cells and in an immature rat model. Data indicate that both botanicals (black cohosh and red clover) upregulate the cellular anti-oxidative response machinery, thus reducing the carcinogenic effect of tamoxifen's reactive metabolites. This proposal will provide an overall picture of the effect of these botanicals and purified compounds on the efficacy of tamoxifen and on tamoxifen induced endometrial cancer, which is of importance considering the increasing number of breast cancer survivors and women at high risk undergoing tamoxifen treatment. The significance of the application is that this proposal hypothesizes that red clover and black cohosh, both frequently used for the alleviation of menopausal symptoms, will reduce tamoxifen-induced endometrial cancer due to their cancer chemopreventive properties.

Title: **NIR Hypoxia Imaging of Breast Tumor Response to Neoadjuvant Chemotherapy in Vivo**
P.I.: **Shudong Jiang**
Institution: **Dartmouth College, Hanover, NH**
Grant No.: **1R21CA135303-01A1**
Award: **$199,595**

Near-infrared (NIR) multi-spectral imaging is a unique tool for characterizing tissue composition in the female breast. The major advantage of this modality is its ability to provide images of tissue oxygen saturation (StO_2) as well as total hemoglobin concentration (HbT), water fraction (H_2O percent) and elastic scattering parameters. Because microcirculation and oxygenation play such major roles in tumor progression and regression, assessing their variation in response to neoadjuvant chemotherapy may reveal early prognostic biomarkers of treatment response that could be used to alter and/or optimize the course of treatment on a more individualized patient basis. Assessing dynamic contrast enhancement in tumor

oxygenation after hyperoxic gas inhalation with NIR spectral tomography appears to be feasible and may provide easily- acquired, low cost image signatures for predicting therapeutic response to chemotherapy in the breast. The overall goal of this proposal is to develop and evaluate dynamic NIR tomographic oximetry for characterizing the response of locally advanced breast cancers to neoadjuvant chemotherapy by assessing the temporal variation in tumor oxygenation during hyperoxic gas inhalation. Dartmouth College, through the Norris Cotton Cancer Center at the Dartmouth-Hitchcock Medical Center, has significant resources to leverage in order to conduct the proposed study. A group of investigators which includes clinical specialists in diagnostic radiology, surgical oncology, medical oncology, surgical pathology, and medical engineering has been configured to develop and evaluate technology for breast imaging for cancer detection, diagnosis and therapy monitoring since 1999. The proposed project is an important component of the research of this group. The significance of the application is that this project will develop and evaluate dynamic NIR tomographic oximetry for characterizing the response of locally advanced breast cancers to neoadjuvant chemotherapy by assessing the temporal variation in tumor oxygenation during hyperoxic gas inhalation. NIR oximetry acquired longitudinally during the course of therapy will be correlated with pathological endpoints in order to determine whether early prognostic biomarkers of treatment response can be identified in the dynamic NIR oxygenation signatures that could be used to customize breast cancer treatment decisions to individual patients in the future.

Title: **Reactivation of Breast Cancer Micrometastases by Senescent Bone Marrow Stroma**
P.I.: **Robert Wieder**
Institution: **University of Medicine/Dentistry of New Jersey, New Jersey Medical School**
Grant No.: **1R21CA142537-01A1**
Award: **$205,920**

More than a third of stage I-III breast cancer patients have bone marrow micrometastases at the time of diagnosis providing a source of recurrence. Most recurrences occur in postmenopausal women. Mechanisms of dormancy and recurrence are not well understood, but data suggest a dependence on a close association with bone marrow stroma. The applicants hypothesize that stromal cells undergo senescence due to aging and/or postmenopausal estrogen deprivation and begin to secrete inflammatory cytokines that can stimulate dormant cancer cells to reawaken. The broad, long-term goals of the proposed investigations are to define mechanisms that govern the establishment of the dormant state in breast cancer cells in the bone marrow and to determine factors and mechanisms responsible for their re-awakening and recurrence of disease. The study will determine if bone marrow stroma can undergo senescence when deprived of estrogen or treated with cytotoxins in vitro and in vivo in a murine model. The outcomes of these studies will establish a way of thinking about dormancy as a function of the senescent microenvironment and seek to reverse estrogen-deprivation-induced inflammation to maintain it. The significance of the application is that the study proposes to investigate the induction of senescence in mouse bone marrow stroma by estrogen deprivation in vitro and in vivo as manifested by the secretion of inflammatory cytokines and loss of the capacity to support dormancy of breast cancer cells in an in vitro model and the loss of the capacity to support the dormancy of xenografted human breast cancer cells in the bone marrow microenvironment. Experiments will determine if treatment with estrogen or anti-inflammatory agents can restore the capacity of senescent stroma to support dormancy.

Title: **Caregivers' Strengths-Skills: Managing Older Cancer Patients**
P.I.: **Victoria H. Raveis**
Institution: **Columbia University Health Sciences, New York, NY**
Grant No.: **5R01CA115315-05**
Award: **$46,488**

This project will implement and evaluate the efficacy of a short-term, problem-solving skills training program for familial caregivers to lower income older (60+) post-treatment cancer patients. The goal of the intervention is to equip family caregivers with problem-solving skills and knowledge that will provide them with a more adaptive means of attending to any symptoms their elderly relative may experience during the cancer survivorship period. By focusing attention on families' potential role in palliative care efforts during the post-treatment period, they propose that they will be able to impact patients' health related quality of life, by fostering enhanced symptom recognition, improved symptom control, advocacy with health professionals, and adherence to symptom management options. Familial caregivers to older cancer patients who have completed active treatment will be accrued from Community/ Migrant Health Centers (C/MHCs). Caregivers and patients will be followed for ten months. The Specific Aims are to: (1) deliver a brief problem-solving training program with regard to symptom management (problem-solving) to enhance caregiver skills (i.e., perceived self-efficacy, social problem-solving and communication) of familial caregivers to older post-treatment cancer patients; (2) evaluate the efficacy of problem-solving in enhancing caregiver skills, relative to participating in a caregiver support group (support): (a) assess short- and long-term change in caregiver skills reported by caregivers assigned to either the problem-solving condition or the support condition; and (b) compare change reported by caregivers in the problem-solving condition, relative to reports by those in the support condition; (3) assess the impact of change in caregiver skills on: (a) change in patients' symptomology and physical functioning, depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with care (patient outcomes); (b) change in caregivers' depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with patient care (caregiver outcomes); (4) disseminate information that informs family training in palliation and symptom control to participating C/MHCs and other C/MHCs serving these populations, contingent on demonstrating beneficial program outcomes.

Title: **BRCA1, Sporadic Breast Cancer, and Aging Women**
P.I.: **Hava Karsenty Avraham**
Institution: **Beth Israel Deaconess Medical Center, Boston, MA**
Grant No.: **1R21CA135226-01A1**
Award: **$149,600**

By defining the targets that are altered in mutated BRCA1-linked breast and ovarian cancers and providing insights into the BRCA1 pathways, this study may lead to potential new therapeutic strategies for the prevention, early diagnosis, and treatment of familial breast and ovarian cancers. In addition, results from this work will enhance their understanding of the molecular events that drive breast and ovarian cancers in aging women, and may link BRCA1 and beta-catenin to oxidative stress and breast oncogenesis. The risk of developing breast cancer increases as women get older. The maintenance of DNA represents a fundamental and continuous challenge to every cell in the body. Genomic instability is a hallmark of most cancers as well as a hallmark in aging. Recent evidence strengthened the link between the maintenance of genome integrity, cancer susceptibility, and aging. These conditions can be caused by germline mutations in BRCA1, which is an essential caretaker protein in the surveillance of DNA damage. Impaired oxidative stress response plays an important role in breast oncogenesis. Beta-catenin was shown to be a cofactor for the FOXO family, which promotes survival by inducing

cell cycle arrest and quiescence in response to oxidative stress. They observed that wild-type (WT) BRCA1, but not mutated BRCA1, interacts with beta-catenin and increases beta-catenin protein expression by promoting lysine-6-linked ubiquitination. Oxidative stress reagent H2O2 increased colocalization and the interaction of BRCA1 with beta-catenin in the nucleus. WT-BRCA1, but not mutated BRCA1, protected the nuclear active form of beta-catenin during oxidative stress responses. The expression of this form of beta-catenin was lower or absent in most of BRCA1 familial breast cancer tissues. Therefore, they hypothesize that: (1) BRCA1 acts as a sensor in regulating beta-catenin mediated oxidative stress and FOXO function; and (2) low expression of WT-BRCA1 or mutations in BRCA1 leads to impaired response to oxidative stress and causes genomic instability, resulting in increased risk of breast cancer in women. Therefore, they aim to examine the effects of BRCA1 on beta-catenin protein expression and stability and to analyze the role of BRCA1 in beta-catenin mediated oxidative stress response. Thus, they specifically propose the following aims: Aim 1: To investigate the role of BRCA1 in the expression and distribution of beta-catenin and its targets (cyclin D1 and c-Myc) during mammary gland development in BRCA1 mutant mice, in which BRCA1 exon 11 is specifically deleted from the mammary glands by using the Cre-loxP system. Aim 2: To characterize the role of BRCA1 as a sensor in regulating the beta-catenin and FOXO interaction during oxidative stress signaling. Results from this work will enhance their knowledge of the molecular events that drive sporadic breast and ovarian cancer development and progression in aging women.

Title: **Targeting the Phosphoinositide Kinase Chain to Prevent Breast Cancer Metastasis**
P.I.: **Jeannette Kunz**
Institution: **Baylor College Of Medicine, Houston, TX**
Grant No.: **1R03CA139545-01**
Award: **$76,750**

Breast cancer is the most commonly diagnosed form of cancer in women 40-55 years of age and it is the second major cause of cancer deaths behind lung cancer for all women. Metastatic breast cancer, where cancer cells spread by motile mechanisms and establish tumors at distant vital sites, is much harder to eradicate and is the primary cause of patient death from breast cancer. Understanding the molecular principles that determine the efficiency of tumor metastasis is therefore critical to the prevention and treatment of breast tumors. Traditional cancer therapeutics are aimed at preventing tumorigenesis of normal breast tissue and inhibiting growth of established cancers. However, few therapeutic strategies target cell migration and invasion, although the pathological deregulation of these processes is a major cause of morbidity associated with the disease. Cell migration and invasion are coordinately regulated by the small GTPase Rac1 and the localized production of the lipid phosphatidylinositol-4,5-bisphosphate (PI4,5P2). The hyperactivation of Rac1 signaling has been observed in many cancers, particularly in cancers of the breast, and this is directly linked to increased metastatic potential and poor patient survival. A role for PI4,5P2 signaling in cancer progression has so far not been reported. However, recent evidence described in the preliminary studies section of this proposal has established that PIPK1a, a member of the Type I phosphatidylinositol-4-phosphate kinase family, which generates PI4,5P2, is a critical regulator of cell migration and cell-matrix adhesion. They have defined a biochemical pathway in which PIPK1a mediates Rac1 activation in response to integrin and growth factor signals. Rac1, in turn, controls signaling to downstream effectors, including a second member of the PIPKI family, PIPK1b, to promote the assembly of F-actin and of focal adhesion sites necessary for migration and invasion. These results therefore establish a pathway in which PIPK1a is the pinnacle of a signaling cascade that links transmembrane receptors to the regulation of actin and focal adhesion assembly during cell motility. Because cell migration and adhesion are critical for cancer metastasis, PIPK1a may be a target for the prevention of cancer progression.

The long-term goal of these studies is to validate PIPK1a as a target for therapeutic intervention in metastatic disease using tissue culture cell models and the athymic nude mouse model of breast cancer. The proposed research also involves pilot studies designed to assess the efficacy of a newly identified natural small-molecule inhibitor of PIPK1a in the control of breast cancer progression. They will use a combination of basic research, chemical genetic, and in vivo approaches to systematically address the role of the PIPK1a pathway in cell migration and invasion in a 3-dimensional matrix, in anchorage-independent growth, and in cancer progression in vivo using the athymic nude mouse. The proposed research not only has the potential to impact therapeutic design to prevent breast cancer metastasis, but will also advance their understanding of signaling mechanisms that may be critical for breast cancer metastasis.

Title: **Development and Pilot Test of an Elective BSO Decision Support Guide**
P.I.: **Miriam Kuppermann**
Institution: **University of California, San Francisco**
Grant No.: **1R21CA141241-01**
Award: **$203,940**

Results of this study will contribute to the small literature on women's preferences and attitudes toward bilateral salpingo-oophorectomy (BSO). This study will generate a clinically useful BSO Decision Support Guide that women of varying literacy levels and diverse cultural backgrounds can use to help them participate in shared decisions about use of BSO. It will also generate questionnaires and data to be used in planning future evaluations of the impact of the guide on informed decisionmaking regarding and use of and satisfaction with BSO concomitant to hysterectomy among average risk women. Ovarian cancer is a common and often fatal condition. More than 600,000 women undergo hysterectomy each year, 90 percent of which are done for noncancerous conditions. Historically, many of these women have undergone BSO to decrease the risk of ovarian cancer and/or to avoid possible morbidities and future surgery related to benign ovarian neoplasms, endometriosis, and pelvic pain. However, BSO results in a permanent loss of ovarian estrogen and androgens that are known to be associated with maintenance of cardiovascular health, bone health, sexual functioning, and overall health-related quality-of-life. As a result, consideration of ovarian retention for premenopausal women who are not at increased genetic risk of ovarian cancer has been advocated, although no clear guidelines have been established regarding how decisions should be made regarding whether or not to perform elective BSO and the time of hysterectomy for benign condition. Decision aids have been developed and their use has been encouraged, in a number of areas to help patients and providers share in making informed decisions, particularly in situations that include more than one approach to care, uncertain outcomes, and benefits and harms that people value differently. Clearly, decisionmaking around BSO is an area the meets these criteria. They therefore propose to conduct formative research and use it to develop and pilot test a BSO Decision Support Guide, to help patients share with their providers in making informed, preference-based decisions regarding whether or not to undergo BSO concomitant to hysterectomy to prevent ovarian cancer. To accomplish these goals, they will conduct a series of focus groups and one-on-one qualitative interviews to assess how women who will be undergoing, or who have recently undergone, hysterectomy for noncancerous conditions view elective BSO and to assess their information needs and desires regarding shared decisionmaking in this context. They will then create a draft BSO Decision Support Guide using information obtained from the literature, from their formative research, and the experience of providers who have counseled women about this choice. After pilot testing the BSO Decision Support Guide among 62 women scheduled to undergo hysterectomy for benign conditions to assess its usefulness and usability for patients and their providers, they will generate a final version that will be ready for use in future studies of the impact of the intervention on decision quality and use of BSO.

Title: **Spore in Endometrial Cancer**
P.I.: **Paul Goodfellow**
Institution: **Washington University in St. Louis, MO**
Grant No.: **P50CA134254-01A1**
Award: **$200,000**

This Specialized Program of Research Excellence (SPORE) in Endometrial Cancer is submitted by Washington University in St. Louis, the Siteman Cancer Center at Barnes-Jewish Hospital, and Washington University School of Medicine. It includes four research projects, three supportive cores, and research and career development programs. This proposal brings together basic and applied investigators to conduct innovative and diverse translational investigations aimed at preventing, diagnosing, and treating endometrial cancer. The four projects in their application have been carefully designed to have significant potential to change clinical practice within five years. Project 1: FGFR2 as therapeutic target in endometrial cancer; Project 2: Methylation markers for prognosis in endometrioid endometrial cancers; Project 3: Identifying inherited endometrial cancer and the environmental and genetic factors contributing to somatic loss of mismatch repair; Project 4: Novel effectors of ERK signaling and their potential roles in the treatment of endometrial cancer. The four projects represent carefully chosen marriages between selected endometrial cancer research priorities and the strengths of Washington University and their collaborators. The critical objectives that they have chosen to focus on are to: (1) improve the treatment of patients with persistent or recurrent endometrial cancer using a molecularly targeted therapy and determine if upfront adjuvant biologic therapies hold promise for improving outcomes in the general endometrial cancer population; (2) develop prognostic markers to help guide the treatment of women with the most common form of uterine tumors, endometrioid endometrial cancer; (3) optimize detection of those women with inherited forms of endometrial cancer so they and their at-risk family members can receive risk-appropriate (intensified) cancer surveillance; and (4) elucidate the role novel effectors of ERK signaling play in uterine cancer and assess opportunities for targeting these in the treatment of endometrial cancers. Three cores will support these projects: administration, tissue and pathology, and biostatistics. The Developmental Research Program will support a pathway for continued identification and support of diverse research that could replace or improve current projects, and a Career Development Program will recruit and support candidates committed to training in translational research in endometrial cancer.

Title: **Immunogenicity of Quadrivalent Human Papilloma Virus Vaccine (HPV Types 6, 11, 16, 18) in Recipients of Reduced Intensity Hematologic Stem Cell Transplantation (Bench to Bedside Program)**
P.I.: **A. Chenoy, et al.**
Institution: **NHLBI/NICHD Intramural Program**
Grant No.: **Y2OD9147**
Award: **$100,000**

This project investigates the use of the recently licensed quadrivalent human papilloma virus (HPV) vaccine against HPV types 6, 11, 16, 18 in females age 12 years or older undergoing allogeneic, hematopoietic stem cell transplantation (HSCT) as an approach to reduce post-transplant HPV-related comorbidity, anogenital dysplasia and malignancy. This population is at excess risk for HPV-related anogenital dysplasia and malignancy following transplantation and stands to benefit greatly from prophylactic HPV vaccination. In addition to determining whether the quadrivalent vaccine is immunogenic in the post-transplant population, this investigation will also determine, in a subset of patients, whether there are differences in HPV vaccine immunogenicity in individuals with identical T cell immunity that have non-identical host cell backgrounds i.e. HSCT donors (male or female) and their respective/paired female transplant recipients.

Title: **Improving Flexible Sigmoidoscopy in Women by Optical Analysis of Microvasculature**
P.I.: **Vadim Backman**
Institution: **Northshore Univ Healthsystem Research Institute, Evanston, IL**
Grant No.: **1R21CA140936-01**
Award: **$214,425**

Despite a myriad of screening tests available, colorectal cancer (CRC) remains the second leading cause of cancer deaths among Americans. Approximately half the population does not undergo any CRC screening because of cost, access, and concerns about discomfort with both the procedure and colonic purge. Flexible sigmoidoscopy (endoscopic evaluation of the distal colon) is performed in the community and has many advantages over other recommended tests (e.g. colonoscopy, CT colography) such as being relatively inexpensive, more widely available (performed by primary care physicians) and proven efficacy at decreasing both CRC mortality and incidence. However, flexible sigmoidoscopy is insensitive in women given their predilection for proximal neoplasia. Indeed, while flexible sigmoidoscopy identifies two-thirds of advanced adenomas in men, it only detects one-third in women highlighting the need for adjunctive approaches. Their multi-disciplinary CRC prevention group has focused on bridging novel optical technologies to clinical practice. Using 4-dimensional elastic light scattering fingerprinting (4D-ELF), they published that in CRC models, the peri-cryptal capillary blood content was increased prior to any histological abnormalities (a phenomena they termed EIBS (early increase in blood supply). They developed an endoscopically- compatible fiber-optic probe and demonstrated that EIBS was detectable at a distance from neoplastic lesions. In the rectum, EIBS was detectable in patients harboring advanced neoplasia elsewhere in their colon. Importantly, rectal EIBS was more robust in women (~60 percent increase versus neoplasia-free controls) than men (~25 percent) for proximal advanced neoplasia (that was not visualizable by flexible sigmoidoscope). They, therefore, hypothesize that rectal EIBS measurement will detect advanced proximal neoplasia in women. They will obtain rectal EIBS analysis on women undergoing colonoscopy. They will identify diagnostic EIBS parameters and determine the impact of demographic factors (e.g., age, race, smoking, medication use) on these markers. This data will be used to formulate a prediction rule for advanced proximal adenomas. They will then prospectively validate this prediction rule on a separate cohort of women simulating real world flexible sigmoidoscopy screening conditions prior to full colonoscopy. This will provide the rationale to performing future multicenter trials of rectal EIBS as an adjunct to flexible sigmoidoscopy in women. If successful, this practical and relatively inexpensive approach may be pivotal for the resurgence of flexible sigmoidoscopy as an accurate, cost-effective and patient-friendly CRC screening option in women.

Title: **Regulation of Breast Cancer Progression by FAK Expression in Tumor Macrophages**
P.I.: **Amy H. Bouton, J. Thomas Parsons**
Institution: **University of Virginia, Charlottesville**
Grant No.: **1R21CA135532-01A1**
Award: **$198,087**

The growth and metastatic spread of solid tumors is controlled by signals emanating from tumor cells as well as by immune cells and fibroblasts in the surrounding stroma, components of the extracellular matrix, and soluble growth factors and cytokines. While this complexity creates challenges for therapeutic intervention, it also provides unique opportunities by making available a number of distinct cellular and molecular targets that can be exploited to control tumor growth and progression. The focus of this proposal is on Focal Adhesion Kinase (FAK), a protein tyrosine kinase whose expression is significantly increased in many late-stage cancers,

including breast cancer. The applicants hypothesize that FAK expression in two components of the tumor microenvironment, the tumor cells and tumor-associated macrophages (TAMs), plays a critical role in promoting breast tumor progression and metastasis. The applicants will use mouse models of breast cancer to gain an understanding of how FAK expression in breast carcinoma cells and/or the ancillary tumor-associated macrophages controls primary breast tumor growth and metastatic spread. Globally, knowledge will be about mechanisms through which tumor cells and other cells within the tumor microenvironment communicate to promote breast tumor growth and metastasis. The significance of the application is that the study proposes to focus on the role of FAK in both macrophages and tumor cells, this work will uncover novel features of macrophage - tumor cell synergy that contribute to breast tumor behaviors. In addition to providing critical information about how FAK inhibitors should be used to treat breast cancer patients, this work will potentially identify new strategies for targeting distinct cellular compartments within the tumor that can be exploited therapeutically to control tumor growth and progression. It is anticipated that, through the knowledge gained from these studies, there will be a significant reduction in mortality from breast cancer.

Title: **Role of MicroRNAs in Initiation and Progression of Breast Cancer**
P.I.: **Lorenzo Sempere**
Institution: **Dartmouth College, Hanover, NH**
Grant No.: **R03 CA141564-01**
Award: **$79,000**

Breast carcinoma (BrCa), which is the second most prevalent cancer in women, is a complex, inadequately understood, and often fatal disease when not detected at early stages. A more detailed understanding of the molecular mechanisms and regulatory pathways at work will enormously assist in improving the design and target selection of therapeutic strategies. MicroRNAs (miRNAs) are evolutionarily conserved, short noncoding regulatory RNAs that post-transcriptionally modulate gene expression by binding to their cognate target mRNAs via pervasive and versatile mechanisms. Altered expression of specific subsets of miRNAs has been linked to different types of hematologic and solid tumors. Independent studies using BrCa clinical specimens have identified a small subset of miRNAs, which are differentially detected between normal and tumor tissue specimens. Thus, the clinical value of these miRNAs as novel biomarkers for different aspect of BrCa management is being actively investigated. Importantly, functional analyses in cell line systems and xenograft transplantation in mouse models have revealed tumor suppressive and oncogenic functions of some of these miRNAs. This proposal focuses on miRNAs as potential tumor suppressive mechanisms to prevent breast carcinogenesis. The applicants expect that results of this proposal will uncover an etiological contribution of miRNAs and validate the use of these mouse models for future studies concentrating on the role of individual miRNA in BrCa and development of miRNA-based therapeutic strategies. The significance of this proposal is that the in situ hybridization technology offers spatial resolution of miRNA expression unsurpassed by other techniques, which could be readily adapted to routine clinical practice to benefit patients and assist physicians in making crucial decisions.

Cardiovascular Disease

Title: **Cardiovascular Events in Women's Ischemia Syndrome Evaluation**
P.I.: **Sheryl F. Kelsey**
Institution: **University of Pittsburgh, PA**
Grant No.: **5R03AG032631-02**
Award: **$20,000**

Much attention has been focused on the differences between men and women presenting with heart attacks and angina pain. The Women's Ischemia Syndrome Evaluation (WISE) study has been a successful and productive four-center prospective study of women clinically referred for coronary angiography for evaluation of symptoms suggestive of ischemia. The goals of WISE were to improve diagnostic testing for ischemic heart disease and to explore female-specific ischemic heart disease pathophysiology. A National Death Index (NDI) search will be used to extend mortality followup for WISE women to an average of eight years (maximum 10). Experienced site coordinators will prepare materials to submit to NDI and send results to the coordinating center where updated mortality data will be added to the WISE database. Using the existing database, coronary risk factors, hormonal status, psychosocial, genetic factors, and results of diagnostic tests will be evaluated as predictors of long-term mortality. Initiated in September 1996, recruitment of 936 women was completed in a timely manner by March 2000. Support was awarded for an additional five years of followup, and the database was closed in March 2006. A rich longitudinal database on these women is thus available. Patient names reside at the clinical sites, but to maintain confidentiality, are not included in the WISE database at the coordinating center. Extension of cardiovascular mortality data will more clearly define prognostic factors for long-term mortality in women with ischemia with and without obstructive disease. With an additional targeted analysis, development of a simple, reproducible, angiographic technique to identify micro-vascular dysfunction, by correlating TIMI Frame Count with Doppler Wire determined coronary flow reserve measured in response to adenosine in WISE women with suspected ischemia but no significant coronary artery disease is possible. Availability of a simple diagnostic technique allows clinicians to target these women for aggressive medical therapy aimed at early coronary artery disease and improved prognosis.

Title: **Role of 15-Lipoxygenase in Enhanced Pulmonary Vasoconstriction in Females**
P.I.: **Sandra L. Pfister**
Institution: **Medical College of Wisconsin, Milwaukee**
Grant No.: **1R21HL093181-01A1**
Award: **$220,200**

Pulmonary arterial hypertension encompasses a group of diseases characterized by high pulmonary artery pressure and pulmonary vascular resistance. Vasoconstriction, vascular remodeling, and thrombosis all contribute to the increased vascular resistance. Central to the proposed studies is that while relatively rare, idiopathic pulmonary arterial hypertension is a medically significant disease that occurs more frequently in young women. The disease is usually catastrophic for those afflicted. Mechanisms to explain the sex- difference in pulmonary arterial hypertension have not been well studied. The main focus of the grant application is to use a rabbit model to explore the role of sex in a novel signaling pathway that regulates pulmonary vascular tone. Results will lay the fundamental conceptual groundwork for future studies to understand more completely the pathogenesis of pulmonary hypertension in women. Furthermore, this work is intended to advance new concepts in women's health research and the study of sex and gender differences. Specifically, prior research by the investigators provided the first evidence that in pulmonary arteries obtained from female rabbits, endothelium-dependent contractions to both arachidonic acid (AA) and methacholine

were enhanced when compared to responses in males. Pharmacological studies with inhibitors of AA metabolism indicated that the factor was a lipoxygenase metabolite. The investigators showed in their prior studies that lipoxygenase metabolites are increased in females compared to males and the protein expression of 15-lipoxygenase is greater in female pulmonary arteries. While sex differences in vascular responses to various vasoactive agents have been documented, no studies have investigated the role of sex differences on lipoxygenase metabolism of AA in pulmonary arteries. This proposal is designed to explore the specific hypothesis that differences in AA metabolism by 15-LO contribute to the increased endothelium-dependent pulmonary vasoconstriction in females compared to males. To further develop this novel hypothesis, studies will be performed in pulmonary artery vascular preparations using chemical, biochemical, physiological and pharmacological approaches. These proposed studies will not only provide new insights into the role of endogenous arachidonic acid-derived factors in the pathogenesis of pulmonary arterial hypertension but will also advance their knowledge in women's health research by identifying possible mechanisms that contribute to sex-related differences in the incidence of pulmonary arterial hypertension. Significance of the Application: While relatively rare, idiopathic pulmonary arterial hypertension is a medically significant disease that occurs more frequently in young women. The disease is usually catastrophic for those afflicted. Identifying endogenous pulmonary factors that may predispose females to the development of pulmonary hypertension is timely and important considering the abundance of clinical data indicating sex differences in vascular disease. Furthermore, this work is intended to advance new concepts in women's health research and the study of sex/gender differences.

Title: **Mechanisms Underlie Inverse Gender Discrepancy in Ischemic Protection**
P.I.: **Nian-Qing Shi**
Institution: **University of Wisconsin-Madison**
Grant No.: **1R21HL093626-01A1**
Award: **$222,750**

The proposed research will employ KATP channel mutant mice that are defective in the sulfonylurea receptor 2 (SUR2) to evaluate gender difference in ischemic protection, regulation of estrogen in sarcolemmal and mitochondrial SUR2 forms and obtain new insights in ion channel regulation in cardiovascular diseases. Myocardial infarction (MI) is a major health problem worldwide due to its acute nature and lack of effective prevention schemes. Gender difference in ischemic protection exists, with relatively lower MI incidences in pre- menopausal females than age-matched males. Emerging evidence indicates that the female-specific advantage in ischemic protection is mediated by estrogen. In the ischemic protection network, KATP channels (KATP) are postulated to play protective roles, but their relative importance remains controversial. Composed by a Kir6.2 pore and an SUR2 regulatory subunit, KATP activity is recorded in cardiac sarcolemmal or mitochondrial inner membrane. Their recent data show that disrupting the SUR2 gene at an earlier exon 3 causes an early lethality and the mutants only lived 8 days. However, disrupting SUR2 at middle exons 12-16 interrupts the SUR2 long forms, but the novel SUR2 short forms remain expressed. They have identified 2 splice variants that are generated by a rare intra-exonic splicing (IES) event in SUR2 mRNA to produce transcripts encoding the 55-kDa SUR2 short forms in heart mitochondria. Characterization of SUR2 KO has revealed an inverse pattern of gender difference in cardioprotection. Completed tests in KO males show that they are constitutively protected, with reduced infarcts after ischemia, while KO females have larger infarcts and cannot be preconditioned. mRNA levels of both IES variants markedly increase in the preconditioned KO males but they reduce dramatically in the preconditioned KO females. This interesting discrepancy offers a new platform of using SUR2 mutant mice to investigate gender difference

in ischemic protection. The proposed research intends to explore the molecular mechanisms underlying gender difference in cardioprotection in relation to KATP channels, especially mitochondrial KATP. They hypothesized that estrogen modulates expression of sarcolemmal and mitochondrial SUR2 forms in mice. They further hypothesized that levels of the IES variants encoding the mitochondrial SUR2 short forms are critical to protection. In Aim 1, they will characterize ischemic protection in both genders of WT and KO mice, and study whether estrogen modulates expression of the SUR2 forms. In Aim 2, estrogen regulation in mitochondrial SUR2 will be investigated, and a 55A "rescued" female mouse model will be tested whether they can improve protection. Interactions of estrogen receptor 2 and the IES variants will be explored. Results from this research not only provide new insights in gender-specific response to cardioprotection but also identify new drug targets for future clinical treatments against MI.

Title: **Weight, Diet, Genes, and CVD Risk Factors (Hypertension and Diabetes)**
P.I.: **Nanette Requintina Lee**
Institution: **University of San Carlos, Cebu, Philippines**
Grant No.: **1R01TW008288-01**
Award: **$50,000**

This study will examine the independent and combined effects of genetic predisposition and modifiable factors such as weight and dietary patterns on the risks of having hypertension and diabetes, two major cardiovascular disease (CVD) risk factors. The demographic and health trends in the Philippines exemplify those of other developing Asian countries where CVD-related morbidities and deaths are prevalent and increasing. Thus, studying the mechanisms that can lead to the development of hypertension and diabetes among Filipinos can provide critical information that may guide more tailored prevention efforts for these populations, potentially narrowing global health disparities. Cardiovascular diseases (CVD) are the leading causes of morbidity and mortality in the world. Hypertension and diabetes, two of the major CVD risk factors, are complex diseases caused by the combined actions of genetic and environmental factors. Few studies have examined the interaction of these factors and fewer, if any, have looked at their effects in populations of developing Asian countries that are plagued with increasing levels of obesity and rapidly changing food environments. The information gap may be due to the lack of population-based studies with adequate depth and detail. There is a paucity of information on dietary and adiposity trends derived from longitudinal studies and there are inadequate genetic data, especially among Asians who tend to develop CVD risk factors at lower body mass index thresholds. Aims and Methods: The proposed study aims to understand how weight history, dietary patterns, and genetic variants independently and jointly affect blood pressure and fasting glucose among adult Filipino women (38–71 years in 2007) using the Cebu Longitudinal Health and Nutrition Survey (CLHNS), an ongoing community-based study of over 2,000 women (and their infants) which began in 1983. This is a unique dataset that contains not only rich genetic information on these women but also dietary and anthropometric measurements obtained since baseline, recent blood pressure (1998-2007) and fasting glucose (2005) measurements, and other individual-, household-, and community-level data collected over a span of 24 years of rapid countrywide socio-economic changes. Specifically, using multivariate regression methods they will determine the: (a) effect of weight history (i.e. duration of overweight) on the risk of having hypertension and/or diabetes; (b) association between dietary patterns (identified through cluster analysis) and hypertension and/or diabetes; (c) independence and co-occurrence of hypertension and diabetes and how these relate to weight and dietary patterns; and (d) effects of genetic variants on hypertension and diabetes, focusing on gene variants that have been associated with hypertension or diabetes by previous association studies. Further, the study will explore significant interaction of effects among genetic variants, overweight history, and dietary patterns in affecting hypertension or diabetes.

Title: **Sex Differences in Myocardial Ischemia Triggered by Emotional Factors after MI**
P.I.: **Viola Vaccarino**
Institution: **Emory University, Atlanta, GA**
Grant No.: **1R21HL093665-01A1**
Award: **$232,500**

Coronary heart disease (CHD) is the major cause of death in American women, and every year a similar number of women and men die due to CHD. Growing evidence supports important differences in the pathophysiology, clinical presentation, and prognosis of CHD between women and men; yet much remains to be learned about the unique characteristics of CHD in women. Young and middle-aged women have higher mortality and complication rates after an acute myocardial infarction (MI) compared with men of similar age. Reasons for these differences are unknown; they are not explained by traditional CHD risk factors, other comorbidity or treatments, and occur despite the fact that women have less coronary atherosclerosis and more preserved ventricular function than men. One third to two thirds of patients with CHD have myocardial ischemia that is induced by psychological stressors. Such ischemia is often painless and unrelated to severity of coronary artery disease; nonetheless it is associated with adverse outcomes. Emotional factors such as depression and psychological trauma are more common in women with CHD than in men and may predispose women to stress-induced ischemia. Depression, for example, is present in up to 40 percent of women with MI younger than 60 years. However, emotionally-triggered ischemia has hardly been studied in women before. The overall objective of this proposal is to evaluate differences in stress-induced ischemia between 50 women and 50 men younger than 60 years who were hospitalized for acute MI in the previous 6 months in Emory-affiliated hospitals. They hypothesize that myocardial ischemia due to emotional factors is more common in women than in men, while exercise-induced ischemia is as common, or even less common, in women. The aims of this study are to: (1) use single photon emission tomography (SPECT) [Tc-99m] sestamibi myocardial perfusion imaging, to compare myocardial perfusion during rest, during exercise, and during an emotionally stressful challenge in women and men; (2) investigate biological mechanisms for the sex differences in ischemia induced by emotional stress, including differences in hemodynamic (blood pressure, heart rate), neurobiological (cortisol and autonomic nervous system), and inflammatory responses to the stressful challenge; (3) investigate behavioral and psychosocial explanatory factors for the sex differences in ischemia induced by emotional stress (depression, history of trauma, and socio-economic environment). Younger women with MI represent an understudied patient group despite their higher rate of adverse events compared with men. Investigation of this group will provide critical information for the prevention of CHD in women. Their study may uncover a unique pathway which may explain sex differences in the outcome of MI.

Title: **Sex Differences in Myocardial Ischemia Triggered by Emotional Factors After MI**
P.I.: **Viola Vaccarino**
Institution: **Emory University, Atlanta, GA**
Grant No.: **3R21HL093665-01A1S1**
Award: **$291,952**

Coronary heart disease (CHD) is the major cause of death in American women, and every year a similar number of women and men die due to CHD. Growing evidence supports important differences in the pathophysiology, clinical presentation and prognosis of CHD between women and men; yet much remains to be learned about the unique characteristics of CHD in women. Young and middle-aged women have higher mortality and complication

rates after an acute myocardial infarction (MI) compared with men of similar age. Reasons for these differences are unknown; they are not explained by traditional CHD risk factors, other comorbidity or treatments, and occur despite the fact that women have less coronary atherosclerosis and more preserved ventricular function than men. One third to two thirds of patients with CHD have myocardial ischemia that is induced by psychological stressors. Such ischemia is often painless and unrelated to severity of coronary artery disease; nonetheless it is associated with adverse outcomes. Emotional factors such as depression and psychological trauma are more common in women with CHD than in men and may predispose women to stress-induced ischemia. Depression, for example, is present in up to 40 percent of women with MI younger than 60 years. However, emotionally-triggered ischemia has hardly been studied in women before. The overall objective of this proposal is to evaluate differences in stress-induced ischemia between 50 women and 50 men younger than 60 years who were hospitalized for acute MI in the previous 6 months in Emory-affiliated hospitals. They hypothesize that myocardial ischemia due to emotional factors is more common in women than in men, while exercise-induced ischemia is as common, or even less common, in women. The aims of this study are to: (1) use single photon emission tomography (SPECT) [Tc-99m] sestamibi myocardial perfusion imaging, to compare myocardial perfusion during rest, during exercise, and during an emotionally stressful challenge in women and men; (2) investigate biological mechanisms for the sex differences in ischemia induced by emotional stress, including differences in hemodynamic (blood pressure, heart rate), neurobiological (cortisol and autonomic nervous system) and inflammatory responses to the stressful challenge; (3) investigate behavioral and psychosocial explanatory factors for the sex differences in ischemia induced by emotional stress (depression, history of trauma, and socio-economic environment). Younger women with MI represent an understudied patient group despite their higher rate of adverse events compared with men. Investigation of this group will provide critical information for the prevention of CHD in women. Their study may uncover a unique pathway which may explain sex differences in the outcome of MI.

Chronic Fatigue Syndrome

Title: **Autonomic Nervous System in Chronic Fatigue Syndrome**
P.I.: **Italo Biaggioni**
Institution: **Vanderbilt University, Nashville, TN**
Grant No.: **1R01NS055670-01**
Award: **$383,438**

The overall goal of this application is to determine the role of the autonomic nervous system in the abnormalities associated with chronic fatigue syndrome (CFS). They propose to test the hypothesis that the sympathetic nervous system contributes to the cardiovascular and inflammatory abnormalities present in CFS and in particular in the subset of patients characterized by postural tachycardia (POTS). CFS and POTS are seen mostly in otherwise normal young women, and are the cause of significant disability. Their preliminary study indicates a decrease in plasma volume in patients with POTS, which can contribute to, and be the consequence of, sympathetic activation. Their preliminary studies also indicate an interaction between the sympathetic nervous system and nitric oxide mechanisms; this may also create a negative feedback mechanism whereby a decrease nitric oxide results in sympathetic activation, and increased sympathetic activity results in impaired nitric oxide mechanisms. They have developed a paradigm that will allow us to define selectively the contribution of endothelial nitric oxide to blood pressure regulation and will apply this approach to patients with CFS and POTS. In addition, their preliminary studies indicate that sympathetic activity is associated with inflammatory processes. In particular, C-reactive protein are increased in patients with POTS and, conversely, decreased in patients with low sympathetic tone due to pure autonomic unsuccessful undertaking. They propose to measure validated

indices of sympathetic activity, inflammation and oxidative stress in patients with CFS and POTS, and compare them to appropriate control groups, including patients with CFS without POTS, POTS without CFS, and normal controls. If their hypothesis is correct, and sympathetic activity contributes to the pathophysiology of CFS, then chronic inhibition of sympathetic tone will result in improvement of symptoms, cardiovascular alterations, volume defects, and inflammatory abnormalities present in CFS.

Title: **HERV-K18 as a Risk Factor for CFIDS**
P.I.: **Bridgitte T. Huber**
Institution: **Tufts University, Boston, MA**
Grant No.: **1R01AR053821-01A2**
Award: **$146,500**

The etiology of Chronic Fatigue Syndrome (CFS) is far from understood and is likely due to multiple genetic components. Infection with Epstein-Barr virus (EBV) and treatment with IFN-a have been implicated in the pathogenesis. Their laboratory has shown that EBV infection, and exogenous IFN-a, activate transcription of the env gene of a human endogenous retrovirus, HERV-K18. This provirus is normally silent, but when induced it encodes a superantigen (SAg), which is a class of proteins that is capable of deregulating the immune system. Three alleles of HERV-K18 env have been documented, K18.1, K18.2, K18.3, whose gene products have SAg activity, but are predicted to differ biochemically and functionally. Their working hypothesis is that HERV-K18 is a risk factor for CFS. In a pilot study, the allele and genotype distributions of the HERV-K18 env gene were compared between various groups of CFS patients and healthy controls. Although only a limited number of samples were available in the various cohorts, the odds ratios that were obtained were statistically significant. The most intriguing interpretation of these data is that they provide genetic evidence for the unique etiology of at least one group of CFS patients. Thus, it may be possible to delineate different subtypes of CFS, depending on the clinical history of the patients. It is now proposed to substantiate these pilot results, using a much larger cohort of 400 CFS patients associated with EBV that has been assembled by the co-investigator, Dr. Renee Taylor. Dr. Ben Katz, board certified in both Pediatrics and Pediatric Infectious Diseases, will clinically evaluate the patient cohort, and Dr. Inga Peter, a genetic epidemiologist and biostatistician, will oversee the statistical analyses. In addition, the expression pattern of the HERV-K18 SAg during active disease versus intermission will be measured. Furthermore, T cell stimulatory activity of this SAg, expressed on peripheral blood lymphocytes of patients during the course of the disease, will be tested ex vivo, using a T cell hybridoma reporter assay that has been developed in their lab. Since SAg-activated T cells produce massive quantities of chemokines, lymphokines and neurokines, the expression of the HERV-K18 SAg could influence not only the immune system, but other organs as well. A positive association between CFS and either HERV-K18 alleles or expression patterns would open new avenues for the development of clinical treatments of this chronic disease. CFS is a disease that affects a significant number of people worldwide, yet the underlying mechanism(s) of pathogenesis remains unclear. The herpes virus EBV and IFN-a have been suggested to be associated with CFS, although these concepts are far from accepted. They propose a novel genetic aspect in the EBV/CFS association, namely the presence of certain HERV-K18 alleles that differ in their superantigen activity.

Title: From Infection to Neurometabolism: A Nexus for CFS
P.I.: Jan A. Witkowski
Institution: Cold Spring Harbor Laboratory, NY
Grant No.: 1R13NS066634-01
Award: $10,000

The Centers for Disease Control and Prevention (CDC) defined chronic fatigue syndrome (CFS) as unremitting fatigue often accompanied by chronic widespread pain, cognitive impairment, and sleep disturbance and post-exertion malaise. Last year, the CDC estimated that at least 4 million American adults suffer with CFS. Population based studies of CFS have found at least 2 million adults with CFS are either receiving disability or are unemployed. Further, economic impact studies have determined that costs to the U.S. economy are in excess of $20 billion each year. The past 20 years of NIH-funded research on CFS resulted in more than 5,000 peer reviewed biomedical publications describing the biology of CFS including infection, genetic polymorphisms, and brain metabolism. Research of current CFS investigators is rooted in the two decades of accumulated knowledge. Ongoing research and results can be coordinated in order to expedite control and prevention strategies for CFS. To do this, they are organizing a small, 3-day workshop for 30 scientists at the Banbury Center at Cold Spring Harbor Laboratory. The Banbury Center meetings are recognized internationally as being among the world's best discussion workshops for a variety of topics ranging from neuroscience to science policy. Investigators funded by the NIH as well as the CFIDS Association of America and conducting research on biomarkers for early detection, objective diagnosis, and treatment of CFS will be invited to participate. Domain experts in infectious disease, physiology, and neuroscience will be invited to chair sessions and evaluate the work presented by the CFS researchers. There are three objectives to this workshop: (1) to have funded CFS investigators present their latest research; (2) to identify common interests and study synergies; and (3) to coordinate CFS-funded investigators into an expanded research network. The anticipated outcome of this meeting is the identification of CFS investigators interested in collaborating in an ongoing CFS research network. This project is directly applicable to the NIH mission "to advance significantly the Nation's capacity to protect and improve health".

Title: Cognitive Behavioral Stress Management for Chronic Fatigue Syndrome
P.I.: Michael H. Antoni
Institution: University of Miami, Coral Gables, FL
Grant No.: 1R01NS055672-01
Award: $343,219

This is a 4-year study that uses a 10-week, telephone-based, cognitive-behavioral stress-management intervention (T-CBSM) to illuminate neuroimmune mechanisms underlying the effects of stress and stress management on physical health status and immune regulation in individuals with chronic fatigue syndrome (CFS) relative to participants receiving a health promotion telephone (T-HP) intervention. CFS is characterized by physical symptoms which bring about severe limitations in lifestyle behaviors and vocational activities. Associated symptoms include debilitating fatigue, low grade fever, lymph node pain and tenderness, cognitive difficulties, and mood changes. There is growing evidence that CFS patients may also show abnormalities in HPA axis functioning and on several indices of immune functioning. Chronic stress is also associated with a flattened diurnal secretion pattern for cortisol. An inability to maintain regulation in the HPA axis may contribute to the pathophysiology of CFS via diminished control of pro-inflammatory cytokines and associated physical symptoms related to chronic immune activation and inflammation. Given the debilitating nature of CFS, they propose to deliver the T-CBSM intervention through a telecommunications system

(i.e. Telecare) designed to enhance access to formal and informal care for a population that may have difficulty accessing traditional psychotherapeutic settings. In their prior work with individuals with CFS, they have shown that individuals in a structured group CBSM intervention report significantly improved quality of life, perceived stress, fatigue, memory, muscle pain, and post-exertional malaise compared to individuals in the control condition. The Telecare system has been successful in delivering a supportive intervention for older caregivers of dementia patients. This study is novel in expanding their prior work to individuals with CFS who have reported difficulty participating in structured groups due to physical burden. The study design is a 2 X 3 randomized experimental design with group (T-CBSM, n=60 vs. T-HP, n=60) as the between-group factor, and time (Pre-intervention, Post-intervention and 6 month followup) as the within-group factor. Their primary objective is to evaluate the extent to which a T-CBSM intervention aimed at building skills in anxiety reduction, distress tolerance, stressor appraisals, and adaptive coping strategies may improve physical health status and immune regulation in CFS by modulating neuroimmune interactions.

Craniofacial

Title: **Estrogen and Psychological Stress in Temporomandibular Joint Disorder Pain**
P.I.: **David Bereiter**
Institution: **University of Minnesota Twin Cities**
Grant No.: **2R01DE012758-11A1**
Award: **$200,000**

Pain in the jaw joint and muscles of mastication is the most common form of persistent facial pain. Female gender and co-occurrence with depressive illness and psychological stress are recognized risk factors in developing persistent jaw pain. Their understanding of the neurobiology of persistent jaw pain will be improved by the use of new animal models that consider these known risk factors. Temporomandibular joint/muscle disorders (TMJD) represent a family of conditions that present with pain in the temporomandibular joint (TMJ) and muscles of mastication. Chronic TMJD occurs mainly in young women and is strongly associated with elevated levels of psychological stress. Chronic TMJD patients display minimal signs of tissue injury and benefit little from conventional anti-inflammatory drug therapies. The symptoms of chronic TMJD suggest a central neural dysfunction or problem of pain amplification. By contrast, most animal models of TMJ nociception rely on overt inflammation and do not account for known risk factors (i.e., estrogen status and stress). In this application they will use an established model of psychological stress, the repeated forced swim test (FST), known to induce persistent hyperalgesia and will determine its effects on TMJ nociceptive processing in female rats under high and low estrogen conditions. They will test the hypothesis that changes in estrogen status and psychological stress act through the periaqueductal gray-rostral ventromedial medulla (PAG-RVM), the main supraspinal pain modulatory system, to influence TMJ nociception. Since serotonergic (5HT) mechanisms mediate a significant portion of PAG- induced effects on spinal systems, they will test if specific 5HT receptors are involved in modulation of TMJ nociceptive processing at the dorsal horn level. They will stimulate TMJ afferent fibers by injection of the noninflammatory agent, ATP, and record single neuron activity at the trigeminal subnucleus caudalis/upper cervical dorsal horn region (Vc/C1-2), the principal site of termination for TMJ nociceptors. Masseter muscle electromyographic (EMG) activity will allow us to assess treatment effects on a peripheral behavioral correlate of TMJ nociception. Three specific aims are proposed. Aim 1 will determine if estrogen status alters PAG-induced modulation of TMJ-evoked unit activity, masseter muscle EMG and c-fos immunoreactive neurons at the Vc/C1-2 region in sham and FST-conditioned rats. Aim 2 will determine if local actions of 5HT receptors at the caudal brainstem level contribute to PAG-induced modulation of TMJ nociception. Aim 3 will determine if local actions of 5HT receptors

alone at the caudal brainstem level modify the responses to TMJ stimulation independent of overt PAG stimulation. These studies will provide new information on the influence of estrogen status and psychological stress on the neurobiology of brainstem systems thought to be critical for TMJD pain.

Diabetes

Title: **Post-Diabetes Prevention Program Followup Study**
P.I.: **Sarah E. Fowler**
Institution: **George Washington University, Washington, DC**
Grant No.: **5U01DK048489-16**
Award: **$870,000**

The Diabetes Prevention Program (DPP) is a multicenter controlled clinical trial examining the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 American Diabetes Association criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2–5 years) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the lifestyle intervention and metformin-treated groups (58 percent and 31 percent reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45 percent minorities, is the largest impaired glucose tolerance (IGT) population ever studied. Moreover, the subcohort that has developed diabetes (approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured, and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early-onset type 2 diabetes. Specific aims include: 1. examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding micro-vascular and neurologic complications; 3. determine the incidence of cardiovascular disease (CVD), CVD risk factors, and atherosclerosis in new-onset type 2 diabetes and IGT; and 4. examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP.

Title: **Gestational Diabetes Awareness Campaign (Support Services for the National Diabetes Education Program)**
Institution: **NIDDK**
Award: **$1,000,000**

Based on the results of DPP, ORWH partnered with NIDDK to create a gestational diabetes mellitus (GDM) awareness campaign. GDM is a form of diabetes that occurs in some pregnant women, affecting 7 percent and possibly as many as 18 percent of U.S. pregnancies. Immediately after pregnancy, 5 to 10 percent of women with GDM are found to have diabetes, usually type 2. In addition, women with a history of GDM have a 35- to 60-percent chance of developing diabetes within the next 10 to 20 years. Based on the public health implications,

ORWH and NIDDK developed materials for distribution and provided experts for interviews across the United States. The GDM campaign created a national radio interview outreach in FY 2010 that reached almost 3 million listeners.

Title: **Gender-Specific Complications of Diabetic Autonomic Neuropathy: A New Mouse Model**
P.I.: **Jonas Bernard Galper**
Institution: **Tufts Medical Center, Boston, MA**
Grant No.: **1R21HL093699-01A1**
Award: **$238,500**

Diabetic Autonomic Neuropathy (DAN) is characterized by impairment of autonomic responsiveness of the heart. DAN has been associated with an increased incidence of arrhythmia and sudden death in diabetics. Although the overall incidence of sudden death is lower in women than in men, the risk of sudden death associated with diabetes in women is greater than in men. Studies in postmenopausal women demonstrated that combined estrogen/progestin therapy reduced the incidence of diabetes. Comparison of heart rate variability showed that the parasympathetic response of the heart was increased in young women compared with men; this difference was attenuated after menopause, but maintained in women on hormone replacement therapy (HRT). These data suggested the hypothesis that menopausal women might be more likely to develop DAN and that HRT might protect the heart from development of DAN and decrease the incidence of arrhythmia and sudden death. The Akita mouse manifests a gender difference in the development of diabetes: males develop severe hyperglycemia and secondary effects of diabetes, while females exhibit only a mild hyperglycemia. Using male Akita mice, they had previously developed an animal model for DAN that is characterized by the appearance of spontaneous ventricular arrhythmias following myocardial infarction (MI). Here they propose to test the hypothesis that the female Akita mouse might serve as an animal model for the study of gender specific complications of DAN. Specifically, they will test the hypotheses that: (1) ovariectomy of female Akita mice results in the development of the diabetic phenotype and secondary effects of diabetes as demonstrated by the development of hyperglycemia, proteinuria, and a decreased parasympathetic inhibition of Isoproterenol-stimulated L-type Ca2+ currents, and that estrogen reverses this effect; (2) estrogen replacement protects ovariectomized female Akita mice against the development of spontaneous ventricular arrhythmias following MI; and (3) gene array studies will establish a subset of genes that are differentially expressed in ovariectomized mice who develop arrhythmias following MI, which might serve as candidate genes for the treatment and prevention of this effect of diabetes in women. Studies in this application propose to establish a unique animal model, which might offer a new gender specific therapeutic approach to diabetes and the complications of DAN.

Title: **Look AHEAD: Action for Health in Diabetes**
P.I.: **Mark Andrew Espeland**
Institution: **Wake Forest University, Winston-Salem, NC**
Grant No.: **5U01DK057136-11**
Award: **$100,000**

Look AHEAD is a randomized clinical trial examining the long-term health effects of an intensive weight loss intervention in approximately 5,145 overweight volunteers with type 2 diabetes. Participants are randomized to an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity, or to a control program of diabetes support and education. The primary outcome of Look AHEAD is the aggregate occurrence of severe cardiovascular events (fatal and non-fatal myocardial infarction

(MI) and stroke and cardiovascular deaths) over a planned followup of 11.5 years. The original grant application provided funding for the first 7 years of the study (1 year for study design and 6 for execution of the trial). The present grant application is for an additional 7 years of funding to complete the Look AHEAD trial. All aspects of the study have proceeded extremely well. The sample of 5,145 was recruited on time, retention has been excellent, and the intervention has been effective in producing initial weight loss and maintaining it over time. All 16 clinical sites have been successful in recruitment, retention, and delivery of the intervention and the DSMB has been very positive about the execution of the trial. The present application reviews the overall design of Look AHEAD, progress to date, and plans for the future. Specific aims are to retain the cohort over time, continue to complete annual in-person visits and semiannual telephone interviews for outcome assessments and continue to administer the lifestyle intervention. These procedures will enable us to analyze the effects of the intervention on serious cardiovascular-related factors and complications, and cost-effectiveness of the intervention.

Title: **Obesity, Inflammation, and Thrombosis: Look AHEAD**
P.I.: **Christie Ballantyne**
Institution: **Baylor College of Medicine, Houston, TX**
Grant No.: **5R01HL090514-03**
Award: **$20,000**

The increased number of obese diabetic individuals, coupled with their high cardiovascular morbidity, mortality, and healthcare expenditures, poses an enormous public health problem for the United States. Obese diabetic patients have increased inflammation and impaired coagulant balance, which are both thought to contribute to increased risk for atherothrombotic events. Although lifestyle modification with diet therapy, exercise, and weight management is recommended as foundation therapy by multiple national organizations, there are no prospective clinical trials that have shown significant cardiovascular event reduction by weight loss achieved by any modality. The Look AHEAD (Action for Health in Diabetes) study is a large multicenter trial designed to examine whether weight loss through intensive lifestyle intervention (ILI) with both diet and exercise will reduce cardiovascular events in obese diabetic individuals compared with a control group that receives diabetes support and education (DSE). The Look AHEAD trial has quantitatively assessed which aspects of lifestyle were modified by individuals (diet, physical activity) and effects on adiposity, fitness, and traditional risk factors (blood pressure, lipids, glycemic control). The proposed aims have been designed in conjunction with the Look AHEAD investigators to examine the effects of diet and exercise on inflammation and impaired coagulant balance. In this grant, they propose the following aims: (1) examine the association between measurements of obesity (weight, body mass index, waist, etc.) at baseline and levels of proinflammatory (IL-6, CRP) and anti-inflammatory (adiponectin isoforms) adipocytokines and parameters of impaired coagulant balance (PAI-1, fibrinogen, D-dimer, TAFI) in 50 percent of patients enrolled in the Look AHEAD trial and how this relationship is influenced by dietary intake, physical activity, fitness, gender, ethnicity, and presence of cardiovascular risk factors and disease; (2) compare the effects of ILI versus DSE on changes in inflammatory markers and impaired coagulant balance between baseline and year 1 and examine how changes are related to changes in adiposity, dietary intake, fitness, and physical activity; (3) examine how greater reductions in weight loss lead to greater changes in parameters that measure pathways of inflammation, oxidative stress, neurohormonal regulation, and impaired coagulant balance in a case-control study.

Title: **Gene X Behavior Interaction in the Look AHEAD Study**
P.I.: **Rena R. Wing (contact), Jeanne M. McCaffery**
Institution: **The Miriam Hospital, Providence, RI**
Grant No.: **3U01DK056992-11S1**
Award: **$301,213**

The interplay of genetic and behavioral factors is critical to understanding obesity and behavioral weight loss intervention has emerged as a key strategy in combating obesity. In this application, they propose to identify specific genes that predict individual differences in weight loss in response to behavioral intervention to help identify individuals that struggle with weight loss despite behavioral efforts. Obesity is a major public health problem, with millions of Americans suffering from weight-related health complications, including Type 2 diabetes, coronary heart disease, hypertension, and osteoarthritis. Behavioral weight loss intervention has emerged as a key strategy in combating obesity and the associated health consequences. However, individuals differ in their degree of success in these programs and genetic factors are known to play a role. In this application, they propose to identify specific genes that predict individual differences in weight loss in response to behavioral intervention to help identify individuals who struggle with weight loss despite behavioral efforts. Specifically, they will determine whether obesity genes interact with lifestyle intervention in predicting weight loss at year 1 of the Look AHEAD trial (U01DK056992), an NIH-funded, multicenter randomized controlled trial with the primary goal of determining whether weight loss achieved through an intensive lifestyle intervention can reduce cardiovascular morbidity and mortality among persons with type 2 diabetes. At year 1, participants assigned to Intensive Lifestyle Intervention (ILI), focusing on changes in diet and physical activity, lost an average of 8.6 percent of their weight (N= 2,496; 97.1 percent followup) relative to losses of 0.7 percent among individuals assigned to the Diabetes Support and Education (DSE) group (N= 2,463, 95.7 percent followup), who received diabetes support and education groups alone. Consent for genetic analyses was provided by 3,759 participants. Genotype data from the IBC chip, including over 4,000 markers within genes previously associated with obesity, will allow us to test their central hypothesis that genes that predispose to obesity interact with lifestyle treatment to influence weight loss following intensive lifestyle intervention. They conduct these aims with the explicit goal of bringing together a team with expertise in behavioral research, genetic epidemiology, and molecular biology to create transdisciplinary researchers who are able to bridge across the disciplines and identify key gene x behavior interactions in the context of the Look AHEAD trial.

Dietary Supplements/Complementary and Alternative Medicine

Title: **Botanical Dietary Supplements for Women's Health**
P.I.: **Norman R. Farnsworth**
Institution: **University of Illinois, Chicago**
Grant No.: **5P50 AT000155-10**
Award: **$95,158**

The UIC/NIH Center for Botanical Dietary Supplements Research was established in the fall of 1999 to address the issues of standardization, quality, safety, and efficacy of botanical dietary supplements. The Center then adopted and will continue to implement an interdisciplinary strategy to achieve its basic and clinical research objectives. Participating faculty co-investigators and collaborators are drawn from the Departments of Medicinal Chemistry and Pharmacognosy and Biopharmaceutical Sciences in the College of Pharmacy; the Department of Medicine (Section of Endocrinology and Metabolism) in the College of Medicine; and the Department of Math, Statistics, and Computer Science in the College of Liberal Arts. The Center studies botanicals with potential benefits for women's health, focusing on plants that are reported to alleviate the symptoms of menopause and premenstrual syndrome. Botanical extracts are

subjected to rigorous chemical evaluation followed by both in vitro and in vivo biological testing. Standardized botanical extracts that appear efficacious and demonstrate adequate safety profiles in in vitro and animal models will be candidates for clinical, Phase I trials. Hops (Humulus lupulus L.) will undergo Phase I evaluation in this grant cycle. In order to achieve this comprehensive agenda for the development of chemically- and biologically-standardized botanical dietary supplements, the renewed BRC research program will be organized as follows: Standardization of Botanicals; Mechanism of Action of Botanicals (Menopause); Studies of Metabolism, Bioavailability, and Toxicity. Two additional programs will be undertaken: a Pilot Project Program and a Training and Career Development Program. The experiments proposed in this application will greatly enhance their understanding of the mechanism of action of botanicals and whether they are safe and efficacious for women's health.

Genitourinary

Title: **Urinary Incontinence Treatment Network: Data Coordinating Center**
P.I.: **Sharon L. Tennstedt**
Institution: **New England Research Institutes, Inc., Watertown, MA**
Grant No.: **3U01DK058229-09S2**
Award: **$250,000**

This proposal is submitted in response to RFA-DK-06-501 for continuation of the Urinary Incontinence Treatment Network (UITN) Data Coordinating Center (DCC) at New England Research Institutes, Inc. (NERI). The DCC is responsible for the scientific management of the studies, including directing, training, and monitoring the performance of clinical centers in enrollment, data collection, and data management as well as for all data analysis, and reports to the Data and Safety Monitoring Board. In Phase I and continuing to Phase II, NERI has provided several unique and innovative tools and capabilities, including a proprietary Web-based data management system, an automated patient randomization system, and an electronic repository for urodynamic studies tracings. The DCC is also responsible for network communications and meeting support and provides a secure study website and a public website. DCC scientists play a leadership role in all network activities, including protocol development, standing committees and work groups, manuscript development and presentations. Phase II will focus on conduct of the trial of mid-urethral slings (TOMUS) as well as continuation of the observational followup studies for the SISTEr and BE-DRI studies (i.e., E-SISTEr and E-BE-DRI) of Phase I. Primary aims of TOMUS are to compare objective and subjective cure rates for stress incontinence at 12 and 24 months between the retropubic and transobturator midurethral sling procedures. Performance of these procedures is increasing rapidly with limited data available on safety and efficacy. Therefore, this study will compare the efficacy and safety of the retropubic and transobturator (inside-out and outside-in) procedures in a 2-arm RCT; 588 women with stress Ul will be enrolled. Primary Aim of E-SISTEr is to compare long-term (60 mos.) effectiveness and durability of the Burch colposuspension and autologous fascial sling for treatment of stress Ul in a randomized cohort of 655 women. Primary Aim of E-BE-DRI is to examine long-term (26 mos.) durability of the addition of behavioral treatment to drug therapy for treatment of urge Ul in a randomized cohort of 307 women. The UITN is a multi-disciplinary, multicenter group of Investigators dedicated to high impact clinical research regarding the prevention, evaluation and management of Ul to improve the quality of life for adults. The UITN is conducting 3 studies of treatments for both stress and urge urinary incontinence.

HIV/AIDS

Title: Gender Differences Among Women and Men Enrolled in China's National Free Antiretroviral Treatment
P.I.: Fujie Zhang
Institution: National Center/AIDS/STD Control/Prevent, Beijing, China
Grant No.: 5R03TW008203-02
Award: $56,206

The aims of this application are to: (1) evaluate gender differences in antiretroviral treatment outcome; and (2) if gender differences are detected, examine factors associated with these differences. Specific Aim 1 will be accomplished by testing a set of hypotheses that women differ from men on the following measures of response to first-line antiretroviral therapy (ART) including: (a) all-cause and HIV-related mortality in the first 24 months after initiating therapy; (b) immunologic response, as measured by change in CD4+ cell count in the first 24 months; (c) virologic response as measured by the proportion of patients who reached the undetectable level of viral load in the first 24 months; (d) ART-related side effects associated with different regimens, including symptoms and laboratory-based diagnoses within the first 24 months; and (e) time to stopping first-line ART after initiating therapy. Specific Aim 2 will be accomplished by performing multivariable analysis for any outcome found to differ significantly between women and men. Covariates that might explain the treatment outcome differences will be examined to determine if they differ in proportion between women and men. Those that do will be inserted into the multivariate model to determine if any are statistically significant. All analyses will be conducted using a national ART Database established by the China Center for Disease Control and Promotion (China CDC). This large database collects demographic and clinical care information on all patients participating in the free-ART program, which provides a unique resource for examining gender- related differences in community-based HIV treatment outcomes. Determining whether these differences exist and understanding their causes will benefit HIV-infected individuals not only in China but perhaps throughout the developing world. China has successfully implemented an antiretroviral treatment (ART) program, but many challenges remain in managing the program. The proposed study is a secondary data analysis of the China National Antiretroviral Treatment Database. The findings from the proposed analysis will provide invaluable information on the understanding of treatment differences between HIV-infected women and men in community-based ART programs and will assure the future success of the ART program in China. The analysis may also provide much-needed information to guide the assessment of other community-based HIV treatment programs in developing countries.

AIDS International Training and Research Program (AITRP)

This program supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries to conduct multidisciplinary biomedical and behavioral research to address the AIDS epidemic in their country. Grants are awarded to U.S. institutions with strong HIV-related research training experience and with HIV-related research collaborations with institutions in low- and middle-income countries. These institutions—in partnership with their foreign collaborating institutions—identify health scientists, clinicians, and allied health workers from the foreign countries to participate in their joint research training programs. For FY 2009, several awards were made to programs in Haiti, China, Malawi, Cameron, Brazil, and India.

Title: **AIDS International Training and Research Program**
P.I.: **Adaora A. Adimora**
Institution: **University of North Carolina, Chapel Hill**
Grant No.: **2D43TW001039-11**
Award: **$20,000**

Fogarty International Center trainees are serving in key leadership positions and are in the center of exciting and critical research activities. Working with their collaborating institutions they have assessed the priority health needs of their partner countries and propose a research training program that addresses the countries' research needs as well as the developmental plans of their collaborating institutions. This is the second competitive renewal application for the University of North Carolina (UNC) AIDS International Training and Research Program (AITRP). They propose to continue to provide training in three countries: The Peoples Republic of China, Malawi, and Cameroon. Investigators at UNC have worked in China since 1979, Malawi since 1989, and Cameroon since 1998. The UNC AITRP has embraced several guiding principles. First, they use training to build strong ties to key in-country organizations. Trainees with guaranteed return jobs in these organizations are preferentially selected. Second, their training opportunities build on funded research projects and bridge many of the strengths of UNC. Wherever possible they combine basic, clinical and epidemiological training and research in order to build critical mass. Third, they have used the Fogarty training to promote international research, working with many collaborators and funding agencies. Fourth, they have developed south-to-south and international collaborations to facilitate training and ongoing research opportunities. For example, University of the Witwatersrand is a training site for Malawi personnel, and they have developed a strong collaboration with the London School of Hygiene and Tropical Medicine for training of physicians from Malawi (a former British protectorate). Fifth, they have looked for opportunities for evolution and innovation. Such efforts have been particularly important in the development of a new Department of Public Health at the Malawi College of Medicine (which has received dedicated Fogarty support), extensive research ethics and Institutional Review Board training in China, and rapid technology transfer in all three UNC AITRP countries. Sixth, they are committed to in-country leadership and ongoing mentorship after the trainee has completed their program.

Title: **Emory AIDS International Training And Research Program**
P.I.: **Carlos Del Rio**
Institution: **Emory University, Atlanta, GA**
Grant No.: **2D43TW001042-11**
Award: **$20,000**

Located in Atlanta, the Emory AIDS International Training and Research Program (AITRP) has established itself as an interdisciplinary training environment that is producing highly qualified HIV/AIDS researchers. The collaborating countries of the Emory AITRP proposed for this application are Mexico, Georgia, Vietnam, Rwanda, and Zambia. The Specific Aims of the research training program include: 1. to build academic capacity in partner countries through the support of in-country education and training 2. to build HIV/AIDS research human resource capacity through the support of degree-seeking, long-term training 3. to fill identified gaps in partner country research training capacity through the provision of specialized medium and short-term training. 4. to build in-country capacity to conduct implementation science research that will allow their trainees to become involved in the evaluation of the impact of a variety of interventions that are currently occurring in their collaborating countries such as PEPFAR.

Title: **AIDS International Training and Research Program**
P.I.: **Lee Harrison**
Institution: **University of Pittsburgh, PA**
Grant No.: **2 D43 TW001038-11**
Award: **$20,000**

The proposed AIDS International Training and Research Program (AITRP) will substantially enhance the ability of Brazil, Mozambique, and India to conduct crucial HIV prevention research. They propose to continue the AITRP at the University of Pittsburgh. Their mission is to provide Brazilian, Indian, and Mozambican health professionals with interdisciplinary tools needed to conduct cutting-edge HIV prevention research in their countries. The director and codirector are, respectively, Dr. Lee Harrison, Professor of Epidemiology and Medicine, and Dr. Phalguni Gupta, Professor of Infectious Diseases and Microbiology. An exciting change in their program is the addition of a site in Beira, Mozambique, which has striking training needs and where the university has established close collaborations with the Universidade Catolica de Mozambique. The addition of Mozambique and the training of a large cadre of well-trained Brazilian investigators over the past ten years allow them to dramatically reduce their training efforts in Brazil and shift resources to Mozambique. As a component of their training program, they will leverage the extensive training already provided to Brazil by conducting south-to-south training between these two Portuguese-speaking countries. Ongoing research in Brazil includes HIV vaccine trials, studies of effectiveness of antiretroviral therapy in public clinics, and changes in causes of death among HIV-infected patients. In India, ongoing projects include studies of genetic heterogeneity of Indian HIV strains, CDS suppression of HIV, HIV incidence studies to identify high-risk populations, and development of a novel Clostridium perfringens-based oral HIV vaccine. Research at their new site in Mozambique is currently limited and they will use the training provided by the University of Pittsburgh AITRP to jump-start a much-needed research agenda there. Trainees from all three countries will have access to the substantial HIV research activities at the University of Pittsburgh, including research in epidemiology, behavioral sciences, and laboratory sciences. During the next five years, they propose to establish an extensive training program in Mozambique; provide limited, selected training for Brazil; and provide laboratory and behavioral sciences training for India. Their successful track record during the first 10 years, the excellent training opportunities they propose, and collaboration with key institutions in their three countries assure that their program will continue to be highly productive.

Title: **Vanderbilt University-CIDRZ AIDS International Training and Research Program**
P.I.: **Sten H. Vermund**
Institution: **Vanderbilt University, Nashville, TN**
Grant No.: **2D43TW001035-11**
Award: **$20,000**

The Vanderbilt University Center for Infectious Disease Research in Zambia (VU-CIDRZ) training partnership with their international collaborators is designed to strengthen both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care in developing countries. The Vanderbilt University (VU) Center for Infectious Disease Research in Zambia (CIDRZ) AITRP, formerly the VU-University of Alabama at Birmingham AITRP, seeks renewal of its grant, now in its 10th year due to an NIH-initiated 1-year extension. They contribute research training to both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care. The VU-CIDRZ training partnership with their international collaborators is designed to train foreign scientists and key research support staff

to conduct independent research and training in their home countries, as well as perform at an internationally credible level in collaborations with local and foreign scientists. They now seek to renew their AITRP with a continued focus on Zambia (since 1998), Pakistan (since 1994), India (since 2000), China (since 2000), and their newest partnership in Mozambique (VU training partnership since 2006 and developmental AITRP engagement since 2007). They have completed their older training commitments in Mongolia, Jamaica, and Russia and will complete their training commitments for Bangladesh upon the graduation of a current doctoral training (anticipated in 2011). They have restricted their AITRP training partnerships to five focus cities in order not to dilute their impact to where they have funded overseas research and strong research training partners. At the same time, they have leveraged support in each of the five venues such that their AITRP resources will go much further than permitted by the grant's funding alone. They will continue to provide a diverse portfolio of long-, medium-, and short-term training options. To date 58 trainees have received graduate degrees, 97 percent of whom have returned to work in their home countries, eight are currently in degree programs and more than 2,000 have been trained through their in-country advanced short courses. They believe VU remains an ideal university partner for this initiative for several significant reasons. The migration of the training program to VU offers the opportunity for trainees to receive the absolute highest quality of graduate training and exposure to innovative HIV/AIDS-, STD-, and TB-related research, resources, and faculty mentors. The program is uniquely positioned within the infrastructure of the VU Institute for Global Health (VU-IGH), directed by Dr. Vermund with its "center-without-walls" philosophy that nurtures noncompetitive partnerships among and within VU and with partner institutions around the globe. They feel that the innovative features of their renewal and their proven track record address the unmet needs in international AIDS training.

Microbicides Innovation Program (MIP)

In collaboration with the NIH Office of AIDS Research (OAR), National Institute of Allergy and Infectious Diseases (NIAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH), ORWH has funded a number of R21/R33 innovation projects to support exploratory and developmental research on new microbicides and microbicides strategies and technologies in the goal of advancing promising strategies and technologies into the preclinical and clinical development of new agents. RFAs, all using the title Microbicides Innovation Program (MIP), have been issued in recent years to expand the research base in this area. The development of safe, effective, acceptable topical microbicides to prevent the sexual transmission of HIV could play a major role in worldwide reduction of new HIV infections. An effective and acceptable microbicide potentially could save millions of lives. Topical microbicides are agents that can result in inhibition of the transmission of HIV and/or other sexually transmitted infections (STIs), which may be cofactors in HIV transmission. The purpose of the MIP is to support novel and underexplored strategies in the field of topical microbicides.

Summaries for the individual MIP awards follow:

Title:	**Mucus-Penetrating Nanoparticles for Sustained Microbicide Delivery**
P.I.:	**Richard A. Cone, Justin S. Hanes (contact)**
Institution:	**Johns Hopkins University, Baltimore, MD**
Grant No.:	**5R21AI079740-02**
Award:	**$13,637**

They have developed mucus-penetrating nanoparticles (MPP) suitable for sustained delivery of small-molecule microbicides (Lai et al [2007]. *Proceedings of the National Academy of Sciences, 104*(5),1482-1487). Conventional particles (CP) are mucoadhesive and stick to the outer layers of

mucus that are shed most rapidly out of the vagina. By densely coating MPP with low molecular weight polyethylene glycol (PEG) they found that unexpectedly large MPP 100–500 nm in diameter can be engineered to rapidly penetrate human cervicovaginal (CV) mucus and thereby reach the unstirred layer of mucus adhering to the epithelial surface. These MPP will likely significantly increase vaginal residence time and improve epithelial microbicide distribution. The aim of this R21/R33 project is to develop MPP for the sustained delivery of small-molecule microbicides to increase their protective efficacy, acceptability, and user reliability. 'User failure' is the primary failure mode of barrier methods, and microbicides are likely to be used more reliably if applied daily on a coitally-dissociated basis. Another failure mode well-documented in animal models is inadequate microbicide distribution - the infectious inoculum reaches surfaces unprotected by the microbicide. MPP can provide a once-a-day, coitally-dissociated method that is likely to achieve complete and essentially uniform epithelial distribution. MPP will not likely provide the month-long delivery of a vaginal ring, but MPP have advantages that are not immediately apparent, as follows: (1) the vaginal epithelium is highly permeable to small water-soluble molecules, thus uniform epithelial distribution can best be achieved by uniform sustained delivery of small water soluble microbicides directly to the entire epithelial surface, not just to the vicinity of a vaginal ring; (2) uterine peristalsis exposes the upper reproductive tract to vaginally deposited pathogens, and reliable protection of the upper tract is more likely to be achieved by MPP that can transport, and then locally deliver, small water-soluble molecules to the epithelia surfaces of the upper tract. In the R21 phase they propose to develop acyclovir-loaded MPP to evaluate in their mouse herpes simplex virus (HSV) models for efficacy, duration, vaginal distribution, and toxicity. The MPP will be composed of biodegradable copolymers that they have shown are capable of sustained delivery of a wide range of bioactive molecules. The key milestone for R21 will be to develop acyclovir-MPP that provide at least one day of protection in the mouse. In the R33 phase, they will use the knowledge gained from the R21 phase to speed the development of an anti-HIV MPP for sustained release of the best anti-HIV microbicide candidate then available (fall 2010), with tenofovir being a likely choice. The R33 anti-HIV MPP will be optimized for drug delivery based on R21 results, and be tested for toxicity in mouse models and for efficacy in the Hu-BLT-SCID mouse/HIV model by Dr. Victor Garcia at University of Texas Southwestern. World-wide, there is a great need for methods women can use to protect against AIDS and other sexually transmitted diseases. Several small-molecule vaginal microbicides are being developed that block HIV from infecting and/or replicating in target cells. The aim of this project is to enhance the protective efficacy of these small-molecule microbicides by developing mucus-penetrating nanoparticles that will improve coverage of susceptible tissues to increase reliability of protection, and to increase duration of protection so that the microbicides can be applied regularly, on a daily basis, and not require coitally-related applications.

Title: **Novel Mucosal Models Predictive of Microbicide Safety**
P.I.: **Betsy C. Herold (contact), Marla J. Keller**
Institution: **Yeshiva University, Bronx, NY**
Grant No.: **5R21AI079763-02**
Award: **$13,637**

The proposed Microbicide Innovation Program fosters the development of new model systems (dual chamber and murine) that have the potential to substantially advance microbicide science. This approach is designed to improve methods for assessment of microbicide safety. The optimal microbicide should protect against infection without disrupting the mucosal environment or its mediators of host defense. The clinical trial failures with nonoxynol-9 and cellulose sulfate highlight the challenges in microbicide research and the need to establish better markers predictive of microbicide safety. The proposed studies address this gap. The primary objective of the R21 component is to establish two synergistic models of microbicide safety: (1) an in vitro dual chamber model using primary human cervical epithelial cells and

(2) a murine model. Preliminary findings with these models demonstrate that the models would have predicted the increase in HIV acquisition observed in recently completed clinical trials. The microbicides disrupt the epithelium in vitro, as evidenced by a loss in transepithelial electrical resistance and in structural proteins and these changes are associated with an increased migration of cell-free HIV across the epithelium. In parallel studies, the drugs also trigger substantial changes in genital tract tissue architecture in mice following repeated vaginal application and the observed changes are associated with an increased susceptibility to genital herpes infection. Establishment of these two complementary models will contribute to efficient assessment of microbicide safety. During the R33 phase, both models will be translated into the preclinical pipeline by evaluating leading microbicide candidates, singly and in combination. Candidate microbicides will be introduced in the presence of cervicovaginal secretions and challenged in vitro with virus introduced in semen. The migration of both cell-free and cell-associated HIV will be tested in the dual chamber model system. In addition, during the R33 phase, the in vitro model will be expanded to assess the impact of microbicides on cells derived from women with human papillomavirus (HPV) associated dysplasia. While it is critical to assess the effect of microbicides on healthy genital tract cells and mucosa, it is highly likely that many women who choose to use a microbicide will be infected with a sexually transmitted infection. HPV is the most common sexually transmitted infection worldwide and changes in genital tract epithelium in response to microbicides may differ in women with HPV. These results will provide critical new data on microbicide safety in women with a sexually transmitted infection. Biomarkers predictive of microbicide safety are urgently needed. Tissue and murine models may provide more efficient strategies to assess microbicide safety by expanding existing models to include testing of primary cells. Development of an effective dual chamber and murine model may prove to be important in determining which candidate microbicides to move forward in the development pipeline. In addition, these models may provide a means to test the safety of microbicides in healthy women as well as those with underlying STIs.

Title: **Novel Vaginal Microbicides Based on Stable AAV-Neutralizing Antibody Gene Transfer**
P.I.: **Wayne A. Marasco**
Institution: **Dana-Farber Cancer Institute, Boston, MA**
Grant No.: **5R21AI079767-02**
Award: **$13,637**

In the global AIDS pandemic, more than half of new HIV-1 infections are acquired by women through intravaginal HIV exposure. Although cervicovaginal epithelial cells lining the mucosal surfaces of the female lower genital track provide the initial defense system against HIV-1 infection, the protection is often incomplete. Transport of HIV-1 across this mucosal barrier is absolutely critical for HIV-1 colonization and subsequent virus dissemination and thus, enhancing anti-HIV-1 humoral immunity at the mucosal cell surface by the local expression of anti-HIV-1 neutralizing antibodies (nAbs) that block epithelial cell attachment and virus entry may provide an important new intervention that could slow the spread of HIV/AIDS. This R21/R33 project represents the combined efforts of the Marasco (Antibody Engineering, Gene Therapy), Anderson (Mucosal Immunity) and Mansfield (HIV/AIDS Macaque Model) laboratories to investigate whether stable adeno-associated virus (AAV)-nAb gene transfer to the cervicovaginal epithelial stem cells can provide a strategy that will lead to durable protection against HIV-1. In the R21 phase, they will first determine which of nine AAV serotypes provides optimal gene transfer of GFP without toxicity to primary human (Hu) and rhesus macaque (Rh) primary genital epithelial cells (PGECs) comprising endocervical, ectocervical and vaginal epithelial cells with special focus on stable gene transfer into p63+CK17+epithelial stem cells which are capable of renewing stratified epithelium. Persistence

of AAV-GFP transduction, potential toxicities and effects of proinflammatory cytokines, hormonal conditions, semen and vaginal secretions on transduction efficiency and transgene persistence will be examined. They will construct a miniaturized version (minibody) of broadly neutralized human anti-gp120 Mab b12 in both the IgG1 and dimeric IgA2 format and assess b12 neutralizing activity against HIV-1/SHIV by both Ab treatment studies and AAV gene delivery to organotypic human vaginal and endocervical models and Hu and Rh PGECs. Upon successful demonstration of in vitro protection, the R33 phase will begin where they will first conduct an AAV-transduction dose escalation study in Rh (n=12) to evaluate depth, uniformity and extent of p63+,CK17+ stem cell transduction, the PK of b12scFv-FcG1 and b12scFv-FcA2 secretion, and toxicity. This will be followed by a second intravaginal transduction study with the optimal dose of the two AAV-b12scFv vectors each alone and together followed by vaginal challenge with SHIV (Rh=15-16). Finally, they will evaluate enhanced SHIV protection through mixtures of gel-forming polymers and AAV to increase in vivo AAV transduction and b12scFv-Fc secretion (Rh=9). Overall, 13 hypotheses will be tested. These important studies fulfill a major objective of the R21/R33 program to support research that may be high risk/impact and have the potential to advance AIDS microbicide strategies. Given the safety profile, low immunogenicity and rapid advancement of AAV-based gene therapy in numerous clinical trials, it is likely that success of this novel approach could be quickly translated to human studies. HIV-1 infections are acquired most often through sexual contact and more than half of new infections are acquired by women through intravaginal HIV exposure. They propose to develop a genetic microbicide that when delivered to the mucosal surface of the cervix and vagina will allow the lining cells to stably produce a neutralizing human anti-HIV antibody that blocks HIV-1 attachment and infection. A protective genetic microbicide delivered to the female lower genital track could dramatically slow the spread of HIV/AIDS.

Title: **HIV Integrase as a Target for Topical Microbicide Development**
P.I.: **Mary E. Klotman**
Institution: **Mount Sinai School of Medicine of New York University**
Grant No.: **5R21AI079776-02**
Award: **$13,637**

Over 4 million individuals were newly infected with HIV in 2006 with sexual transmission the predominant mode of infection worldwide, highlighting the need for effective prevention strategies. Unfortunately clinical trials to date, with the first generation of candidate topical microbicides to block sexual transmission, have been disappointing as both nonoxynol-9 (N-9) and more recently cellulose sulfate (CS) either did not block transmission or actually enhanced transmission. These results highlight the continued need for highly efficacious and safe microbicide candidates. This project will address the safety and efficacy of a new class of specific anti-retrovirals as topical microbicide candidates, integrase inhibitors. The integrase inhibitor, GS-9160, is a potent inhibitor of HIV which has been extensively studied in animals and most recently in a Phase I human trial and has had no significant toxicity. The potential of this drug as a candidate microbicide will be evaluated in two phases. In the R21 phase, a candidate gel formulation of GS-9160 will be generated in collaboration with Gilead Sciences and evaluated for in vitro drug loading and stability. The drug and candidate formulation with favorable loading will be evaluated in cervical and vaginal epithelial cell monolayers and cervicovaginal explants for release and uptake, cytotoxicity, and efficacy against primary and laboratory isolates. The parallel evaluation of gene expression induced by formulated GS-9160 in human and rhesus macaque (RM) cervicovaginal explants along with a similar analysis of tissue and cervical vaginal lavage (CVL) fluid derived from in vivo RM studies in the R33 phase will validate the cervicovaginal explant model as a screen for host responses in vivo. If the candidate formulation has an acceptable safety profile as determined by the absence of a proinflammatory response (comparable to N-9) and inhibits HIV infection in the explant

model, the R33 phase will be initiated with testing of local and systemic pharmacokinetics and toxicity associated with vaginal delivery of formulated GS-9160 in RM followed by an efficacy study in RM vaginally challenged with R5 SHIV. The proposed studies will directly address whether integrase inhibitors as a class should be added to the pipeline for microbicide development. In addition, studies proposed will validate the genital explant model as a screen for host responses in vivo.

Title: **Combinations of Entry Inhibitors as Anti-HIV-1 Microbicides**
P.I.: **Patricia J. Liwang**
Institution: **University of California, Merced**
Grant No.: **5R21AI079777-02**
Award: **$13,637**

Given the high rate of sexual transmission of HIV-1, particularly in the developing world, the need for a topical microbicide is critical. The long term goal of this research is to develop an anti-HIV microbicide using HIV-1 fusion inhibitors. In particular, they have found that the combination of certain chemokine variants with gp41-binding proteins results in highly potent inhibition of HIV-1, both in fusion assays (IC50=1 pM) and in viral assays in PBMC (IC50=0.7 nM, R5 tropic strain Ba-L). The Aims of the proposal are as follows: First, combinations of CCR5 binding proteins and gp41-binding peptides will be tested in both fusion assays and in viral assays with multiple clades of HIV as well as primary strains in order to determine which combinations provide the most potent protection. Then it will be determined if a higher level of inhibition efficiency can be obtained by combining both a variant chemokine and a gp41-binding protein on a single polypeptide chain. During the R33 phase of the project, it is proposed to carry out pre-clinical evaluation of the most potent inhibitors and combinations, including, stability to pH and ionic strength, cell toxicity, and irritation in animal models. The most promising inhibitors will then be tested in two different ways. In Aim 4 they will be expressed by Lactobacillus jensenii, an organism that is naturally found in vaginal mucosa, and as such represents a method of delivery of protein microbicides having great potential. Finally, in Aim 5, the best entry inhibitors will be evaluated in a humanized mouse model that has been shown to be able to be infected with HIV. Anti-HIV microbicides are molecules that can be used topically to prevent the spread of the HIV-1 virus through sexual transmission. The proposed experiments will study the combination of CCR5-binding proteins and gp41-binding proteins to synergistically inhibit HIV and as components of a microbicide.

Title: **Scalable Production of Recombinant Protein Microbicides**
P.I.: **Julian Ma**
Institution: **St. George's Hospital Medical School, London, UK**
Grant No.: **5R21AI079785-02**
Award: **$13,637**

HIV microbicides are designed to be applied topically before sexual intercourse to inactivate the virus and prevent infection. Some of the most promising microbicide candidates have been proteins, but their clinical development and evaluation has been hampered by the lack of available material and/or the prospect of having to manufacture vast quantities of recombinant protein very cheaply. Plant biotechnology offers some potential solutions. Whilst the production of microbicides at agricultural scale is a long-term aim, it is likely that the first generation products will emerge from plants grown in containment, under conditions more recognizable as conventional medicine production systems. It has long been established that recombinant proteins can be expressed in all tissues of the plant, including roots. Indeed, some recombinant proteins produced by transgenic plants are actively secreted from the root system in a process known as rhizosecretion. This gives rise to the possibility that transgenic

plants could be grown in greenhouses under hydroponic conditions, using a defined culture medium. Moreover, the microbicide product could be harvested from hydroponic culture medium, rather than plant tissue, which would greatly simplify purification, and allow harvest over the lifetime of the plant. Hydroponic cultivation of plants is already a well-established technique in the horticultural industry and is also currently used for the production of natural medicinal compounds. The objective of this proposal is to establish a contained hydroponic tobacco plant culture approach for production of two microbicide protein candidates, cyanovirin-N and MAb 4E10, and to develop optimization strategies for growth and production that will deliver previously unavailable protein microbicides at a level to allow clinical evaluation. They will establish production at small commercial scale. In the first (R21) phase of the proposal, they intend to demonstrate feasibility of the approach and have established production-driven milestones for entry into the second (R33) phase, in which they will develop manufacturing and purification according to good practice regulatory requirements ultimately to deliver protein microbicides for clinical trials. Cyanovirin-N and MAb 4E10 are two of the most promising protein microbicide candidates currently available. However, the clinical development of both has been held back by production difficulties, and their efficacy and safety profiles are still to be determined. This project is aimed at developing a production platform for CV-N, MAb 4E10 and ultimately other recombinant protein microbicides, which will advance these products to human clinical trials.

Title: **Intravaginal Ring Microbicide Formulations Comprising Multiple Anti-HIV Agents**
P.I.: **Thomas J. Smith**
Institution: **Oak Crest Institute of Science, Pasadena, CA**
Grant No.: **5R21AI079791-02**
Award: **$13,637**

The broad long-term goal of this project is to empower women to protect themselves from HIV infection through the development of improved vaginal ring formulations for microbicides based on the sustained release drug delivery of antiviral agents. Their clinically proven sustained release drug delivery platform uniquely allows them to deliver drugs of both high- and low-aqueous solubility. The ganciclovir intraocular implant,Vitrasert, approved for the treatment of AIDS-related cytomegalovirus (CMV) retinitis, releases the relatively soluble antiviral ganciclovir into the eye for a period of eight months. Retisert releases the relatively insoluble steroid fluocinolone acetonide for up to three years. They propose to utilize this platform technology to develop long-term vaginal ring formulations for the potential microbicides tenofovir and TMC-120. In the first two years of this project (R21) they will evaluate the hypothesis that, when incorporated into a ring formulation, the prodrug tenofovir disoproxil fumarate is superior to the parent drug tenofovir as candidate microbicide. In the second phase of the project (R33) they will manufacture and test ring formulations containing multiple antiviral agents. They hypothesize that, using their unique drug delivery platform, there will be no loss of elution characteristics with the incorporation of multiple drugs into their system. The successful completion of this project will result in the submission of an investigational new drug exemption (IND) leading to clinical trials for these formulations. Each day 15,000 people are infected by HIV, the majority in sub-Saharan Africa and a growing percentage of women infected though heterosexual sex.

Title: HIV Sexual Transmission in Mice: Study Of Microbicide Efficacy
P.I.: Mary Jane Potash
Institution: St. Luke's-Roosevelt Institute for Health Sciences, New York, NY
Grant No.: 5R21AI079792-02
Award: $13,637

This application is submitted in response to RFA-AI-07-034. They have constructed a model of systemic infection of immunocompetent mice by chimeric HIV-1, EcoHIV. Their previous studies indicate that EcoHIV replicates in lymphocytes and macrophages in infected mice, infection in mice is sensitive to antiretroviral drugs, productive infection persists for months inducing immune responses, and HIV-1 DNA vaccination can block infection in mice. Preliminary results reported here show that sexual transmission of EcoHIV in mice is rapid and efficient. Their overall goal in this application is to develop the mouse infection system to investigate the mechanisms of sexual transmission of HIV-1 as a platform to test efficacy of candidate microbicides. The Specific Aims of are: (1) to optimize conditions for sexual transmission of EcoHIV in mice and evaluate interventions; (2) to identify the cell types involved in sexual transmission of EcoHIV; 3) to test the inhibition of sexual transmission of EcoHIV by antiretroviral-based microbicides; 4) to determine the HIV-1 subtype dependence of sexual transmission and efficacy of antiretroviral based microbicides against different HIV-1 subtypes; 5) to determine whether combination administration of an HIV-1 DNA vaccine followed by a microbicide can prevent sexual transmission of subtype B EcoHIV. Chimeric HIV-1 will be transmitted to conventional, immunocompetent female mice by mating with males infected through inoculation. Virus burden in multiple organs will be measured by real-time PCR and productively infected cells will be identified by flow cytometry and confocal microscopy. Accomplishment of Aims 1–3 will provide a firm foundation for and justification to extend the model to Aims 4–5 in studies directly relevant to the current HIV-1 epidemic and to develop realistic means to control the epidemic. HIV-1 infection continues to spread worldwide, primarily by sexual transmission. The public health community responded to this pandemic by research into microbicides, compounds that women can apply to prevent transmission of HIV-1 during intercourse. Unfortunately, there is no simple way to determine which of many microbicides being developed actually blocks HIV-1 transmission until women begin their use. Some of the first to be tested by women in clinical trial actually increased HIV-1 transmission. This application is designed to develop a system for preclinical testing of microbicides in mice to determine their ability to reduce or prevent sexual transmission of HIV-1. They have shown that a form of HIV-1 that they genetically engineered to infect mice is very easily transmitted during mating. They propose to optimize this system to determine how well microbicides block sexual transmission of HIV-1. They shall also test in mice how the forms of HIV-1 that are widely distributed today can be controlled by microbicides. They have already shown that vaccination can reduce susceptibility to HIV-1 in mice. They also plan to both vaccinate mice and then treat with microbicides to determine if it is possible to completely prevent sexual transmission of the virus. Their hope is that the model of sexual transmission of HIV-1 in mice can accelerate the development of safe and effective microbicides that can be used to control the AIDS pandemic.

Title: **HIV Microbicides and the Vaginal Microbiome**
P.I.: **Steven L. Zeichner (contact), Jacques Ravel**
Institution: **Children's Research Institute, Washington, DC**
Grant No.: **5R21AI079798-02**
Award: **$13,637**

Vaginal HIV microbicides offer great promise to reduce HIV transmission, but phase 3 microbicide trials have failed. In some studies, patients using the microbicides had higher HIV transmission rates than did subjects using placebos. There is no clear explanation for these failures, but one hypothesis holds that microbicides alter the vaginal microbial flora in ways that increase inflammation or activate potential HIV host cells, enhancing transmission. Studies examining the effects of microbicides on the vaginal flora found few significant effects on the microbiome, but they used conventional culture techniques. Recent studies using molecular, culture-independent techniques showed that the flora in many human microbial environments, including the vagina, is much more complex than previously appreciated and that conventional culture techniques only detect a small fraction of the microbes in the environment. They propose to use these new culture-independent techniques to explore the hypothesis that microbicides alter the vaginal microbiome in ways that can potentially enhance HIV transmission via these Specific Aims: (1) examine the vaginal microbial flora before and after microbicide application in a CONRAD repeat phase 1 study of nonoxynol-9 (N-9), cellulose sulfate (CS), and placebo using Affymetrix PhyloChip microarrays; (2) examine the portfolio of expressed genes in the vaginal microbiome before and after microbicide application using microbial cDNA sequencing in the phase 1 study; (3) examine the microbial species composition before and after microbicide application in the CONRAD CS phase 3 study that failed using the PhyloChip and direct 16S rRNA gene sequencing. The main milestone they propose as a transition from the initial R21 phase of the project to the R33 phase is the demonstration that microbicide use leads to a significant alteration in the vaginal flora as assessed by the PhyloChip. Determining whether microbicide application is associated with vaginal microbiome changes that could enhance HIV transmission would aid understanding of the failure of the previous phase 3 trials and would help future microbicide development efforts because, if harmful changes in vaginal flora are associated with microbicide use, future microbicide development efforts would require careful measures to avoid inducing potentially harmful changes in the vaginal microbiome. Vaginal microbicides for the prevention of HIV sexual transmission offer great theoretical promise to reduce HIV sexual transmission and blunt the HIV pandemic, particularly in regions with the highest HIV prevalence rates. Unfortunately, several large late phase trials of HIV microbicides have failed for unknown reasons, with the research subjects using the microbicides having rates of HIV transmission higher than subjects using placebos. They hypothesize that one factor contributing to the failure of the microbicides is that their use produces a harmful change in the microbial flora living in the vagina, which leads to inflammation or activation of the cells that HIV replicates in, increasing the risks of HIV transmission. In their study, they propose to use new molecular biological techniques to comprehensively catalog essentially all of the microbes living in the vagina and determine how the use of HIV microbicides alters the population of the microbes. Determining that the use of HIV microbicides lead to a significant, potentially harmful alteration in the population of vaginal flora would help explain the failure of the existing microbicides to prevent HIV transmission and may help enable the development of new, more effective HIV microbicides.

Title: **Microbicide Properties of RT Inhibitor Combinations**
P.I.: **Michael A. Parniak**
Institution: **University of Pittsburgh, PA**
Grant No.: **5R21AI079801-02**
Award: **$13,637**

Topical microbicides are an important strategy to minimize heterosexual transmission of HIV. Several single-agent microbicides are in clinical trials, including one based on the nonnucleoside reverse transcriptase inhibitor (NNRTI) UC781 that they discovered as a potential microbicidal agent. However, combination microbicides may be preferable, yet only a single combination microbicide is currently under evaluation. There is also an urgent need to identify new pipeline microbicidal agents. They have found that the nucleoside RT inhibitor (NRTI) 4'-ethynyl-2-fluoro-deoxyadenosine (4'E-2FdA) provides a potent and prolonged barrier to HIV- 1 infection of cells in the subsequent absence of exogenous drug, a property previously only noted for NNRTI such as UC781. The memory effect barrier is imparted by 4'E-2FdA at drug levels orders of magnitude less than those needed for protection by the nucleotide tenofovir, currently in clinical assessment for microbicide use. They hypothesize that microbicides comprising combinations of different classes of highly potent RT inhibitors, namely the NNRTI UC781 and an NRTI such as 4'E-2FdA, will provide an optimal barrier to HIV-1 transmission. They therefore propose these Specific Aims for this R21/R33 phased innovation application: R21 Aim 1. To evaluate the in vitro (cell-based) microbicidal properties of NRTI and UC781 alone and in combination. These studies include assessment of antiviral activity and memory effect protection imparted by NRTIs and UC781 alone and in combination using primary cells (PBMCs, CD4+ T-cells, macrophages) and different HIV drug-sensitive and drug-resistant strains, isolates and clades. R21 Aim 2. To elucidate the mechanism of 4'E-2FdA (and analogs) induced protective barrier or memory effect in HIV susceptible cells. These studies include characterization of uptake, conversion to triphosphate, and intracellular stability of the NRTI-TPs, as well as detailed kinetic evaluations of the NRTI substrate activity with enzymes involved in metabolism of the NRTIs. R21 deliverables: identification of a lead NRTI and two backups for use with UC781 for development as a combination microbicide. R33 Aim 1. To formulate the NRTI/NNRTI combinations selected in the R21 phase into an appropriate delivery system for vaginal topical use. NRTIs and NNRTIs have different chemical properties, thus appropriate delivery systems must be identified to enable incorporation and release of the active agents. They will prepare and evaluate both gel and rapidly dissolving film formulations for the combination microbicide. R33 Aim 2. To evaluate the anti-HIV microbicidal activity of formulated NRTI/NNRTI combinations in an ex vivo cervical explant tissue model. These studies will use a newly developed physiologically relevant polarized cervical tissue model to assess the impact of formulated microbicides alone and in combination on HIV transmission and infectivity. R33 Deliverables: identification of an appropriate delivery formulation for the selected NRTI/NNRTI combination for entry into subsequent preclinical safety and efficacy studies. This project seeks to develop anti-HIV microbicides based on the non-nucleoside RT inhibitor UC781 in combination with novel 4'-substituted nucleosides, a combination found to provide profound and protracted protection of susceptible cells against HIV infection in vitro. Their studies will provide potent new formulations to the microbicide development pipeline for entry into clinical evaluation.

Title: **New SHIV R5 Envs (Based On All Subtypes) for Effective Microbicide Testing**
P.I.: **Eric J. Arts**
Institution: **Case Western Reserve University, Cleveland, OH**
Grant No.: **5R21AI079852-02**
Award: **$13,637**

SIV strains containing HIV-1 env genes (SHIVenv) have been successfully employed to infect macaques through intravenous and mucosal routes. These macaque models have been crucial for studies on HIV pathogenesis, vaccine, and microbicide testing. However, few SHIVenv strains can maintain stable and prolonged infections. Several challenges are apparent in the testing of anti-HIV-1 microbicides and many of these stem from poor animal models to test efficacy. In the R21 proposal, they have outlined a system to construct and test the infectivity of SHIV based on the env and pol genes of subtype A, B, C, and D from acute/early infections. In aim 1, they will utilize a rapid yeast recombination cloning approach to shuttle approximately 400 HIV-1 env genes into an HIV-1NL4-3 or SIV backbones of mac239 and KB-9. The HIV-1 subtype A, C, and D env genes will be PCR amplified from the endocervix or blood of Ugandan and Zimbabwean women within three months or after three years of infection. Over 20 HIV-1 env chimeric viruses have already been constructed and tested using env genes from these patient samples. HIV and SIV env chimeric viruses will be included in subtype-specific pools if the clone is capable of replication on cell lines expressing human or rhesus CD4/CCR5 (respectively) and in human or rhesus PBMCs (respectively). In aim 2, the pathogenicity of these pools will then be accessed (1) using vaginal explants and (2) through vaginal exposure in macaques. The clones that establish infection in both the explant tissue and macaques can then be reconstituted into the pathogenic subtype A, B, C, and D pools for the microbicide studies described in the R33 section of this proposal (aim 3). First, they will determine if higher concentrations of cmpd167 or PSC-RANTES are required to inhibit the pathogenic subtype A, B, C, and D pools of HIV or SHIVs (as compared to the standard SHIVSF162-P3) in human or rhesus vaginal explant tissues. They determine the identity of any HIV or SHIV clone(s) that are capable of infection even in the presence of the drug. These specific HIV-1 clones (produced from original DNA clones) can then be tested for sensitivity to CMPD167 and PSC-RANTES and to determine if infection was related to drug resistance. Finally and most importantly, microbicides CMPD167 and PSC-RANTES will be vaginally applied to rhesus macaques prior to exposure with the infectious subtype A, B, C, and D pools as well as the standard SHIVSF162-P3. They suspect that the majority of the treated macaques will be protected from SHIVSF162-P3 infection. In contrast, the protective effects of the microbicides may be reduced and in some animals, a slight delay in viremia (as compared to untreated animals) may be the result of infection by specific clone in the SHIV pool with reduced sensitivity to CMPD167 and PSC-RANTES. Vaginal microbicides provide an excellent method to protect women from HIV-1 infection but testing these products prior to human use remains a challenge. A monkey species (e.g. Rhesus macaques) and virus cousin of HIV-1 (SHIV) are used to test the level of protection by these compounds. In this proposal, they have designed new SHIVs that are more closely related to HIV-1 and provide more stringent testing of microbicides for future human use.

Title: **Development of a Novel Semen-Activated Prodrug as an Anti-HIV Microbicide**
P.I.: **Robert W. Buckheit, Jr.**
Institution: **Imquest Biosciences, Frederick, MD**
Grant No.: **1R21AI079772-01A1**
Award: **$37,500**

The S-acyl-2-mercaptobenzamide thioester (SAMT) inhibitors are low-molecular-weight compounds which target multiple steps in the HIV replication pathway, but primarily function to specifically inactivate cell-free HIV immediately upon exposure to the reactive compounds and to suppress the production of infectious HIV from virus-infected cells. These NCp7-targeted, virus inactivating compounds act by stripping coordinated zinc ions from the nucleocapsid (NC) protein in the infectious virion or maturing virus particle. In the process, the compounds irreversibly cross-link the nucleocapsid proteins rendering the virion noninfectious and defective. Thus, the NCp7 inhibitors interfere with two potential virus transmission mechanisms required for the infection of target cells in the vaginal environment. In the R21 phase of this proposal they propose to develop new microbicides composed of polymeric prodrugs for delivery of the SAMTs. This delivery mechanism limits the tissue absorption of the SAMT until it comes in contact with the viral inoculum in semen by attaching it to a high molecular weight biocompatible polymer. They will conjugate the SAMT inhibitors to the polymer carrier through enzyme-cleavable linkages that will release the active drug product in the presence of specific enzymes in semen. This delivery approach offers several advantages in the context of microbicide action since (1) the NCp7 inhibitors can inactivate cell-free and cell-associated virus in semen, they will target the virus before it can diffuse in an infectious form to or into tissue; (2) they will add moieties to the polymer backbone that will increase the stability of the SAMT inhibitors by decreasing the pH local to the conjugated drug by the Donnan effect; and (3) since microbicides will be used by women repeatedly over many years, a polymeric prodrug approach will allow precise control over the tissue concentrations and exposure to anti-HIV compounds, limiting the chance to develop viral resistance and limiting toxicity. Critical to the development of this prodrug approach, biological evaluations will be performed to confirm the efficacy of the SAMTs in the presence of seminal plasma and vaginal fluids. Additionally, the enzymatic activation of the compound from its prodrug form will be evaluated in specially designed in vitro assays to mimic the events which must occur in the vagina and to quantify the kinetics of drug activation and virus inactivation in the presence of semen and other appropriate biological matrices. Finally, the biological properties of both semen and vaginal fluids on the efficiency of transmission of HIV to target cells will be evaluated to define the potential synergies between the antiviral activity of constituents of semen and the biological activity of the thioester inhibitors.

Title: **Microbicide Delivery System to Target Lymphoid Organs**
P.I.: **Mohamed Labib**
Institution: **Advanced BioDevices, Princeton, NJ**
Grant No.: **1R21AI082738-01**
Award: **$37,500**

Sexual transmission of HIV-1 involves complex processes involving exposure of the female genital tract to virus or infected cells and their transport to other sites, including local lymph nodes, where the virus replicates and establishes infection. It has been shown that Langerhans cells (LC) and dendritic cells (DC) capture the virus either from the vaginal surface or from top epithelium layers and transport it to draining and local lymph nodes, where it infects CD4+ T cells. Intense development of topical microbicides is underway with the ultimate goal of decreasing the sexual transmission of HIV-1. Current efforts have been directed to inactivating

the virus either at the surface of the vagina before entry, or in the squamous or stroma layers of the vaginal epithelium. Their physical transport modeling predicts that molecular drugs delivered as topical gels cannot reach draining or local lymph nodes. One possible way to deliver drugs to lymphoid sites surrounding the vagina is to use drug-loaded nanoparticles. Their preliminary results provide evidence indicating that nanoparticles can be delivered to local lymph nodes via vaginal application in a mouse model. To further develop this platform for use as a microbicide or prophylactic strategy, they propose the following plans for the R21/R33 application. In the R21 phase, they will study the delivery of quantum dots having different surface chemistry, including conjugation with targeting molecules, to determine the mode of their transport to different lymphoid sites. In the R33 phase, they will use drug-loaded nanoparticles and verify the applicability of this platform to target important sites in the female genital tract. Physical models will be developed to understand the transport processes and to guide the development of the nanoparticle delivery system

Title: **Small-Molecule Inhibitors of Gp41-Mediated Fusion as HIV-1 Topical Microbicides**
P.I.: **Min Lu**
Institution: **Cornell University, New York, NY**
Grant No.: **1R21AI079771-01A1**
Award: **$37,500**

In the continuing absence of an effective vaccine, topical microbicides offer a credible alternative preventive strategy to reduce sexual transmission of HIV-1. Several viral fusion and entry inhibitors have been shown to prevent SHIV infection of rhesus macaques by the vaginal and/or rectal routes and are in preclinical and early clinical development as microbicide candidates. HIV-1 membrane fusion is mediated by a series of large-scale structural transitions in the gp41 envelope glycoprotein. Evidence indicates that a transient gp41 species known as the prehairpin intermediate is a potential target for drugs that inhibit HIV-1 entry. The long-term goal of this research plan is to use modern molecular and structural methods to identify and develop a novel small-molecule gp41 fusion inhibitor for inclusion in a topical HIV-1 microbicide. To achieve this, they will capitalize on specific surface features revealed by their recent structure determination of an autonomously folded, trimeric coiled-coil subdomain of gp41 that provides an atomic model for the putative prehairpin conformation, as well as small-molecule lead compounds developed by means of an innovative structure-based drug design technology. They propose the following Specific Aim for the R21 component of this project is to identify and optimize two series of novel small-molecule compounds that inhibit HIV-1 membrane fusion by targeting the gp41 prehairpin intermediate. They will design and synthesize two sets of analogs of active triazinone and biphenyl compounds, characterize the equilibrium properties of interactions with the N-trimer coiled coil, and evaluate their anti-HIV-1 activity and mechanism of action. Bound inhibitors will be visualized by x-ray crystallography in order to allow refinement of binding affinity. The Specific Aims of the R33 phase of the project are: (1) To characterize the specificity, potency, and toxicity of improved small-molecule compounds with enhanced gp41 inhibitory activity. They will conduct in vitro studies in primary cells and human cervicovaginal tissue explants to determine the virucidal activity of select small-molecule gp41 inhibitory compounds against diverse primary HIV-1 isolates, and their potentially toxic or inflammatory effects. They will also use the rabbit vaginal irritation model to evaluate the irritation potential of the fusion inhibitors. (2) To assess the in vivo potency and breadth of activity of optimized small-molecule fusion inhibitors alone and in combination with entry inhibitors targeting HIV-1 gp120 (BMS-378806) and CCR5 (CMPD167) using the NOD/SCID-hu BLT mouse vaginal transmission model. They will evaluate the protection of humanized BLT mice from vaginal challenge with multiple

HIV-1 variants by small-molecule fusion inhibitors alone and in synergistic combination with BMS-378806 and CMPD167. Their emphasis is to identify a new class of potent HIV-1 fusion inhibitors suitable for development as a component of a microbicide formulation.

Title: **Gp-340 and Syndecan Inhibition-Based Microbicide for HIV**
P.I.: **Drew Weissman**
Institution: **University of Pennsylvania, Philadelphia**
Grant No.: **1R21AI082701-01**
Award: **$37,500**

Education and microbicides active against HIV represent the best approaches to controlling the epidemic worldwide in the absence of a protective vaccine. Their research program studies the earliest events in genital tract transmission. They have identified a protein expressed by genital tract epithelial cells that could serve as a potential target for inhibition of transmission of HIV called gp-340. They have demonstrated that gp-340 is expressed on the cell surface of vaginal and cervical epithelial cells, in vivo, in vitro, and ex vivo and binds HIV envelope. Of significance to genital tract transmission, gp-340 binding of virus leads to an increase in both the infectivity and half-life of the virus. Gp-340 expressed by genital tract tissue and cell lines also mediates transcytosis of HIV, the vesicular transport of macromolecules from one side of a cell to the other. A second molecule called syndecan has been studied and shown to have similar transinfection and transcytosis properties and is also expressed by genital tract cells. They have identified a peptide inhibitor of envelope binding to gp-340 that blocks both gp-340 mediated transinfection and transcytosis in in vitro and ex vivo models of genital tract transmission. This peptide contains a portion of a motif that inhibits syndecan mediated transinfection, as well, and they will modify this peptide to inhibit envelope binding to both macaque gp-340 and syndecan and develop it into a microbicide. This potential role of gp-340 and syndecan to act at a stage of infection after delivery to the lumen of the genital tract but prior to interaction with and infection of target cells is very attractive and novel in microbicide design. They hypothesize that interfering with this process will inhibit or block genital tract transmission. In the initial R21 portion of this proposal, they will establish in vitro macaque systems of genital tract transmission. If they demonstrate that macaque gp-340 and syndecan mediate transinfection and transcytosis and V3 loop derived peptides or improved versions block macaque gp-340 and syndecan mediated transinfection and transcytosis, they will proceed with the R33 portion of the grant. The Specific Aims of this are: microbicide development with in vitro testing and to test the effect of blocking gp-340 and syndecan-HIV Env interaction on genital tract SIV transmission in the rhesus macaque vaginal transmission model. Through these Specific Aims, they will develop a new type of microbicide and determine the role of genital tract gp-340 and syndecan in HIV transmission. If successful, these studies will deliver a new microbicide based on host cell interactions with HIV that promote genital tract transmission to preclinical trial studies.

Title: **Research Support Services for the DAIDS**
P.I.: **Garrison Arlondria, Robert Hockensmith**
Institution: **B L Seamon Corporation, Greenbelt, MD**
Grant No.: **N01AI60017-4-0-1**
Award: **$5,000**

This contract provides research support services that are critical to the research mission of the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases. This contract provides the following services: travel support and meeting and conference support, administrative and technical support.

Title: **Haiti AIDS Research Training: Models to Implementation**
P.I.: **Jean William Pape**
Institution: **The GHESKIO Centers, Port-au-Prince, Haiti**
Grant No.: **2U2RTW006896-06**
Award: **$20,000**

The specific areas of integrated clinical, operational, and health services research that will form the basis of the proposed ICOHRTA training program include: (1) adult antiretroviral treatment; (2) prevention of mother-to-child HIV transmission and antiretroviral treatment of HIV-infected mothers and infants; (3) tuberculosis with emphasis on multidrug resistant TB and HIV coinfection; (4) AIDS malignancies; (5) adolescents and HIV/AIDS; and (6) behavioral research. Research training will focus on translating models of HIV and TB care and prevention to large-scale national implementation. The goal of GHESKIO-Cornell ICOHRTA training program is to increase capacity in integrated clinical, operational, and health services research in support of Haiti's national scale-up of HIV and tuberculosis services. Haiti is the poorest country in the Western Hemisphere and has the highest rates of both HIV infection and tuberculosis. It is estimated that 3 percent of the adult population is HIV-infected and that the prevalence of tuberculosis is 402/100,000 population (100 times the U.S. rate). In response to this epidemic, the Haitian Ministry of Health asked GHESKIO to form a national HIV and TB Network, a collaboration of 32 public and private health care organizations across the country that is charged with "scaling up" to provide a standardized package of HIV and tuberculosis services to 500,000 persons by 2014. The services include voluntary counseling and HIV testing, management of tuberculosis and sexually transmitted infections, prevention of mother-to-child HIV transmission, and comprehensive HIV care of children, adolescents, and adults. The Haitian Ministry of Health has asked GHESKIO (Haitian Study Group for the Study of Kaposi's Sarcoma and Opportunistic Infections) to lead this network through training, supervision, monitoring, and evaluation, and through the conduct of operational and health services research. GHESKIO is an international research and training institution that has benefited from 25 years of uninterrupted NIH funding and research capacity building with Cornell University, and support from the Fogarty International Center. GHESKIO is recognized as a center of research excellence, and is a member of the NIH HIV Vaccine Trials Network (VTN), the AIDS Clinical Trials Group (ACTG) and a recipient of support from the United Nations Global Fund for AIDS, TB and Malaria and the President's Emergency Plan for AIDS relief (PEPFAR). In the current proposal, GHESKIO will continue as the primary training institution and extend research capacity to other organizations in Haiti that are participating in the GHESKIO HIV and Tuberculosis Network. The program will continue to emphasize medium- and long-term training in Haiti. Since its inception four years ago the ICOHRTA has provided training to 120 Haitian biomedical personnel, all of whom are working in Haiti, providing HIV/TB services and conducting operational and health services research. GHESKIO, in collaboration with Haitian and International partners, will develop training curricula in clinical, operational, and health services research methodology and in ethics, program management, and scientific writing. A Masters in Public Health Degree program, established with ICOHRTA support, will continue to be offered in Haiti by Quisqueya University, in partnership with GHESKIO and Cornell University.

Immunity/Autoimmunity

Title: **Predictors of Pregnancy Outcome in Systemic Lupus Erythematosus and Antiphospholipid Syndrome**
P.I.: **Jane E. Salmon**
Institution: **Hospital for Special Surgery, New York, NY**
Grant No.: **5R01AR049772-07**
Award: **$200,000**

Pregnancy complications in women with the antiphospholipid syndrome (APS) and/or systemic lupus erythematosus (SLE) include recurrent miscarriage, preeclampsia, placental insufficiency, and intrauterine growth restriction (IUGR). The mechanisms leading to placental and fetal injury in vivo are incompletely understood and treatment remains suboptimal. They have identified complement as an early effector in pregnancy loss and/or IUGR associated with placental inflammation in a mouse model of APS and shown that complement activation causes the release of anti-angiogenic factors and abnormal placental development. The PROMISSE Study (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) is a first-time effort to translate their novel findings in mice to humans and determine if elevations of complement split products predict pregnancy complications in patients with antiphospholipid (aPL) antibodies and/or SLE. In the first 4 years of this prospective, observational study of pregnant patients grouped and analyzed according to the presence or absence of aPL antibodies and preexisting SLE, they have enrolled 342 pregnant patients in 7 centers, obtained detailed medical and obstetrical information monthly, and serially collected plasma, serum, DNA, RNA, and urine. Preliminary data suggest that elevated levels of complement activation products antecede and predict poor fetal outcome, consistent with their hypothesis that complement is a proximal mediator of fetal loss and IUGR. They propose to increase their target sample size from 400 to 700 pregnant patients to maintain study power given lower than expected outcome rates, and to leverage the infrastructure and rich collection of patient data and samples by expanding the array of biomarkers and scope of adverse pregnancy outcomes. Specifically, in Aim 1 they will determine whether elevations of split products generated by activation of complement pathways predict poor fetal and/or maternal outcome in patients with aPL antibodies and/or SLE and, in Aim 2, whether the balance of circulating angiogenic and antiangiogenic factors predicts preeclampsia or delivery of IUGR infants. In Aim 3, a new direction, they will use the PROMISSE cohort to affirm in humans their recent findings in mice, that certain anti-DNA antibodies cross-react with N-methyl D-aspartate receptors (NMDAR) and cause neuronal death with ensuing cognitive and behavioral impairment. They propose to quantitate anti-NMDAR antibody levels throughout pregnancy in PROMISSE SLE patients and test the hypothesis that in utero exposure to maternal anti-NMDAR antibodies alters behavior and cognitive development in offspring by evaluating cortical function tasks in 12 month and 3.5 year old children. This competitive renewal and extension of the PROMISSE Study provides an outstanding opportunity to translate knowledge from mouse models to patients, define pathogenic mechanisms, identify predictors of poor pregnancy outcome in APL and/or SLE, and define novel therapeutic targets to prevent such outcomes.Patients with systemic lupus erythematosus (SLE) and/or antiphospholipid (aPL) antibodies are at increased risk for miscarriage, preeclampsia and fetal growth restriction - major causes of maternal, fetal, and neonatal morbidity and mortality in the US and worldwide - whose etiology and mechanism remain unknown and for which therapy is limited. In addition to causing placental dysfunction, maternal autoantibodies may also directly impair fetal brain development. Identification of biomarkers that predict poor pregnancy outcome in these patients will elucidate mechanisms of disease, define targets for treating patients, and generate clinically applicable indicators to permit initiation of interventional trials in patients at greatest risk for pregnancy complications.

Title: **Role of Sex Differences in the Expression and Function of Regulatory T Cells in Systemic Lupus Erythematosus**
P.I.: **Ram Pyare Singh**
Institution: **University of California, Los Angeles**
Grant No.: **1R21AI083894-01**
Award: **$192,500**

Regulatory CD4+ T cells and CD8+ T cells have important roles in suppressing autoimmune disease in the peripheral immune system. Impaired function of regulatory/suppressor T cells contributes to development of autoimmunity. The goal of this project will be to study the quantities and functions of T regulatory cells in healthy controls and patients with SLE, comparing males to females in both groups (given the fact that lupus disease is much more frequent in females than in males). The first aim is to quantify, immunophenotype, and perform functional analysis of the T regulatory cell subsets in healthy controls, and in male lupus versus female lupus. The second aim is to compare gene expression profiles of CD4+ CD25+ hiTreg and CD8+ T cells in male versus female lupus patients and to compare them with healthy controls. Finally, the investigators will test the effect of testosterone and estradiol in these cells in vitro to see their effects on cell phenotypes, gene expression, signaling and regulatory functions. The overall purpose is to understand the molecular network of these CD4+ T regulatory cells and CD8+ suppressor cells in systemic autoimmunity. The significance of the application is that the applicants propose to study regulatory T cells (CD4 and CD8) (comparing male to female SLE patients and male to female healthy individuals) for quantities, suppressive capacities, and differences in gene expression. The ability of sex hormones to change T regulatory numbers, functions, and gene expression will be studied.

Title: **NARAC—The Genetics of Rheumatoid Arthritis**
P.I.: **Peter K. Gregersen**
Institution: **Feinstein Institute for Medical Research, Manhasset, NY**
Grant No.: **5R01AR044422-11**
Award: **$182,442**

This renewal application has the overall goal of identifying all of the major common genetic variants that underlie susceptibility to rheumatoid arthritis (RA), and to begin to identify rare susceptibility alleles, if they exist. In preliminary data they have identified a number of candidate genes and regions on the basis of linkage analysis in multiplex RA families, as well as by whole genome association studies using approximately 550,000 SNPs on a panel of over 900 RA patients and matched controls. They now wish to identify the specific causal variants and understand their mode of action. In Specific Aim 1 they will identify the causal genetic variants within the common genes that confer risk for rheumatoid arthritis. They have already identified several genes and regions of interest, including STAT4 on chromosome 2q. In Specific Aim 1a they will replicate these initial associations in case-control datasets totaling up to 5,000 patients. Various methods of genomic control for population stratification will be utilized for these replication studies. In Specific Aim 1b they will carry out fine mapping of candidate regions. This will generally involve haplotypic analysis using custom sets of SNP markers. In Specific Aim 1c they will utilize various approaches to identify the likely causative genetic variants in the gene under study. Examples of the approaches to be used in Specific Aim 1c are given for STAT4. In Specific Aim 2, they will apply a staged approach to identify gene-gene and gene-environment interactions that contribute to RA susceptibility. The top performing markers in the univariate analyses of Specific Aim 1a and 1b will be examined for interactions using Classification and Regression Tree (CRT) as well as traditional logistic regression methods. Top performing models will be tested in replication datasets of cases and controls. In Specific Aim 3, they will identify rare genetic variants that contribute to RA susceptibility. This Specific

Aim is based on preliminary analysis indicating that slightly deleterious SNPs (sdSNPs) are a significant component of the genetic burden underlying complex disease. These sdSNPs are enriched in the low frequency (MAF < 5 percent) component of the SNP population. They will initially investigate a limited number of candidate genes with high-throughput sequencing on the Solexa platform, along with followup analysis in large case-control datasets. Larger scale and more comprehensive approaches to this issue may be employed in the later years, depending on technical advances in the field.

Title: **International Research Registry Network for Sjögren's Syndrome**
P.I.: **Troy Daniels, John Greenspan**
Institution: **University of California, San Francisco**
Grant No.: **N01-DE-32636**
Award: **$300,000**

This contract focuses on the continuation of the International Research Registry Network for Sjögren's syndrome. As part of this registry, key elements being collected include using a set of standardized diagnostic criteria for the recruitment of Sjögren's syndrome patients; the collection, processing, storage, shipment and analysis of clinical information and biological specimens (tissue, blood, saliva, and tears) from patients and families with Sjögren's syndrome; and to disseminate to researchers clinical information and biological specimens from patients with Sjögren's syndrome. During this year, all research sites are focused on enrolling eligible study participants and have begun the process of 2-year recall evaluations of the pSSw and level 2 controls (called partial SS phenotype) groups. Enrollment of blood relatives and unrelated DNA control donors also is continuing. Currently, data analysis has begun to assess the progress towards developing a framework for the classification criteria.

Title: **OGT Overexpression in Women with Lupus**
P.I.: **Bruce C. Richardson**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **5R21AR056370-02**
Award: **$20,000**

Lupus afflicts women nine times more often than men. Estrogen contributes to lupus severity, but does not completely explain the increased risk. Impaired DNA methylation, a repressive epigenetic modification, causes overexpression of T cell genes that contribute to lupus. DNA methylation also silences one X chromosome in women. CD40LG is an X-linked gene known to be overexpressed in lupus and contribute to autoantibody production, on the inactive X demethylates and is overexpressed in women but not men with lupus, predisposing women to lupus. Other X-linked genes may also demethylate, predisposing to autoimmunity. The investigators surveyed methylation sensitive T cell genes, and identified O-linked N-acetylglucosamine transferase (OGT) as another X-linked gene overexpressed in demethylated female T cells. OGT couples N-acetylglucosamine (GlcNAc) to serines and threonines in a variety of proteins including signaling molecules, modifying function in a manner analogous to phosphorylation and referred to as the hexosamine signaling pathway (HSP). HSP abnormalities are implicated in diabetes and neurodegeneration, but little is known regarding their roles in T cells. The researchers hypothesize that demethylation of OGT on the inactive X results in overexpression in women, altering HSP signaling and contributing to pathogenic T cell function by modifying signaling. The investigators plan to test this hypothesis by: (1) comparing OGT mRNA and protein levels in control and demethylated CD4+ and CD8+ T cells from healthy men and women with levels of CD4+ and CD8+ T cells from men and women with inactive lupus, active lupus, and disease/age controls, and confirming OGT demethylation by bisulfite sequencing; (2) determining if OGT overexpression

impairs T cell ERK, JNK and/or p38 pathway signaling and modifies T cell gene expression patterns; and (3) determining the functional significance of T cell OGT overexpression on the development of autoimmunity using transgenic mice with a T cell specific inducible OGT transgene. These studies will characterize a new pathway regulating T cell gene expression, and characterize how abnormalities in the pathway may predispose women to autoimmunity.

Title: **Do Estrogen Receptors in B Cells and Dendritic Cells Mediate Sex Bias in Murine Lupus?**
P.I.: **A. Darise Farris, Susan Kovats**
Institution: **Oklahoma Medical Research Foundation, Oklahoma City**
Grant No.: **5R21AI079616-02**
Award: **$193,750**

Systemic lupus erythematosus (SLE) is an autoimmune disease that preferentially affects women (9:1) in their reproductive years, indicating that sex-specific factors including the sex hormone estradiol play an important role in lupus pathogenesis. Murine models of lupus show natural earlier expression of disease and ensuing mortality in female mice. The Sle1 and Sle3 lupus susceptibility loci present in NZM2410 mice direct increased penetrance of disease in females, which is consistent with studies showing that elevation of systemic estradiol or exposure to estrogenic environmental compounds accelerate lupus development. An understanding of the mechanisms underlying the female preponderance of SLE requires that they precisely determine how endogenous estrogens and estrogen receptors (ER) regulate the function of immune cells such as B lymphocytes and dendritic cells (DC), which express ER and have been implicated in lupus pathogenesis. However, current models for the study of estrogen effects on immune cells often have involved systemic exposure to supra-physiological levels of estradiol or global loss of ER, which creates hormonal imbalances. Elevated systemic levels of estradiol result in a profound depletion of hematopoietic progenitors, leading to alterations in numbers and phenotype of B cells and DC. To circumvent these effects of ER ligands on immune cell development, the study proposes to develop and use a novel model of murine lupus in which ER alpha expression may be specifically ablated in differentiated B cells or DC. The investigators will use lentiviral transgenesis to deliver Cre recombinase driven by the CD19 or CD11c promoters to lupus prone B6.Sle13 bicongenic mice bearing a conditional ER-alpha allele. This approach will determine whether aberrant DC or post-bone marrow B cell phenotypes associated with the sex sensitive Sle1 and Sle3 loci are mediated by direct effects of endogenous estrogens on B cells or DC. Aim 1 will determine if the elevated DC numbers or hyperactivated DC phenotypes leading to proinflammatory cytokine production in female B6.Sle13 bicongenic mice are a result of the direct action of endogenous estrogen on DC. Aim 2 will determine whether perturbations in transitional B cell subsets and subsequent enhanced loss of serologic tolerance in female B6.Sle13 bicongenic mice are a result of the direct action of endogenous estrogen on committed B cells and/or DC. The successful implementation of this lentiviral transgenesis strategy to delete ER-alpha in specific cell types will establish a versatile model that could be used to study the role of ER-alpha signaling in any cell type during the development of lupus nephritis. This knowledge will help to understand why autoimmune diseases preferentially afflict women.

Title: **Sociodemographic Disparities in Lupus Nephritis: Healthcare Access and Outcomes**
P.I.: **Karen Costenbader**
Institution: **Brigham and Women's Hospital, Boston, MA**
Grant No.: **1R01AR057327-01**
Award: **$200,000**

Systemic lupus erythematosus (lupus) is an autoimmune disease that mainly afflicts disadvantaged groups in the United States, often causing kidney failure. The reasons why some groups suffer worse outcomes are not known. They will investigate how differences in healthcare access are related to gaps in outcomes for lupus kidney disease. Access to quality healthcare is a challenge for minority and disadvantaged groups in the United States Lupus, a complex autoimmune disease, can cause nephritis and, in severe cases, end-stage renal disease. Lupus nephritis is a potentially preventable outcome that disproportionately afflicts vulnerable groups: women, racial and ethnic minorities, the poor, those lacking medical insurance and education, and children and the elderly. They have found that the incidence of lupus end-stage renal disease rose dramatically from 1995–2004 in the United States, in particular among those 20–39 years old, women, and racial and ethnic minorities. More new cases now occur among Blacks than whites. The causes of these growing disparities are unknown. They hypothesize that multiple barriers to quality healthcare for lupus nephritis exist for disadvantaged patients and are responsible for premature, excess, and avoidable morbidity and mortality. Their goals are to identify and prioritize potentially remediable barriers to healthcare access for lupus nephritis and end-stage renal disease, leading to both future research and policy interventions. Their uniquely qualified interdisciplinary research team will address nationwide sociodemographic variation in lupus nephritis health care and the potentially modifiable factors responsible for outcome disparities. They will constitute two nationwide cohorts: one with >5,000 patients with incident lupus nephritis from 2000–2004, and a second with >14,000 patients with incident lupus end-stage renal disease from 1995–2009 and investigate the factors that contribute to access to care and disparities. They have developed a conceptual model for understanding the determinants of health disparities in lupus nephritis and posit that potentially modifiable factors, such as subspecialist care, provider and medical center volume, medical insurance, and adherence to therapy, contribute to long-term outcomes in lupus nephritis, including the development of end-stage renal disease and death. Lupus patients from the affected communities will likely have great insight into their findings and should be involved in the development of strategies for overcoming observed barriers. They will perform focus groups of community lupus patients and investigate the barriers to quality healthcare for lupus nephritis and end-stage renal disease from patients' perspectives. The interdisciplinary research team will be composed of investigators with expertise in healthcare disparities research, biostatistics, pharmaco-epidemiology, administrative claims data, lupus epidemiology, and quantitative research methodologies. The findings will be widely disseminated to the lupus community, physicians, and healthcare workers. The results will provide guidance to clinicians and policymakers on strategies to reduce barriers and improve access to care and outcomes for all Americans with lupus nephritis.

Title: **Longitudinal Determination of Outcomes of Adolescents with Fibromyalgia**
P.I.: **Susmita Kashikar-Zuck**
Institution: **Children's Hospital Medical Center, Cincinnati, OH**
Grant No.: **1R01AR054842-01A2**
Award: **$200,000**

This project will be the first controlled prospective longitudinal study of adolescents with juvenile primary fibromyalgia syndrome (JPFS). The results will greatly increase their knowledge about the prognosis for patients with JPFS, and the complex relationship between physical and emotional symptoms in fibromyalgia syndrome. Findings will be of direct clinical relevance with respect to knowledge about physical, emotional, and social outcomes for JPFS patients, and early identification of those who may be at risk for long-term suffering and disability. The study will lay the groundwork for future clinical trials aimed at early and targeted interventions for JPFS. Fibromyalgia syndrome (FMS) is a chronic and often debilitating condition that results in marked difficulties in daily functioning, psychiatric comorbidity, and decreased quality of life. Many adult FMS patients report that their symptoms began earlier in life, when the symptoms may have been more amenable to early intervention. However, the developmental course of FMS and its associated symptoms from adolescence through adulthood has never been documented. Prospective longitudinal studies of patients diagnosed with fibromyalgia in adolescence are urgently needed. In this study, they propose to prospectively follow 96 patients diagnosed with JPFS and 48 healthy controls into their young adult years. These participants are currently enrolled in their completed and ongoing JPFS research, and have completed baseline assessment (Time 1, mean age 15 years). A Time 2 protocol has been recently implemented to assess current functioning (mean age 19 years). So far they have demonstrated excellent cohort retention (90 percent), and preliminary results suggest that as a group, JPFS patients continue to have significant physical and emotional difficulties, but there is considerable variability in outcomes. Participants are now approaching the crucial young adult years, a time of rapid change and new challenges that places greater stress on coping resources for those who are already dealing with chronic pain. They are proposing two additional assessments for the entire cohort in the young adult years (Time 3, mean age=22 years; and Time 4, mean age=24 years). In this controlled, prospective longitudinal study, the primary objective is to first establish whether JPFS patients continue to have greater physical symptoms and impairment, psychiatric symptoms and social difficulties in young adulthood than healthy controls. The secondary objective is to examine developmental trajectories of two key outcomes: physical impairment and depressive symptoms, from adolescence through young adulthood. For each outcome, they hypothesize three distinct trajectories: those who show low initial impairment and continue to show little impairment into young adulthood, those who are initially impaired and get worse over time, and those who are initially impaired but improve over time. They will test whether trajectories of physical impairment and depressive symptoms are independent of one another, and in doing so, they will be able to disentangle aspects of mood from impairment associated with FMS. Moreover, they will test whether change in FMS symptom severity is differentially associated with physical impairment or depressive symptoms. Finally, they will test whether treatment via cognitive-behavioral therapy in adolescence has any persisting effects on long-term outcomes. Information will be gathered from participants and family member/ significant others via on-line surveys. Psychiatric interviews and tender point exams will be conducted in person. The long-term goal is to develop more refined methods to identify patients who are at risk for negative trajectories of physical and emotional outcomes and to design early, targeted interventions.

Autoimmunity Centers of Excellence

The Autoimmunity Centers of Excellence (ACE) focus on supporting clinical trials and mechanistic studies, pilot research projects, and other group activities such as working groups or subcommittees formed by the Steering Committee with narrow focus and short duration (e.g., establishing immunocompetence criteria or comparing measurements of regulatory T cells).

Title: **Autoimmunity Center of Excellence at Stanford**
P.I.: **Charles Fathman**
Institution: **Stanford University, Stanford, CA**
Grant No.: **1U19AI082719-01**
Award: **$30,000**

The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune disease. The major theme of the Stanford Autoimmunity Center of Excellence (the Center) is the study of the regulation of CD4 T cells in pathogenesis and treatment of autoimmune diseases. The Center will support and be supported by other ACE groups across the United States and will take advantage of Stanford's documented leadership in basic and clinical research, technology development, and education in clinical immunology. Success of the Center will be supported by the interrelationships previously established at Stanford among clinician scientists from multiple departments studying autoimmune diseases in multiple organs and tissues. The Stanford ACE will be composed of outstanding basic and clinical investigators from multiple disciplines at Stanford Medical School. Stanford ACE proposes both a basic research project, centered on CD4 T cell unresponsiveness, and a translational research project to study a new T cell lineage (termed Th17 cells) that is characterized by the ability of these lymphocytes to secrete high levels of the proinflammatory cytokine interleukin-17 (IL-17). Proposed clinical research projects encompass three different autoimmune diseases [diffuse systemic sclerosis (SSc), psoriatic arthritis, and systemic juvenile idiopathic arthritis (SJIA)] that afflict adults and children, as well as organ systems including joints, skin, blood elements, and blood vessels, and will test the efficacy of therapy and develop tests to characterize the mechanisms of action of these therapeutics. The proposed pilot and feasibility project proposes a 2-year research plan in SJIA patients to identify and validate urine peptide biomarkers that predict (a) response to TNF inhibition; (b) response to IL-1 inhibition; (c) impending disease flare. In addition, this proposal will provide other ACE groups access to cutting-edge reagents and technology platforms for studying human autoimmune diseases, and dissemination of educational materials that can be used by other ACEs to teach clinical immunology concepts to high school, undergraduate, graduate, postgraduate, and clinical fellows and faculty. The Stanford ACE proposes to support integrated basic, pre-clinical, and clinical research by proposing and then conducting basic and translational research into the mechanism of CD4 T cell unresponsiveness; two clinical trials that include novel therapies and mechanistic studies of these therapies for autoimmune diseases; and a pilot proposal that intends to develop new biomarkers of disease. PROJECT 1A: Clinical Component (Genovese, M): Stanford University Medical Center (SUMC) has an extraordinary tradition of medical, translational, and basic science research. An outstanding array of resources, faculty, and facilities will be available to support the proposed ACE site at Stanford University. This proposal brings together a skilled group of translational researchers with a track record of productivity in both laboratory and clinical research focusing on human autoimmune mediated diseases. Stanford has brought together various disciplines to demonstrate both accomplishment and ability to work together with the following fields represented: adult rheumatology, dermatology, pulmonary medicine, and pediatric rheumatology. The projects chosen for this submission highlight the significant collaborations that exist between rheumatology (adult and pediatric), dermatology and pulmonary medicine. Both clinical trials projects explore dermatologic and rheumatologic

manifestations of diseases such as psoriatic arthritis and systemic sclerosis. Clinical Trial Concept 1: The use of an anti-IL-17 mab in the treatment of active psoriatic arthritis primary hypothesis: The proportion of patients achieving the ACR 20 response from baseline to week 14 among active psoriatic arthritis (PSA) subjects treated with IL-17 mab is larger than the proportion achieving ACR 20 response from baseline to week 14 among active PSA subjects treated with placebo. Objectives: The goal of this study is to determine the safety and efficacy of a monoclonal antibody to Interleukin-17 (IL-17 mab) in the treatment of PSA with active skin and joint disease. Clinical Trial Concept 2: The use of CTLA-4lg (abatacept) in subjects with diffuse systemic sclerosis primary hypothesis: Given several lines of evidence supporting the role of activated T cells in affected skin, they hypothesize that inhibiting T cell activation may lead to significant clinical improvement in skin manifestations in patients with diffuse systemic sclerosis (dSSc), and that changes in tissue and blood autoantibody and cytokine profiles will be associated with clinical response. Objectives: The primary goal of this study is to determine the safety and efficacy of CTLA-4lg for the treatment of cutaneous manifestations of dSSc. Relevance: The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune disease. The Stanford ACE proposes clinical research projects that encompass three different autoimmune diseases (SSc, psoriatic arthritis, and SJIA), and proposes to study the MoA of therapeutics for preventing or treating different autoimmune diseases.

Title: **Oklahoma Autoimmunity Center of Excellence**
P.I.: **Judith James**
Institution: **Oklahoma Medical Res Foundation, Oklahoma City, OK**
Grant No.: **1U19AI082714-01**
Award: **$30,000**

The Oklahoma Medical Research Foundation is home to outstanding clinical and basic science investigators who have research interests in the etiology and pathogenesis of autoimmune diseases and seek to identify novel therapeutics for more effective patient treatments. The scientific expertise, extensive clinical trial experience, access to geographically distinct patient populations, as well as unique patient registries, repositories, and core technologies provide a solid foundation for the Oklahoma Autoimmunity Center of Excellence (ACE) application to which they have added an interdisciplinary team of clinical and basic science investigators. The focus of the Oklahoma ACE application is on expediting the translation of scientific discoveries in autoimmunity to clinical application in the diagnosis and treatment of systemic autoimmune diseases. To accomplish this, the Oklahoma ACE comprises two research projects, a proposed pilot research project, a Clinical Center (Joan Merrill, PI) and an administrative core (Judith James, PI). The research projects focus on thrombotic thrombocytopenic purpura (TTP), systemic lupus erythematosus, and Sjögren's syndrome, which are also focuses of the Clinical Center. Multiple sclerosis, rheumatoid arthritis (RA), pediatric arthritis, insulin-dependent diabetes, idiopathic thrombocytopenia and pediatric lupus are other key disease emphases of the Clinical Center. Two complimentary, but unique, research projects focus on understanding early events in the development of lupus autoimmunity and in defining targetable genetic associations in Sjögren's syndrome. The pilot project uses complementary methods to address roles of elevated interferon activity in patients with TTP and a novel animal model of thrombocytopenia. In addition, two clinical trials are proposed; both of which enhance or build upon the basic science projects. The first studies efficacy and mechanistic affects of anti-IFN in select SLE patient subsets by applying a patient centric, dose optimization strategy. The second tests the efficacy and early MRI changes of a novel MEK1/MEK2 inhibitor in RA with additional mechanistic studies. The administrative core will provide leadership and management through acting on behalf of the Oklahoma ACE members within the ACE Network and NIH Program, ensuring fiscal responsibility for the ACE, and providing an

educational foundation for a multidisciplinary approach to autoimmune disease research. Thus, the Oklahoma ACE will unite Oklahoma-based clinical and basic science experts to facilitate access to unique patient populations for participation in clinical trials and to understand basic mechanisms of etiology and pathogenesis.

Title: **A Systems Biology Approach For Pediatric and Adult Autoimmune Diseases—ACE**
P.I.: **Maria Virginia Pascual**
Institution: **Baylor Research Institute, Dallas, TX**
Grant No.: **1U19AI082715-01**
Award: **$30,000**

They propose to create an Autoimmunity Center of Excellence that will incorporate the efforts of clinicians, human immunologists (both basic and translational), physician-scientists with clinical expertise and research experience in autoimmunity, bioinformaticians, and geriomics/ systems biologists. Together, the assembled group has an extensive background in clinical trials and a proven track record for merging basic and clinical science. This team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. Within this collaborative setting, a systems biology approach is proposed to focus on both pediatric and adult autoimmune diseases. The goals of the Center are: (1) to assess the efficacy of novel targeted therapies; (2) to develop simple and robust biomarkers using state-of-the-art genomic approaches: (3) to understand the role of recently identified T cell subsets in disease pathogenesis, and (4) to assess antigen-specific responses in pediatric and adult autoimmune diseases. These projects will provide a better understanding of the pathogenesis of specific autoimmune diseases and allow us to develop a strategy to assess disease activity based on novel transcriptional markers as well as to identify autoantigen-specific immune responses. The Center will deliver: (1) innovative clinical trials targeting specific cytokines in psoriasis & dermatomyositis; (2) development of biomarkers for dermatomyositis, psoriasis, lupus and multiple sclerosis; (3) identification of novel therapeutic targets in dermatomyositis; (4) development of assays to test autoantigen-specific immune responses; (5) development of a unique microarray database of human autoimmune diseases. Clinical component (Cush, J): Baylor Institute for Immunology Research aims to bring together a distinguished team of clinical investigators to conduct cutting-edge clinical trials on specific autoimmune diseases. This unique group of investigators and clinicians has appointments at Baylor University Medical Center, UT Southwestern Medical Center, Texas Scottish Rite Hospital in Dallas and Northwestern University. These talented individuals have been enlisted from diverse programs with subspecialties in dermatology, rheumatology, neurology, pediatrics, and human immunology. They provide a set of inimitable resources for clinical trials and have a proven track record for merging basic and clinical science. Indeed, this team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. With such outstanding collaborative players, a systems biology approach is proposed here which investigates both pediatric and adult autoimmune disease. To this end, two Phase II randomized, double-blind, placebo-phase controlled clinical trials are proposed. The first trial investigates whether blocking IL-1 with Anakinra will result in objective disease improvement for patients with Juvenile Dermatomysitis (JDM). The trial design will demonstrate: (1) if the time to improvement for patients receiving Anakinra early in the study will be earlier than those who receive later treatment; and (2) if the proportion of patients improved at week 8 of the blinded phase will be significantly greater in the early treatment group. Mechanistic studies will utilize gene expression profiling assays to find a novel diagnostic test for JDM as well as disease activity measures and biomarkers to follow and predict patients' response to therapy. The second clinical project proposes to use a-IL-17 in patients with plaque psoriasis as well as psoriatic arthritis. Specifically, this study will assess the safety and efficacy of a-IL-17

in these patients and determine both the time to achieve endpoints of a PASI 75 or ACR20 and sustainability of such responses at 24 weeks. Associated studies will establish blood transcriptional markers to predict clinical responses in patients treated with a-IL-17, determine if transcriptional scores can be used to assess disease activity, and analyze the effect(s) of IL-17 blockade on B and T cell subsets. A dynamic team of clinical investigators assembled at BUR to conduct state-of-the-art clinical trials on autoimmune disease would be of great value and accelerate the process of bringing research from the laboratory bench to the bedside. This team proposes two important trials that will assess a-IL-1 treatment in Juvenile Dermatomyositis and IL-17 blockade in psoriatic diseases.

Title: **Mechanisms of Beta Cell Responses In Autoimmune Disease—ACE**
P.I.: **Eugene W. St. Clair**
Institution: **Duke University, Durham, NC**
Grant No.: **2U19AI056363-06**
Award: **$30,000**

This application is a competitive renewal of the Autoimmunity Center of Excellence (ACE) at Duke. Its research focus will continue to be modulation of B cell responses in autoimmune disease. The ACE will be under the leadership of Dr. E. William St. Clair, Professor of Medicine and Immunology. For the past 5 years, Duke has been a productive member of the ACE network, contributing new insights into the developmental pathways of B cells and the mechanisms of B cell directed therapy. The proposed ACE builds on these discoveries and will support two new basic science projects, five ongoing and two new clinical trials, and an administrative core, and continue to emphasize a strong and fluid integration between the bench and the bedside. Tedder and colleagues have recently found that a phenotypically unique subset of B cells secreting IL-10 (called B10 cells) serve as critical negative regulators during adaptive CD4+ T cells responses, and dramatically suppress Th1 immune responses and autoimmune disease in mice. For Basic Research Project 1, they will examine the hypothesis that antigen-specific regulatory B10 cells modulate autoimmune responses in mice and man and that they can be manipulated for therapeutic gain. A picture is gradually emerging about the precursors of self-reactive B cells in autoimmune disease. Kelsoe and coworkers in Basic Research Project 2 will investigate developmentally regulated expression of activated cytidine deaminase (AID) in human fetal and neonatal pre-, pro, and immature/transitional B cells and its relationship to the generation of self-reactive B cells in human autoimmune disease, potentially eludidating another pathway of B cell self-reactivity outside the confines of normal tolerance mechanisms. They propose two new clinical trials to investigate lymphotoxin-beta receptor fusion protein as a treatment for primary Sjögren's syndrome, and rituximab therapy for bullous pemphigoid. A pilot research project is also proposed to engineer tetramers of self-antigen enabling the identification and characterization of self-reactive B cells, which will have implications for the goals of the clinical and other basic research projects. Overall, the Duke ACE will bridge these basic and clinical studies to advance their understanding of autoimmune disease. The B cell is a type of immune cell essential to autoimmunity. The goal of the proposed Autoimmunity Center of Excellence at Duke is to improve their understanding of the roles played by B cells in human autoimmune disease. The projects are designed to be highly integrative between the bench and the bedside, with collaborations between basic and clinical scientists. These studies may lead to better treatments. Clinical component (St. Clair, E.W.): The clinical research component of the Autoimmunity Center of Excellence shares with the basic research component an overall goal of advancing their understanding about the role of B cells in the pathogenesis of autoimmune diseases. This component will be directed by Dr. E. William St. Clair. During the past 5 years, the Duke ACE has brought 3 new clinical trial concepts to the ACE Steering Committee, resulting in one completed trial, one ongoing trial, and one protocol in development. They are also participating in three

other ongoing ACE-sponsored clinical trials. Therefore, substantial clinical research activity will carry over to the next funding cycle. Their center is organized to support clinical trials in rheumatology, dermatology, gastroenterology, hematology, and neurology. They have access to several large patient populations, including patients with rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome, scleroderma, autoimmune blistering disease, psoriasis, inflammatory bowel disease, autoimmune hepatitis, anti-phospholipid antibody syndrome, and myasthenia gravis. Each of these disease areas has leadership from one or more physician-investigators with significant clinical trial experience, including an example of a productive inter-institutional collaboration. The physician leadership is supported by an ample infrastructure that provides clinical research space, infusion facilities, experienced clinical coordinators, and an Immune Monitoring Component. The Clinical Research Component aligns with the ACE at a thematic level, with substantial collaborations between basic and clinical scientists. To this end, the proposed clinical trial concepts will focus on B cell directed therapy. In one case, they propose to examine the clinical efficacy of lymphtoxin-beta receptor fusion protein in the treatment of primary Sjögren's syndrome, and have already secured commitment from the industry sponsor to provide study drug for this trial. The other application will investigate rituximab as initial therapy for bullous pemphigoid. The mechanistic studies for these proposed trials as well as current trials are highly integrated with the basic research projects. The Clinical Research Component will make a significant contribution to the ACE enterprise during the upcoming funding cycle. The Clinical Research Component will support clinical trials sponsored by the Autoimmunity Centers of Excellence in several disease areas, including rheumatology, dermatology, gastroenterology, hematology, and neurology. It has been productive during the current funding cycle, and has the capability, as shown in this application, to generate new ideas for clinical trials that can be translated into well-designed studies.

Title: **Molecular Epidemiology of Drug Resistance and Population Genetic Structure of *Plasmodium falciparum* and *Plasmodium vivax***
P.I.: **Fangli Lu**
Institution: **Sun Yat-Sen University School of Medicine, China**
Grant No.: **1R01TW008151-01A1**
Award: **$50,000**

This project will be of significant benefit to public health programs aimed at identifying and combating drug-resistant malaria, and have the potential to benefit the health of a substantial proportion of the world's population. The data will provide valuable information for extending the lifespan of individual antimalarial drugs and developing more appropriate malaria control policies in China. Malaria remains a serious public health problem in China. In the subtropical Yunnan Province and the tropical Hainan Island of China, malaria has been the most endemic with high transmission of both *Plasmodium falciparum* and *P. vivax*. However, most of the attention in terms of research and interventions has been focused in Africa and Southeast Asia, while very few studies of malaria in China have been conducted. Because of extensive use, chloroquine (CQ) has now lost its efficacy due to the emergence of resistant strains in most parts of the world. Meanwhile, suspension of the use of CQ has resulted in reappearance of CQ sensitivity. However, there were differences in the evolution of CQ resistance between parasites from Yunnan and Hainan, the exact mechanism needs to be investigated. Sulfadoxine-pyrimethamine (SP) targets the dhfr and dhps genes of *P. falciparum*, and point mutations that confer resistance have been widely reported worldwide. Documenting the identity and extent of SP resistance is also critical for policy decisions regarding antimalarial drugs. In addition, *P. vivax* causes a large burden of morbidity in the world including China but traditionally has been understudied. Based on these, their long-term goal of this proposal is to: (1) identify single-nucleotide polymorphism (SNP) and characterize the geographic distribution of genetic

diversity, population structure, and haplotype variability at drug resistant loci of *P. falciparum* from Yunnan and Hainan, China; (2) examine the geographic population structure and levels of genetic diversity of *P. vivax* using microsatellite and SNP; and (3) yield valuable information for making more effective malaria control policies in China. In the past several years they have developed the molecular methods to study the genetics, population diversity, and evolution of malaria parasites, and have done some preliminary studies on malaria field isolates from Yunnan and Hainan using genetic markers, thus enabling us to study the molecular epidemiology of these important malaria parasites in this proposal. The Specific Aims are to: (1) determine genetic polymorphisms associated with CQ resistance (CQR) in *P. falciparum* field isolates from Yunnan and Hainan provinces in China; (2) determine the point mutation prevalence in the dhfr (pyrimethamine drug resistance) and dhps (sulfadoxine drug resistance) genes associated with SP resistance in *P. falciparum* field isolates from Yunnan and Hainan provinces in China; and (3) assess the changes of *P. vivax* genotypes using pvcsp, pvmsp1, and pvmsp3-1 genes and microsatellite markers and determine the geographic structure and specific epidemiological characteristics of *P. vivax* transmission in Yunnan and Hainan, China.

Menopause

Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH Network)

Women going through the menopause transition may experience a variety of symptoms, ranging from vasomotor symptoms (hot flashes and night sweats) to sleep disturbance, mood disorders, loss of sexual desire, and vaginal dryness. As many as two-thirds of all women report vasomotor symptoms, and more than 85 percent report at least one menopausal symptom as they transition through menopause. For the 25 percent of women whose symptoms are severe, the resulting discomfort greatly diminishes their quality of life. For many decades, menopausal hormone therapy (MHT) using estrogen (or, in a woman with a uterus, a combination of estrogen and a progestin) has been the therapy of choice for relieving menopause-related symptoms. But recently, several large clinical trials, and in particular, the Women's Health Initiative, have found an increased risk of serious health problems, such as blood clots, stroke, heart disease, breast cancer and cognitive impairment in women using estrogen-progestin regimens. Not surprisingly, women are reluctant to use MHT for menopausal symptoms and in search of alternative strategies to improve their quality of life.

The primary goal of the MsFLASH Network is to conduct multiple collaborative clinical protocols to evaluate a variety of strategies (e.g., pharmacological, botanical, behavioral, etc.) to alleviate vasomotor symptoms (VMS) and to assess the role of these strategies and changes in the burden of VMS on menopause-related sleep disturbance, mood disorders and vaginal dryness. Secondary objectives of the Network include the following:

- Provide necessary interdisciplinary scientific input in reproductive endocrinology, gynecology, oncology, behavioral medicine, psychiatry, sleep, physiology, biostatistics, psychometrics, pharmacology, complementary and alternative medicine (CAM) and clinical trials methodology.
- Implement the rapid identification and development of standard definitions and terminology, data collection instruments and needed new methodologies for assessment and analysis of participant outcomes.
- Ensure the success of recruitment by providing access to a broad base of populations of interest—different race/ethnicities, types of menopause (e.g., spontaneous or induced by surgeries), treatments, and conditions that propel women of reproductive age into the menopause transition.

- Establish a knowledge base that will advance therapeutic decisionmaking through a better conceptualization of menopausal symptoms, testing of promising strategies, and advancement of strategies shown to be efficacious and safe.
- Establish collaborations between the practice community and the clinical field sites.
- Disseminate validated findings to the medical and scientific communities.

A number of different treatment strategies are under consideration. Possible treatments to be studied during the 5-year project period include the following:

- Antidepressants such as paroxetine (Paxil) or escitalopram (Lexapro)
- Paced respiration (slow deep breathing also known as relaxation breathing)
- Yoga
- Low-dose estradiol patch and low-dose estradiol gel
- Exercise programs, both moderate and vigorous

MsFLASH centers include the following:

Title:	**Menopausal Symptoms Initiative—Finding Lasting Answers for Sweats and Hot Flashes**
P.I.:	**Andrea Z. LaCroix**
Institution:	**Fred Hutchinson Cancer Research Center, Seattle, WA**
Grant No.:	**5 U01AG032699-02**
Award:	**$200,000**

The long-term objective of NIA's RFA-AG-08-004 entitled, New Interventions for Menopausal Symptoms (U01) is to accelerate progress in identifying effective remedies for vasomotor symptoms (VMS) in women going through the menopausal transition. They have created a network of scientists who are highly knowledgeable about the menopausal transition and experienced in the conduct of women's health trials to fulfill this mission. This data coordinating center (DCC) application is being submitted in conjunction with the network entitled The Menopausal Symptoms Initiative-Finding Lasting Answers to Sweats and Hot Flashes (MsFLASH). Their DCC will be jointly led by Andrea LaCroix and Garnet Anderson who have served together as Co-Principal Investigators (PIs) of the Women's Health Initiative Clinical Coordinating Center (Seattle) for more than a decade. The MsFLASH network has five clinical sites located in Boston (Lee Cohen and Hadine Joffe, PIs), Indianapolis, IN (Janet Carpenter, PI), Oakland, CA (Barbara Sternfeld and Bette Caan, PIs), Philadelphia (Ellen Freeman, PI) and Seattle (Katherine Newton and Susan Reed, PIs). This interdisciplinary investigator group proposes five randomized controlled trials testing a range of behavioral, mind-body, hormonal and pharmacologic interventions to treat hot flashes. The specific objectives of the DCC are to: (1) provide and coordinate all necessary leadership activities to facilitate collaboration and productivity among network scientists during all phases in the lifecycle of VMS clinical trials from hypothesis formulation to publication, dissemination, and data sharing; (2) build upon 15 years of experience and well established human and operational resources to coordinate five or more multi- site randomized trials including support of protocol development, recruitment, intervention, data collection and management, and statistical analysis; and (3) create the infrastructure to involve an expanded network of scientists from the US and worldwide to facilitate the development and use of common methodologies and measurements for VMS trials inside and outside of this trial network so that emerging new treatments for hot flashes can be rapidly identified and rigorously tested for efficacy and safety with comparable results.

Title: **MsFLASH: An RCT of Yoga And Ultra-Low-Dose Estrogen Gel for Vasomotor Symptoms**
P.I.: **Katherine M. Newton**
Institution: **Group Health Research Institute, Seattle, WA**
Grant No.: **5U01AG032682-02**
Award: **$95,148**

In this site application they propose a multicenter, factorial design, RCT of yoga, ultra low-dose estradiol (E2) gel and placebo gel to be conducted in Seattle, Indianapolis and Boston. The primary aims are to: (1) evaluate the effects of yoga vs. no yoga on a) subjective VMS frequency and b) VMS bothersomeness; and (2) evaluate the effects of ultra-low-dose estrogen (E2) gel vs. placebo gel on (a) subjective VMS frequency and (b) bothersomeness. Their hypotheses are that (1) the effect of yoga will be greater than no yoga on (a) subjective VMS frequency and (b) VMS bothersomeness; and (2) the effect of ultra-low-dose E2 gel will be greater than no E2 gel on (a) subjective VMS frequency and (b) bothersomeness. Their secondary aims are: (1) to evaluate the effects of yoga and ultra-low-dose E2 gel on other common menopause outcomes including (a) objective VMS frequency (Bahr monitor), (b) sleep (PSQI, Actigraph), and (c) mood (CESD, HADS); and (2) to examine whether the combined effect of yoga and ultra-low-dose E2 on their primary and secondary outcomes is greater than the effect of either alone. To accomplish their Specific Aims they will: (1) recruit and randomize 400 women to one of four treatment arms for 12 weeks (placebo gel, yoga + placebo gel, ultra-low-dose E2 gel, yoga + ultra-low-dose E2 gel); (2) measure primary and secondary outcomes at baseline and 12 weeks; (3) compare changes in outcomes in yoga and ultra low-dose E2 gel groups to placebo; and (4) compare changes in primary and secondary outcomes for yoga + ultra low-dose E2 gel to the effects of either intervention alone (if yoga alone is efficacious).

Study of Women's Health Across the Nation

Title: **SWAN: Study of Women's Health Across The Nation**
P.I.: **Joel S. Finkelstein**
Institution: **Massachusetts General Hospital, Boston**
Grant No.: **3U01AG012531-16A1S1**
Award: **$75,000**

The Study of Women's Health Across the Nation (SWAN) is a multicenter, multiethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. The goals of the original RFA were to answer the following questions: How do hormones change with the menopausal transition? What factors affect the timing of the transition? What are the symptoms that accompany menopause and who is at risk? How do cardiovascular risk factors change with the transition and is there ethnic variation? What are the rates of bone loss with the transition? When does bone loss begin and what are the risk factors? What are the health consequences of menopause and who is at risk? SWAN is compiling the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. SWAN is now poised to study the effects of these menopause-related changes on subsequent healthy aging and on age-related diseases in the post-reproductive period. SWAN I was first funded in September 1994 by the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the Office of Research on Women's Health (ORWH) in response to RFA AG-94-002, Menopause and Health in Aging Women. The first competing continuation of SWAN (SWAN II) was funded in 1999 and the second (SWAN III) in 2004. SWAN I, II and III have been supported by a cooperative agreement mechanism, with nine funded components: seven clinical centers, a central reproductive hormone laboratory

(CLASS), and a coordinating center. A second central laboratory (MRL) was originally funded as a subcontract to the coordinating center (CC). In addition, a core repository of serum, plasma, and urine specimens and a DNA repository were established in June 2000 under separate funding (U01 AG 17719, PI: Dr. MaryFran Sowers). For non-study-related reasons, site operations at New Jersey Medical School stopped in April 2004. The basis of this action was allegations made by two study employees who resigned abruptly. The SWAN principal investigator (PI) and study coordinator were subsequently exonerated from these allegations. (Please see Appendix 12 for a more complete report.) The grant was transferred to the Albert Einstein College of Medicine in 2005. Since that time, the New Jersey PI and project director have worked tirelessly to overcome the obstacles to re-implement the study. As of June 1, 2008, a total of 155 women have successfully completed their clinic visit and five more visits are scheduled. They project that by the end of SWAN III, data will be available for 250 women. This has been very encouraging and thus Nanette Santoro, PI of the New Jersey SWAN site has been approved by the NIA to prepare a U01 application to cover further contacts for the Hispanic women. Please note that the SWAN IV project applications pertain to the remaining six sites only. Information relative to the New Jersey site is covered in the separate application submitted by Dr. Nanette Santoro. From over 16,000 women aged 40–55 years who were screened during 1995–1997, 3,302 women aged 42–52 years were enrolled in SWAN's longitudinal cohort (approximately 450 at each of seven clinical centers). They completed their baseline clinic visit during 1996–1997. Of the 3,302 women enrolled, 1,550 were Caucasian, 935 African American, 286 Hispanic, 250 Chinese, and 281 Japanese. A subset of 880 menstruating women was enrolled in the Daily Hormone Study (DHS) started in 1997, which is designed to examine cyclical daily hormone and symptom patterns during the menopausal transition.

Title: **Study of Women's Health Across the Nation III**
P.I.: **Kim Sutton Tyrrell**
Institution: **University of Pittsburgh, PA**
Grant No.: **3U01AG012553-15A1S2**
Award: **$125,000**

The Study of Women's Health Across the Nation (SWAN) is a multicenter, multiethnic, community based longitudinal study designed to characterize the biological, symptomatic, and psychosocial changes that occur during the menopausal transition and the effects of these changes on women's health during and after the transition. Current and prior funding (SWAN I and II) has supported a baseline and six annual followup examinations during which 895 (48 percent) women will have transitioned to postmenopause. This application requests funding to complete four additional followup visits (SWAN III) to allow an adequate evaluation of the late perimenopause and early postmenopause, a period that has not been well studied, particularly among non-white women. They will continue their current tracking of changes in reproductive hormones, bleeding patterns, symptoms, bone loss, cardiovascular (CV) risk factors, blood pressure, body size, and other related characteristics and will undertake new scientific endeavors in targeted areas. These include measurement of vascular stiffness to assess early CV disease, assessment of vertebral morphometry at four sites using DEXA technology, and the addition of one cognitive function test. In addition, they will focus on linking the midlife experience to age-related outcomes (e.g. cognitive function, urinary incontinence) and chronic diseases (e.g. fractures, diabetes and hypertension). Specimens from the additional followup visits will continue to contribute to the SWAN biological specimen repository (annual blood and urine samples as well as DNA and immortalized cells). This is a separately funded component that broadens the opportunities to address future hypotheses about health and disease in aging women. As women reach the end of early postmenopause (two years following the final menstrual period), they will shift from an annual to a biannual followup examination schedule with mail and telephone contact in the alternating years. This will permit cost-

effective and less intensive followup. SWAN's organization and operations have been modified to enhance productivity and they are poised to publish important biological, symptom, and behavioral results pertaining to the menopause transition. With SWAN III, many of the original goals of SWAN will be brought to fruition. They will build upon the rich foundation developed during SWAN I and II and link these data to important menopause-related and health outcomes in SWAN II.

Other Menopause Research

Title: **Neurobiology of the Menopausal Transition**
P.I.: **Yolanda R. Smith**
Institution: **University of Michigan, Ann Arbor**
Grant No.: **5R01AG027675-04**
Award: **$47,579**

This project is part of an RFA jointly funded by the National Institute on Aging and the Office of Research on Women's Health on the biology of the perimenopause, impact on health and aging in nonreproductive somatic and neuronal tissues. This and other projects funded under this RFA focus on increasing their understanding of the underlying biologic mechanisms associated with the increased risk for, or decreased protection leading to, health problems and conditions associated with the menopausal process in middleaged women. The focus is on how the hypothalamic-pituitary-ovarian axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within nonreproductive somatic and neuronal target tissues, the role of steroid hormone biosynthesis and/or metabolism within non-reproductive somatic and neuronal tissues on pathophysiologic processes within these tissues across the perimenopause, and the role of aging on these pathophysiologic processes.

Title: **Biological Mechanisms of Arterial Stiffening with Age and Estrogen Deficiency**
P.I.: **Kerrie Moreau**
Institution: **University of Colorado, Denver**
Grant No.: **5R01AG027678-04**
Award: **$47,579**

The purpose of this project is to determine the key functional mechanisms by which the loss of female sex hormones, particularly estradiol (E2), contribute to the age-related decrease in large artery compliance. The overall hypothesis is that basal large artery compliance will decrease in response to acute sex hormone suppression in pre- and perimenopausal women due in part to a decrease in vascular endothelial-dependent vasodilatory tone mediated, in part, to the development of vascular oxidative stress. However, E2 administration during sex hormone suppression will decrease vascular oxidative stress, improve endothelial vasodilatory tone and restore arterial compliance to basal levels. Secondary and tertiary hypotheses are that the changes in arterial compliance and vasodilatory function with sex hormone suppression and E2 will be related to unfavorable, and favorable, respectively, changes in vascular endothelial cell protein expression including oxidant (e.g., NADPH) and antioxidant (e.g., glutathione peroxidase) enzymes, vasoconstrictors (endothelin-1), and estrogen receptor alpha (ERalpha). To test these hypotheses, healthy pre-, peri-, and postmenopausal women will be studied at, before, and following acute sex hormone suppression (gonadotropin releasing hormone antagonist [GnRHant]) with or without E2 add-back therapy. The GnRHant intervention will enable us to study the direct mechanisms associated with sex hormone deficiency and the E2 add-back intervention will enable us to isolate the independent effects of E2. Insight into the molecular

mechanisms mediating the decrease in large artery compliance will be obtained using a novel translational research technique to determine changes in vascular endothelial cell protein expression of genes involved in the regulation of cellular and systemic adaptations to aging and sex hormone deficiency including oxidative stress, nitric oxide bioavailability, and the potent transcription factor ERalpha proteins. The results should provide new insight into the integrative biological mechanisms by which sex hormone deficiency modulates the age-related reduction in large artery compliance in women as they transition through the menopause.

Title: **Impact of Endocrine Aging on Brain and Immune Responses**
P.I.: **Farida Sohrabji**
Institution: **Texas A&M University Health Science Center, College Station, TX**
Grant No.: **5R01AG027684-04**
Award: **$47,579**

This project seeks to determine the mechanisms by which reproductive aging and estrogen replacement alter the inflammatory response and consequently the neuronal environment. In a series of studies, they have established that estrogen replacement to young adult animals increases trophic support in the forebrain and attenuates inflammation following neural injury. However estrogen replacement at reproductive senescence, which is physiologically akin to menopause, fails to increase trophic factors and paradoxically, increases inflammatory mediators following neural injury. Collectively these data suggest that the timing of estrogen replacement in relation to reproductive aging may critically determine whether estrogen has a benign or deleterious outcome. Their central hypothesis is that the age-related decline in endogenous hormones triggers compensatory changes in estrogen receptor systems in specific immune cells, thus increasing the central and peripheral inflammatory response. This hypothesis will be tested in three Specific Aims, using animal and human tissue models that span the reproductive spectrum, namely, normally cycling (pre-menopause), irregularly cycling (perimenopause), and reproductive senescent (postmenopause). In Specific Aim 1 they will test the hypothesis that permissive changes in the blood-brain barrier will cause a more rapid and robust neural inflammation in reproductive senescent animals as compared to normally cycling or irregularly cycling animals. Animals will be injected systemically with the bacterial pathogen lipopolysaccharide (LPS) and inflammatory mediators will be measured in peripheral organs and the brain. Additionally, they will examine endothelial cells of the blood-brain barrier for reproductive age-related changes in this barrier. In Specific Aim 2 they will determine if the inflammatory response of peripheral blood mononuclear cells (PBMC) is affected by clinically-relevant variables namely, the route of hormone administration (oral versus transdermal) and diet (regular versus high cholesterol). The response quotient, derived from an ex vivo LPS challenge assay, will be measured in rat and human blood samples to determine if salient lifestyle variables increase the risks associated with reproductive aging. Finally, in Specific Aim 3 they will test the hypothesis that compensatory alterations of the estrogen receptor system, resulting from ovarian decline, is a principal mechanism underlying estrogen's deleterious effects in reproductive senescence. Changes in the pattern and levels of estrogen receptor (ER)-alpha will be evaluated by immunohistochemistry and Western blots, while functional changes will be evaluated using signaling arrays. Human and rodent PBMC's and rodent cerebral endothelial cells from each reproductive stage will be studied. Collectively, these studies will test the hypothesis that in order for estrogen replacement to be beneficial, therapy must be initiated before compensatory responses to ovarian decline.

Title: **Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO**
P.I.: **Puliyur S. Mohankumar**
Institution: **Michigan State University, East Lansing**
Grant No.: **5R01AG027697-04**
Award: **$47,579**

This project is part of an RFA jointly funded by National Institute on Aging and the Office of Research on Women's Health on the biology of the perimenopause, impact on health and aging in nonreproductive somatic and neuronal tissues. This and other projects funded under this RFA focus on increasing their understanding of the underlying biologic mechanisms associated with the increased risk for, or decreased protection leading to, health problems and conditions associated with the menopausal process in middle-aged women. The focus is on how the hypothalamic-pituitary-ovarian axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within nonreproductive somatic and neuronal target tissues, the role of steroid hormone biosynthesis and/or metabolism within non-reproductive somatic and neuronal tissues on pathophysiologic processes within these tissues across the perimenopause, and the role of aging on these pathophysiologic processes.

Title: **Estrogen: Neuroprotection in the Perimenopause**
P.I.: **Anne M. Etgen**
Institution: **Yeshiva University, Bronx, NY**
Grant No.: **5R01AG027702-04**
Award: **$47,579**

Alterations in the hypothalamic-pituitary-ovarian axis in perimenopausal women are associated with multi- organ risk factors for disease, yet the biological mechanisms underlying this increased disease risk are largely unknown. This proposal addresses unanswered questions regarding the vulnerability of the middle- aged brain to global ischemia. In young female rats, the presence of physiological levels of estradiol before and after global ischemia, as might occur during cardiac arrest, reduces hippocampal CA1 neuron loss and associated cognitive impairments. Whether estradiol retains its neuroprotective actions in middle-aged females, and whether the age-related decline in insulin-like growth factor-l (IGF-I) increases vulnerability to ischemia-induced neurodegeneration and cognitive impairment, are unknown. This proposal examines the roles of age, estrogen, and IGF-I in the survival and function of hippocampal neurons in a rat model of global ischemia. The underlying hypotheses are that: (1) the middle-aged brain retains its responsiveness to the neuroprotective actions of estradiol if the duration of estrogen withdrawal is brief (critical period hypothesis) or circulating levels of IGF-I are maintained; (2) estrogen acts in the middle-aged brain to activate specific cell survival pathways and thereby intervenes in apoptotic cascades to prevent death of neurons otherwise destined to die. Specific Aim 1 uses stereological cell counting and behavioral tests to evaluate the outcome of global ischemia in middle-aged female rats that are intact, ovariectomized at various intervals prior to insult, or ovariectomized and treated with estradiol at various intervals after ovariectomy. If estradiol does not preserve neurons and cognitive function in older hormone-deprived animals, they will also determine if IGF-I can reinstate estrogen protection. Specific Aim 2 examines the apoptotic death cascades triggered by global ischemia and identifies the site at which estrogen intervenes in these cascades. They will examine: (1) mitogen-activated protein kinase and cAMP response element binding protein at early times after ischemia; (2) the anti-apoptotic gene Bcl-2 and activation of caspase 3 at later times after ischemia; (3) inactivation of Akt and subsequent activation of the forkhead transcription factor FKHRL1 at

early times after ischemia. These experiments will provide new information on the potential for hormone therapy instituted during the perimenopausal transition to protect the brain from damage due to global ischemia.

Title: **Menopause: Decreased Response to Increasing Inflammation**
P.I.: **Adriana Caterina Maggi**
Institution: **University of Milan, Italy**
Grant No.: **5R01AG027713-04**
Award: **$46,199**

The long-term goal of their research is to find treatments for the prevention of the disorders associated with menopause which are safer and more efficacious than present hormone replacement therapy (HRT). The failure of present HRT to fulfill medical and women's needs has to be ascribed to an insufficient knowledge of the biology of menopause. The aim of their research is focused on understanding the consequences of cessation of ovarian functions on the physiology of nonreproductive organs such as bone, brain, arteries, and fat. In particular their studies and the studies proposed in the present project will focus on the effects of estrogen decreased production at menopause transition and after in nonreproductive organs. Given recent results demonstrating that in nonreproductive organs of fertile female mice estrogen receptors (ERs) are activated by factors other than estrogens, their Specific Aim 1 will focus on assessing the extent to which ERs are transcriptionally active during menopause transition and after. They will then try to identify the factor(s) involved in ER activation. This part of the project relates to questions which so far could be addressed only partially with the current technology. The generation of a novel model of reporter system, the ERE-Luc mouse, will enable us to precisely quantify ER activity in the organs of interest and facilitate the search of factors involved in ER unliganded activation. Specific Aim 2 will give us the opportunity to test an original hypothesis that would explain the widespread protective effects provided by the estrogen-ER system. This hypothesis is based on numerous very recent observations made in their group and several other groups showing that estrogens and cognate receptors may exert a strong anti-inflammatory action by inhibiting the immune response of cells of the monocyte lineage. They here propose that menopause consists of a decreased response to increased inflammation. They will test this hypothesis by the direct assessment of ER relevance on macrophage activity through the generation of a novel conditional ERalpha knockout mouse. Furthermore, using brain as a paradigmatic nonreproductive organ, they will measure basal and induced activity of brain inflammatory cells. Finally, the specific involvement of ER anti-inflammatory activity in the development of menopause-associated diseases will be tested with the study of the activity in menopause of another class of intracellular receptors devoted to the control of inflammation, the PPARs.

Title: **Genetics of Reproductive Life Period and Health Outcomes**
P.I.: **Joanne M. Murabito**
Institution: **Boston University Medical Campus**
Grant No.: **5R21AG032598-02**
Award: **$241,900**

The overall research objective of this grant is to elucidate the contribution of menopause and reproductive factors versus aging per se to health conditions common in women in later life. More than half the variation in age at menarche and menopause is attributable to genetic factors yet the genes regulating these traits remain largely unknown. Data from longitudinal studies, such as the Framingham Heart Study (FHS), provide a wealth of data across adulthood including reproductive factors, disease occurrence, and health behaviors in both women and men. The FHS is multigenerational and includes an extensive genetics database with extant

genotyping from a 550K genomewide scan obtained through the the National Heart, Lung and Blood Institute's SNP Health Association Resource (SHARe) project. They postulate that novel genetic variants influencing the age of menarche and natural menopause can be identified using a dense genomewide association study (GWAS). This proposal aims to identify genetic variants that influence age at menarche and age at natural menopause through a GWAS using extant 550K genotyping data; to perform in silico replication of significant associations in independent samples; to examine the associations between genetic variants and osteoporosis-related traits obtained using dual x-ray absorptiometry (DXA) and hand radiogrammetry, in women as well as in men; to perform a phenome scan using the genotypes associated with reproductive aging to identify other associated phenotypes that may provide additional insights into underlying biological mechanisms mediating the associations in women. The phenome scan will also be performed in men to explore sex-specific associations. The use of the 550K genotyping will be resource effective and their work will be publicly available through the FHS SHARe Project located at the National Center for Biotechnology Information (NCBI) permitting investigators around the world to embark on this research. Insights from this project may lead to the discovery of genes related to female reproductive aging and associated health outcomes and in turn lead to innovative diagnostic and therapeutic interventions to improve the overall health of women and possibly of men.

Mental Health

Title: **Novel Approaches to Understanding Mental Disorder, Substance Abuse, and HIV Risk Among Homeless Women**
P.I.: **Leslie B. Whitbeck**
Institution: **University Of Nebraska, Lincoln**
Grant No.: **1R21HD058989-01A1**
Award: **$145,180**

This R21 application seeks two years of support to develop state-of-the-science methodologies to address four important needs in existing research with homeless women: (1) to capture the diversity of circumstances among a fluid and hard-to-access population; (2) to increase their understanding of mental and substance use disorders (particularly personality disorders) across the diversity of homeless women; (3) to improve their understanding trajectories to homelessness through development of an innovative event history calendar approach; (4) to advance knowledge of homeless women's health and HIV-risk by circumstance and trajectories to homelessness. This research will provide measurement development and preliminary studies for a multistate longitudinal R01 designed to advance their understanding of mental and substance use disorders among homeless women, their movement into and out of homelessness, the consequences of homelessness for women and minor children in their custody, and women's health, HIV-risk, and HIV testing behaviors. The planned longitudinal research will focus on a growing but poorly understood population of the nation's most vulnerable women. The Specific Aims of this R21 developmental application are to: (1) develop and pilot a sampling plan that will better reflect the diversity of homeless women; (2) develop and pilot an innovative events history calendar for use with homeless women; (3) program and pilot Axis 1 (UM-CIDI) and Axis II (DIPD-IV) diagnostic interview schedules for computer-assisted personal interviews with homeless women; (4) develop and program women's health and HIV-risk measures; and (5) pilot the measures with 200 homeless women in two Midwestern cities.

Title: **Race and HIV Risk: Contextual and Neurocognitive Influences on Sex Partnerships**
P.I.: **Leah Floyd**
Institution: **Johns Hopkins University, Baltimore, MD**
Grant No.: **1R21DA025543-01**
Award: **$204,426**

The primary aim of this R21 application in response to the National Institute on Drug Abuse's Advancing Novel Science in Women's Health Research Initiative (PAS-07-381) is to address gaps in literature focused on HIV risk and disparities among females. In the United States, as rates have increased among females, the rate of HIV/AIDS diagnoses for African-American females approaches 25 times the rate for white females. Despite the broad base of findings documenting health disparities in HIV, extant studies cannot explain why African Americans continue to be disproportionately affected. Currently, there is a hidden HIV epidemic among young adult African-American females with no history of substance abuse. These women are at increased risk for contracting HIV by virtue of their social networks. The proposed study requests 2 years of support for a cross-sectional epidemiologic examination of racial/ethnic differences in sexual partnerships among 220 females (110 Black and 110 White) residing in low socioeconomic status (SES) neighborhoods. Guided by ecosocial theory, they seek to explain why these differences exist across race/ethnicity. They will consider the extent to which neighborhood social and economic factors (e.g., drug markets) interact with race/ethnicity to produce different levels of HIV risk. They will expand drug abuse and HIV prevention research by, in addition to considering individual differences, examining the influences of neighborhood drug markets on the sexual behaviors, sexual partnerships, and rates of a sexually transmitted disease among young adult females residing in disadvantaged neighborhoods. Finally, the proposed study will move beyond descriptive social epidemiology and into identifying neurocognitive processes that mediate/moderate relationships between neighborhood factors and individual behavior. As a small yet growing base of research suggests, to the extent that individuals are able to make decisions, solve problems and control impulses, neurocognitive functions may serve as protective factors or pathways through which external social factors influence individual behavior. Identifying social factors that influence partner selection and individual level factors that may serve to reduce the adverse effects of living in disadvantage neighborhoods will inform HIV prevention interventions for African-American and underserved women. If successful, the proposed research project: (1) should provide insight into why African-American females have higher rates of HIV than their white counterparts; (2) highlight the importance of considering the contextual influences of drugs, that is, the influence of drug markets on social structures and sexual norms and behaviors; and (3) identify modifiable individual level factors linking neighborhood social and economic factors to individual HIV risk behaviors.

Title: **Antimanic Use During Pregnancy**
P.I.: **Katherine L. Wisner**
Institution: **University of Pittsburgh, PA**
Grant No.: **5R01MH075921-04**
Award: **$200,000**

Bipolar disorder (BP) is a serious psychiatric condition that affects 0.5–1.5 percent of individuals in America. The age of onset of BP is during the initial childbearing years. Seventy percent of women with established BP will suffer recurrent episodes post-birth. Continuous medication administration is the mainstay of treatment for BP. Although the information available to physicians who treat pregnant women with unipolar depression has increased over the past decade, data to inform decisions about treatment of BP has not advanced similarly.

Information about anticonvulsant use during pregnancy has been garnered solely from the study of women with epilepsy, who have increased risk for malformations independent of drug treatment. Data about atypical antipsychotic use in pregnancy is almost non-existent in either women with BP or schizophrenia. The majority of studies have not included the range of outcome measures that comprise the contemporary portfolio of the reproductive toxicity outcomes. Pharmacologists have produced data for altered physiologic states (renal or hepatic disease) and for other patient subpopulations (children and elderly). The need for similar studies in pregnancy is certainly no less than for these populations. New information must be obtained to guide risk-benefit decisionmaking to a new level of sophistication. This is a prospective observational study of women with BP during pregnancy and the mother-infant pairs in the first postpartum year. They plan to enroll 200 women with BP and 58 women without BP (for 140 and 40 completers, respectively). Decisions about treatment during pregnancy will be made by the woman with her physician (not associated with the study) prior to study enrollment. The major aims of the study are to define a cohort of pregnant women with DSM-IV defined BP and to: (1) Characterize the BP illness course in the population through pregnancy and the first postpartum year, with careful documentation of treatment(s) and gestational timing; (2) Evaluate function in the maternal role as well as occupational, educational and social domains. (3) Define pregnancy and infant outcomes in both medicated and unmedicated women with BP and compare them to those of unmedicated women without BP. Separation of the effects of medication from the disorder is critical to advance risk assessment. (4) Assess the infants' development through the first year of life. (5) Perform serum levels at 20, 30, and 36 weeks gestation to allow level/dose ratio monitoring for women who take medications during childbearing. The mother-infant serum levels of women with BP who breastfeed their infants also will be assayed. 6) Conduct pharmacokinetic (PK) studies on the subset of women who take lithium, the most common drug used to manage BP during pregnancy in their Center, at 20–24 weeks, 32–36 weeks, and 12–16 weeks after birth. No such PK data are currently available.

Title: **Sex Stress Emotional Disorders: Uniting Preclinical and Epidemiologic Research**
P.I.: **Elizabeth J. Costello**
Institution: **Duke University, Durham, NC**
Grant No.: **5R21MH083964-02**
Award: **$20,000**

The overall research objective of this grant is to (1) bring together researchers who have made important advances in preclinical, experimental, and epidemiological research on stress responsitivity and psychopathology; (2) to integrate their findings across disciplines and identify key questions related to gender disparities; and (3) to plan a new program of research that takes a developmental approach to sex differences in stress responsivity as they affect depression and anxiety disorders in young people. The program of work has three aspects: (1) Two annual meetings of the workgroup members to identify key questions and plan a program of analysis of existing data sets. Meetings will be designed so that participants will learn as well as teach. At the second meeting, each workgroup member to commit to be first author on one or more specific papers. (2) A program of data analysis to be carried out at the Center for Developmental Epidemiology, Duke University. Analyses will be reported to the group by email; group members can request additional followup analyses. Monthly conference calls between meetings will discuss output of analyses and plan further work. (3) An application for an Interdisciplinary Developmental Science Center for Mental Health (IDSC) or similar mechanism, to be submitted in October 2010. Questions to be addressed include the following: (1) what has been learned from animal research about sex differences in the effects of early adversity on neurobiological parameters, such as the HPA axis, the autonomic nervous system, and neural systems implicated

in psychopathology; (2) what has been learned from laboratory and epidemiological research with humans about sex differences in the effects of early adversity on neurobiological parameters, such as the HPA axis, the autonomic nervous system, and neural systems implicated in anxiety and depression in the first decades of life; (3) where do these bodies of work agree, where do they conflict, and where are the most important gaps. They expect that the answers to questions 1–3 will lead to the planning of a Center application to focus on such questions as: (4) how does gender moderate the effects of childhood stress on mental health and neurobiological function, i.e., what are the interactions between stress response systems and sex steroids; (5) what are the sex-specific effects of stress and life events in different developmental stages or during transitions between stages (e.g., puberty) on risk for anxiety and depression; (6) how does the timing of differences in onset of anxiety and depression in males and females relate to sex differences in psychological and neurobiological functioning?

Title: **Sex Differences in the Entorhinal Cortex**
P.I.: **Helen E. Scharfman, Nathan S. Kline**
Institution: **Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY**
Grant No.: **5R21MH084215-02**
Award: **$20,000**

This project will evaluate whether sex differences exist in a part of the brain where they have not previously been recognized, the entorhinal cortex, and address their implications. They hypothesize that there is increased neuronal activity in the female medial entorhinal cortex and this disrupts processing of new information, particularly spatial information. Based on preliminary findings, estrogen appears to play a key role by facilitating NMDA-eceptor-mediated activation of entorhinal neurons. The implications are important because they could help address sex differences in cognitive function, and lead to new considerations for treatment of learning disorders. There are many differences between females and males in the brain, behavior, and disease. One of these is established in rodents as well as man: spatial memory. What could be the underlying basis? In this project they test the hypothesis that there are robust sex differences in the rodent medial entorhinal cortex that could explain sex differences in spatial memory. The medial entorhinal cortex seems a logical candidate given it is critical to spatial representation in the rat, and lies in an ideal anatomical position because it is situated between hippocampus and cortex. Their preliminary data, using slices of entorhinal cortex, shows a sex difference in evoked responses to afferent input in entorhinal cortex: in slices from females, responses are repetitive or prolonged relative to males, a sex difference that is blocked by the NMDA receptor antagonist D-APV. When estrogen levels are high, these events are most robust, and when estrogen is low, or a prepubertal animal is evaluated, they are relatively rare. They hypothesize that the responses of entorhinal neurons to afferent input are increased in the female rat relative to males, and this disrupts information processing and synaptic plasticity, i.e., long-term potentiation (LTP). Because the difference appears to be localized to superficial layers, the perforant path projection to hippocampus may be selectively influenced, and this is important because the perforant path is the major afferent system to hippocampus from entorhinal cortex. In this proposal, they will establish the cellular physiology in slices of entorhinal cortex of female and male rats, test sex differences in LTP in the entorhinal cortex and hippocampus, and address whether puberty and estrogen are key factors, as preliminary data suggest. Together the results will shed light on an area of the brain where sex differences are relatively unexplored, and could have important implications for understanding cognitive function, as well as treating learning disorders.

Title: **Emotions are Emergent Events Constrained by Affective and Conceptual Processes**
P.I.: **Lisa Barrett**
Institution: **Boston College, MA**
Grant No.: **5DPOD003312-03**
Award: **$391,250**

Emotional states are central to mental and physical health. NIH invests tremendous resources in research on emotion, much of it devoted to animal models. Ironically, this research is guided by a scientific paradigm that is grounded in human experience. People experience fear and see it in others, so scientists assume there must be a literal (modular) neural circuit for fear in the mammalian brain. Rats freeze when they hear a tone paired with a foot shock, so they are presumed to be in a state of fear (versus surprise, anger, or even a general state of alarm) and undergoing "fear learning." Scientists also presume that a map of the neural circuitry of freezing behavior will yield a neural mechanism for fear that is largely preserved in humans, and a decade of neuroimaging studies have focused on locating a homologous neural circuit in the human brain. In the last five years, the researcher has traced the roots of this "natural kind" model, conducted a comprehensive review of the literature to examine its veracity, and found it wanting. In response, I have fashioned a new systems-level model, called the Conceptual Act Model, grounded in the neuroanatomy of the human brain. The researcher's model parsimoniously incorporates neuroscience findings from rats, primates, and humans, and explains the mechanisms that produce the range and variety of behavioral and introspective instances that they call "emotion.". The Conceptual Act Model asks different—and perhaps better—questions about what emotions are and how they function in mental and physical health. The NIH Director's Pioneer Award will allow the researcher the intellectual freedom and resources to continue building evidence for the Conceptual Act Model of emotion, thereby shaping a new paradigm to guide the scientific study of emotion.

Musculoskeletal Systems

Title: **Function and Behavior Phenotype of Inflammatory Arthritis in the Rat Knee and Temporomandibular Joint**
P.I.: **Kyle Allen**
Institution: **Duke University, Durham, NC**
Grant No.: **1K99AR057426-01**
Award: **$74,540**

Degenerative joint disorders, such as arthritis, affect a substantial percentage of the U.S. population and have a significant economic burden. The focused use of disease modifying drugs and cellular strategies for tissue regeneration offer great potential to treat these disorders; however, the safety and efficacy of these treatment strategies must first be evaluated in preclinical models. The purposes of this proposal, and the career aims of the principal investigator, are to create and refine techniques to evaluate joint function and symptoms in preclinical animal models of arthritis and to investigate the potential for disease-modifying therapeutics to modify functional and symptomatic sequelae associated with arthritis. This proposal begins with the mentored phase where interleukin 1p (IL-lp) overexpression in the knee joint will be used as a rat model of unilateral inflammatory arthritis. The functional and symptomatic sequelae of this arthritis will be evaluated using custom-designed gait and pain sensitivity tests. Moreover, two IL-1p antagonists, interleukin 1 receptor antagonist (Il-1 Ra) and soluble interleukin 1 receptor type II (slHRII), will be evaluated for their ability to modify functional and symptomatic sequelae associated with knee arthritis. The principal investigator (PI) will then transition skills and knowledge gained during the mentored phase to the study of temporomandibular joint (TMJ) disorders and their functional and symptomatic sequelae.

In the independent stage, techniques and methods to assess the sequelae of TMJ disorders will be developed for rodent models, including systems to evaluate orofacial sensitivity, bite force, dietary habits, and sleep patterns. The intra-articular IL-1p overexpression model will then be adapted to initiate TMJ arthritis, and the developed technologies will be applied and assessed for their ability to modify the associated functional and symptomal sequelae. This proposal addresses the developments of novel treatment and assessment strategies for knee arthritis and TMJ disorders, drawing significantly on the PI's experience in TMJ research and the mentor institution's expertise in osteoarthritis and drug delivery. Moreover, this research plan will assist the PI in transitioning to a faculty position and establish an independent research program evaluating therapeutic interventions for TMJ disorders and degeneration.

The Osteoarthritis Initiative

Knee osteoarthritis (OA) is the most common cause of disability in adults. The Osteoarthritis Initiative (OAI): A Knee Health Study is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA. Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury, or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and follow participants who have knee OA or are at high risk for developing knee OA for at least a 4-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and X-rays will be completed at each of four annual followup visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee OA. Levels of knee pain and physical disability will be assessed at study start and at each of the followup visits by questionnaire and examination. The four clinical centers include the following:

Title: **Clinical Centers for the Osteoarthritis Initiative: Rhode Island**
P.I.: **Charles B. Eaton**
Institution: **Memorial Hospital of Rhode Island, Pawtucket**
Grant No.: **N01AR22262-12-0-1**
Award: **$162,500**

Title: **Clinical Centers for the Osteoarthritis Initiative**
P.I.: **Marc Hochberg**
Institution: **University of Maryland, Baltimore**
Grant No.: **N01AR22259-12-0-1**
Award: **$162,500**

Title: **Clinical Centers for the Osteoarthritis Initiative**
P.I.: **Rebecca Jackson**
Institution: **Ohio State University, Columbus**
Grant No.: **N01AR22261-13-0-1**
Award: **$162,500**

Title: **Clinical Centers for the Osteoarthritis Initiative**
P.I.: **Kent Kwoh**
Institution: **University of Pittsburgh, PA**
Grant No.: **N01AR22260-13-0-1**
Award: **$162,500**

Neurology/Neuroscience

Title: **Identification and Validation of Human Hypothalamic Nuclei In Vivo and Ex Vivo Using 7 Tesla MRI**
P.I.: **Nikolaos Makris**
Institution: **Massachusetts General Hospital, Boston**
Grant No.: **1R21MH084041-01A1**
Award: **$265,125**

There is increasing evidence regarding the importance of the hypothalamus for understanding women's health and sex differences in relation to neurological, psychiatric, endocrine, and sleep disorders. In fact, hypothalamic nuclei, key regulators of autonomic and endocrine functions, are some of the most highly sexually dimorphic nuclei in the brain and implicated in psychiatric and medical disorders with known sex differences. They would argue that an understanding of hormonal effects on the brain and the regulation of other organs and/or systems, such as the cardiovascular and reproductive systems, are critical as downstream effects of hypothalamic activity. Thus an understanding of the neuroanatomy of hypothalamic nuclei and how they are differentially disrupted in men and women in specific disorders will contribute to elucidating sex differences in clinical medicine. However, the identification of hypothalamic nuclei in vivo in humans has not been realized. This is important since studies have shown the association of the hypothalamus, endocrine dysfunction and sex differences in psychiatric disorders. In fact, the paraventricular hypothalamic nucleus (PVN) is enlarged in patients with major depressive disorder (MDD), in PVN neurons that are dense in corticotropin releasing hormone (CRH) and estrogen receptor (ER)1. In their recent work in schizophrenia (SCZ) they identified structural abnormalities using MRI in the hypothalamus particularly in the PVN in women. Furthermore, in healthy women they showed, using functional MRI, regulation of brain activity in hypothalamic nuclei such as the PVN, dependent on gonadal hormone changes over the menstrual cycle. The principal focus of this study is to use a new in vivo methodology for the assessment of the hypothalamus comparing neuroimaging data using 7 Tesla magnetic resonance imaging (MRI) and human postmortem validation. The proposed study aims to identify the PVN in vivo and ex vivo in the human hypothalamus using high field MRI, to investigate the relationship of the MRI methodology and the histological technique, and to establish the correlates of the histological structures with the MRI representations. In addition to the PVN, which is critical for its role within the hypothalamic-pituitary-adrenal (HPA) axis and its dysfunction in MDD and SCZ, they will identify the supraoptic nucleus, which will be used as a control region. High-resolution 7 Tesla MRI will be carried out in 30 healthy subjects, and four ex vivo human hypothalamic samples. Their overarching goal is an innovative methodological one: to identify the PVN of the human hypothalamus in healthy adult women and men in vivo. They expect this method, once defined, to be applied clinically in subjects with MDD and SCZ.

Title: **Cellular and Molecular Basis Of Hippocampal Atrophy in Depressed Female Monkeys**
P.I.: **Carol A. Shively**
Institution: **Wake Forest University Health Sciences, Winston-Salem, NC**
Grant No.: **1R21MH086731-01**
Award: **$222,000**

Clinical and experimental studies suggest that hippocampal volumes may be smaller in individuals with depression, although the cellular mechanisms underlying this relationship are unclear. Stressful life events are associated with an increased risk of depression, and animal models, exposed to chronic stress have been used previously to investigate hippocampal shrinkage in depression. Although the data from preclinical stress models are compelling, the degree to which stress responses in animal models are relevant to human depression remains controversial, particularly since women are at two-fold greater risk of depression and the animal models are mostly male rodents. Evaluation of the causes of reduced hippocampal volume in an experimental model that more closely resembles human depression would be valuable. They have developed a primate model of depression in adult female cynomolgus monkeys which closely resembles human depression, and recently observed that depressed monkeys have relatively small anterior hippocampi (HC). The overall goal of this proposal is to evaluate hippocampal morphologic, cellular, and molecular characteristics in depressed and nondepressed female monkeys to determine whether the smaller hippocampi of depressed female monkeys are accompanied by reductions in neuropil and synaptic, spinous, and dendritic integrity. They have a unique and valuable collection of fixed, frozen hippocampi derived from the population of adult female monkeys in which the behavioral and physiological characteristics of depression were studied premortem for 4 years. Using the tissue from eight depressed and eight nondepressed monkeys they will determine astrocyte, pyramidal, and granule neuron size and number, and protein and mRNA levels of markers of synaptic, spinous, and dendritic integrity in the cornu ammonis (CA) CA1, CA2, CA3, and dentate gyrus of the anterior and posterior HC of behaviorally depressed and nondepressed monkeys. The results of this study will establish the use of the model in future investigations of the mechanisms of depression and the efficacy of interventions for depression. The research is particularly responsive to the FOA entitled "Advancing Novel Science in Women's Health Research" (PAS-07-381). The results of the proposed study will be used in support of a competitive NIH application.

Title: **Sex-Specific Gene Regulation of Neuronal Chloride Co-Transporter Kcc2**
P.I.: **Wolfgang B. Liedtke**
Institution: **Duke University, Durham, NC**
Grant No.: **1R21NS066307-01**
Award: **$234,000**

Chronic pathological pain and certain epileptic syndromes are neuropsychiatric disorders that share an increased female prevalence and refractoriness to treatment. The latter feature is considered to be linked to pathologically increased neuronal excitability caused by increased neuronal chloride (Cl-), which in turn is rooted in down-regulation of the dominant neuronal Cl--transporter, kcc2, which extrudes Cl-. Here they propose experiments to elucidate sex-specific regulation of the kcc2 gene by estrogens, based on a hypothesis that neuronal Cl- is dysregulated in response to neuronal injury in a sexually dimorphic manner, with the consequence of rendering women more susceptible to the above diseases. They have obtained exciting preliminary results (1) showing that kcc2 transcription is regulated by the repressor REST/NRSF which binds to a novel RE1/NRSE DNA binding site in kcc2 regulatory regions;

(2) demonstrating this regulation to underlie the early developmental transformation of GABAergic transmission from excitatory to inhibitory; (3) developing a novel method to culture cortical primary neurons from individual rat E17 embryos which are being sex-typed by X- and Y-chromosome specific DNA markers. The latter method, straightforward yet possibly a groundbreaking novelty, permits strictly separate female versus male primary cortical neuronal culture. They intend to elaborate molecular mechanisms how neuronal Cl- and kcc2 are regulated sex-specifically by exposing male vs. female neurons to 17-β-estradiol and xenobiotic estrogen-mimetics. For this, they will electroporate kcc2 reporter gene constructs, wildtype and mutated for binding sites, driving a secreted luciferase reporter, which will facilitate establishment of a time-course of kcc2 transcription. For direct determination of Cl-, the fluorescent Cl--indicator clomeleon will be co-transfected. Cultures will be exposed to physiologically relevant concentrations of estradiol and practically relevant concentrations of xeno-estrogens (coumestrol, bisphenol-A, dieldrin). Use of the latter compounds will allow us to address modulation of estrogen responses by these ubiquitous compounds. Any sex-specific regulation will be confirmed in primary cultures derived from gene-targeted mice (estrogen receptor (ER)-α, -β and nonclassical-ER-knockin). These experiments will be conducted in a highly collaborative environment at Duke University, involving molecular and physiology neuroscience labs, in addition to molecular endocrinology and environmental toxicology input. Results can be expected to shed new light on a fundamental matter, neuronal Cl--regulation, which very likely has sex-specific regulation as a basis for increased female prevalence in therapy-refractory neuropsychiatric diseases

Title: **Respiratory Plasticity Following Spinal Cord Injury**
P.I.: **Gordon Mitchell**
Institution: **University of Wisconsin-Madison**
Grant No.: **5R37HL069064-08**
Award: **$20,000**

The fundamental hypothesis guiding this proposal is that chronic treatments, known to enhance serotonergic modulation of respiratory motor output, strengthen respiratory synaptic pathways to spinal (phrenic) motoneurons, thereby improving respiratory function during recovery from spinal cord injury. In specific, they will investigate the effects of chronic intermittent hypoxia (CIH) and spinal deafferentation via cervical dorsal rhizotomy (CDR) on synaptic pathways to phrenic motoneurons prior to acute spinal hemisection or following chronic spinal hemisection. Their laboratory has previously shown that both CIH and CDR enhance serotonergic modulation of phrenic motor output, but appear to do so by different mechanisms. They have also shown that spinal serotonin receptor activation enhances both functional and ineffective (crossed-spinal) synaptic pathways in rats. Thus, they will apply these unique models of serotonin-dependent respiratory plasticity to test the hypothesis that they will restore respiratory drive to phrenic motoneurons on the injured (hemisected) side, and enhance respiratory drive to phrenic motoneurons on the uninjured (non-hemisected) side. In Aims 1 and 2, they will test the hypotheses that pretreatment with either CIH or CDR enhances evoked and spontaneous phrenic activity in intact and crossed-spinal pathways in anesthetized rats. In the:next three aims, they will apply CIH following chronic spinal hemisection to test the hypotheses that CIH enhances evoked and spontaneous phrenic activity in anesthetized rats (Aim 3), restores ventilatory responses to chemoreceptor stimulation in unanesthetized rats (Aim 4), and increases ventral spinal concentrations of brain derived neurotrophic factor below the hemisection (Aim 5). This study provides an unprecedented opportunity to determine whether two unique experimental treatments restore respiratory motor function below a well-defined cervical spinal injury, and provides the basis for highly novel therapeutic approaches in the treatment of respiratory insufficiency following spinal cord injury.

Nutrition

Title: National Food and Nutrient Analysis Program
Institution: National Cancer Institute, U.S. Department of Agriculture
Grant No.: Y1CN5010-52-0-1
Award: $25,000

The National Food and Nutrient Analysis Program (NFNAP) is a research program that seeks to achieve sound estimates of dietary components and thus, improvements in nutrient values with particular focus on components with possible roles in human health. The project, directed by the Nutrient Data Laboratory (NDL), Agricultural Research Service, U.S. Department of Agriculture (USDA), was initiated in 1997 and recently renewed in collaboration with the NIH National Cancer Institute (NCI) and the Office of Dietary Supplements, ORWH, and other supporting NIH Offices, Institutes, and the FDA. The primary outcome of the program will be a body of nutrient data representative of the U.S. population intake and consumption patterns with unprecedented analytical quality. This is a collaborative, interdisciplinary project with the NFNAP. Specifically, the two leading causes of death in women in the United States are: (1) cardiovascular disease and (2) cancer. The NFNAP may prove particularly relevant to these women's health issues because the food consumption and composition databases target those foods that are major contributors of public health significance in the United States Specifically, the five objectives of the NFNAP are to: (1) sample and analyze selected key foods; (2) institute a monitoring program for key foods; (3) develop databases for foods consumed by U.S. ethnic subpopulations; (4) develop and update databases for bioactive food components; and (5) develop and validate databases for dietary supplement composition. Moreover, the NFNAP may be significant to research on women's health on several different levels. Better estimates of the mean nutrient content of foods and variance indicators will permit more accurate assessment of nutrient intakes by individuals. This will improve the ability to detect etiologic relationships, delineate biologic mechanisms, assess time trends in nutrient intake, and define populations at nutritional risk. Further, the NFNAP may provide background data supporting nutritional guidance and communications focused specifically on women.

Obesity/Overweight

Title: Intervening on Spontaneous Physical Activity to Prevent Weight Regain in Women
P.I.: Barbara J. Nicklas
Institution: Wake Forest University Health Sciences, Winston-Salem, NC
Grant No.: 1R21HL097252-01
Award: $205,728

Recommendations for more effective long-term weight loss strategies may need to consider the role of gender differences. If, as shown in female versus male animal models, negative energy balance resulting in weight loss results in greater compensatory reductions in energy expenditure in women compared to men, obesity treatments may need to be tailored in women to override these reductions in total energy expenditure. Their approach focuses on a behavioral strategy (self-monitoring) to eliminate the compensatory reduction in non-exercise 'spontaneous' physical activity (SPA) seen in women who lose weight by means of a hypocaloric diet and structured exercise training. Their long-term research goal is to establish empirical evidence for innovative treatment options that are more effective in producing weight loss and preventing weight regain in women. The main goal of this pilot is to provide preliminary data and effect estimates to begin to test their overall hypothesis that prevention of weight loss-induced reductions in SPA will be more beneficial for long-term maintenance of weight loss in women than in men. They propose to conduct a pilot study using a two-

arm, 10-month design in 72 obese, older (55–70 yrs) men and women (n=36 per group). Participants will be randomized to a 5-month standardized weight loss intervention involving a hypocaloric diet and aerobic exercise (DIET+EX) or to the same weight loss intervention with addition of a behavioral component that targets self-monitoring (SM) of SPA (SM+DIET+EX), and then followed for another 5 months after weight loss. The Specific Aims of this R21 exploratory/developmental application are: Primary-To examine whether SPA self- monitoring results in less body weight regain in the followup phase in both men and women; Secondary-To examine whether: (1) women regain more weight than men in the followup phase; (2) SPA self-monitoring and gender have an effect on change in weight in the intensive weight loss phase; (3) SPA self-monitoring and gender have an effect on change in SPA in the intensive weight loss phase; and (4) there is an association between SPA changes in the weight loss phase and weight regain in the followup phase. They anticipate that the results will lead to a larger and longer trial to definitively test their hypothesis, which could potentially provide evidence against the current standard of care (i.e., exclusive prescription of structured moderate-intensity exercise) for obesity therapy in women and may lead to sex-specific treatment guidelines.

Title: **DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women**
P.I.: **Theresa L. Powell, Debra Ann Krummel**
Institution: **University of Cincinnati, OH**
Grant No.: **5R21HL093532-02**
Award: **$234,000**

Obesity prevalence is increasing worldwide and with the difficulty to treat this condition, the need for early intervention is urgent. Obesity in pregnancy is rapidly becoming a major obstetric complication because it increases the risk of gestational diabetes and pre-eclampsia and predisposes the mother for later metabolic and cardiovascular disease. A common problem for the baby is fetal overgrowth, which is associated with traumatic birth injuries and the development of the metabolic syndrome in childhood or later in life. The obese, pregnant woman has increased serum levels of proinflammatory cytokines and low circulating levels of adiponectin leading to decreased insulin sensitivity, which has been suggested to link obesity in pregnancy to metabolic and cardiovascular disease later in life. Fetal growth is determined by placental nutrient supply and our preliminary data show that placental nutrient transport is increased in obesity. Upregulation of placental nutrient transporters in obesity may be caused by the abnormal maternal metabolic profile, since high insulin and proinflammatory cytokines and low adiponectin have been shown to stimulate placental nutrient transport. Approximately one third of all women enter pregnancy being obese and despite the serious adverse consequences for the health of the woman and her child, no specific treatment is currently available. The aim of our study is to supplement the diet of obese pregnant women with docosahexaenoic acid (DHA), a safe, low cost, readily available dietary component that we have shown is extremely low in the diet of our midwestern urban population (10 percent of recommended levels for pregnancy). This omega-3 fatty acid has been shown to have a significant impact on improving insulin sensitivity and circulating levels of proinflammatory cytokines and adiponectin in nonpregnant obese women. DHA has been studied extensively as a dietary supplement in pregnancy as a potential mechanism to improve cognitive function in children. However, the effect of DHA maternal metabolic status and placental function has not been previously reported. We hypothesize that DHA supplementation will improve maternal insulin sensitivity, reduce proinflammatory cytokines, increase circulating adiponectin, downregulate placental nutrient transport, and reduce fetal growth. Our approach for this pilot study will be to recruit 90 obese (BMI 30–45), pregnant women in mid-gestation and randomize these subjects into placebo or DHA treatment (800 mg/day) groups. Subjects will be studied again in late gestation after 12 weeks of supplementation. In Aim 1 we will determine the effect of DHA supplementation on maternal inflammatory status and insulin sensitivity.

In Aim 2 we will establish the impact of DHA supplementation in obese pregnant women on placental nutrient transport and fetal growth. We propose that improved maternal metabolic status and reduced nutrient delivery to the fetus will result in a significant improvement in the long term health of women and their children. Public Health Relevance: Obesity in pregnancy is a major concern for women's health because no specific treatment is currently available for this common condition. Obesity in pregnancy increases the risk for pregnancy complications and predisposes both the woman and her child to develop diabetes and cardiovascular disease later in life. This project will study the effect of a safe dietary supplement, the long chain polyunsaturated fatty acid DHA, on the obese woman's metabolic status during pregnancy, the transport of nutrients to the fetus by the placenta, and the size of the baby at birth. The proposed research is relevant to public health because we expect that it may lead to the development of a novel treatment, which could prevent a number of perinatal complications as well as metabolic disease later in life in women and their children.

Title: **DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women**
P.I.: **Debra Ann Krummel**
Institution: **University of Texas, San Antonio**
Grant No.: **3R21HL093532-02S1**
Award: **$169,872**

This project augments the parent grant (5R21HL093532-02) in order to recruit more Hispanic and African-American participants.

Pain

Title: **Sex Differences in Acute Pain and Analgesic Responses: Psychosocial and Genetic Influences**
P.I.: **Barbara A. Hastie**
Institution: **University of Florida, Gainesville, FL**
Grant No.: **1R21DE019267-01A1**
Award: **$218,495**

Pain is one of the most costly and pervasive public health problems, with women and minorities facing increased risk for under-treated and mismanaged pain. Women, compared to men, report more frequent and intense pain and have increased prevalence of debilitating pain across a multitude of conditions. Women also represent the majority of the 40 million outpatient and ambulatory surgeries conducted each year. Acute post-operative pain and under-treatment of pain are well-documented and lead to prolonged recovery and potentially to development of chronic long-term pain conditions. Despite incongruent findings of sex differences in analgesic efficacy, consistent reports show that women experience between 30 percent and 75 percent more adverse drug reactions (ADRs) compared to men. ADRs can lead to life-threatening complications, discontinuation of pain treatment, prolonged recovery and non-compliance. Recent pharmacogenomic studies have demonstrated that genotype may contribute to sex differences in pharmacokinetic (PK) and pharmacodynamic (PD) responses to certain drugs. Genetic and nongenetic contributions to sex differences in opioid analgesia, related side effects, and treatment outcome have received limited attention in the field of pain research. This study will use a common acute clinical pain model to identify and characterize psychosocial, physiological, and genetic factors that contribute to sex differences in pain perception, analgesia, and side effects. Aim 1 will determine sex differences in perceptual and physiological responses to acute post-operative pain and will examine how those are related to genetic, pre-operative psychophysical and psychosocial factors. Aim 2 will determine sex differences in opioid analgesia and side effects and will examine genetic, PK, PD, and

psychosocial factors that explain group differences in analgesic responses. One hundred and forty male and female patients (age range 16–45) who undergo third molar extraction will be included in this study. Preoperatively, they will assess experimental pain responses and psychosocial measures. They will monitor post-operative pain levels along with PK/PD responses to the opioid fentanyl. They will examine sex differences in post-operative pain, analgesic responses and side effects immediately and for several hours post-surgery and for 3 days post-procedure. The study is designed to build a foundation for a R01 grant proposal supporting an independent line of clinically-relevant experimental pain research. This project will enhance understanding of translational research in pain as well as biopsychosocial factors that contribute to health disparities in pain and its treatment, particularly for women. Additionally, this study will provide insight into the complex genetic, PK/PD processes involved in postoperative pain and analgesic responses and will elucidate biopsychosocial contributions to sex differences in pain and side effects. The ultimate goal is to develop translational research that will reduce the increased burden of clinical pain in women through the development of tailored interventions designed to enhance the quality of life for women, consistent with priorities of the NIH Office of Research on Women's Health.

Title: **Using fMRI to Evaluate Cognitive-Behavioral Therapy Treatment Response for Patients with Chronic Pain**
P.I.: **Magdalena R. Naylor**
Institution: **University of Vermont and St. Agric College, Burlington, VT**
Grant No.: **5R21AR055716-02**
Award: **$112,875**

This proposed study will test the hypothesis that cognitive-behavioral therapy (CBT) can modify the dysfunctional neural circuitry associated with chronic pain. Because chronic pain is considered a complex sensory and emotional experience they expect that an intervention such as CBT could alter patients' responses to both painful and emotionally provocative stimuli and thus the underlying neural circuitry tested by fMRI. They believe that their paradigm represents a valuable strategy for advancing their understanding of the neurobiology of emotional control related to pain and the effects of CBT in the group setting. The primary goal of this revised R21 application is to investigate whether a psychotherapeutic approach, group Cognitive Behavioral Therapy (CBT), modifies the dysfunctional emotional and sensory neural circuitry associated with chronic pain as examined by functional magnetic resonance imaging (fMRI). They propose to apply previously tested and accepted paradigms for symptom provocation (acute pain and negative emotional stimuli) to investigate CBT effects on neural correlates of chronic pain. Because chronic pain is not just an isolated sensory event but rather a complex sensory and emotional experience, it is reasonable to expect that an intervention which improves chronic pain such as CBT will alter responses to both painful and emotionally provocative stimuli and thus the underlying neural circuitry. The efficacy of a group CBT treatment modality for chronic pain patients has been well established. In addition, their fMRI pilot study results revealed that the exaggerated amygdala response to negative emotional stimuli in chronic pain patients was normalized after 12 weeks of group CBT, suggesting that CBT may affect at least the emotional component of the pain process. Forty subjects who meet inclusion and exclusion criteria for the fMRI study will be randomly assigned to two study conditions: 12-week group CBT treatment condition and attention control condition. Each participant will undergo two fMRI examinations (before and after group interventions) to explore two study goals: (1) whether CBT treatment changes the function of brain neural circuitry in response to application of acute noxious stimuli and emotional (fearful) stimuli; and (2) whether there is a relationship between altered activation in brain areas associated with the attentional, affective, and sensory aspects of chronic pain and quantifiable improvement in clinical measures reported at the conclusion of group CBT. Their approach is novel as there are

no published studies that explore the neurobiological effects of psychotherapeutic approaches in chronic pain. By combining a noxious pain stimulation paradigm, an emotional stimulation paradigm, and brain imaging, and putting this approach into a clinical framework, they will open important, new avenues of research on chronic pain. Their approach may represent a valuable strategy for advancing their understanding of the neurobiology of emotional control related to pain and the effects of cognitive-behavioral therapy in the group setting. Measuring directly the effects of CBT on brain function could ultimately improve clinical decisionmaking and contribute to development of the individualized treatment of patients with chronic pain.

Title: **Pain and Endometriosis: Effects on Ectopic Cyst Innervation and Axons**
P.I.: **Geoffrey M. Bove**
Institution: **University of Southern Maine, Portland**
Grant No.: **1R21HD053510-01A2**
Award: **$219,832**

Women with endometriosis often have significant pain. Modern studies have implicated the neo-innervation of endometrial cysts as a primary source of this pain. However, the presence of nerve fibers does not necessarily specify their function and cannot determine whether, or in which situations, they are active. There has been no investigation to functionally characterize the effect of endometrial lesions on nerves or on axons. The applicant's laboratory has focused on the effects of inflammation on axons. They have shown that nerve inflammation induces ectopic mechanical sensitivity of nociceptor axons, which are not normally sensitive. Their data also indicate that nerve inflammation induces ongoing activity that arises from both the inflamed site and/or the cell body, and that sympathetic neuronal activity is decreased during nerve inflammation. Recently they adapted the model of rat endometriosis to involve the sciatic nerve. This model is very similar to the rat endometriosis model where a section of uterus is transplanted to a intraperitoneal site. Using immunohistological methods, they will determine the extent of neutrophil and macrophage invasion of the nerve-uterus complex. They will also determine if axons are damaged using ninjurin and fluoro-jade, assessing the presence in both axons and dorsal root ganglion cells. These studies will determine the function and thus the importance of the ectopic innervation of endometrial cysts, as well as the effects of the lesions on through-conducting axons. The results of this study will impacts the understanding of endometriosis pain and seed further research into the pain mechanisms of endometriosis. The significance of this proposal is that it proposes to make novel inquiries regarding the etiology of endometriosis-related pain. The information that this study will yield stands to improve diagnostic awareness and mechanistic understanding, and thus therapeutic approaches, of the treatment of the symptoms of endometriosis. As a result of this research, consideration and specific examination of nerves within the pelvis during ablative laparoscopic techniques may become an important additional diagnostic procedure for women with endometriosis.

Title: **N6F-Dependent Sensitization of Nocioceptors by Opiate**
P.I.: **Frank Porreca**
Institution: **Arizona Health Sciences Center, Tucson**
Grant No.: **3R01DA023513-02S1**
Award: **$20,000**

Opiate-induced hyperalgesia has been reported in humans and in animals. Continuous opiate administration for several days produces pronociceptive neuroplastic adaptations in both the peripheral and central nervous systems which likely underlie the observed hypersensitivity. Despite the potential clinical significance of such changes, specific mechanisms of opiate-induced hypersensitivity are unknown. Injury to tissues can result in sensitization of nociceptors, resulting in enhanced response to noxious and normally non-noxious stimuli (i.e.,

hyperalgesia and allodynia, respectively). They hypothesize that opiate-induced hyperalgesia and allodynia may result from sensitization of nociceptors. Importantly, they hypothesize that sensitization of nociceptors by opiates can occur in the absence of tissue injury. Two specific questions are addressed by the experiments proposed in this application: (1) can opiates induce nociceptor sensitization without tissue injury and (2) is opiate-induced nociceptor sensitization the result, in part, of an NGF-dependent process. Behavioral, neurochemical, immunohistochemical and electrophysiological studies will test the hypothesis that opiates (a) act at opiate receptors to produce hypersensitivity and an increase in expression of NGF in peripheral tissues; (b) increase NGF-dependent phosphorylation of p38 MAPK (pp38 MAPK) in TrkA-positive cells; (c) increase NGF-dependent and pp38 MAPK-dependent trafficking of the TRPV1 channel to the periphery; (d) upregulate CGRP and substance P (SP) expression in TrkA-positive cells in an NGF-dependent, and pp38 MAPK-dependent fashion; and (e) produce NGF-, pp38 MAPK- and TRPV1-dependent hypersensitivity. The consequences of opiate-induced neuroplasticity raise questions of whether unintended harm to patients might actually occur. Given the prevalent reliance on opiates for treatment of severe pain, understanding of the fundamental biological mechanisms associated with prolonged exposure to these drugs is essential. Additionally, mechanisms underlying possible nociceptor sensitization occurring in the absence of tissue injury may ultimately lead to insights into clinical conditions of prominent pain without apparent tissue injury including, for example fibromyalgia, IBS, CRPS-1 and perhaps migraine. The consequences of opiate-induced neuroplasticity raise questions of whether unintended harm to patients might actually occur. Given the prevalent reliance on opiates for treatment of severe pain, understanding of the fundamental biological mechanisms associated with prolonged exposure to these drugs is essential. Additionally, mechanisms underlying possible nociceptor sensitization occurring in the absence of tissue injury may ultimately lead to insights into clinical conditions of prominent pain without apparent tissue injury including, for example, fibromyalgia, IBS, CRPS-1 and perhaps migraine.

Reproductive Health/Developmental Biology

(Please see Menopause section above for additional projects)

Title: **Compromised Microcirculation in Women with Polycystic Ovary Syndrome**
P.I.: **Nina Stachenfeld**
Institution: **John B. Pierce Laboratory, Inc., New Haven, CT**
Grant No.: **1R21HL093450-01A1**
Award: **$256,203**

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinopathy in young women, affecting 6–10 percent of women of reproductive age. Obesity, insulin resistance, hyperandrogenism and hyperestrogenism are core functional disorders of PCOS and place women at increased risk for microvascular dysfunction. Women with PCOS have greater circulating concentrations of endothelin-1 (ET-1), a potent vasoconstrictor in the microcirculation (including that of the skin), which can increase blood pressure and lead to endothelial damage. The central hypothesis of this proposal is that testosterone effects on ET-1 mediate the peripheral microvascular dysfunction associated with PCOS. This hypothesis will be tested using a prolonged skin heating model to study peripheral microvascular responsiveness. Local skin heating has been used extensively to study mechanisms controlling peripheral microcirculation under a number of physiological conditions, including obesity, insulin resistance and hypertension. The impact of testosterone or ET-1 on microvascular responsiveness to local heating has not been studied in women with or without PCOS. This proposal seeks to provide this missing information via pursuit of two Specific Aims. Specific

Aim 1 will apply dose-response curves to examine the mechanism by which ET-1 influences peripheral vasodilation. Specific Aim 2 will determine the mechanism by which testosterone affects peripheral microcirculatory responsiveness in women with and without PCOS. These studies will have broad public health implications because their findings on the effect of hyperandrogenism on endothelial function may provide insights applicable to cardiovascular health in women and men.

Title: **Advancing Research on the Sexually Transmitted Female "Nuisance" Pathogen *Trichomonas vaginalis***
P.I.: **Jane Carlton**
Institution: **New York University School of Medicine**
Grant No.: **1R21AI083954-01**
Award: **$253,688**

Trichomoniasis is the most common nonviral STD, estimated to cause ~174 million infections worldwide each year. The *Trichomonas vaginalis* parasite resides in the urogenital tract of both sexes and can cause vaginitis in women and urethritis and prostatitis in men. However, the disease is known more as a female "nuisance" condition, which has resulted in a lack of scientific and medical attention and scant interest by public health officials in developing trichomoniasis control programs. Acute infections among women are associated with pelvic inflammatory disease and adverse pregnancy outcomes. Most alarming is the recognition that *T. vaginalis* infection appears to increase women's susceptibility to HIV-1 infection. Because of the association between *T. vaginalis* and risk for HIV-1 acquisition, interventions to reduce *T. vaginalis* infection and transmission would likely result in fewer HIV-1 infections. Completion of the *T. vaginalis* genome sequence in 2007 has significantly increased their knowledge concerning the biology and mechanisms of pathogenesis of the parasite, but significant gaps remain. In particular, the genetic diversity of the parasite is not known, i.e., whether the parasite is maintained as a clonal population or whether genetic exchange occurs between parasites in the urogenital tract. The extent of genetic diversity has implications for the control of the disease, for example it determines how virulent parasites spread or how they may evade a vaccine. The focus of this R21 proposal is to examine the genetic diversity of *T. vaginalis* infecting women attending eight New York City Bureau of STD clinics in inner city areas, and to use some of these isolates to develop a standardized and accessible in vitro model system for the study of colonization of the vagina by the parasite. A panel of polymorphic genetic markers—microsatellites and single copy genes—will be developed using the *T. vaginalis* genome sequence, and used to genotype *T. vaginalis* isolates identified in vaginal swabs taken from women attending the clinics. Knowledge of the genetic diversity and colonization characteristics of the parasite will provide important data points for subsequent studies, for example determining associations between *T. vaginalis* genotypes and the commensal microbes that make up the vaginal "microbiome".

Title: **Human Papillomavirus Epidemiology and Response to Screening (HEARTS)**
P.I.: **Elise D. Riley**
Institution: **University of California, San Francisco**
Grant No.: **1R21AI079439-01**
Award: **$188,034**

Human papillomavirus (HPV) vaccine development and clinical research have focused on women from the general population and little is known about HPV among indigent women, many of whom experience repeated risk for sexually transmitted infections that continues through the span of their lives. The impact of repeated exposure to HPV, as well as the

impact of co-infections like HIV, HCV, gonorrhea, and chlamydia on the natural history of HPV infection and HPV-associated disease, is unclear in this population. Moreover, the prevalence of HPV subtypes in this population is unknown, which precludes estimates of potential vaccine effectiveness. A better understanding of HPV among indigent U.S. women could have implications for improvement in health care delivery, particularly regarding HPV vaccine uptake and effectiveness. They propose an exploratory study to assess the prevalence and variability of cervical HPV and cervical HPV disease (cervical intraepithelial neoplasia); associations with co-infections (i.e., HIV, HCV, gonorrhea and chlamydia) and drug use (e.g., tobacco and crack cocaine); and the feasibility of a larger randomized study among homeless and marginally housed women. Individuals will be recruited from homeless shelters, free-food programs and low-income single room occupancy hotels. In this way, study participants will not be limited to individuals who visit specific institutions, thus facilitating reliable estimates from a community-based sample.

Title: **Physiological Reactivity to Acute Stress during Pregnancy**
P.I.: **Lisa Michelle Christian**
Institution: **Ohio State University, Columbus**
Grant No.: **1R21HD061644-01**
Award: **$181,209**

Preterm delivery, an increasingly frequent occurrence in the United States, is associated with significant family burden and an estimated societal cost of at least $26 billion per year. In the United States, the preterm birth rate is 12–13 percent as compared to 5–9 percent in other developed countries. Persistent racial disparities contribute to this discrepancy. Psychosocial stress and related physiological sequelae may contribute to preterm birth overall, as well as to racial disparities in preterm birth. The experience of chronic stress, such as that conferred by racial minority status, may sensitize physiological stress responses. Indeed, as compared to Caucasians, African Americans exhibit greater cardiovascular reactivity to a variety of acute stressors. Importantly, blood pressure, glucocorticoid, and catecholamine responses to acute stress are attenuated during healthy pregnancy as compared to nonpregnancy. This adaptation may protect the mother and fetus from potentially detrimental effects of maternal physiological activation. Thus, women who exhibit greater and more extended physiological reactions to everyday stressors may be at increased risk for negative perinatal outcomes. Notably, no studies of acute stress during pregnancy have examined inflammatory immune responses or mechanisms underlying blood pressure change (i.e., cardiac output, total peripheral resistance). Moreover, limited information is available regarding effects of race on physiological adaptation to pregnancy. The current study will address important gaps in the literature by examining cardiovascular, endocrine, and immune reactivity to acute stress among 40 healthy pregnant women (20 Caucasian, 20 African American) and 40 demographically matched nonpregnant control women. This research is designed to ultimately lead to the identification of women at greater risk for negative perinatal outcomes and elucidation of mechanisms underlying increased risk, providing a basis for individualized health care services. Specific Aim 1: To utilize more comprehensive and advanced methodology to assess physiological reactivity during pregnancy versus nonpregnancy, including measures of inflammation, impedance cardiography, and glucocorticoid receptor function. Hypothesis 1: Pregnant women will show attenuated physiological responses to acute stress as compared to nonpregnant women. Specific Aim 2: To examine racial differences in physiological reactivity during pregnancy versus nonpregnancy. Hypothesis 2: As compared to Caucasian women, African-American women will exhibit greater physiological reactivity to stress during pregnancy and nonpregnancy. Specific Aim 3: To examine psychosocial correlates of physiological reactivity during pregnancy and nonpregnancy. Hypothesis 3: Women reporting greater distress will exhibit greater

physiological reactivity during pregnancy and nonpregnancy. Specific Aim 4: To examine associations between physiological reactivity and length of gestation. Hypothesis 4: Greater physiological reactivity to acute stress will predict shorter gestational length.

Title: **A Study of the Factors Influencing Women's Decisions about Childbirth**
P.I.: **Mary J. Regan**
Institution: **University of Maryland Baltimore**
Grant No.: **1R21HD059074-01A1**
Award: **$238,251**

Cesarean section (CS) is currently used at over twice the rate recommended by the World Health Organization; use of the procedure has almost doubled in the last two decades for reasons that are as yet poorly understood. Overutilization results in avoidable morbidity and mortality and higher health costs related to childbirth. Many causes for the increased use of CS have been suggested, including growth in the number of "maternal requests," that is, healthy women asking for CS in the absence of medical indications. An NIH expert panel explored maternal request CS and concluded that at this time there is insufficient evidence to warrant CS on maternal demand without medical indications and recommended "increased research devoted to strategies to predict and influence the likelihood of successful vaginal birth." Using the same data, the American College of Obstetrics and Gynecologists (ACOG) concluded that there is no reason to deny a surgical birth to a healthy mother as long as she is well informed. The divergence between these positions points to a critical gap in knowledge about the factors that drive CS rates, including the influence of maternal demand on the use of CS. Despite this recent focus on maternal demand, there is scant research on what women want from their birthing experience, including their reasons for choosing one mode of childbirth over another. The purpose of their proposed research is to answer the question: What factors influence women's decisions about how their babies will be born? Women's hopes and desires for their first birth experience are influenced by what they know both consciously and unconsciously. Because people are only partly aware of the attitudes and beliefs that inform their hopes and desires, this proposal will use three methods of data collection. The first is a projective method commonly used in the social sciences to access knowledge that exists outside of consciousness. The second is a focus group method that provides a venue for birthing women to articulate the conscious basis for their ideas about childbirth and allow participants to compare their ideas with others. Third, all women will be interviewed after the baby is born to build understanding about how their experiences influence future birthing choices the women make. Participants will be 50 primigravid women with uncomplicated pregnancies, aged 21 or older. This proposal builds on the researchers' previous work related to the use of CS. It is one step in a defined program of research directed towards improving the health of mothers and their children by optimizing care during pregnancy, labor, and birth.

Title: **Modulation of Polycyclic Aromatic Hydrocarbon Ovarian Toxicity by Biotransformation Enzyme Polymorphisms**
P.I.: **Ulrike Luderer**
Institution: **University of California, Irvine**
Grant No.: **1R21ES016846-01A1**
Award: **$229,745**

Infertility or impaired fecundity affects 12 percent of American women. Ovarian dysfunction, including premature ovarian failure is a major cause of infertility. It is likely that exposure to environmental toxicants is responsible for many more cases of impaired ovarian function than is currently appreciated. Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous

environmental contaminants, which are known to impair ovarian function and cause ovarian failure in rodents and are probable ovarian toxicants in women. Tobacco smoke, foods, and air pollution are among the sources of exposure to PAHs. The mechanistic basis for interindividual variation in susceptibility to PAH ovarian toxicity is not understood, but polymorphisms in enzymes that metabolize PAHs likely play an important role. The work outlined in this proposal will demonstrate the feasibility of a larger study to test the hypothesis that genetic variations in Phase 1 and Phase 2 biotransformation enzymes involved in metabolizing PAHs modulate the ovarian toxicity of PAHs in women. Specific Aim 1: To test the feasibility of prospectively measuring time to pregnancy and PAH exposure and of using genomewide genotyping methods to determine PAH biotransformation enzyme polymorphisms for a study analyzing the associations between PAH exposure and biotransformation enzyme polymorphisms and fecundability (time to pregnancy). Specific Aim 2: To test the feasibility of using microelectronic dipstick monitors to measure daily urinary reproductive hormone concentrations over multiple menstrual cycles for study of the associations between PAH metabolizing enzyme polymorphisms and PAH exposure and menstrual cycle abnormalities. Specific Aim 3: To pilot test serum anti-Müllerian hormone, follicle stimulating hormone, and inhibin B concentrations as markers of ovarian reserve for study of the associations between PAH exposure and diminished ovarian reserve.

Title: **Neuroactive Steroids and Seizure Control during Pregnancy in Women with Epilepsy**
P.I.: **Page Buckhannan Pennell**
Institution: **Brigham and Women's Hospital, Boston, MA**
Grant No.: **1R03NS063233-01A1**
Award: **$102,626**

Epilepsy is a common disorder, affecting approximately 1.3 million women of child-bearing age in the United States. Seizures during pregnancy can cause increased risks to both the mother and fetus. These risks have to be balanced against the known teratogenic effects of antiepileptic drugs (AEDs). During pregnancy, the sex steroid hormones estradiol and progesterone increase dramatically. Sex steroid hormones and the metabolic byproducts that are capable of modifying neural activity are classified as neuroactive steroids (NAS). Animal models demonstrate modulation of seizure activity by the NAS 17β-estradiol (EST), progesterone (PROG), and allopregnanolone (ALLO). In women, fluctuations in these NAS have been implicated in seizure control in the non-pregnant state, with worsening seizures at certain times of the menstrual cycle (catamenial epilepsy). Human studies have demonstrated an increase in seizure frequency with elevated EST/PROG ratios and with declining or low PROG levels. This has not been studied during pregnancy in women with epilepsy. This proposed study will utilize serum samples (n=810 samples) already collected from 135 women with epilepsy during different stages of pregnancy during a Specialized Center of Research in Women and Gender Issues program project grant. These women were enrolled prospectively with tracking of seizures and medications. Collection of plasma samples occurred at multiple points in each trimester. Based on variable points of enrollment (< 20 weeks gestation), they have increased observations/samples in the later trimesters of pregnancy. Seizure frequency will be analyzed during the second and third trimesters of pregnancy and compared to the nonpregnant baseline for each subject. Consistent with the R03 mechanism, the current application will extend the analysis of these existing data/samples via measurement of the neuroactive steroids EST, PROG, and ALLO. The working hypotheses are: (1) during pregnancy, changing concentrations of EST and PROG influence seizure control; (2) the progesterone metabolite, ALLO, mediates the seizure-reducing effect of PROG. The following will be analyzed in relationship to change in seizure frequency during pregnancy: EST/PROG ratio, the rate of rise of PROG, and the rate of rise of ALLO. Additionally, given that labor and

delivery is a particularly vulnerable time for increased seizures; ALLO and PROG levels will be compared between women who had peripartum seizures and those who did not. This study can ultimately lead to a better understanding of the NAS regulation of seizure control during pregnancy. Insights gained from this study could provide the impetus for further development of NAS analogs, with treatment benefits extending to both genders and across all ages. During pregnancy, treatment with supplemental progesterone could allow for decreased levels of fetal exposure to AEDs in utero, with improved seizure control and reduced anatomical and neurodevelopmental teratogenicity.

Title: **Research to Improve Preconception Health of Adolescent Women**
P.I.: **Sara Jumping Eagle**
Institution: **Oglala Lakota Oyate, Pine Ridge, SD**
Grant No.: **1S06GM087165-01**
Award: **$121,622**

The Oglala Sioux Tribe, in partnership with Stanford Research/University of South Dakota School of Medicine and the Oglala Lakota College, will be addressing priority health issues identified by the tribe and to support and expand the research capacity and infrastructure that will build on the research foundation that has been developed within the tribe over the past decade.

Title: **Uterine Leiomyoma Research Center Program**
P.I.: **Serdar E. Bulun**
Institution: **Northwestern University, Chicago, IL**
Grant No.: **1P01HD057877-01A2**
Award: **$250,000**

Uterine leiomyomata (fibroids) represent the most prevalent benign gynecologic disorder in the US. The cellular and molecular mechanisms regulating the development and growth of leiomyoma are not well understood. Their interdisciplinary team has designed three well-integrated projects focusing on interactions between biologically critical hormonal pathways in uterine leiomyoma involving the transcription factors progesterone receptor (PR) and FOXO, the signaling pathway PI3K/AKT and the pro-fibrotic factor TGF-beta. Project I (Bulun) will be pursued to understand the mechanisms as to how anti-progestins such as RU486 reduce tumor size. They hypothesize that progesterone regulates a number of critical genes, that favors increased proliferation and decreased apoptosis of leiomyoma smooth muscle cells, whereas anti-progestins reverse this effect by enhancing apoptosis and decreasing proliferation. Project II (Kim/Chakravarti) will determine the role of the PI3K/AKT/F0X0 signaling pathway regulating leiomyoma cell growth and survival in response to progesterone. They hypothesize that progesterone induces proliferation of leiomyoma cells through activation of the PI3K/AKT/F0X0 signaling pathway and that inhibitors of the AKT pathway should override the proliferative effects of progesterone and promote apoptosis. Project III (Nowak) will define the mechanisms as to how antifibrotic drugs regulate leiomyoma growth. They hypothesize that the increased proliferation exhibited by leiomyoma smooth muscle cells is due to a major shift in the extracellular matrix environment caused by increased synthesis of new, monomeric collagen type I by these cells. They will determine whether antifibrotic drugs may be an effective new treatment for leiomyomas. These projects are supported by an administrative core (Bulun) and tissue procurement and cell culture core (Kurita). Overall, as part of their long range goal, all projects investigate local hormonal signaling regulating apoptosis and proliferation as biologic endpoints and test existing and upcoming pharmaceutical compounds that target these pathways in uterine leiomyomata. Relevance: Symptomatic uterine leiomyomata affect millions of U.S. women and cause irregular uterine bleeding, anemia, recurrent pregnancy loss leading to more than 200,000 hysterectomies per year. Available treatments are limited due in large part to the fact that the

mechanisms regulating the development and growth of these tumors are unclear. They propose integrated molecular, cellular and translational studies that should lead to a better understanding and future development of novel therapeutics for uterine leiomyomata.

Title: **The Role of GPR54 Signaling in Pubertal Disorders**
P.I.: **Suzy Drumond-Carvalho Bianco**
Institution: **University of Miami School of Medicine, Coral Gables, FL**
Grant No.: **5R21HD059015-02**
Award: **$20,000**

The long-term goal of this project is to identify factors that regulate the timing of pubertal onset and reproductive maturation. The identification of GPR54, a G-protein coupled receptor, and its ligand, kisspeptin, as upstream regulators of GnRH secretion has led to intense research to elucidate their roles in the regulation of the reproductive axis. Inactivating mutations in GPR54 cause failure to undergo puberty and infertility. In contrast, early stimulation of this receptor triggers precocious puberty in mice. Preliminary results indicate that GPR54 is desensitized and internalized in response to continuous kisspeptin stimulation, and that a GPR54 amino acid substitution identified in a female patient with central precocious puberty (a disorder with disproportionately high female incidence) increases GPR54 responsiveness by delaying the desensitization of the receptor. The hypothesis is that the timing of signaling and desensitization of GPR54 is critical for its role in controlling puberty and reproduction, and that amino acid substitutions in GPR54 may affect its responsiveness by interfering with signaling or desensitization, thereby contributing to the clinical presentation. Although G-protein coupled receptor desensitization is generally strongly regulated, no data have been published on GPR54 desensitization. The short term goal of this project is to define the mechanisms underlying GPR54 desensitization, in order to understand how genetic mutations of this receptor affect these mechanisms and hence the timing of pubertal onset and sexual maturation. A thorough understanding of the mechanisms underlying GPR54 signaling may uncover the basis of gender differences in normal and abnormal pubertal development, as well as reveal a new array of potential targets of pharmacological manipulation for the treatment and prevention of abnormal pubertal development and possibly other reproductive disorders.

Title: **Obstetric-Fetal Pharmacology Research Units Network**
P.I.: **Gary D. Hankins**
Institution: **University of Texas Medical Branch, Galveston**
Grant No.: **5U10HD047891-05S2**
Award: **$235,025**

The University of Texas Medical Branch (UTMB) has the capability to participate actively as a member of the Obstetric-Fetal Pharmacology Research Units (OPRU) Network. Gary Hankins, M.D., as principal investigator (PI), is responsible for the proposed clinical trial on the use of hypoglycemic drugs in the treatment of diabetes during pregnancy. He has extensive experience within several NIH multicenter trials, e.g., First and Second Trimester Evaluation of Risk of Aneuploidy (FASTER), Beneficial Effects of Antenatal Magnesium Sulfate Study (BEAM), and the Vaginal Ultrasound Cerclage Trial. Dr. Hankins has achieved successful patient recruitment and retention by involvement with UTMB's Regional Maternal and Child Health Program (RMCHP). All RMCHP clinics follow protocols established by the Maternal-Fetal Medicine division, headed by Dr. Hankins. More than 12,000 pregnant women are cared for annually within the RMCHP clinic system, approximately 7,000 of whom deliver at UTMB. The Pharmacology/Pharmacokinetics (PK) co-investigator, Mahmoud S. Ahmed, Ph.D., has more than 25 years of expertise in utilizing human placenta and derived preparations in his investigations. Dr. Ahmed is a laboratory-pioneered investigator in placental receptors,

their natural ligands and mediated responses, as well as the mechanism of hCG release from trophoblast tissue. They investigated the effects of in vitro and in vivo chronic administration of opiates on placental physiology and maternal-neonatal outcome. Utilizing dual perfusion of placental lobule, they demonstrated the influence of efflux protein and placental metabolic enzymes on the PK for placental transfer of opiates. They identified placental aromatase as a drug-metabolizing enzyme and are investigating its polymorphism. Kenneth D. Carey, D.V.M., Ph.D., as animal model co-investigator, is responsible for coordinating the baboon studies to be conducted at the Southwest National Primate Research Center (SNPRC) in San Antonio. A population of normal and diabetic baboons will be studied. Dr. Hankins is an adjunct investigator at the SNPRC and has had extensive involvement with the primate research staff. The Department of Obstetrics and Gynecology has well-funded scientists with expertise in areas relevant to this RFA including infection, vascular physiology, and placental functions. Clinical PK co-investigators Susan Abdel-Rahman, Pharm.D., and Wayne Snodgrass, M.D., Ph.D., have more than 30 years of combined experience in the development of protocols for PK studies, evaluation of data obtained, and PK/PD modeling. The Division of Neonatology, the GCRC, and other departments at UTMB will provide support for this project.

Title: **The History of Emergency Contraception**
P.I.: **Heather M. Prescott**
Institution: **Central Connecticut State University, New Britain, CT**
Grant No.: **5G13LM009242-02**
Award: **$75,530**

The National Library of Medicine Grant for Scholarly Works in Biomedicine and Health will be used to research and write a book-length project on the history of emergency contraception from the 1960s until the present. Postcoital methods of contraception were first developed in the early 1960s as part of a larger movement to provide reproductive health care to adolescent and young adult women. This project will explore the multiple constituencies involved in the development and marketing of emergency contraceptives since the 1960s. It will draw upon the personal papers of major reproductive scientists, gynecologists, population groups, and feminist activists. This study will emulate the method used by social historians of medicine, which views the history of medicine as a negotiated process between experts and clients. Therefore, a major focus of the project will be the role women patients played in the dissemination of this technology. This project will show women not only as test subjects for this new method of birth control but also as active health care consumers.

Title: **ORWH–NICHD Leiomyoma Tissue Bank**
P.I.: **James Segars**
Institution: **NICHD Intramural program**
Grant No.: **Z01HD008737-09**
Award: **$85,000**

The health of 30–50 percent of women in the United States is adversely affected by uterine leiomyoma (fibroids). Uterine fibroids are a health disparity issue that disproportionately affects African-American women. Research into causes and treatment has lagged behind other disciplines, in part due to lack of available tissues, since surgical samples are often not made available to scientists. To address the problem of tissue availability, and promote research on this condition, this project proposes to establish a fibroid tissue bank as an initiative in the intramural program of NICHD. This tissue bank will provide samples to NIH-funded investigators and DoD-funded investigators to support work on this condition. The Leiomyoma Tissue Bank (LTB) will be physically located in space assigned to Dr. Segars of NICHD. The LTB

will be structured after RStaR-banks for endometrium and ovary established by the Specialized Cooperative Program in Reproductive Research. Computerization of sample inventory will be performed with software provided by NICHD.

Title: **Activin Target Genes in the Ovary: Regulation of Ovarian Follicle Development**
P.I.: **Jingjing Kipp**
Institution: **Northwestern University, Chicago, IL**
Grant No.: **1K99HD055357-01A2**
Award: **$83,333**

These proposed studies will increase their understanding on the mechanisms of activin regulation of normal ovarian follicle development, and provide new insights into this important reproductive process and hence fertility control, infertility treatment, and human health related diseases including cancer. Normal development of ovarian follicles is critical for female reproduction and endocrine function, as it prepares and provides healthy and fertilizable eggs and ensures normal production of steroid and peptide hormones. This process is finely regulated by various intrinsic and endocrine factors. Factors produced by granulosa cells include the TGF-beta superfamily member activin and the steroid hormone estrogen, both of which have been demonstrated to play an intra-ovarian role in regulating ovarian follicle development. I have revealed a linkage between activin and estrogen signaling pathways in the ovary. Mice treated neonatally with activin show an increase in follicle formation and activin stimulates mouse granulosa cell proliferation in vitro. The mechanisms that mediate these events are not known. The researcher has identified Cyp26b1 as the gene that was most significantly suppressed by activin and confirmed its expression in the postnatal ovary. Cyp26b1 degrades the potent morphogen retinoic acid which has been suggested to regulate ovary development. Therefore, the central hypothesis of this proposal is that activin modulates ovarian follicle development through regulation of gene expression profiles of a subset of targets including ERa, ERP and Cyp26b1. The studies proposed will test this hypothesis through three Specific Aims. Aim 1 will investigate the mechanism(s) underlying activin regulation of ER expression. This will be accomplished by examining involvement of the activin signaling proteins Smad2/3 in activin stimulation of ER expression, and identifying binding site(s) of Smad protein complexes to the ER promoter and determining their functional importance. Aim 2 will identify novel activin regulated genes in the ovary. This will be accomplished by microarray gene expression profiling using neonatal whole ovary cultures and by further verification of the results with real time RT-PCR. Aim 3 will investigate the roles of C3T326b1 and activin in regulating RA environment in the ovary and how Cyp26b1 and RA may affect ovarian follicle formation and development. Together with these experimental studies, the proposal includes a logical plan for further training and mentoring of the applicant, leading to a successful transition to an independent academic career.

Title: **Improving Contraceptive Use in High-Risk Women**
P.I.: **Tina Raine-Bennett**
Institution: **University of California, San Francisco**
Grant No.: **1K24HD057086-01A1**
Award: **$144,892**

Little is known about interventions that work to improve contraceptive use and decrease unintended pregnancy. Information that can be obtained from high-quality clinical trials will be generalizable and provide evidence based guidance for providers in public clinic settings. It is important to mentor the next generation of obstetricians and gynecologist trained in epidemiologic research and clinical trials methodology. Early unintended pregnancies

have significant consequences and occur at disproportionately higher rates in young, poor, uneducated, and minority women. The overall goals of this proposal are to: (1) lay the groundwork for conducting a high-quality, large-scale, theory driven intervention to improve contraceptive use and reduce unintended pregnancy rates among young, low-income, and minority women receiving care at family planning clinics; and (2) engage fellows and junior faculty in the development of patient oriented research to improve contraceptive use behavior among women at high-risk for unintended pregnancy. Formal training in health services research methods through a Robert Wood Johnson (RWJ) Clinical Scholars post-doctoral fellowship and a Mentored Minority Medical Faculty Development Award provided skills and experience to become an independent investigator and build a productive research agenda in patient-oriented research. Principal findings from the analysis of data from my current NICHD-funded longitudinal cohort study of teens and young women who initiate hormonal contraceptives will provide the guiding concepts that will determine the content of a multi-component, clinic-based intervention aimed at multiple relevant modifiable factors. The dataset will form the basis of the qualitative analyses in the research plan and will serve as a key teaching tool for fellows needing to learn epidemiological research skills. They will perform primary and secondary analyses examining individual-level data (demographic, personal, and reproductive characteristics) as well as a wide range of information on contextual factors such as relationships, family, peer and community norms that influence contraceptive method choice and continuation. This will be followed by formative qualitative work and pilot studies to develop a relevant and operationally feasible intervention. The work in this proposal is intended to bridge the gap between collecting observational behavioral data and implementing theory driven patient oriented research to modify behaviors. The K24 award will strengthen the researcher's scholarly potential and contribution by expanding the scope of her current patient-oriented research and allowing her to focus more explicitly and directly on mentoring and developing beginning investigators in patient-oriented research in family planning.

Title: **Malaria in Pregnancy: Nutrition and Immunologic Effects**
P.I.: **Wafaie Fawzi**
Institution: **Harvard University School of Public Health, Cambridge, MA**
Grant No.: **1R01HD057941-01A2**
Award: **$200,000**

Vitamin A and zinc supplementation during pregnancy have the potential to boost the immune response to prevent placental malaria and/or avoid clinical complications associated with it such as maternal anemia and low birth weight in the infants. However, the safety and efficacy of such supplements in pregnant women has not been examined. The proposed study will address this research question and will provide evidence that may lead to an optimization of international guidelines on vitamin A and zinc supplementation in pregnant women that will be important for more than 25 million women becoming pregnant in malaria-endemic regions in Africa every year. Malaria in pregnancy is a major public health problem in Tanzania and many other countries in sub-Saharan Africa. Malaria is associated with tremendous morbidity in the mother including severe anemia, and in the fetus in the form of low birth weight and fetal loss. Vitamin A and zinc deficiencies are specific factors which can modulate the clinical course of malaria and exacerbate associated complications. The published literature suggests that these two micronutrients favor a reduction in risk of placental malaria and related clinical outcomes including malaria and anemia among women, and low birth weight. They propose to study the efficacy of zinc and/or vitamin A supplementation in reducing the risk of placental malaria and other maternal/fetal outcomes. They will recruit 9,000 women of reproductive age and follow them up on monthly basis for pregnancy status, and identify and randomize their target sample of 2,500 pregnant women. Subjects eligible for randomization will be HIV-negative women who are at or before 8 weeks of gestation. Women will be enrolled using a

factorial design and assigned to receive zinc alone, vitamin A alone, both zinc and vitamin A, or placebo. All women will receive daily folate and iron supplements as per standard prenatal care. Women, and after delivery babies, will be followed up until 6 weeks after delivery. Compliance with supplement use will be assessed by direct questioning of women and pill count at monthly clinic visits. Biochemical assessment of compliance will also be assessed measuring the plasma concentration of vitamin A and zinc in a random subsample of 400 women at randomization, at 30 weeks of gestation, and at delivery. The primary endpoint is placental malaria, and secondary endpoints include maternal malaria, maternal anemia, and low birth weight. They propose to examine key aspects of the humoral and cell-mediated immune response to malaria in a sub-study. The program will be carried out by Harvard School of Public Health in collaboration with Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania.

Title: **Midcareer Investigator Award in Patient-Oriented Research**
P.I.: **Kurtt Barnhart**
Institution: **University of Pennsylvania, Philadelphia**
Grant No.: **1K24HD060687-01**
Award: **$187,466**

Recruitment and retention of productive junior investigators is a priority of academic medical institutions and the research community, and a strong mentoring relationship will increase the likelihood of success. The purpose of this Mid-career Investigator Award in Patient-Oriented Research is to provide support for Kurt Barnhart, M.D., M.S.C.E., a reproductive endocrinologist and epidemiologist at the University of Pennsylvania. Dr. Barnhart is an accomplished clinical investigator with continuous NIH support since he joined the faculty at Penn in 1996. He has also been recognized as an outstanding mentor. The candidate's immediate and long-term career goals center on his desire and intention to continue to evolve and mature as a patient-oriented researcher, teacher, and mentor. In doing so, he needs to be able to enhance and focus his efforts on conducting patient-oriented research (POR), and building a clear training and mentoring path for those interested in POR in women's health. This award will allow him to achieve these goals by protecting 50 percent of his time through a reduction in his clinical and administrative duties. He will also reduce effort on some of his funded projects while concomitantly increasing the effort of junior faculty he currently mentors. Mentoring: Dr. Barnhart will focus his mentoring on scholars enrolled in the Masters of Science in Clinical Epidemiology (M.S.C.E.) supported by the NIH T32 Reproductive Epidemiology training grant. Candidates for this program include fellows in sub-specialties in women's health, family medicine and pediatrics. Dr. Barnhart was one of the first trainees of this grant and is currently the co-principal investigator. Other mentees will include junior faculty, fellows in Reproductive Endocrinology and Infertility, residents in Ob/Gyn and medical students. He plans to serve as primary thesis mentor for some, a research mentor for others, and will direct the Ob/Gyn resident research program at Penn. Dr. Barnhart is committed to the career development of clinician investigators. Research Plan: The Specific Aims proposed in this application will evaluate the short and long term consequences of assisted reproductive technology (ART), a priority area of research for NIH. The three Specific Aims which investigate the association of ART with short term perinatal morbidity and childhood development provide the perfect opportunity to mentor young investigators on the design and conduct of a hypothesis-driven clinical research that will serve as the basis for future studies. Complementary and diverse research methods have been proposed to address this important research area. Aim 1 will use the national SART database to test the hypothesis that supra-physiologic conditions associated with a fresh IVF cycle may be associated with perinatal morbidity. Aim 2 will use a three-arm cohort study assessing childhood development in children conceived with IVF, superovulation or without medical assistance. Aim 3 will use a large administrative dataset to link mothers and

children and assess for autism spectrum disorder in a true population setting. These aims not only address an important question but also are designed to advance the skills of the principal investigator, enhance interdisciplinary research and provide optimal opportunity for training and mentorship. Finally, these aims will likely provide evidence to be used to design larger trials, hopefully by the growing cadre of reproductive epidemiologists and POR researchers in women's health nationwide, many of whom will have been mentored by Dr. Barnhart.

Title: **Identification of Genes Predisposing to Pelvic Floor Disorders**
P.I.: **Lisa A. Cannon-Albright**
Institution: **University of Utah, Salt Lake City**
Grant No.: **1R01HD061821-01**
Award: **$66,667**

This research has a major potential to affect public health in the prevention of pelvic floor disorders (PFDs): they may be able to identify high-risk populations who can be identified at a young age, studied and possibly targeted for prevention; and at a later stage in the development of PFDs, special interventions can be studied and possibly implemented in women at risk for recurrence of their condition. Someday, identification of these high-risk populations may be as general as familial risk, or as specific as specific gene screening. The investigators propose a unique and powerful collaboration between basic and clinical scientists in Utah to identify genes affecting predisposition to pelvic organ prolapse (POP). The co-principal investigators both have significant experience, Dr. Norton in PFD genetics and Dr. Cannon-Albright in predisposition gene identification. The investigators will access the Utah Population Database, a computerized genealogy of Utah combined with decades of medical data from the two largest healthcare systems in Utah (serving 90 percent of the state), to identify and recruit surgically treated cases of POP (1,250 cases in 5 years). All POP cases sampled will be genotyped with the Illumina 610Q SNP marker set. The PIs will apply multiple different genetic analyses to this resource of genotyped POP cases to aid in the identification of predisposition genes. The record linkage of medical procedure codes (identifying surgeries performed on each patient) to individual genealogy data allows us to identify all genetic relationships among the POP cases. They will perform genomewide association analysis, using software they have developed which allows inclusion of both independent and related cases. They will identify all genetic relationships between the sampled POP cases and perform linkage analysis in informative, high-risk POP pedigrees. They will identify chromosomal regions shared Identical by Descent (IBD) in very distantly related cases in these pedigrees, and they will identify IBD sharing within the small subset of POP cases (2 percent) who are inbred. Initial collaborative analysis of data obtained by Dr. Norton's NIH funded study of affected PFD sib-ships has already provided significant evidence for a predisposition gene localization on chromosome arm 9q, and suggestive evidence for at least one other locus on chromosome 1. In summary, they will create a population-based resource of surgically treated POP cases, they will pursue established and new methods to identify and localize predisposition genes affecting POP, and they will begin a detailed search for the chromosome 9 gene they have localized.

Title: **Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team**
P.I.: **Pamela A. Moalli**
Institution: **Magee-Women's Research Institute and Foundation, Pittsburgh, PA**
Grant No.: **1R01HD061811-01**
Award: **$66,666**

Prolapse (i.e., abnormal descent) of the pelvic organs is a common costly condition that negatively impacts the lives of millions of women worldwide. Biologic and synthetic meshes are often used in the surgical repair of prolapse due to improved anatomical outcomes over native tissue repairs; but with little scientific data on which to base the selection of a particular product. Unfortunately, the complications associated with certain meshes cause unacceptably high rates of morbidity including infection, tissue contraction, vaginal discharge, and pain. In this proposal, they aim to establish a comprehensive mesh testing center in which previously or newly marketed prolapse meshes can be objectively tested and the next generation of prolapse meshes can be developed based on specific scientific criteria. Each year roughly 200,000 U.S. women undergo a surgery to repair pelvic organ prolapse. Biologic and synthetic meshes are widely used in prolapse repairs to improve anatomical outcomes over native tissue repairs which currently have a failure rate of more than 30 percent. To date, however, there is little scientific data to guide surgeons in the selection of a particular product. As a result, meshes are used based on the recommendations of a local vendor and consequently, are placed in women on a trial and error basis. There is growing evidence, however, that the complications associated with prolapse meshes cause unacceptably high rates of morbidity including infection, mesh shrinkage, mesh erosion, mesh exposure, pelvic, rectal, and bladder pain, and dyspareunia. Such complications have become significant enough for the FDA to recently release a warning about mesh use, especially when it is placed transvaginally. In this proposal, they therefore, aim to establish an interdisciplinary team of scientists dedicated to the comprehensive testing of previously or newly marketed prolapse meshes and for the development of the next generation of graft materials based on specific scientific criteria. In the first phase of the study, they determine how biochemical and structural changes in the prolapsed vagina impact passive and active mechanical behavior so as to develop a mesh in which these deficiencies are repaired or compensated for, allowing us to restore the prolapsed vagina to the nonprolapsed condition. In the second phase, they hypothesize that the shortcoming of current prolapse meshes is that they are too stiff. While this results in a repair with increased tensile strength, it occurs at the expense of tissue function with accelerated tissue contraction, decreased elasticity and compliance, and deterioration of smooth muscle function. To test their hypothesis, they implant commonly used synthetic prolapse meshes into the vagina of nonhuman primates with prolapse using the gold standard surgical procedure (the abdominal sacrocolpopexy) and then define the cellular, biochemical and biomechanical impact on the vagina at 6 months post implantation. Eventually, they will implant meshes transvaginally to characterize the distinct host response to this surgical approach. In the third phase, they explore the development of future grafts for prolapse surgery. They hypothesize that because of its bioinductive effects, a combined biologic/synthetic mesh will be superior to a synthetic mesh alone in restoring vaginal structure and function. They propose that a key yet poorly developed component of prolapse repairs is the re-establishment of smooth muscle reactivity and therefore, test the use of a temporary biologically active scaffold in achieving this process. In this way, this grant proposal provides a mechanism to establish the first team of scientists dedicated to the comprehensive unbiased evaluation of prolapse meshes as a means of educating both current and future prolapse surgeons, and the public regarding potential problems associated with certain materials. Indeed, the development of such a group is imperative for protecting the health of women.

Title: **Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and its Association with Incidence, Progression and Recurrence of Pelvic Floor Disorders**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah, Salt Lake City**
Grant No.: **1R01HD061787-01**
Award: **$66,667**

The effect of strenuous physical activity on new or recurrent pelvic floor disorders is unknown. They developed an intravaginal pressure sensor to measure intra-abdominal pressure. They will perfect the wireless technology needed to use the sensor remotely so that they can understand how different activities done in real-world settings affect intra-abdominal pressures and pelvic floor disorders. Pelvic floor disorders affect one in four American women. Few modifiable risk factors have been identified that might reduce the incidence or progression of pelvic floor disorders. Popular wisdom and scant clinical data suggest that strenuous activity causes or promotes pelvic floor disorders. Given the health benefits of activity, women should be encouraged to be maximally active unless there is scientific evidence to the contrary. Existing physical activity instruments are largely designed to assess cardiovascular exertion and are validated using activity diaries, accelerometers, and step counters. Such measures may not accurately measure activities that increase loading on the pelvic floor (such as lifting). After researching available technologies, they concluded that a tool to understand how physical activities impact abdominal pressure in the real world does not exist. Over the past 18 months, their interdisciplinary team of bioengineers, urogynecologists, electrical engineers, and exercise scientists developed and validated the performance of a prototype for an intravaginal abdominal pressure sensor that accurately measures pressure in the upper vagina, an easily accessible space that records pressures similar to the true intra-abdominal pressure. In this proposal, they plan first to further develop an integrated system (the "WRAPS", Wireless Remote Abdominal Pressure System) to monitor intra-abdominal pressure outside of the clinical setting. This system will consist of three key elements: an intravaginal pressure sensor with wireless data transmission capability, a small portable data monitoring and storage unit, and computer based data translation software for downloading and managing the pressure data. In a controlled exercise laboratory setting, they will then use intra-abdominal pressure data generated by the WRAPS to determine the reproducibility of intra-abdominal pressures measured during specific types of physical activity and will finalize development of a valid questionnaire that categorizes the magnitude of intra-abdominal pressures during activities. Finally, in a real-world setting in which participants wear the intravaginal sensor during waking hours for four 1-week periods over the course of a year, they will characterize intra-abdominal pressures experienced by women of varying degrees of habitual physical activity and, using WRAPS data as the gold standard, determine whether activity can be appropriately categorized in terms of pelvic loading by means of self-administered questionnaires, the current standard. Obtaining future evidence about the impact of physical stressors on pelvic floor disorders relies on their ability to measure the risk factor in question. This innovative translational collaboration will remove a critical barrier to progress in understanding the etiology of pelvic floor disorders in women.

Title: **Pregnancy and Drug Metabolizing Enzymes and Transporters**
P.I.: **Steve Caritis**
Institution: **Magee-Women's Research Institute, Pittsburgh, PA**
Grant No.: **3U10HD047905-05S2**
Award: **$285,225**

The purpose of this proposal is to establish an Obstetric-Fetal-Pharmacology Research Unit (OPRU) at the University of Pittsburgh and to summarize the components of the applicant's OPRU. They will demonstrate their willingness to cooperate with other OPRUs to establish a network of OPRUs to identify and study common problems related to the use of pharmacologic agents during pregnancy. They provide three protocols for assessment by the network for future exploration. The Pittsburgh OPRU is composed of a large clinical facility (Magee-Womens Hospital) with more than 8,000 deliveries and a wide array of women with medical or obstetric complications. A CRC satellite at Magee provides an optimal site for recruitment and study of pregnant women. These clinical facilities are linked to the Center for Clinical Pharmacology (CCP), which provides a core laboratory for classical pharmacology analyses and a pharmacogenetic laboratory for genotyping, mRNA expression and sequencing endpoint measurements. A proteomics laboratory is also linked to the CCP. In addition to these clinical and analytical resources is a breeding rhesus monkey colony housed at Magee-Womens Hospital. A basic science component completes the Pittsburgh OPRU. A diverse group of basic scientists and clinical researchers has been interacting through the CCP and will add considerable breadth and depth to their OPRU. The leadership of the Pittsburgh OPRU provides a diverse and experienced group of researchers with a long history of collaboration and investigation in the area of maternal-fetal pharmacology. The leadership has experience in collaborative endeavors and is prepared to cooperate with other OPRUs to conduct collaborative research.

Title: **University of Washington Obstetric-Fetal Pharmacology Research Unit**
P.I.: **Mary Hebert**
Institution: **University of Washington, Seattle**
Grant No.: **3U10HD047892-05S2**
Award: **$235,000**

The overall objective of this grant proposal is to establish an Obstetric-Fetal Pharmacology Unit at the University of Washington. The major goal of the pharmacology unit will be to characterize the pharmacokinetics and pharmacodynamics of drugs that are of therapeutic value during pregnancy and whose clinical pharmacology is altered by the pregnant state. The general research focus will be cytochrome P450 enzymes and membrane transporters. This proposal describes the available environment and resources at the University of Washington for establishing a successful and productive Obstetric-Fetal Pharmacology Research Unit. As a demonstration of their research interests and capabilities the following translational research studies that integrate their strengths in clinical and basic sciences are proposed to evaluate the following study aims. 1. They aim to determine whether the in vivo activities of CYP2C9 and organic cation transporter (OCT) are altered through stages of pregnancy using the following phenotype markers: glyburide for CYP2C9 and metformin for OCT. Phase I (population pharmacokinetic analysis) and Phase II (pharmacokinetic/pharmacodynamic analysis) studies are proposed to investigate the effects of pregnancy on the aforementioned drug-metabolizing enzymes and transporters (second and third trimesters vs. 3 months postpartum period). 2. They aim to determine the efficacy and safety of insulin vs. glyburide vs. glyburide plus metformin for treatment of gestational diabetes mellitus. A Phase III efficacy and safety trial is proposed to evaluate the effects of gestational diabetes as well as the treatments on maternal, fetal and infant and child developmental outcomes.

Pelvic Floor Disorders Network

Title: **The Cleveland Clinic Clinical Site**
P.I.: **Matthew Barber**
Institution: **The Cleveland Clinic Clinical Site, OH**
Grant No.: **5U10HD054215-04**
Award: **$25,000**

Pelvic floor disorders (PFD) including urinary incontinence, pelvic organ prolapse (POP), and fecal incontinence affect a substantial proportion of women in the United States. PFD result in significant psychosocial costs to an individual and their aggregate social and economic costs to society are enormous. Despite their substantial health impact, the quality of the evidence supporting most of the commonly used treatments, especially surgical interventions, is limited by the lack of standardization of diagnostic and therapeutic interventions, use of non-standardized and non-validated outcome measures, poor quality research designs, and inadequate power to detect clinically meaningful differences. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with PFD using the highest quality research methods available. The Specific Aims of this application are to: (1) demonstrate that the Cleveland Clinic Foundation (CCF) possesses the personnel, patient, clinical, and administrative resources needed for successful participation as a Clinical Site in the PFDN; and that their participation would be advantageous to the successful attainment of the Network's scientific goals; and (2) to present a concept application for potential conduct by the PFDN. The broad, long-term objectives of their concept application are to: (1) compare sacrospinous ligament fixation (SSLF) to uterosacral vaginal vault fixation (USWS) and (2) assess the role of perioperative pelvic floor physiotherapy (PFPT) in women undergoing transvaginal surgery for apical or uterine POP. Their Specific Aims are to: (1) compare the anatomic outcomes of SSLF to USWS in women undergoing transvaginal surgery for Stage 2–4 POP involving the vaginal apex or uterus 3 years after surgery; (2) compare functional, sexual, and health-related quality of life (HRQOL) outcomes of SSLF to USWS in the same women 3 years after surgery; (3) assess whether short-term functional, sexual, and HRQOL outcomes improve in women receiving PFPT perioperatively compared to those who receive surgery alone; (4) assess whether perioperative PFPT improves anatomic, functional, sexual and HRQOL outcomes 3 years after surgery (long-term) compared to surgery alone; and (5) determine the incremental cost-effectiveness of perioperative PFPT at the time of transvaginal surgery for POP. They present a collaborative multicentered randomized trial comparing SSLF to USSVS with or without perioperative PFPT using a 2x2 factorial study design. A standardized common protocol for enrollment, treatment and data collection will be employed by 6–8 Clinical Sites within the PFDN coordinated by the data coordinating center.

Title: **The Pelvic Floor Disorders Network**
P.I.: **Linda Brubaker**
Institution: **Loyola University, Chicago, IL**
Grant No.: **5U10HD041250-09**
Award: **$25,000**

Loyola is a productive, innovative clinical research institution that has contributed to the first cycle of the Pelvic Floor Disorders Network and they are eager to build on the PFDN's excellent start. Their application documents: (1) Loyola is a qualified and committed institution with an interdisciplinary faculty and key personnel with experience in clinical trials design and conduct. A highly qualified and committed research team led by the same principal investigator, Dr. Brubaker, this research team contains urogynecologists and urologists. Two of the faculty members received master's degrees in clinical research design and statistical analysis and one

is currently in this degree program. A cadre of study coordinators are cross-trained to meet the needs of the PFDN study roster. The team has excellent collaborations within the Loyola faculty. (2) Loyola's Participation in PFDN protocols and procedures: Loyola has demonstrated high-quality participation in PFDN protocols with excellent and consistent recruitment. They also demonstrate their consistent contributions in PFDN work, including dissemination of PFDN scientific findings. Loyola has been productive and has worked well with the PFDN team. Their first cycle application proposed the essence of the CARE trial, which was completed ahead of schedule and is under consideration for publication. 3) A Feasible, Scientifically Relevant Concept Protocol (Randomized Surgical Trial): They believe they have demonstrated their ability to design and conduct high-quality clinical trials. This application also describes a randomized surgical trial for women who select vaginal apical reconstruction. A comparison of the two most common techniques may inform a future study which seeks to determine which route of surgery (abdominal vs. vaginal) is best suited for an individual woman. This trial is a feasible, scientifically relevant randomized surgical trial. The draft protocol is suitable for PFDN Steering Committee discussion and revision, prior to implementation.

Title: **Pelvic Floor Disorders Network**
P.I.: **Charles William Nager**
Institution: **University of California, San Diego**
Grant No.: **5U10HD054214-04**
Award: **$25,000**

The objectives and aims of this application are for San Diego to become the first western United States clinical site in the Pelvic Floor Disorders Network (PFDN). The San Diego Clinical Site is a collaboration of three medical centers: (1) the University of California, San Diego (UCSD), (2) Kaiser Permanente, San Diego (Kaiser), and (3) Naval Medical Center, San Diego (NMCSD). This same collaboration in the Urinary Incontinence Treatment Network (UITN) led all sites in patient recruitment for the UITN SISTEr (Stress Incontinence Surgery Treatment Efficacy) trial. The efficiency of the San Diego Clinical Site's efforts was recognized by the PFDN and they were asked to become a subcontract site for the University of Alabama for the Colpopexy and Reduction Efforts (CARE) study. In the brief nine months available before the CARE study ended, San Diego (UCSD and Kaiser only) recruited 19 patients to CARE. This total was more than all but one center during those nine months. They were the third UITN site to reach recruitment goals in the UlTN's BE-DRI (Behavior Enhances Drug Reduction Incontinence) study. Additionally in the UITN, their site has led efforts in the design, protocol development, and workgroup leadership for the UlTN's current study, TOMUS (Trial Of Mid-Urethral Slings). Urodynamic studies are commonly performed in the United States at an annual cost of approximately $400 million. These urodynamic studies are routine preoperative investigations in most centers that have urodynamic capability, yet they do not have evidence that these tests improve outcomes. The concept proposal is a randomized trial of preoperative urodynamic studies in women with predominant stress urinary incontinence. The primary aim is to determine if preoperative urodynamic studies improve treatment success rates in all women considered candidates for SUI surgery after an office evaluation. They believe that this proposed urodynamics study requires a multicenter randomized clinical trial and has significant relevance to the appropriate evaluation and care of women with pelvic floor disorders, namely urinary incontinence. The proposed study also has potential significant importance for national health care resource allocation and expenditures. The work that the San Diego investigators have done for the UITN in the last five years to develop standardized, quality urodynamic studies make them the ideal investigators to lead this effort. They believe that the PFDN will benefit greatly by the proven ability of the San Diego Clinical Site's demonstrated energy, skills, and leadership.

Title: **Utah Pelvic Floor Disorders Network**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah, Salt Lake City**
Grant No.: **5U10HD054136-04**
Award: **$25,000**

Pelvic floor disorders are common, bothersome, and inadequately treated. The overarching aim of the investigators from the proposed University of Utah Pelvic Floor Disorders Clinical Site is to improve women's health in the area of pelvic floor dysfunction. To this end, site Specific Aims include: (1) identifying priority areas of research, (2) developing assessment tools, (3) developing and implementing PFDN protocols, (4) recruiting and enrolling subjects in PFDN protocols, (5) achieving on-target recruitment goals and high subject retention, (6) ensuring high-quality data, (7) transmitting data accurately to the data coordinating center, (8) participating in data analysis, (9) disseminating results to the research community, and (10) producing high-quality publications. The broad scientific aim for the randomized clinical trial outlined in this proposal is to evaluate whether post-operative pelvic floor muscle training following surgery for pelvic organ prolapse and/or stress urinary incontinence improves post-operative outcomes (anatomic, symptomatic, and quality of life outcomes) at 3 months, 1 year, and 2 years postoperatively.

Title: **Perioperative Pelvic Floor Rehab: A Randomized Trial**
P.I.: **Holly E. Richter**
Institution: **University of Alabama at Birmingham**
Grant No.: **5U10HD041261-09**
Award: **$25,000**

Surgical techniques for the treatment of stress incontinence (SUI) have significantly evolved over the last 100 years. The gold standard Burch urethropexy and pubovaginal sling procedures are now being performed less frequently, with the increased use of the newer minimally invasive mid-urethral sling procedures, the most common being the tension-free vaginal tape procedure (TVT). The TVT procedure is comparable in efficacy to the open Burch procedure with low morbidity and fewer complications. Because the sling is placed at the level of the mid-urethra under no tension, it was thought that the TVT would yield fewer postoperative lower urinary tract symptoms. However, a review of the literature has not borne this out, with postoperative storage symptoms reported in up to 42 percent of women. The primary purpose of the proposed randomized clinical trial is to test whether a perioperative behavioral/pelvic floor muscle training program can reduce the occurrence of these postoperative storage symptoms and voiding dysfunction in women undergoing a TVT procedure for SUI. Behavioral interventions are known to be effective for treating urge incontinence and voiding dysfunction unrelated to surgery, but have not been tested as a preventive adjunctive strategy. Approximately 400 subjects will be randomized to a perioperative behavioral program or usual care. The intervention will be implemented 2 weeks preoperatively, and reinforced before leaving the hospital and two weeks postoperatively. The primary outcome will be complaints of urgency, frequency, nocturia and urge incontinence using the overactive bladder questionnaire (OABq). Evaluations will be performed at 2 and 6 weeks, 3, 6, and 12 months postoperatively, and will include the OABq, questionnaire for urinary diagnosis (QUID), urogenital distress inventory (UDI), pelvic organ prolapse/urinary incontinence sexual function questionnaire (PISQ), patient global impression of severity (PGI-S) and SF-36. Subjects will also complete a 7-day bladder diary to assess frequency of storage symptoms. Secondary aims are to determine whether this intervention reduces time to voiding and symptoms of voiding dysfunction, whether it impacts on patient satisfaction and quality of life, and to identify predictors of

postoperative storage symptoms and voiding dysfunction symptoms. This type of information will allow physicians to more effectively counsel and treat their incontinent female patients to further enhance long-term quality of life.

Title: **Pelvic Floor Disorders Network**
P.I.: **Joseph I. Schaffer**
Institution: **University of Texas Southwestern Medical Center, Dallas**
Grant No.: **5U10HD054241-04**
Award: **$25,000**

This application describes the qualifications and experience of the urogynecology and urology faculty and research teams at the University of Texas Southwestern (UT Southwestern) Medical Center and Parkland Hospital and the facilities and patient population available to carry out clinical protocols sponsored by the Pelvic Floor Disorders Network. In 2004, there were more than 2,100 women with pelvic floor disorders seen in their clinics and 617 women underwent surgical procedures for correction of pelvic floor disorders. The Departments of Obstetrics and Gynecology and Urology have increasingly collaborated since 1997 to offer comprehensive care of women with pelvic floor disorders. In addition to urogynecology and urology, collaboration includes faculty from colorectal surgery, radiology, physical therapy, and maternal-fetal medicine. The clinical research teams described in this application have successful prior as well as on-going experience in NIH sponsored national multicenter trials. Centerpieces in this application are two existing research clinics, one targeted at private patients (operated by the Urology Department) and the other focused on medically indigent patients (operated by the Obstetrics and Gynecology Department). Also included in this application is a concept application for a randomized trial designed to assess the efficacy of end-to-end versus overlapping repair of the external anal sphincter lacerated during childbirth. The primary outcome is anal incontinence which is a significant consequence of such lacerations. This trial would permit accurate evaluation of the outcome of specific surgical procedures which is one of the prime areas of interest leading to creation of the Pelvic Floor Disorders Network. They are of the view that along with strategies for prevention of anal sphincter laceration during childbirth, optimal management of the torn sphincter should also be studied since more than 200,000 women sustain such pelvic floor injuries each year in the United States.

Title: **Pelvic Floor Disorders Network—Data Coordinating Center**
P.I.: **Catherine A. Spino**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **5U01HD041249-09**
Award: **$25,000**

Pelvic floor disorders such as urinary incontinence, pelvic organ prolapse, and fecal incontinence are common and significant health-related problems for women in the United States. Outcomes following surgical and non-surgical intervention for pelvic floor disorders have not been adequately evaluated. As a result, data necessary to fully inform patients and to make important policy decisions are unavailable. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to systematically evaluate these outcomes. This application to be the data coordinating center (DCC) for the pelvic floor disorders network brings together experienced investigators from biostatistics, urogynecology, urology, quality of life and health services research to prospectively assess the outcomes from various surgical interventions for female pelvic floor disorders. The Specific Aims of the DCC are to: (1) assist in protocol development by providing expertise in the design, conduct and analysis of clinical trials conducted by the PFDN; (2) provide expertise in measurement of quality of life and in the selection of the appropriate instruments to assess treatment outcomes and, when appropriate,

to perform the interviews; (3) coordinate the implementation of the study protocols approved by the steering committee, including design of the case report forms and interviewing protocols, development of a manual of operations, centralized database management with either centralized or remote data entry, submission of an IND to the FDA when necessary, and by organizing training and certification sessions, as needed; (4) establish a database for each study conducted by the PFDN; (5) implement either centralized or web-based data entry and verification; (6) monitor the clinical sites with respect to data quality; (7) provide infrastructure for monitoring adverse events and regulatory oversight for the network;(8) provide logistical support for the steering committee, advisory board and DSMB, for both face-to-face meetings and teleconferences; (9) maintain a website for the PFDN that includes web pages with content for the public, and a password-protected site with all study documentation and databases; and (10) manage and distribute protocol funds to the clinical centers. To illustrate the work of the DCC, a randomized clinical trial is proposed to compare surgical procedures for pelvic organ prolapse using a vaginal approach.

Title: **Pelvic Floor Disorders Network**
P.I.: **Anthony G. Visco**
Institution: **Duke University, Durham, NC**
Grant No.: **5U10HD041267-10**
Award: **$25,000**

Women's health research at the University of North Carolina (UNC) is sophisticated and widespread with many committed investigators addressing issues of fundamental importance to women. UNC has a tradition of excellence in clinical care, training, and research in pelvic floor disorders and includes one of the nation's first accredited fellowship programs in the Division of Urogynecology and Reconstructive Pelvic Surgery. They offer comprehensive evaluation and treatment options in a high-volume care setting that serves as a tertiary referral center for women from across the state. Women sought consultation or treatment for more than 2,700 pelvic floor disorders by Urogynecologists at UNC in the previous 2 years. Seventy-eight percent of the women were Caucasion and 15 percent were African American, predominantly from rural and suburban communities with stable care and followup patterns. Approximately 427 women had multichannel urodynamic studies annually. UNC providers have extensive expertise in both surgical and nonsurgical management of urinary incontinence, pelvic organ prolapse, and defecatory dysfunction. The Division of Urogynecology performs an average of 106 surgical procedures for the primary indication of urinary incontinence, 300 for prolapse and provides medical management for more than 1,464 women with these conditions each year. The UNC Pelvic Floor Disorders Research Collaborative, led by the Division of Urogynecology is an interdisciplinary team of outstanding investigators in urogynecology, urology, gastroenterology, radiology, maternal-fetal medicine, and clinical research methodology. They have a history of strong clinical ties and dedication to interdisciplinary research. Diagnostic resources include muti-channel urodynamic testing, cystoscopy, defecography, pelvic MRI, 360-degree endoanal ultrasound, anal manometry and needle electromyography. Clinical services include surgical treatment of complex pelvic floor disorders and a wide range of non-surgical options. As an active PFDN clinical network site, UNC has an established research infrastructure with the proven ability to support large-scale, multicentered clinical research. The collaborative is well-equipped and uniquely qualified to continue as a valuable member of the Pelvic Floor Disorders Network. Given the exceptional quality of the research opportunities and resources available at UNC, the stable and diverse patient population, the strength of the investigator pool, their proven high-level recruitment and the commitment of the institution to the stated goals of this RFA, they look forward to continuing to make substantial contributions to advancing women's health related to pelvic floor disorders.

APPENDIX C

ORWH-Cofunded Research Summaries, FY 2010

Adolescent Health

Title: **The National Longitudinal Study of Adolescent Health**
P.I.: **Kathleen M. Harris**
Institution: **University of North Carolina, Chapel Hill**
Grant No.: **5P01HD031921-15**
Award: **$200,000**

The National Longitudinal Study of Adolescent Health (Add Health) is currently funded for Wave IV data collection. At the time the project began in 1994–1995, investigators selected a nationally representative sample of adolescents in grades 7–12. Participants have been followed through adolescence and the transition to adulthood with three in-home interviews. Wave IV will include additional information that encompasses social, behavioral, and biological data. In addition to data contributed in earlier surveys, these subjects, who are now between the ages of 23 and 31 years, will provide biological data to capture the prevailing health concerns as well as biological markers of future chronic health conditions.

Title: **An Integrative Intervention for Binge Eating among Adolescent Girls**
P.I.: **Suzanne Mazzeo**
Institution: **Virginia Commonwealth University, Richmond**
Grant No.: **1R34MH086922-01A2**
Award: **$200,000**

Many adolescents struggle with overeating (binge-eating). Adolescents with these eating problems are more likely than their peers to be depressed, anxious, and feel badly about their appearance. African-American girls are especially at-risk for these eating problems. Effective treatments are urgently needed. This study will develop and evaluate an innovative intervention, Linking Individuals Being Emotionally Real (LIBER8), for ethnically diverse adolescent girls. This intervention will focus on teaching girls skills that help them reduce their problematic eating behaviors and improve their overall well-being. Binge and loss of control (LOC) eating affect a significant number of adolescents of all ethnicities and are associated with numerous psychological problems, including depression, anxiety, low self-esteem, body dissatisfaction, and weight concerns. African-American women appear to be particularly vulnerable to binge eating disorder, and LOC and binge eating are prevalent among African-American girls. However, empirically validated culturally sensitive treatments for these disordered eating behaviors are not available. Thus, this R34 application aims to develop a manualized and culturally sensitive intervention, LIBER8, for African-American and White adolescent girls targeting binge and LOC eating. They will target the intervention to adolescents with either or both behaviors. This intervention will integrate components of dialectical behavior therapy tailored to adolescents who engage in binge and LOC eating, such as mindfulness and distress tolerance skills training, with a core of cognitive-behavioral therapy (CBT). They will seamlessly integrate a key adolescent communication strategy, namely text-messaging, into therapeutic self-monitoring. They will evaluate the feasibility and acceptability of the intervention in a controlled pilot trial. This study is designed explicitly to gather preliminary data to inform a subsequent larger randomized controlled trial. They hypothesize that this intervention will

serve to reduce binge and LOC eating, as well as improve psychosocial functioning as evidenced by decreased depression, anxiety, eating disorder cognitions, and impulsivity, and improved quality of life.

Title: **NHANES Project For Adolescents And Girls**
P.I.: **Rick Troiano**
Institution: **National Cancer Institute, Bethesda, MD**
Award: **$300,000**

NHANES data from 2003–2006 show a dramatic decline in physical activity, especially for girls, as children move into adolescence. Poor sleep and loss of muscle strength are issues for women as they age. The NHANES will measure physical activity, sleep, and muscle strength for women and men across the lifespan from a nationally representative sample.

Aging

Title: **National Social Life, Health, and Aging Project**
P.I.: **Linda J. Waite**
Institution: **National Opinion Research Center, Chicago, IL**
Grant No.: **5R37AG030481-03**
Award: **$200,000**

They propose to collect a second wave of the National Social Life, Health and Aging Project (NSHAP) to obtain data on social networks and social support, marital and cohabitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. The primary objective of the National Social Life, Health and Aging Project (NSHAP) is to establish an innovative, high-quality dataset for use by researchers studying the relationships between social processes and health among older adults. Wave I obtained questionnaire and biomeasure data on a nationally-representative sample of 3,005 community-dwelling adults ages 57–85 in 2005 and 2006. They propose to collect a second wave in NSHAP to obtain data on social networks and social support, marital and cohabitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. They propose to revisit respondents 4 years after their initial interview. Using these data, they can describe and model the distribution of changes in health, well-being, social networks, social participation and social context. In each case, they shall examine the distributions both for the entire sample and within subgroups defined by key sociodemographic characteristics such as gender, race and ethnicity, and socioeconomic status. They also propose to augment the sample by interviewing the spouse or cohabitating romantic partner. These data will allow them to characterize the impact of marital and romantic relationships on health by examining the effects of one person's characteristics and behaviors on the health of the other. They will also analyze the partnerships themselves, and assess the relationship between characteristics of the partnership, such as support, closeness, and mistreatment, and the health of each of the

partners. In sum, they will explore their overarching hypothesis that older adults with strong functioning intimate relationships will show more positive (or less negative) health trajectories that those who have weaker relationships or lack such relationships altogether.

Alcohol and Other Substance Abuse

Title: **An Ethnographic and Economic Investigation of the Fresh Start Program (Detroit)**
P.I.: **Juliette Kathryn Roddy**
Institution: **University of Michigan, Dearborn**
Grant No.: **5R21DA027145-02**
Award: **$154,500**

Treatment professionals and substance abuse researchers agree that both successful drug abuse recovery and exiting street prostitution require changes in social networks and accompanying economic independence. These changes can be both quantitatively and qualitatively described by studying street prostitutes who are engaged in the treatment and recovery process through the application of ethnographic and economic instruments and an accompanying mapping of changing social networks. The proposed work has implications for women's health and welfare and the prevention and treatment of sexually transmitted disease. Aside from journalistic accounts detailing the pitfalls of drug treatment, little research has been done on the recovery process as it actually proceeds within particular programs. Research is not always well incorporated into treatment settings, which may resist innovations due to internal organizational factors. Conducting research in criminal justice settings, including drug courts or programs administered through drug courts, is also problematic. Nonetheless, more such research is needed as treatment and recovery services become central features of the national response to substance abuse, especially in an era of prison downsizing. This will also require research that actively engages with communities and institutions. The proposed research will work collaboratively with multiple agencies to investigate the process of treatment and recovery as it occurs in women who participate in Fresh Start. Fresh Start is a substance abuse intervention program for female street sex workers who have come into repeated contact with law enforcement. Fresh Start is a coercive recovery-based program that serves as a direct contrast to voluntary, traditional, treatment-based programs. The program serves as an alternative to jail time for these women, who are arrested in periodic sweeps of neighborhoods where street prostitution is common. They predict that, prior to entering residential treatment through Fresh Start, women will have daily routines dominated by "street" networks that are relatively constricted and immersed in drug use and drug-using contexts. For those that enter residential treatment and stay in the program for a year, they predict that networks will remain relatively constricted, but will instead be largely immersed in treatment-dominated contexts. In the recovery stage, women will be engaging with the larger community, that is, interacting with more people who are not in treatment or recovery. In this stage, they predict that networks may grow more extensive and variable, as women begin to explore new avenues of social interaction and opportunity. Using interdisciplinary methods, they will seek evidence of desired change in social networks, sociospatial contexts, and economic behaviors, resources, and outcomes.

Title: **Interactive Effects of Ethanol and Estrogen on Brain Vasopressin During Puberty**
P.I.: **Toni R. Pak**
Institution: **Loyola University, Chicago, IL**
Grant No.: **5R21AA018398-02**
Award: **$186,875**

Women who abuse alcohol are twice as likely to develop anxiety disorders compared with men, a phenomenon in which the underlying biological mechanisms are unknown. Their overall objective is to identify the interactive effects of alcohol and estrogen on arginine vasopressin (AVP), a well-established key molecular mediator of anxiety, in order to elucidate the molecular mechanisms predisposing women to increased risk of anxiety disorders. Adolescent binge drinking is a potential risk factor for the development of adult anxiety disorders due to the heightened stress reactivity that occurs as a direct result of increased circulating estrogens during pubertal development. Little is known about the long-term neurobiological consequences of alcohol consumption during puberty, which is a dynamic and important period of brain development that involves changes in cortical gray matter, synaptic connectivity, and increased neurogenesis. Exposure of alcohol during this critical period of extensive brain remodeling may result in permanent neuronal damage or disruptions in the formation of new neuronal connections, which might manifest as adult behavioral psychoses, including anxiety disorder. Their preliminary data show that alcohol exposure during puberty increased AVP gene expression in specific regions of the brain. Therefore, the experiments proposed in Specific Aim 1 will directly test the hypotheses that there is a critical window of time during pubertal development when the AVP system is most vulnerable to the effects of alcohol. The preliminary data also showed that estrogen exacerbates the effects of alcohol on AVP gene expression. And finally, their preliminary data demonstrated that alcohol treatment and estrogen receptor ligands increased AVP gene expression in neuronal cells derived from the hypothalamus, and gene expression was closely correlated with the activity of the gene promoter. Alcohol also activates estrogen-signaling pathways in the brain, which suggests that the underlying mechanisms for alcohol-induced changes in AVP may be mediated by estrogen signaling pathways. Therefore, the experiments proposed in Specific Aim 2 will directly test the hypotheses that: (1) acute alcohol exposure increases AVP promoter activity in neuronal cells, (2) there are specific regulatory regions of the AVP promoter that interact with alcohol, and (3) estrogen and alcohol interact synergistically to increase AVP promoter activity. To date, specific molecular and neuroendocrine markers that are activated by alcohol during puberty have not been identified. This proposal is focused on a specific candidate gene (AVP) and its downstream signaling pathways that are developmentally shaped during puberty. They expect these studies to show that AVP is permanently altered, either as a direct target for alcohol or indirectly through steroid hormone receptor signaling pathways. Thus, the value of this research lies in the potential for therapeutic approaches that would target specific genes and perhaps reverse brain damage caused by alcohol consumption during pubertal development as well as strengthen reasons for abstaining from alcohol during that time.

Cancer

Title: **A Decisionmaking Framework for Contralateral Prophylactic Mastectomy**
P.I.: **Abenaa Brewster**
Institution: **University of Texas M.D. Anderson Cancer Center, Houston**
Grant No.: **1R21CA149803-01A1**
Award: **$191,327**

The rising incidence of contralateral prophylactic mastectomy (CPM) among patients with sporadic breast cancer for whom there is no established psychosocial or clinical benefit or cost data is a critical area of public health concern. The proposed study will evaluate the clinical benefits, risks and cost of CPM and prospectively evaluate the decisionmaking process leading to CPM among women with sporadic breast cancer. The results of the study will be used to develop a clinical educational instrument that will enable patients with sporadic breast cancer and their providers to make more informed decisions regarding CPM which will serve to improve the quality of life of breast cancer survivors. The two Specific Aims are: (1a) assess the association between CPM and disease-free survival (defined as contralateral breast cancer, distant recurrence and breast cancer mortality), (1b) assess the health care resource utilization associated with CPM, which will include the surgical procedure, management of surgical complications, and subsequent breast reconstruction; (2) prospectively examine the psychosocial characteristics and decisionmaking process of women considering CPM. The hypothesis is that CPM will marginally improve disease-free survival, add substantial costs to the health care system and that patients with more cancer-related distress will be more likely to consider CPM. The findings from this study will form the basis for future research (e.g., intervention and/or observational studies) in this area that may be expanded to include multiple institutions. The proposed study is innovative because there are no studies to date that have prospectively evaluated the psychosocial factors that contribute to the decisionmaking process leading to CPM among patients with sporadic breast cancer. This research is important because of the rising incidence of CPM and the exposure of an increasing number of women to aggressive surgical management without established psychosocial or clinical benefit. The long-term impact of the proposed research is significant because it will lead to the development of an evidence-based clinical educational intervention that will enable patients with sporadic breast cancer and their providers to make more informed decisions regarding CPM and improve the quality of life of breast cancer survivors.

Title: **Can Lifestyle Modify Fatigue in Breast Cancer Survivors?**
P.I.: **Wendy Y. Chen**
Institution: **Brigham and Women's Hospital, Boston, MA**
Grant No.: **1R03CA141572-01A1**
Award: **$89,000**

With over 2 million breast cancer survivors in the United States, the investigators propose to evaluate the determinants of fatigue with a specific focus on new-onset and persistent fatigue among breast cancer survivors and an innovative exploration of dietary modifiers of fatigue. Fatigue is the most common and distressing symptom among breast cancer survivors and can persist for years after treatment, even in those clinically disease-free. Most studies among cancer survivors have evaluated the prevalence of fatigue using a cross-sectional design with limited longitudinal followup and none of the published studies to date have data on subjects before diagnosis. They propose to utilize the prospective Nurses' Health Study (NHS) cohort, which includes data on subjects before and after cancer diagnosis as well as a cancer-free comparison group, to evaluate the prevalence and trajectory of fatigue among breast cancer survivors not currently on treatment and the influence of lifestyle factors affecting the inflammatory pathway,

a possible causative mechanism. They will examine both persistent (present before and after diagnosis) and new-onset fatigue (lack of fatigue before diagnosis and development of fatigue after diagnosis). Strengths of the NHS dataset include data collected prospectively before and after diagnosis, availability of a comparable control group, and extensive information on dietary and lifestyle factors before and after diagnosis with an excellent followup rate. Although the cause of fatigue among cancer survivors is most likely multi-factorial, increasing evidence suggests that inflammation is an important mediator. Breast cancer survivors with fatigue have higher levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-1), and circulating T lymphocytes compared with survivors without fatigue. In addition, dietary intake can modify inflammatory biomarkers relating to cardiovascular disease and the metabolic syndrome. Therefore, if inflammation is a mediator of fatigue, lifestyle factors that modify inflammatory pathways may also influence fatigue among survivors. Using data both before and after cancer diagnosis for survivors and cancer-free comparisons, they propose analyses to characterize risk factors for persistent and new-onset fatigue among breast cancer survivors and lifestyle factors that may modify the development and persistence of fatigue. Their findings could lead to new methods of coping with a debilitating symptom and identifying women who might best respond to interventions to decrease fatigue. Their application is novel in examining dietary modifiers of fatigue. Specifically, they hypothesize that among breast cancer survivors that the prevalence of persistent fatigue is similar to that in matched controls without cancer, but that new-onset fatigue is more common among breast cancer survivors. They hope to identify predictors of new-onset, but not persistent, fatigue, such as age at diagnosis, employment status, and lack of physical activity and overweight at diagnosis. Finally, they will evaluate dietary modifiers of fatigue including a higher intake of cereal fiber, whole grains, and n-3 fatty acids and lower intake of saturated and trans-fatty acids.

Title: **Microbial Exposures across the Lifespan and Cancer Risk in Women**
P.I.: **Christina Clarke**
Institution: **Cancer Prevention Institute of California, Fremont**
Grant No.: **1R21CA152839-01**
Award: **$220,500**

Early-life exposure to harmless microbes, as occurs through exposure to children, pets, and farm animals, is increasingly understood to affect childhood health, and mounting evidence suggests that these exposures also influence health in adulthood. The likely pathway for this influence involves a calibrating effect of early-life microbial exposures on the immune response so as to reduce the likelihood of chronic inflammation in later life. As chronic inflammation is known to interact with hormone levels and is suspected in the cause of several cancers in women, including breast, endometrial, and colon cancers, microbial exposures represent important targets of cancer prevention studies. They have preliminary evidence that early-life exposure to farming and preschool or kindergarten protects against breast cancer risk later in life, justifying more detailed study of these exposures for breast and other cancers, including how the risk associations might vary with age-specific exposures across the lifespan. They have a unique opportunity to examine relationships between microbial exposures and cancer risk in more than 60,000 women participating in the California Teachers Study (CTS), a cohort of female California teachers and administrators followed prospectively for cancer incidence since 1995. Their study aims to measure associations between selected markers of microbial burden at a range of ages and risk of several cancer outcomes, including in situ breast cancer, estrogen receptor (ER)-positive and ER-negative invasive breast cancer, type 1 endometrial cancer, cutaneous melanoma, colon cancer, and, to the extent possible, papillary thyroid cancer. To accomplish these aims, they will conduct a secondary data analysis in the CTS, using a nested case-control design, using exposure data collected from 60,878 cohort members who provided information about five markers for microbial exposure, including characteristics of

their home environment at ages 6 months, 3 years, 5 years, 12 years, and 30 years. They will use unconditional logistic regression to measure associations adjusted for confounders such as age and socioeconomic status. This unified approach will enable us to compare and contrast in a single cohort the associations of early- and later-life markers of microbial exposures with risk of hormone-dependent cancers (e.g., ER-positive breast, endometrial, and papillary thyroid cancers), hormone-independent cancers (e.g., melanoma and ER-negative breast cancer), and cancers linked strongly to chronic inflammation (e.g., breast and colon cancers). If they find that these understudied environmental exposures do reduce risk of specific cancers or groups of cancers, their results could justify the investigation of new cancer prevention strategies using harmless surrogates of important microbial exposures.

Title: **Costa Rica HPV-16/18 Vaccine Trial**
P.I.: **Allan Hildesheim**
Institution: **National Cancer Institute, Bethesda, MD**
Grant No.: **N01CP11005**
Award: **$550,000**

The ORWH has supported infrastructure costs associated with the Costa Rica HPV Vaccine Trial since its inception. In FY09, support in the amount of $400,000 was provided. These funds were utilized to support continued followup and clinical management of the 7,466 women enrolled in this community-based, randomized, phase III clinical trial and for the enrollment of participants into the extended followup phase of the trial (planned for an additional 6 years beyond the initial, 4-year blinded phase). More specifically, funds provided by ORWH in FY09 supported the following activities: (1) continued blinded followup screening of trial participants; (2) referral of participants with evidence of high-grade disease to colposcopy and treatment; (3) initiation of 4-year study visits (final visit under the blinded design—approximately 2,000 such visits of an expected total of 7,000 were performed in FY09); (4) consenting of women into their long-term followup study (approximately 2,000 women of expected total of 7,000 were consented in FY09); (5) initiation of recruitment of new control group for the Long-Term Followup Study (approximately 700 women of expected total of 3,000 were recruited in FY09); and (6) additional collection of specimens from the vulva, anus, and oral cavity to allow for the evaluation of vaccine efficacy at sites other than the cervix. The activities funded by ORWH in FY09 and preceding years have resulted in several important publications in the peer-reviewed literature.

Title: **Nuclear Pore Complex Architecture and Drug Resistance in Ovarian Carcinomas**
P.I.: **Donald Stave Kohtz**
Institution: **Mount Sinai School of Medicine of New York University**
Grant No.: **1R03CA141318-01A1**
Award: **$84,750**

The proposed studies are concerned with a novel mechanism by which ovarian cancinoma cells acquire resistance to cisplatin. While ovarian tumors initially respond well to cisplatin and carboplatin, 70–80 percent of advanced stage ovarian cancers will develop resistance to the drug. The proposed studies will investigate the role of changes in nuclear pore architecture and patterning that may contribute to the acquisition of drug resistance by ovarian cancer cells. While ovarian carcinomas initially respond well to treatment with platinum drugs, the majority relapse and acquire resistance. In ovarian carcinomas, they have observed reductions of NUP62 in resected tumor tissue from ovarian carcinomas, and redistribution of NUP62 among subnuclear fields of nuclear pore complexes (NPCs). Further, enrichment of NUP62-depleted NPCs renders ovarian carcinoma cells resistant to cisplatin in culture. The studies suggest the hypothesis

that survival advantages conferred by the enrichment of NUP62– and/or NUP214+ NPCs may be exploited by tumor cells. To advance this hypothesis, they propose to: (1) investigate alterations in the accumulation and distribution of NUP62 and NUP214 in ovarian carcinomas, to decipher how these factors correspond to tumor parameters, and to investigate how changes in expression or accumulation of either NUP62 or NUP214 influences distribution of the other nucleoporin among NPCs; and (2) investigate how knockdown of NUP62 confers resistance to cisplatin; specifically, to decipher how altering the distribution and prevelance of NUP62+/NUP214– and NUP62–/NUP214+ NPC populations influence survival signaling through NF-κB signaling pathways. The proposed studies impact the basic biology of epigenetic regulation and may also illuminate a new approach to improving the prognosis of ovarian carcinomas treated with platinum drugs. As the patterning and architecture of NPC populations influences the sensitivity of ovarian carcinoma cells to cisplatin, small molecules may be developed that modify NPC architecture to enhance its therapeutic effectiveness. These agents may be employed to reduce the number of cells that survive and/or become latent in response to therapy, and also to chemosensitize relapsed tumors that have acquired platinum resistance.

Title: **Estrogen and Skin Cancer**
P.I.: **Tatiana Oberyszyn**
Institution: **Ohio State University, Columbus**
Grant No.: **1R21CA135570-01A2**
Award: **$228,750**

Americans live in a culture that glorifies youth. According to market researcher FIND/SVP, the anti-aging products market is expected to hit $56 billion by 2007. Studies in postmenopausal women have found that hormone replacement therapy is effective at reversing the dryness and wrinkling that affects aging skin. Based on these studies, there is increasing interest in the use of topical creams containing hormones such as estrogen to prevent or reverse some of the normal cutaneous aging processes in younger premenopausal women. While exposure to these creams may be beneficial cosmetically, the effect of applying estrogen to sun-exposed sites for prolonged periods of time on skin cancer development is not known. Their preliminary studies using female Skh-1 hairless mice found a significant increase in the number of tumors in mice treated topically with estrogen immediately following UVB exposure compared to mice treated with vehicle control. These data indicate that increased levels of estrogen in the skin combined with UV exposure may act to enhance initiation and promotion of UV-induced skin cancers. These findings also suggest that the use of lotions and creams containing estrogenic compounds on sun-exposed sites by younger women may be contributing to the increase in the number of skin tumors being diagnosed in women under the age of 40. Most studies have examined the effects of topical or systemic estrogen on the skin in postmenopausal women, however the reality is that younger premenopausal women are applying topical estrogen containing creams on their faces previously exposed to UV light to prevent/reverse the signs of aging. Two Specific Aims are proposed to test the hypothesis that topical estrogen application to previously UVB-exposed skin accelerates skin carcinogenesis. Studies in Specific Aim 1 will use the Skh-1 hairless mouse murine model of UVB-induced skin carcinogenesis to determine the effects of clinically used topically applied estrogen (Estrogel(R)) on UVB-induced skin tumor development in previously UVB-exposed female skin of intact (premenopausal) and ovariectomized (postmenopausal) mice. Studies in Specific Aim 2 will determine the effects of topically applied estrogen (Estrogel(R)) on UVB-induced skin tumor progression in female Skh-1 skin of intact and ovariectomized mice. The studies carried out in these aims will determine whether topical estrogen increases the number of UVB-induced skin tumors that develop and also whether it differentially enhances the progression of benign UVB-induced tumors to malignant squamous cell carcinomas in intact (premenopausal) and ovariectomized (postmenopausal) mice.

Title: **Family Cancer Literacy to Promote Mammography Screening among Navajo Women**
P.I.: **Christi A. Patten**
Institution: **Mayo Clinic, Rochester, MN**
Grant No.: **1R21CA152433-01**
Award: **$132,301**

Among American Indian and Alaska Native (AI/AN) women, breast cancer is more likely to be diagnosed at an advanced stage and the 5-year breast cancer survival rates are lower than any other ethnic group. Among Navajo women scheduled for a mammography screening appointment, the no-show rate is markedly high (80 percent). This study proposes to develop a family-based cancer literacy intervention that includes culturally and linguistically appropriate education about breast cancer to promote mammography screening among Navajo women. This proposal describes a community-based participatory research study to develop and pilot test a new behavioral intervention to promote mammography screening among Navajo women. From a public health perspective, the intervention has the potential to reach many Navajo women, as 80 percent of women scheduled for mammography appointments do not follow through. These women (over 1,500 each year) are referred to the Nation Breast and Cervical Cancer Prevention Program (NNBCCPP). A key barrier toward implementing cancer prevention and control efforts in the Navajo community is a lack of cancer literacy or cultural and conceptual knowledge regarding cancer. Other barriers to screening are fear of cancer, stigma of cancer (even talking about cancer) often experienced by the patient, family and community, and lack of knowledge about the etiology of cancer and importance of early detection. Therefore, communication about cancer is impeded within Navajo families and the community. This proposal builds on their successful partnership and collaboration with Dini College (the Navajo tribal college). The proposed study is designed to assess the feasibility and potential efficacy of a cancer-literacy focused, family-based intervention on completion of mammography screening for Navajo women. The intervention will include culturally and linguistically appropriate educational materials about cancer (e.g., the Navajo Cancer Glossary). The project will be implemented in two phases. During Phase 1, they will develop the family cancer literacy intervention with feedback from their community advisory committee. In addition, the Cancer Literacy Measure will be adapted for Navajo women through focus groups and individual interviews. Phase 2 will consist of a formative evaluation of the intervention. The NNBCCPP patient and a female family member will be randomly assigned in pairs to the control condition (existing NNBCCPP health education services, N=40 pairs) or to receive these health education services plus the family cancer literacy intervention (N=40 pairs). They will assess the intervention's feasibility and acceptability as indicated by the recruitment and retention rates and qualitative ratings of treatment acceptability. In addition, they will examine the effect of the intervention compared with the control group on the proportion of women who complete mammography screening at 3-month followup documented by NNBCCPP records. They will also examine changes in Cancer Literacy Measure scores from baseline to 3-month followup among both patients and family members. They expect that as a result of this project, they will have developed a replicable, feasible, and acceptable intervention, the efficacy of which can be tested in future large-scale randomized clinical trials. In addition, the adapted Cancer Literacy Measure could be used in future cancer prevention and control projects within the Navajo Nation. The overall objective is to reduce breast cancer morbidity and mortality among Navajo women.

Title: **Pharmacogenetics of Phase II Drug Metabolizing Enzymes**
P.I.: **Richard Weinshilboum**
Institution: **Mayo Clinic, Rochester, MN**
Grant No.: **2U19GM061388-11**
Award: **$250,000**

Breast cancer is the most frequent cancer of women and depression is the most common major psychiatric illness. Drugs are available to treat both of these serious illnesses, but many patients fail to respond and some suffer serious adverse drug reactions. The Mayo Clinic Pharmacogenomics Research Network (PGRN) will apply modern pharmacogenomic techniques to help make it possible to "individualize" the drug therapy of breast cancer and depression. The Mayo PGRN is an integrated, interdisciplinary, pharmacogenomic research effort based on a decades-long focus at Mayo on the pharmacogenetics of phase II (conjugating) drug metabolizing enzymes. The Mayo PGRN began by applying a "genotype-to-phenotype" research strategy that included, sequentially, gene resequencing, functional genomic, mechanistic and translational studies. During the present funding cycle, the Mayo PGRN has also incorporated the use of genomewide techniques and pharmacogenomic model systems, with a special emphasis on functional mechanisms responsible for genetic effects on drug response. They have used that approach to study the pharmacogenomics of the endocrine therapy of breast cancer and selective serotonin reuptake inhibitor (SSRI) therapy of depression—research that grew out of the contribution of phase II enzymes to the biotransformation of the estrogens that play such an important role in breast cancer and biotransformation of the neurotransmitters that are central to the pathophysiology and treatment of depression. Recently, they have performed pharmacogenomic genomewide association (GWA) studies of breast cancer, and they will soon perform similar studies of the SSRI therapy of depression. They propose to continue this genomewide focus during the next funding cycle, with both clinical and model system GWA studies of the drug therapy of breast cancer and depression, always including replication as well as functional and mechanistic studies. They also propose two "Network Resources", one designed to provide access to "next generation" DNA sequencing for all PGRN Centers and the other focused on pharmacogenomic ontology. In summary, the studies in this application build on Mayo PGRN strengths in DNA sequencing and functional genomics—while incorporating genomewide techniques—to provide insight into the role of inheritance in variation in the efficacy and side effects of drugs used to treat breast cancer and depression.

Title: **Mitochondria: A Novel Genetic Modifier for Breast Cancer Risk**
P.I.: **Hua Zhao**
Institution: **Roswell Park Cancer Institute, Buffalo, NY**
Grant No.: **1R21CA139201-01A2**
Award: **$180,248**

Given the fact that mitochondrial produce energy and generate reactive oxygen species (ROS), inherited variations in mitochondrial DNA (mtDNA) might represent a newly described mechanism of cancer predisposition. Inherited variations in mtDNA may be extremely relevant for breast cancer, as oxidative stress has consistently been regarded as a risk factor for breast cancer. The study will further their understanding of the genetic events leading to the development of breast cancer; explore the genetic basis linking mitochondrial, ROS, and breast cancer; find the clues for breast cancer racial disparity, and eventually provide a means of identifying a subgroup that are most likely to develop breast cancer. From a clinical perspective, the long-term application of this information to risk assessment and thus to the prevention and early detection of breast cancer in families as well as population will be significant. Somatic mutations in mtDNA have been regarded as a hallmark of cancer. However, the role of germline

variations (polymorphisms) in mtDNA in cancer development is largely unknown. The mitochondrial genome is highly polymorphic among individuals and exhibits significant geographic and racial difference. It has been suggested that some mtDNA variants could have adverse effect by increasing the generation of ROS. The accumulation of those adverse effects over time may increase an individual's cancer risk. Besides the sequence variations in mtDNA, the copy number of mitochondria might also affect cancer risk by disturbing crosstalk between mitochondrial and nucleus and consequently altering nuclear DNA stability. It has been proposed that the copy number of mitochondria per cell reflects the gene—environment interactions between unknown hereditary factors and levels of oxidative stress. However, whether the copy number of mitochondria could be a predictor of human cancer development remains to be determined. Variability in MtDNA sequence and copy number of mitochondria might be extremely relevant to breast cancer because oxidative stress has been suggested to play a significant role in breast cancer etiology. Considerable efforts have been made to discover breast cancer susceptibility genes. However, few have been identified to date. The dilemma might be due to the fact that some of the susceptibility alleles might not reside in nuclear DNA, but in mtDNA. More intriguingly, the geographic and racial difference of mtDNA polymorphisms might have implications in breast cancer racial disparity because African-American women are at disproportionately high risk for many oxidative stress-related medical conditions, including breast cancer. Therefore, the investigation of the role of mitochondrial as a predisposition factor of breast cancer could have a significant impact. In the current proposal, they plan to utilize the valuable biospecimens and data collected through an ongoing case-control study (7R01CA100598) to comprehensively investigate the associations between mtDNA polymorphisms/haplogroups and breast cancer risk in both Caucasian American (CA) and African-American (AA) women. They will also examine the associations between the copy number of mitochondria and breast cancer risk. In further analysis, they will study whether mtDNA polymorphisms/haplogroups and copy number of mitochondria are associated with aggressive clinical characteristics of breast cancer. Because the proposed research is nested within an ongoing study, the objectives can be addressed in a timely and cost-effective manner. The study will further their understanding of the genetic events leading to the development of breast cancer; explore the genetic basis linking mitochondrial, ROS, and breast cancer; find the clues for breast cancer racial disparity, and eventually provide a means of identifying a subgroup that is most likely to develop breast cancer. Such individuals may then be targeted for specific intervention programs such as chemoprevention and dietary modification.

Title: **BRCA1, Sporadic Breast Cancer, and Aging Women**
P.I.: **Hava Karsenty Avraham**
Institution: **Beth Israel Deaconess Medical Center, Boston, MA**
Grant No.: **5R21CA135226-02**
Award: **$149,600**

By defining the targets that are altered in mutated BRCA1-linked breast and ovarian cancers and providing insights into the BRCA1 pathways, this study may lead to potential new therapeutic strategies for the prevention, early diagnosis, and treatment of familial breast and ovarian cancers. In addition, results from this work will enhance their understanding of the molecular events that drive breast and ovarian cancers in aging women, and may link BRCA1 and beta-catenin to oxidative stress and breast oncogenesis. The risk of developing breast cancer increases as women get older. The maintenance of DNA represents a fundamental and continuous challenge to every cell in the body. Genomic instability is a hallmark of most cancers as well as a hallmark in aging. Recent evidence strengthened the link between the maintenance of genome integrity, cancer susceptibility, and aging. These conditions can be caused by germline mutations in BRCA1, which is an essential caretaker protein in the surveillance of DNA damage. Impaired oxidative stress response plays an important role in breast oncogenesis. Beta-

catenin was shown to be a cofactor for the FOXO family, which promotes survival by inducing cell cycle arrest and quiescence in response to oxidative stress. They observed that wild-type (WT) BRCA1, but not mutated BRCA1, interacts with beta-catenin and increases beta-catenin protein expression by promoting lysine-6-linked ubiquitination. Oxidative stress reagent H_2O_2 increased colocalization and the interaction of BRCA1 with beta-catenin in the nucleus. WT-BRCA1, but not mutated BRCA1, protected the nuclear active form of beta-catenin during oxidative stress responses. The expression of this form of beta-catenin was lower or absent in most of BRCA1 familial breast cancer tissues. Therefore, they hypothesize that: (1) BRCA1 acts as a sensor in regulating beta-catenin mediated oxidative stress and FOXO function; and (2) low expression of WT-BRCA1 or mutations in BRCA1 leads to impaired response to oxidative stress and causes genomic instability, resulting in increased risk of breast cancer in women. Therefore, they aim to examine the effects of BRCA1 on beta-catenin protein expression and stability and to analyze the role of BRCA1 in beta-catenin mediated oxidative stress response. Thus, they specifically propose the following aims: Aim 1: To investigate the role of BRCA1 in the expression and distribution of beta-catenin and its targets (cyclin D1 and c-Myc) during mammary gland development in BRCA1 mutant mice, in which BRCA1 exon 11 is specifically deleted from the mammary glands by using the Cre-loxP system. Aim 2: To characterize the role of BRCA1 as a sensor in regulating the beta-catenin and FOXO interaction during oxidative stress signaling. Results from this work will enhance their knowledge of the molecular events that drive sporadic breast and ovarian cancer development and progression in aging women.

Title: **Improving Flexible Sigmoidoscopy in Women by Optical Analysis of Microvasculature**
P.I.: **Vadim Backman**
Institution: **NorthShore University HealthSystem Research Institute, Evenston, IL**
Grant No.: **5R21CA140936-02**
Award: **$167,750**

Flexible sigmoidoscopy as a colorectal cancer (CRC) screening test is widely available but inaccurate at detecting premalignant polyps in women, largely because women's polyps tend to be located out of reach of the flexible sigmoidoscope. They believe that assessing the superficial blood supply in the visually normal rectum may be uniquely able to sense these lesions further up in the colon of women. If successful, this relatively inexpensive, easy-to-use test may be an adjunct to flexible sigmoidoscopy thereby allowing accurate and cost-effective colorectal cancer screening for women. Despite a myriad of screening tests available, CRC remains the second leading cause of cancer deaths among Americans. Approximately half the population does not undergo any CRC screening because of cost, access, and concerns about discomfort with both the procedure and colonic purge. Flexible sigmoidoscopy (endoscopic evaluation of the distal colon) is performed in the community and has many advantages over other recommended tests (e.g. colonoscopy, CT colography) such as being relatively inexpensive, more widely available (performed by primary care physicians) and proven efficacy at decreasing both CRC mortality and incidence. However, flexible sigmoidoscopy is insensitive in women given their predilection for proximal neoplasia. Indeed, while flexible sigmoidoscopy identifies two-thirds of advanced adenomas in men, it only detects one-third in women highlighting the need for adjunctive approaches. Their multi-disciplinary CRC prevention group has focused on bridging novel optical technologies to clinical practice. Using 4-dimensional elastic light scattering fingerprinting (4D-ELF), they published that in CRC models, the peri-cryptal capillary blood content was increased prior to any histological abnormalities, a phenomena they termed early increase in blood supply (EIBS). They developed an endoscopically compatible fiber-optic probe and demonstrated that EIBS was detectable at a distance from neoplastic lesions. In the rectum, EIBS was detectable in patients harboring advanced neoplasia elsewhere in their colon. Importantly, rectal EIBS was more robust in women (~60 percent increase versus neoplasia-free

controls) than men (~25 percent) for proximal advanced neoplasia (that was not visualizable by flexible sigmoidoscope). They, therefore, hypothesize that rectal EIBS measurement will detect advanced proximal neoplasia in women. They will obtain rectal EIBS analysis on women undergoing colonoscopy. They will identify diagnostic EIBS parameters and determine the impact of demographic factors (e.g., age, race, smoking, medication use) on these markers. This data will be used to formulate a prediction rule for advanced proximal adenomas. They will then prospectively validate this prediction rule on a separate cohort of women simulating real world flexible sigmoidoscopy screening conditions prior to full colonoscopy. This will provide the rationale to performing future multicenter trials of rectal EIBS as an adjunct to flexible sigmoidoscopy in women. If successful, this practical and relatively inexpensive approach may be pivotal for the resurgence of flexible sigmoidoscopy as an accurate, cost-effective, and patient-friendly CRC screening option in women.

Title: **Regulation of Breast Cancer Progression by FAK Expression in Tumor Macrophages**
P.I.: **Amy H. Bouton**
Institution: **University of Virginia, Charlottesville**
Grant No.: **5R21CA135532-02**
Award: **$164,700**

By focusing on the role of focal adhesion kinase (FAK) in both macrophages and tumor cells, this work will uncover novel features of macrophage - tumor cell synergy that contribute to breast tumor behaviors. In addition to providing critical information about how FAK inhibitors should be used to treat breast cancer patients, this work will potentially identify new strategies for targeting distinct cellular compartments within the tumor that can be exploited therapeutically to control tumor growth and progression. It is anticipated that, through the knowledge gained from these studies, there will be a significant reduction in mortality from breast cancer. The growth and metastatic spread of solid tumors is controlled by signals emanating from tumor cells as well as by immune cells and fibroblasts in the surrounding stroma, components of the extracellular matrix, and soluble growth factors and cytokines. While this complexity creates challenges for therapeutic intervention, it also provides unique opportunities by making available a number of distinct cellular and molecular targets that can be exploited to control tumor growth and progression. The focus of this proposal is on FAK, a protein tyrosine kinase whose expression is significantly increased in many late-stage cancers, including breast cancer. They hypothesize that FAK expression in two components of the tumor microenvironment, the tumor cells and tumor-associated macrophages (TAMs), plays a critical role in promoting breast tumor progression and metastasis. They will use mouse models of breast cancer to gain an understanding of how FAK expression in breast carcinoma cells and/or the ancillary tumor-associated macrophages controls primary breast tumor growth and metastatic spread. By combining genetic manipulation of these mice with FAK inhibitors currently in Phase I clinical trials, they propose to: (1) determine how the loss of FAK expression in macrophages alters or ablates macrophage functions that drive breast tumor growth/progression and metastasis (Aim 1); (2) assess how the dual modulation of FAK expression in breast tumor cells and in tumor-associated macrophages alters breast tumor growth and metastasis (Aim 2A); and (3) assess how systemic inhibition of FAK expression alters breast tumor growth and metastasis (Aim 2B). Successful completion of this study will provide new insights into features of the tumor that can predict a clinical response to the FAK-targeted drugs currently in clinical trials and the optimal timing for these treatments. More globally, they will learn about mechanisms through which tumor cells and other cells within the tumor microenvironment communicate to promote breast tumor growth and metastasis.

They anticipate that this work will help to move the paradigm for breast cancer treatment away from the tumor cells per se and toward the full complement of factors that contribute to tumor growth and metastasis.

Title: **Chemoprevention of Tamoxifen-Induced Endometrial Cancer by Black Cohosh and Red Clover**
P.I.: **Birgit Maria Dietz**
Institution: **University of Illinois at Chicago**
Grant No.: **5R21CA135237-02**
Award: **$172,698**

The selective estrogen receptor modulator, tamoxifen, is very effective in treatment and prevention of breast cancer; however, it causes menopausal symptoms and has carcinogenic effects on the endometrium. They hypothesize that red clover and black cohosh, both frequently used for the alleviation of menopausal symptoms, will reduce tamoxifen-induced endometrial cancer due to their cancer chemopreventive properties. Breast cancer is the most common cancer in women. The selective estrogen receptor modulator tamoxifen, which antagonizes estrogen in breast tissue, is efficacious in the treatment and prevention of breast cancer. In tamoxifen-treated patients, botanical dietary supplements such as red clover and black cohosh extracts are frequently used for the alleviation of tamoxifen related menopausal symptoms. Very few studies about the modifying effects of these botanicals on tamoxifen's safety and efficacy have been reported. Tamoxifen's major side effect is an enhanced endometrial cancer risk. Tamoxifen's ER1 mediated uterotrophic activity and its reactive metabolites are believed to be responsible for this effect. Black cohosh and red clover contain anti-oxidative, anti-proliferative, anti-inflammatory, and detoxification enzyme inducing compounds, which could inhibit the initiation or retard the promotion and progression of cancerous cells. The central hypothesis of this project is that black cohosh and red clover reduce the carcinogenic effects of tamoxifen on the endometrium by inhibition of cell proliferation (Aim 1) and through enhancing detoxification pathways (Aim 2). To support this hypothesis they propose two Specific Aims. (1) What is the effect of red clover or black cohosh on tamoxifen-stimulated endometrial cancer? Recent data suggest that black cohosh and red clover can attenuate tamoxifen-stimulated endometrial cancer growth by inhibiting cell proliferation. They will measure the influence of these botanicals on tamoxifen stimulated endometrial tumor growth in ovariectomized athymic nude mice, an established endometrial cancer model for studying estrogenic influences. The mechanism of interaction will be examined by analyzing the expression of pro-proliferative genes and proteins important for tamoxifen mediated tumor promotion in vivo and in vitro. To further identify active compounds, they will examine the anti-proliferative effect of isolated compounds in endometrial cancer cells and in an immature rat model. (2) What is the effect of black cohosh or red clover on detoxification pathways of reactive tamoxifen metabolites? Their data indicate that both botanicals upregulate the cellular antioxidative response machinery, thus reducing the carcinogenic effect of tamoxifen's reactive metabolites. They will study the ability of these botanicals to induce the detoxification enzymes, quinone reductase, and glutathione-S-transferase, in the uterus and liver of adult rats. They will also analyze whether black cohosh and red clover prevent tamoxifen induced oxidative stress in these animals. Additionally, they will examine the effect of the botanicals on tamoxifen's metabolism to active or reactive metabolites in the blood. To elucidate the compounds responsible for the various effects, isolated constituents will be assayed in vitro. The completion of these specific aims will provide an overall picture of the effect of these botanicals and purified compounds on the efficacy of tamoxifen and on tamoxifen-induced endometrial cancer, which is of importance considering the increasing number of breast cancer survivors and women at high risk undergoing tamoxifen treatment.

Title: **NIR Hypoxia Imaging of Breast Tumor Response to Neoadjuvant Chemotherapy In Vivo**
P.I.: **Shudong Jiang**
Institution: **Dartmouth College, Hanover, NH**
Grant No.: **5R21CA135303-02**
Award: **$173,800**

This project will develop and evaluate dynamic near-infrared (NIR) tomographic oximetry for characterizing the response of locally advanced breast cancers to neoadjuvant chemotherapy by assessing the temporal variation in tumor oxygenation during hyperoxic gas inhalation. NIR oximetry acquired longitudinally during the course of therapy will be correlated with pathological endpoints in order to determine whether early prognostic biomarkers of treatment response can be identified in the dynamic NIR oxygenation signatures that could be used to customize breast cancer treatment decisions to individual patients in the future. NIR multispectral imaging is a unique tool for characterizing tissue composition in the female breast. The major advantage of this modality is its ability to provide images of tissue oxygen saturation (StO_2) as well as total hemoglobin concentration (HbT), water fraction (H_2O percent) and elastic scattering parameters. Because microcirculation and oxygenation play such major roles in tumor progression and regression, assessing their variation in response to neoadjuvant chemotherapy may reveal early prognostic biomarkers of treatment response that could be used to alter and/or optimize the course of treatment on a more individualized patient basis. Assessing dynamic contrast enhancement in tumor oxygenation after hyperoxic gas inhalation with NIR spectral tomography appears to be feasible and may provide easily-acquired, low-cost image signatures for predicting therapeutic response to chemotherapy in the breast. The overall goal of this proposal is to develop and evaluate dynamic NIR tomographic oximetry for characterizing the response of locally advanced breast cancers to neoadjuvant chemotherapy by assessing the temporal variation in tumor oxygenation during hyperoxic gas inhalation. They hypothesize that tumors with initially larger and faster changes before and after breathing 100 percent oxygen will have better clinical responses to neoadjuvant chemotherapy. This hypothesis will be quantitatively assessed by: (1) advancing the current NIR multi-spectral tomography system to image dynamic oxygenation changes within the tumor, induced by breathing 100 percent oxygen, with a 0.1 Hz image frame rate; (2) quantifying the tumor oxygenation response with respect to hyperoxic inhalation at different times during the course of therapy; and (3) quantifying the pathological and clinical outcomes of response in order to test for correlation with oximetry changes recorded early in the treatment course. Dartmouth College, through the Norris Cotton Cancer Center at the Dartmouth-Hitchcock Medical Center, has significant resources to leverage in order to conduct the proposed study. A group of investigators which includes clinical specialists in diagnostic radiology, surgical oncology, medical oncology, surgical pathology, and medical engineering has been configured to develop and evaluate technology for breast imaging for cancer detection, diagnosis and therapy monitoring since 1999. The proposed project is an important component of the research of this group. In addition to the principal investigators, Professor Shudong Jiang and Dr. Peter A. Kaufman, M.D., (medical oncology), Professors Keith D. Paulsen, Brian W. Pogue, and Dr. Wendy A. Wells, M.D., (Department of Pathology) will be significant collaborators engaged to accomplish the proposed specific aims, as an adjunct to currently funded grants involving breast imaging research.

Title: **Targeting the Phosphoinositide Kinase Chain to Prevent Breast Cancer Metastasis**
P.I.: **Jeannette Kunz**
Institution: **Baylor College Of Medicine, Houston, TX**
Grant No.: **5R03CA139545-02**
Award: **$76,750**

This research project employs cancer cell lines and mouse models of cancer metastasis to uncover the signaling mechanisms that control a cell's ability to move. The migration of cells is important for proper tissue formation, immune function and wound repair, but when aberrantly regulated can also form the basis of devastating human diseases including cancer, atherosclerosis, and allergies. Their long-term goal is to better understand the signaling mechanisms that control cell migration and to use this information to develop new therapeutic approaches for the prevention of human disease. Breast cancer is the most commonly diagnosed form of cancer in women 40-55 years of age and it is the second major cause of cancer deaths behind lung cancer for all women. Metastatic breast cancer, where cancer cells spread by motile mechanisms and establish tumors at distant vital sites, is much harder to eradicate and is the primary cause of patient death from breast cancer. Understanding the molecular principles that determine the efficiency of tumor metastasis is therefore critical to the prevention and treatment of breast tumors. Traditional cancer therapeutics are aimed at preventing tumorigenesis of normal breast tissue and inhibiting growth of established cancers. However, few therapeutic strategies target cell migration and invasion, although the pathological deregulation of these processes is a major cause of morbidity associated with the disease. Cell migration and invasion are coordinately regulated by the small GTPase Rac1 and the localized production of the lipid phosphatidylinositol-4,5-bisphosphate (PI4,5P2). The hyperactivation of Rac1 signaling has been observed in many cancers, particularly in cancers of the breast, and this is directly linked to increased metastatic potential and poor patient survival. A role for PI4,5P2 signaling in cancer progression has so far not been reported. However, recent evidence described in the preliminary studies section of this proposal has established that PIPK1a, a member of the Type I phosphatidylinositol-4-phosphate kinase family, which generates PI4,5P2, is a critical regulator of cell migration and cell-matrix adhesion. They have defined a biochemical pathway in which PIPK1a mediates Rac1 activation in response to integrin and growth factor signals. Rac1, in turn, controls signaling to downstream effectors, including a second member of the PIPKI family, PIPK1b, to promote the assembly of F-actin and of focal adhesion sites necessary for migration and invasion. These results therefore establish a pathway in which PIPK1a is the pinnacle of a signaling cascade that links transmembrane receptors to the regulation of actin and focal adhesion assembly during cell motility. Because cell migration and adhesion are critical for cancer metastasis, PIPK1a may be a target for the prevention of cancer progression. The long-term goal of these studies is to validate PIPK1a as a target for therapeutic intervention in metastatic disease using tissue culture cell models and the athymic nude mouse model of breast cancer. The proposed research also involves pilot studies designed to assess the efficacy of a newly identified natural small-molecule inhibitor of PIPK1a in the control of breast cancer progression. They will use a combination of basic research, chemical genetic and in vivo approaches to systematically address the role of the PIPK1a pathway in cell migration and invasion in a 3-dimensional matrix, in anchorage-independent growth, and in cancer progression in vivo using the athymic nude mouse. The proposed research not only has the potential to impact therapeutic design to prevent breast cancer metastasis, but will also advance their understanding of signaling mechanisms that may be critical for breast cancer metastasis.

Title: Mitochondrial Catalase as a Treatment for Metastatic Breast Cancer
P.I.: Warren C. Ladiges
Institution: University Of Washington, Seattle
Grant No.: 5R21CA140916-02
Award: $205,823

The project is designed to determine the ability of mitochondrially targeted catalase to suppress metastatic breast cancer in mice. The chance of developing invasive breast cancer during a woman's lifetime is approximately one in eight and more than 40,000 women die of metastatic disease each year. Inherent or acquired tumor drug resistance and dose-limiting toxicity limit many agents used in the treatment of invasive breast cancer. Therefore, an important goal is the development of novel nontoxic therapeutic agents that are active against this deadly disease. They have preliminary data showing that mitochondrial catalase (mCAT) reduces metastatic progression of primary breast cancer in mice, suggesting that targeting mitochondria with catalase could be a potential strategy to treat or prevent metastatic breast cancer in women. The aims of this proposal are to: (1) further characterize the ability of mCAT to suppress breast cancer metastasis in mice; and (2) develop an inducible system in mice for controlling the expression of mCAT in a time- and cell-dependent manner. The data generated in this proposal would confirm their preliminary observations and provide the rationale for developing and/or testing clinically relevant mitochondrial-specific drug delivery systems for treating metastatic breast cancer.

Title: Gender Selectivity to Colon Cancer Chemoprevention by NSAIDs
P.I.: Hemant K. Roy
Institution: NorthShore University HealthSystem Research Institute, Evanston, IL
Grant No.: 5R21CA141112-02
Award: $167,750

Colorectal cancer (CRC) is one of the major public health issues in the United States. The lifetime risk of being diagnosed with this cancer is about six percent. This cancer usually develops slowly (10–15 years) through multiple genetic and phenotypic transitions from normal colonic mucosa to adenoma and then to carcinoma. This protracted progression provides ample time for interventions such as endoscopic screening and removing adenomatous polyps. This has been promising but only about half of the at-risk population (age >50) receive any sort of effective screening. This underscores the need for developing alternate cancer prevention strategies such as chemoprevention. A number of studies show that nonsteroidal anti-inflammatory drugs (NSAIDs) exert chemopreventive benefits against CRC. However, the overall efficacy is relatively modest (30–50 percent risk reduction) and requires more than a decade to show significant benefits. In addition, the use of NSAIDs has been shown to be linked to severe side-effects including ulcers, gastrointestinal bleeding, hemorrhagic strokes, etc., thereby causing some uncertainty in its use for preventing CRC for average risk. To improve the risk-benefit analysis, it is therefore critical to selectively target subjects that can efficiently respond to chemopreventive efficacy of NSAIDs. It has recently been shown that women with CRC may respond to dietary nutrients or pharmacological agents differently than men as they may have differing pathologies, risk factors, and hormone status. The epidemiological studies suggest an improved chemopreventive response in women to NSAIDs although there are discordant reports in the literature. Thus, the issue of whether women are more sensitive to NSAID chemoprevention is unresolved with the possibility that NSAIDs type, dose, etc., may play a role. The proposed studies will address the role of estrogen in gender selective chemopreventive efficacy of NSAIDs. These findings will have an important bearing on the healthcare recommendations for colon cancer chemoprevention which have to be cognizant of this gender selective efficacy for maximum cost–benefit potential of NSAIDs.

Title: **Antagonism of the Ah Receptor in Controlling Breast Cancer Growth and Invasion**
P.I.: **Jennifer J. Schlezinger**
Institution: **Boston University Medical Campus**
Grant No.: **5R21CA134882-02**
Award: **$178,823**

They hypothesize that the hyperexpression of a protein, called the aryl hydrocarbon receptor, and its binding to DNA contributes to the growth and progression of breast tumors. Here they propose that chemicals that impede the function of this receptor (i.e. antagonists) will be effective at downregulating this protein's activity and therefore will suppress breast tumor growth and metastasis. Screening of plant and marine natural product libraries will provide a source of novel antagonists that can be tested for their interaction with this receptor and their mechanism of interference with tumor growth, ultimately resulting in the development of therapeutic agents for the treatment of breast cancer. Historically, the aryl hydrocarbon receptor (AhR) has been studied for its transcriptional regulation of genes encoding cytochrome P450 enzymes, which metabolize environmental and endogenous substrates into toxic and mutagenic intermediates. Accumulating studies support the hypothesis that the AhR also plays an important role in malignant epithelial cell growth and invasion apart from its role in formation of mutagens and in the absence of environmental chemicals. This new paradigm is based on several key observations: (1) AhR expression is increased dramatically in carcinogen-induced rat and mouse mammary tumors and in 'spontaneous' human mammary tumor lines; (2) constitutive AhR activation is indicated by nuclear AhR localization in rat, mouse, and human mammary tumors and by AhR binding to gene promoters in the absence of environmental chemicals; (3) constitutively active AhR regulates the expression of multiple genes, including CYP1B1, CK21, and Slug, a master regulator of tumor invasion; (4) recent studies suggest that increased AhR activity in mammary tumors also contributes to cell migration and invasiveness; and (5) molecular downregulation of the AhR suppresses breast cancer cell proliferation and reverts cells to a non-aggressive phenotype. Molecular and biologic strategies have provided significant evidence that the AhR participates, beyond mutagenesis, in multiple mechanisms that contribute to tumor formation, growth, and invasion. Therefore, they can exploit their ability to examine effects of constitutively active AhR to determine how chemical antagonism of the AhR may translate into breast cancer prevention or a therapeutic approach to suppress tumor progression. Thus, they propose a new hypothesis: Targeting the constitutively active AhR with naturally occurring, nontoxic antagonists represents a feasible therapeutic approach to inhibit breast tumor growth and invasion. Three Specific Aims are proposed: (1) investigate strategies to maximize antagonism of the AhR by examining the potential for synergistic interaction in mixtures of antagonists, performing a high-throughput screen for novel, potent antagonists from natural product extract libraries (National Cancer Institute Natural Products Repository) and examining the 'chemical knockout' approach for improving AhR inactivation; (2) define the molecular mechanisms of chemical antagonism of the constitutively active AhR in a breast cancer model by establishing antagonist effects on AhR transactivation of endogenous gene expression and examining antagonist-mediated changes in AhR-DNA interactions; and (3) establish the functional consequences of chemically antagonizing the constitutively active AhR using optimal AhR antagonists. The translational impact of these studies lies in the ability of known and newly identified antagonists to suppress tumor growth and invasion. Here, potentially therapeutic AhR antagonists will be evaluated for their ability to block the biological outcomes of constitutive AhR activity in human mammary tumor cell lines. Collectively, these studies will provide the foundation for preclinical studies on the potential for potent AhR antagonists to prevent and/or treat breast cancer in vivo.

Title: **Role of MicroRNAs in Initiation and Progression of Breast Cancer**
P.I.: **Lorenzo Sempere**
Institution: **Dartmouth College, Hanover, NH**
Grant No.: **5R03CA141564-02**
Award: **$79,000**

MicroRNAs (miRNAs) are a recently-discovered class of short noncoding RNA genes, which act as post-transcriptional negative regulators of gene expression. MicroRNA-mediated regulation of tumorigenesis is emerging as a new paradigm in the field of cancer biology. Their implemented in situ hybridization technology offers spatial resolution of miRNA expression unsurpassed by other techniques, which could be readily adapted to routine clinical practice to benefit patients and assist physicians in making crucial decisions. Breast carcinoma (BrCa), which is the second most prevalent cancer in women, is a complex, inadequately understood, and often fatal disease when not detected at early stages. A more detailed understanding of the molecular mechanisms and regulatory pathways at work will enormously assist in improving the design and target selection of therapeutic strategies. MicroRNAs are evolutionarily conserved, short noncoding regulatory RNAs that post-transcriptionally modulate gene expression by binding to their cognate target mRNAs via pervasive and versatile mechanisms. Altered expression of specific subsets of miRNAs has been linked to different types of hematologic and solid tumors. Independent studies using BrCa clinical specimens have identified a small subset of miRNAs, which are differentially detected between normal and tumor tissue specimens. Thus, the clinical value of these miRNAs as novel biomarkers for different aspect of BrCa management is being actively investigated. Importantly, functional analyses in cell line systems and xenograft transplantation in mouse models have revealed tumor suppressive and oncogenic functions of some of these miRNAs. This proposal focuses on miRNAs as potential tumor suppressive mechanisms to prevent breast carcinogenesis. They will utilize a genetic approach in mouse models of BrCa to test the hypothesis that global impairment of miRNA functions enhances tumor growth and aggressiveness. Of note, their experimental strategy will be similar to the one successfully used by Tyler Jacks and colleagues to uncover tumor suppressive roles of miRNAs in a K-Ras-driven mouse model of lung cancer. They will target chromosomal deletion of miRNA-processing enzyme Dicer in mammary gland epithelia using the Cre/LoxP system. The effects of global loss of miRNA functions will be studied in well-established mouse models of BrCa. Mammary gland restricted expression of Polyoma virus middle T antigen (PyMT), Neu/HER-2 or Wnt-1 causes BrCa with different latencies and histological features reminiscent of specific human BrCa subtypes. They expect that results of this proposal will uncover an etiological contribution of miRNAs and validate the use of these mouse models for future studies concentrating on the role of individual miRNA in BrCa and development of miRNA-based therapeutic strategies.

Title: **Reactivation of Breast Cancer Micrometastases by Senescent Bone Marrow Stroma**
P.I.: **Robert Wieder**
Institution: **University of Medicine/Dentistry of New Jersey, NJ Medical School**
Grant No.: **5R21CA142537-02**
Award: **$171,600**

The proposed study will investigate the induction of senescence in mouse bone marrow stroma by estrogen deprivation in vitro and in vivo as manifested by the secretion of inflammatory cytokines and loss of the capacity to support dormancy of breast cancer cells in an in vitro model and the loss of the capacity to support the dormancy of xenografted human breast cancer cells in the bone marrow microenvironment. Experiments will determine if treatment with estrogen or anti-inflammatory agents can restore the capacity of senescent stroma to

support dormancy. More than a third of stage I–III breast cancer patients have bone marrow micrometastases at the time of diagnosis providing a source of recurrence. Most recurrences occur in postmenopausal women. Mechanisms of dormancy and recurrence are not well understood, but data suggest a dependence on a close association with bone marrow stroma. They hypothesize that stromal cells undergo senescence due to aging and/or postmenopausal estrogen deprivation and begin to secrete inflammatory cytokines that can stimulate dormant cancer cells to re-awaken. The broad, long-term goals of their investigations are to define mechanisms that govern the establishment of the dormant state in breast cancer cells in the bone marrow and to determine factors and mechanisms responsible for their reawakening and recurrence of disease. They propose to determine if bone marrow stroma can undergo senescence when deprived of estrogen or treated with cytotoxins in vitro and in vivo in a murine model. Their Specific Aims are: (1) to determine if in vitro estrogen deprivation can induce a senescent phenotype in bone marrow stromal cultures incapable of supporting breast cancer dormancy in an in vitro model; (2) to determine if in vivo estrogen deprivation induces a senescent phenotype in bone marrow stroma rendering it incapable of supporting breast cancer dormancy in vitro and in vivo. They will establish and characterize the phenotype of secretory senescence by subjecting stromal monolayers to oxidative and hypoxic stress and estrogen deprivation and measure the expression and activation of TGF-β, Cox-2, IL-6, IL-8 and SA-β-Gal, known markers associated with senescence. They will determine if estrogen deprivation in vitro and in vivo and cytotoxicity in vitro can induce senescence measured by these molecular markers and by the loss of support of breast cancer dormancy in an in vitro clonogenic co-culture model and in a left ventricle injection bone marrow metastasis model. Experiments will also determine whether estrogen deprivation renders stroma more susceptible to chemical injury and whether administration of Cox-2 inhibitors or estrogen can reverse these effects. These studies will establish a way of thinking about dormancy as a function of the senescent microenvironment and seek to reverse estrogen-deprivation-induced inflammation to maintain it.

Title:	**Human Papillomavirus Epidemiology and Response to Screening (HEARTS)**
P.I.:	**Elise D. Riley**
Institution:	**University Of California, San Francisco**
Grant No.:	**5R21AI079439-02**
Award:	**$156,969**

To the best of their knowledge, this is the first study regarding human papillomavirus (HPV) and HPV disease among homeless and marginally housed women. Ascertaining prevalence and risk factors specific to this population will facilitate a better understanding of HPV among indigent U.S. women, which could have implications for improvement in healthcare delivery, particularly regarding HPV vaccine uptake and effectiveness. Given that poor and marginally housed women use health services infrequently, the potential benefits of a prophylactic vaccine are of the utmost importance. HPV vaccine development and clinical research have focused on women from the general population and little is known about HPV among indigent women, many of whom experience repeated risk for sexually transmitted infections that continues through the span of their lives. The impact of repeated exposure to HPV, as well as the impact of co-infections like HIV, HCV, gonorrhea, and Chlamydia on the natural history of HPV infection and HPV-associated disease, is unclear in this population. Moreover, the prevalence of HPV subtypes in this population is unknown, which precludes estimates of potential vaccine effectiveness. A better understanding of HPV among indigent US women could have implications for improvement in healthcare delivery, particularly regarding HPV vaccine uptake and effectiveness. They propose an exploratory study to assess the prevalence and variability of cervical HPV and cervical HPV disease (cervical intraepithelial neoplasia); associations with

co-infections (i.e., HIV, HCV, gonorrhea and Chlamydia) and drug use (e.g., tobacco and crack cocaine); and the feasibility of a larger randomized study among homeless and marginally housed women. Individuals will be recruited from homeless shelters, free-food programs and low-income single room occupancy hotels. In this way, study participants will not be limited to individuals who visit specific institutions, thus facilitating reliable estimates from a community-based sample.

Cardiovascular Disease

Title: **Compromised Microcirculation in Women with Polycystic Ovary Syndrome**
P.I.: **Nina Stachenfeld**
Institution: **John B. Pierce Laboratory, Inc., New Haven, CT**
Grant No.: **5R21HL093450-02**
Award: **$223,143**

Women with Polycystic Ovary Syndrome (PCOS) have greater risk for cardiovascular disease, in particular dysfunction of the peripheral circulation that can lead to hypertension and comprised glucose disposal. This research will determine the role of hyperandrogenism in microvascular responsiveness in women with PCOS, and the mechanisms by which testosterone may impact endothelial function. These studies also have broad public health implications because their findings on the effect of hyperandrogenism on endothelial function may provide insights that can improve cardiovascular health of all obese women and men. PCOS is the most common reproductive endocrinopathy in young women, affecting 6–10 percent of women of reproductive age. Obesity, insulin resistance, hyperandrogenism, and hyperestrogenism are core functional disorders of PCOS and place women at increased risk for microvascular dysfunction. Women with PCOS have greater circulating concentrations of endothelin-1 (ET-1), a potent vasoconstrictor in the microcirculation (including that of the skin), which can increase blood pressure and lead to endothelial damage. The central hypothesis of this proposal is that testosterone effects on ET-1 mediate the peripheral microvascular dysfunction associated with PCOS. This hypothesis will be tested using a prolonged skin heating model to study peripheral microvascular responsiveness. Local skin heating has been used extensively to study mechanisms controlling peripheral microcirculation under a number of physiological conditions, including obesity, insulin resistance, and hypertension. The impact of testosterone or ET-1 on microvascular responsiveness to local heating has not been studied in women with or without PCOS. This proposal seeks to provide this missing information via pursuit of two specific aims. Specific Aim 1 will apply dose-response curves to examine the mechanism by which ET-1 influences peripheral vasodilation. Specific Aim 2 will determine the mechanism by which testosterone affects peripheral microcirculatory responsiveness in women with and without PCOS. These studies will have broad public health implications because their findings on the effect of hyperandrogenism on endothelial function may provide insights applicable to cardiovascular health in women and men.

Title: **Sex Differences in Myocardial Ischemia Triggered by Emotional Factors after MI**
P.I.: **Viola Vaccarino**
Institution: **Emory University, Atlanta, GA**
Grant No.: **5R21HL093665-02**
Award: **$193,750**

Coronary heart disease (CHD) is the major cause of death in American women, and every year a similar number of women and men die due to CHD. Growing evidence supports important differences in the pathophysiology, clinical presentation, and prognosis of CHD

between women and men; yet much remains to be learned about the unique characteristics of CHD in women. Young and middle-aged women have higher mortality and complication rates after an acute myocardial infarction (MI) compared with men of similar age. Reasons for these differences are unknown; they are not explained by traditional CHD risk factors, other comorbidity or treatments, and occur despite the fact that women have less coronary atherosclerosis and more preserved ventricular function than men. One-third to two-thirds of patients with CHD have myocardial ischemia that is induced by psychological stressors. Such ischemia is often painless and unrelated to severity of coronary artery disease; nonetheless it is associated with adverse outcomes. Emotional factors such as depression and psychological trauma are more common in women with CHD than in men and may predispose women to stress-induced ischemia. Depression, for example, is present in up to 40 percent of women with MI younger than 60 years. However, emotionally-triggered ischemia has hardly been studied in women before. The overall objective of this proposal is to evaluate differences in stress-induced ischemia between 50 women and 50 men younger than 60 years who were hospitalized for acute MI in the previous 6 months in Emory-affiliated hospitals. They hypothesize that myocardial ischemia due to emotional factors is more common in women than in men, while exercise-induced ischemia is as common, or even less common, in women. The aims of this study are: (1) to compare myocardial perfusion during rest, during exercise, and during an emotionally stressful challenge in women and men using single photon emission tomography (SPECT) [Tc-99m] sestamibi myocardial perfusion imaging; (2) to investigate biological mechanisms for the sex differences in ischemia induced by emotional stress, including differences in hemodynamic (blood pressure, heart rate), neurobiological (cortisol and autonomic nervous system), and inflammatory responses to the stressful challenge; and (3) to investigate behavioral/psychosocial explanatory factors for the sex differences in ischemia induced by emotional stress (depression, history of trauma, and socioeconomic environment). Younger women with MI represent an understudied patient group despite their higher rate of adverse events compared with men. Investigation of this group will provide critical information for the prevention of CHD in women. Their study may uncover a unique pathway which may explain sex differences in the outcome of MI.

Title: **Weight, Diet, Genes and CVD Risk Factors (Hypertension and Diabetes)**
P.I.: **Nanette Requintina Lee**
Institution: **University of San Carlos, Cebu City, Philippines**
Grant No.: **5R01TW008288-02**
Award: **$50,000**

This study will examine the independent and combined effects of genetic predisposition and modifiable factors such as weight and dietary patterns on the risks of having hypertension and diabetes, two major cardiovascular disease (CVD) risk factors. The demographic and health trends in the Philippines exemplify those of other developing Asian countries where CVD-related morbidities and deaths are prevalent and increasing. Thus, studying the mechanisms that can lead to the development of hypertension and diabetes among Filipinos can provide critical information that may guide more tailored prevention efforts for these populations, potentially narrowing global health disparities. CVDs are the leading causes of morbidity and mortality in the world (1–3). Hypertension and diabetes, two of the major CVD risk factors, are complex diseases caused by the combined actions of genetic and environmental factors (4–8). Few studies have examined the interaction of these factors and fewer, if any, have looked at their effects in populations of developing Asian countries that are plagued with increasing levels of obesity and rapidly changing food environments (9, 10). The information gap may be due to the lack of population-based studies with adequate depth and detail. There is a paucity of information on dietary and adiposity trends derived from longitudinal studies and there are inadequate genetic data, especially among Asians who tend to develop CVD risk factors

at lower body mass index thresholds (11, 12). Aims and methods: The proposed study aims to understand how weight history, dietary patterns, and genetic variants independently and jointly affect blood pressure and fasting glucose among adult Filipino women (ages 38–71 in 2007) using the Cebu Longitudinal Health and Nutrition Survey (CLHNS), an ongoing community-based study of more than 2,000 women (and their infants) which began in 1983. This is a unique dataset that contains not only rich genetic information on these women but also dietary and anthropometric measurements obtained since baseline, recent blood pressure (1998–2007), and fasting glucose (2005), measurements, and other individual-, household-, and community-level data collected over a span of 24 years of rapid countrywide socioeconomic changes. Specifically, using multivariate regression methods they will determine the: (a) effect of weight history (i.e. duration of overweight) on the risk of having hypertension and/or diabetes; (b) association between dietary patterns (identified through cluster analysis) and hypertension and/or diabetes; (c) independence and co-occurrence of hypertension and diabetes and how these relate to weight and dietary patterns; and (d) effects of genetic variants on hypertension and diabetes, focusing on gene variants that have been associated with hypertension or diabetes by previous association studies. Further, the study will explore significant interaction of effects among genetic variants, overweight history, and dietary patterns in affecting hypertension or diabetes.

Title: **Mechanisms Underlie Inverse Gender Discrepancy in Ischemic Protection**
P.I.: **Nian-Qing Shi**
Institution: **University of Wisconsin-Madison**
Grant No.: **5R21HL093626-02**
Award: **$185,625**

The proposed research will employ KATP channel mutant mice that are defective in the sulfonylurea receptor 2 (SUR2) to evaluate gender difference in ischemic protection, regulation of estrogen in sarcolemmal and mitochondrial SUR2 forms and obtain new insights in ion channel regulation in cardiovascular diseases. Myocardial infarction (MI) is a major health problem worldwide due to its acute nature and lack of effective prevention schemes. Gender difference in ischemic protection exists, with relatively lower MI incidences in premenopausal females than age-matched males. Emerging evidence indicates that the female-specific advantage in ischemic protection is mediated by estrogen. In the ischemic protection network, KATP channels (KATP) are postulated to play protective roles, but their relative importance remains controversial. Composed by a Kir6.2 pore and an SUR2 regulatory subunit, KATP activity is recorded in cardiac sarcolemmal or mitochondrial inner membrane. their recent data show that disrupting the SUR2 gene at an earlier exon 3 causes an early lethality and the mutants only lived 8 days. However, disrupting SUR2 at middle exons 12–16 interrupts the SUR2 long forms, but the novel SUR2 short forms remain expressed. They have identified two splice variants that are generated by a rare intra-exonic splicing (IES) event in SUR2 mRNA to produce transcripts encoding the 55-kDa SUR2 short forms in heart mitochondria. Characterization of SUR2 KO has revealed an inverse pattern of gender difference in cardioprotection. Completed tests in KO males show that they are constitutively protected, with reduced infarcts after ischemia, while KO females have larger infarcts and cannot be preconditioned. mRNA levels of both IES variants markedly increase in the preconditioned KO males but they reduce dramatically in the preconditioned KO females. This interesting discrepancy offers a new platform of using SUR2 mutant mice to investigate gender difference in ischemic protection. The proposed research intends to explore the molecular mechanisms underlying gender difference in cardioprotection in relation to KATP channels, especially mitochondrial KATP. They hypothesized that estrogen modulates expression of sarcolemmal and mitochondrial SUR2 forms in mice. They further hypothesized that levels of the IES

variants encoding the mitochondrial SUR2 short forms are critical to protection. In Aim 1, they will characterize ischemic protection in both genders of WT and KO mice, and study whether estrogen modulates expression of the SUR2 forms. In Aim 2, estrogen regulation in mitochondrial SUR2 will be investigated, and a 55A "rescued" female mouse model will be tested whether they can improve protection. Interactions of estrogen receptor 2 and the IES variants will be explored. Results from this research not only provide new insights in gender-specific response to cardioprotection but also identify new drug targets for future clinical treatments against MI.

Title: **Role of 15-Lipoxygenase in Enhanced Pulmonary Vasoconstriction in Females**
P.I.: **Sandra L. Pfister**
Institution: **Medical College of Wisconsin, Milwaukee**
Grant No.: **5R21HL093181-02**
Award: **$190,000**

While relatively rare, idiopathic pulmonary arterial hypertension is a medically significant disease that occurs more frequently in young women. The disease is usually catastrophic for those afflicted. Identifying endogenous pulmonary factors that may predispose females to the development of pulmonary hypertension is timely and important considering the abundance of clinical data indicating sex differences in vascular disease. Furthermore, this work is intended to advance new concepts in women's health research and the study of sex/gender differences. Pulmonary arterial hypertension encompasses a group of diseases characterized by high pulmonary artery pressure and pulmonary vascular resistance. Vasoconstriction, vascular remodeling and thrombosis all contribute to the increased vascular resistance. Central to the proposed studies is that while relatively rare, idiopathic pulmonary arterial hypertension is a medically significant disease that occurs more frequently in young women. The disease is usually catastrophic for those afflicted. Mechanisms to explain the sex difference in pulmonary arterial hypertension have not been well studied. The main focus of the current proposal is to use a rabbit model to explore the role of sex in a novel signaling pathway that regulates pulmonary vascular tone. Results will lay the fundamental conceptual groundwork for future studies to understand more completely the pathogenesis of pulmonary hypertension in women. Furthermore, this work is intended to advance new concepts in women's health research and the study of sex and gender differences. Specifically, their research provided the first evidence that in pulmonary arteries obtained from female rabbits, endothelium-dependent contractions to both arachidonic acid and methacholine were enhanced when compared to responses in males. Pharmacological studies with inhibitors of arachidonic acid metabolism indicated that the factor was a lipoxygenase metabolite. They also present the first data that lipoxygenase metabolites are increased in females compared to males and the protein expression of 15-lipoxygenase is greater in female pulmonary arteries. While sex differences in vascular responses to various vasoactive agents have been documented, no studies have investigated the role of sex differences on lipoxygenase metabolism of AA in pulmonary arteries. This proposal is designed to explore the specific hypothesis that differences in AA metabolism by 15-LO contribute to the increased endothelium-dependent pulmonary vasoconstriction in females compared to males. To further develop this novel hypothesis, studies will be performed in pulmonary artery vascular preparations using chemical, biochemical, physiological and pharmacological approaches. Two Specific Aims will be explored: (1) to chemically identify and biologically characterize the vasoconstrictor 15- lipoxygenase metabolite(s) produced by the rabbit pulmonary artery endothelium and (2) to examine the cellular mechanisms contributing to enhanced 15-lipoxygenase expression in females compared to males. These proposed studies will not only provide new insights into the role of endogenous arachidonic acid-derived factors in the pathogenesis of pulmonary arterial

hypertension but will also advance their knowledge in women's health research by identifying possible mechanisms that contribute to sex-related differences in the incidence of pulmonary arterial hypertension.

Chronic Fatigue Syndrome

Title: **HERV-K18 as a Risk Factor for CFIDS**
P.I.: **Brigitte T. Huber**
Institution: **Tufts University, Boston, MA**
Grant No.: **5R01AR053821-04**
Award: **$164,058**

The etiology of Chronic Fatigue Syndrome (CFS) is far from understood and is likely due to multiple genetic components. Infection with Epstein-Barr Virus (EBV) and treatment with IFN-a have been implicated in the pathogenesis. Their laboratory has shown that EBV-infection, and exogenous IFN-α, activate transcription of the env gene of a human endogenous retrovirus, HERV-K18. This provirus is normally silent, but when induced it encodes a superantigen (SAg), which is a class of proteins that is capable of deregulating the immune system. Three alleles of HERV-K18 env have been documented, K18.1, K18.2, K18.3, whose gene products have SAg activity, but are predicted to differ biochemically and functionally. Their working hypothesis is that HERV-K18 is a risk factor for CFS. In a pilot study, the allele and genotype distributions of the HERV-K18 env gene were compared between various groups of CFS patients and healthy controls. Although only a limited number of samples were available in the various cohorts, the odds ratios that were obtained were statistically significant. The most intriguing interpretation of these data are that they provide genetic evidence for the unique etiology of at least one group of CFS patients. Thus, it may be possible to delineate different subtypes of CFS, depending on the clinical history of the patients. It is now proposed to substantiate these pilot results, using a much larger cohort of 400 CFS patients associated with EBV that has been assembled by the co-investigator, Dr. Renee Taylor. Dr. Ben Katz, board certified in both pediatrics and pediatric infectious diseases, will clinically evaluate the patient cohort, and Dr. Inga Peter, a genetic epidemiologist and biostatistician, will oversee the statistical analyses. In addition, the expression pattern of the HERV-K18 SAg during active disease versus intermission will be measured. Furthermore, T cell stimulatory activity of this SAg, expressed on peripheral blood lymphocytes of patients during the course of the disease, will be tested ex vivo, using a T cell hybridoma reporter assay that has been developed in their lab. Since SAg-activated T cells produce massive quantities of chemokines, lymphokines and neurokines, the expression of the HERV-K18 SAg could influence not only the immune system, but other organs as well. A positive association between CFS and either HERV-K18 alleles or expression patterns would open new avenues for the development of clinical treatments of this chronic disease. CFS is a disease that affects a significant number of people worldwide, yet the underlying mechanism(s) of pathogenesis remains unclear. The herpes virus EBV and IFN-a have been suggested to be associated with CFS, although these concepts are far from accepted. They propose a novel genetic aspect in the EBV/CFS association, namely the presence of certain HERV-K18 alleles that differ in their superantigen activity.

Craniofacial

Title: **Risk Factors for Onset and Persistence of Temporomandibular Disorder**
P.I.: **William Maxiner**
Institution: **University of North Carolina, Chapel Hill**
Grant No.: **3-U01-DE-017018-06S2**
Award: **$150,000**

Risk factors for onset and persistence of myogenous temporomandibular disorder (TMD), with or without arthralgia, ranks second only to headache as the clinical condition most likely to cause craniofacial pain and dysfunction in the U.S. population. During the last decade, a small number of epidemiological studies have attempted to quantify the incidence of TMD in populations of European heritage; however, no investigative team to date has undertaken a large-scale, hypothesis-driven, prospective study designed to identify biopsychosocial and genetic risk factors for the onset and persistence of this vexing pain disorder. They propose to conduct a comprehensive, prospective cohort study of the incidence of TMD in collaboration with an internationally recognized group of epidemiologists, pain researchers, and geneticists. Participants will be enrolled and followed prospectively at four research institutions and by their data coordinating center (Battelle Memorial Institute). Their three goals are to: a) undertake a five-year, prospective cohort study of 3,200 initially TMD-free individuals recruited from major ethnic and racial strata at four study sites, quantifying incidence rates of first-onset-TMD; b) undertake a case-control study by recruiting 200 people with chronically symptomatic TMD identified during cohort recruitment whose history of TMD precludes them from the prospective study; c) to identify in both groups the individual and joint effects of predictors of TMD risk using a conceptual, causal model for TMD that they have developed based on their own studies and other published research. Their preliminary epidemiological findings have led to the central hypothesis that pain amplification and psychological factors, both of which are influenced by genetic variants, represent causal risk factors that influence TMD onset and persistence. The outcomes of their proposed study will identify the primary socio-demographic, clinical, biological, psychological, and genetic risk factors for TMD onset and persistence. In so doing, they will obtain important and novel information regarding the etiopathogenesis of TMD, which will assist with the development of evidenced based pharmacological and behavioral interventions for TMD.

Diabetes

Title: **Gender-Specific Complications of Diabetic Autonomic Neuropathy: A New Mouse Model**
P.I.: **Jonas Bernard Galper**
Institution: **Tufts Medical Center, Boston, MA**
Grant No.: **5R21HL093699-02**
Award: **$198,750**

Diabetic Autonomic Neuropathy (DAN) is characterized by impairment of autonomic responsiveness of the heart. DAN has been associated with an increased incidence of arrhythmia and sudden death in diabetics. Although the overall incidence of sudden death is lower in women than in men, the risk of sudden death associated with diabetes in women is greater than in men. Studies in postmenopausal women demonstrated that combined estrogen/progestin therapy reduced the incidence of diabetes. Comparison of heart rate variability showed that the parasympathetic response of the heart was increased in young women compared with men; this difference was attenuated after menopause, but maintained in women on hormone replacement therapy (HRT). These data suggested the hypothesis

that menopausal women might be more likely to develop DAN and that HRT might protect the heart from development of DAN and decrease the incidence of arrhythmia and sudden death. The Akita mouse manifests a gender difference in the development of diabetes: males develop severe hyperglycemia and secondary effects of diabetes, while females exhibit only a mild hyperglycemia. Using male Akita mice, they have previously developed an animal model for DAN that is characterized by the appearance of spontaneous ventricular arrhythmias following myocardial infarction (MI). Here they propose to test the hypothesis that the female Akita mouse might serve as an animal model for the study of gender specific complications of DAN. Specifically, they will test the following hypotheses: (1) that ovariectomy of female Akita mice results in the development of the diabetic phenotype and secondary effects of diabetes as demonstrated by the development of hyperglycemia, proteinuria and a decreased parasympathetic inhibition of Isoproterenol-stimulated L-type Ca2+ currents, and that estrogen reverses this effect; (2) that estrogen replacement protects ovariectomized female Akita mice against the development of spontaneous ventricular arrhythmias following MI; and (3) that gene array studies will establish a subset of genes that are differentially expressed in ovariectomized mice who develop arrhythmias following MI, which might serve as candidate genes for the treatment and prevention of this effect of diabetes in women. Studies in this application propose to establish a unique animal model, which might offer a new gender specific therapeutic approach to diabetes and the complications of DAN.

Title: **Look AHEAD: Action for Health in Diabetes**
P.I.: **Mark Espeland**
Institution: **Wake Forest University Health Sciences, Winston-Salem, NC**
Grant No.: **5-U01-DK-057136-12**
Award: **$100,000**

Look AHEAD is a randomized clinical trial examining the long-term health effects of an intensive weight loss intervention in approximately 5,145 overweight volunteers with type 2 diabetes. Participants are randomized to an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity, or to a control program of diabetes support and education. The primary outcome of Look AHEAD is the aggregate occurrence of severe cardiovascular events (fatal and non-fatal MI and stroke and cardiovascular deaths) over a planned followup of 11.5 years. The original grant application provided funding for the first 7 years of the study (1 year for study design and 6 for execution of the trial). The present grant application is for an additional 7 years of funding to complete the Look AHEAD trial. All aspects of the study have proceeded extremely well—the sample of 5,145 was recruited on time; retention has been excellent and the intervention has been effective in producing initial weight loss and maintaining it over time. All 16 clinical sites have been successful in recruitment, retention, and delivery of the intervention and the DSMB has been very positive about the execution of the trial. The present application reviews the overall design of Look AHEAD, progress to date, and plans for the future. Specific aims are to retain the cohort over time, continue to complete annual in-person visits and semi-annual telephone interviews for outcome assessments, and continue to administer the lifestyle intervention. These procedures will enable us to analyze the effects of the intervention on serious cardiovascular-related factors and complications, and cost-effectiveness of the intervention.

Title: **Post-Diabetes Prevention Program Followup Study**
P.I.: **Sarah E. Fowler**
Institution: **The George Washington University, Washington, DC**
Grant No.: **5U01DK048489-17**
Award: **$650,000**

The Diabetes Prevention Program (DPP) is a multicenter controlled clinical trial examining the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2–5 years) with a total of approximately 10,000 patient years in the 3,234 volunteers in the three-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the lifestyle intervention and metformin-treated groups (58 percent and 31 percent reductions, respectively) compared with the placebo treated group, the DPP data monitoring board and NIDDK ended the masked treatment phase of the study in May 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45 percent minorities, is the largest IGT population ever studied. Moreover, the sub-cohort that has developed diabetes (approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured, and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific Aims are to: (1) examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; (2) determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; (3) determine the incidence of cardiovascular disease (CVD), CVD risk factors, and atherosclerosis in new onset type 2 diabetes and IGT; and (4) examine topics 1–3 in minority populations, men versus women, and in older subjects in the DPP.

Title: **Sex Hormones and Sex Hormone-Binding Globulin Effects on Diabetes Risk in Women in the Diabetes Prevention Program**
P.I.: **Sarah E. Fowler**
Institution: **The George Washington University, Washington, DC**
Grant No.: **5U01-DK048489-17**
Award: **$350,000**

To date neither phenotypic factors nor genetic factors that may contribute specifically to diabetes risk among women have been explored in the Diabetes Prevention Program (DPP). Associations of low estrogen status with increased diabetes risk, and associations of low concentrations of sex hormone binding globulin (SHBG) with increased diabetes risk, have been observed separately in other studies. However, little published data connects these factors with formally ascertained conversions to diabetes mellitus, and prior studies have not specifically identified women at such high a priori risk as were selected for the DPP. Sex hormone binding globulin is a protein produced by the liver that binds to hormones with a steroid nucleus, with greatest affinity for sex steroids. This protein carries the majority of the circulating sex steroid mass in both men and women. The circulating concentration of SHBG is determined by a number of physiologic factors, in particular by the concentrations

of sex hormones. In these relationships estrogen and testosterone act in opposite directions on SHBG concentration, with higher levels of estrogen resulting in reduced SHBG and higher levels of testosterone resulting in increased SHBG. Genetic effects on SHBG concentration are also recognized, and single nucleotide polymorphisms (SNPs) in the SHBG gene have recently been identified that produce changes in SHBG concentrations or function. The inter-relationships of menopausal status and/or sex hormone concentrations with diabetes risk among women at high baseline risk for diabetes are not well understood. Furthermore, the contributions of genetic effects on SHBG and its relationship with diabetes risk have not been well explored. Here they propose to evaluate associations of sex hormones and SHBG, plus genetic variants that affect SHBG, on diabetes risk in women in the DPP. They will evaluate four main hypotheses: (1) the relationship between baseline SHBG concentrations and risk of progression to prospectively ascertained diabetes differs between premenopausal and postmenopausal women; (2) sex hormone levels will influence diabetes risk through effects on SHBG concentrations, and explain in part the effects of SHBG on diabetes risk in premenopausal and postmenopausal women; (3) race/ethnicity or direct genetic variation in the SHBG gene will alter diabetes risk through effects on SHBG concentrations, independent of effects of sex hormones on SHBG; and (4) the beneficial effects of treatment interventions in DPP are proportional to baseline SHBG and sex hormone concentrations, without differences in this effect across treatment groups.

Dietary Supplements/Complementary and Alternative Medicine

Title: **Identification of Novel Phytoprogestins from Hops and Red Clover**
P.I.: **Joanna E. Burdette**
Institution: **University of Illinois at Chicago**
Grant No.: **1R21AT005377-01A1**
Award: **$235,500**

Women are already taking phytoestrogens in botanical extracts for menopausal symptoms, and the incorporation of progestins may prevent hyperplasia and cancer of the uterus. As women search for more potent alternative estrogens to satisfy the need for menopausal symptom alleviation, the chance for hyperplasia in the uterus increases and makes the characterization of novel phytoprogestins crucial. Hormone replacement therapy (HRT) is the most commonly prescribed medication for the alleviation of menopausal symptoms. Unopposed estrogen replacement therapy increases the risk of developing endometrial cancer by 120 percent for every 5 years of use. To eliminate this risk in women with a uterus, the addition of progesterone to HRT in the form of combined estrogen/progesterone replacement has been implemented. Considerable evidence now indicates that the addition of synthetic progestins to HRT increases the risk of breast cancer as well as many other deleterious side effects. In response to the problems associated with HRT, millions of women are exploring the use of botanicals and dietary supplements for the alleviation of climacteric symptoms. However, the use of botanicals with only plant-derived estrogens in the absence of progestins might increase the risk for developing endometrial cancer similar to estrogen alone. Two common supplements, hops and red clover, contain phytoestrogens that bind and activate estrogen receptors. Interestingly, when hops and red clover are given orally to ovariectomized rats, uterine weights are not significantly increased in animals treated with a crude extract but are significantly increased in animals given an equivalent dose of the pure phytoestrogen. The hypothesis of this grant proposal is that selective natural progesterone compounds can be identified from botanical extracts to generate a combined phytoestrogen-phytoprogestin alternative to traditional hormone replacement therapy. The presence of both estrogen and progesterone receptor agonists in one botanical extract may provide both the benefits of estrogens for alleviation of menopausal symptoms and the progesterone necessary to combat formation of uterine cancers. Selective and safer progestins might also be identified from botanical sources

improving the overall behavior of the progestin used in HRT. In order to provide support for this hypothesis the following Specific Aims are proposed: (1) to determine whether botanical extracts contain phytoprogestins and to identify the pure compounds responsible for the progesterone-like activity; (2) to determine whether phytoprogestins are specific and selective for uterine progesterone receptors; and (3) to determine whether phytoprogestins are protective against uterine hyperplasia in an ovariectomized rat model. These studies will provide a clear justification for the use of botanicals that have the possibility of providing both estrogen and progestin-like activity but with more selective and safer profiles for the treatment of menopausal symptoms. Women are already taking phytoestrogens for menopausal symptoms, and incorporation of progestins may prevent hyperplasia and cancer of the uterus.

Genetics

Title: **Genetics 2010: Model Organisms to Human Biology**
P.I.: **Fred M. Winston**
Institution: **Harvard University Medical School, Boston, MA**
Grant No.: **1R13HG005791-01**
Award: **$5,000**

The Genetics Society of America meeting, "Genetics 2010: Model Organisms to Human Biology," held in June 2010, addressed the value of model organisms for understanding diverse aspects of human biology. This was the third biennial meeting in this area that brought together investigators who study model organisms with investigators who study human biology and disease. The goal of the meeting was to provide a dynamic forum for the exchange of results and ideas between scientists who do not normally interact. Attendees were able to participate in broad subject area sessions to stimulate new ideas that could be brought back to their labs and applied to their organism research and network with potential collaborators. Plenary sessions at the meeting included topics such as sex and gene expression, personal genomics, cancer as a genetic disease, and models of disease, among others. The keynote address was delivered by Nobel Laureate Carol Greider, Ph.D., of The Johns Hopkins University.

Genitourinary

Title: **Translating Unique Learning for Incontinence Prevention: The TULIP Project**
P.I.: **Carolyn M. Sampselle**
Institution: **University of Michigan, Ann Arbor**
Grant No.: **1R01NR012011-01**
Award: **$300,000**

More than one in three US women suffer from the distressing, embarrassing, and often unreported problem of urinary incontinence (UI). A key committee of the 2008 International Consultation on Incontinence concluded that pelvic floor muscle training (PFMT) should be offered as first line therapy to all women with stress, urge, or mixed UI and that bladder training (BT) may be preferred to drug therapy. Conservative strategies are low risk and do not prejudice future treatments. They reasoned that such self-management practices should also prevent UI and conducted a RCT to test a prevention behavioral program. A group session presented an array of conservative self-management practices, PFMT, BT, and the Knack Maneuver, which is a preemptive contraction to decrease stress UI and/or suppress urge UI. At 12-months post-intervention they found a two-fold UI prevention effect. Moreover, they found high and sustained adherence: 82 percent at 3 months post intervention and 68 percent at 12 months. At 4 years followup, sustained adherence of 70 percent was predicted by early self-efficacy. This intervention is novel because it enables women to adopt and sustain efficacious

bladder health practices for incontinence prevention, whereas to date conservative management approaches have focused on treatment. Based on what they now know, these practices should be part of standard well-woman care, but it is not realistic to expect busy clinicians to provide this information within the confines of a brief encounter. They have developed a 15-minute DVD that is a condensed version of the prevention behavioral session; it is culturally sensitive and has yielded comparable levels of knowledge and self-efficacy. Using two sites (Michigan and Pennsylvania), they aim to compare the outcomes of the group behavioral program to the DVD version by randomizing 600 women aged 55 years and older to two arms of a comparative effectiveness trial. Followup will be at 3 months, 12 months, and 24 months post-intervention. (Aim 1). Controlling for age and BMI, they will test the hypotheses HO1: There will be no difference in UI incidence demonstrated between groups (HO). HO2: There will be no difference in post-intervention self-management adherence between groups. HO3: There will be no difference in post-intervention self-efficacy to adopt strategies between groups. They will conduct an economic analysis comparing the two-hour session with the DVD version. (Aim 2). Describing the costs and analyzing the willingness to pay and employment data will be the primary focus of this study in order to create the foundation for a future cost-effectiveness analysis, should trial hypotheses be confirmed. At 36 months post-intervention, they will conduct interviews to learn which intervention elements contributed to sustainability of adherence. (Aim 3). Their long-range objective is to provide a UI prevention intervention suitable for wide-spread translation at the point of well-woman care (annual visit).

Title: **Urinary Incontinence Treatment Network: Data Coordinating Center**
P.I.: **Sharon L. Tennstedt**
Institution: **New England Research Institutes, Inc., Watertown, MA**
Grant No.: **5 U01DK058229-10**
Award: **$100,000**

This proposal is submitted in response to RFA-DK-06-501 for continuation of the Urinary Incontinence Treatment Network (UITN) Data Coordinating Center (DCC) at New England Research Institutes, Inc. (NERI) The DCC is responsible for the scientific management of the studies, including directing, training, and monitoring the performance of clinical centers in enrollment, data collection, and data management as well as for all data analysis, and reports to the DSMB. In Phase I and continuing to Phase II, NERI has provided several unique and innovative tools and capabilities, including a proprietary Web-based data management system, an automated patient randomization system, and an electronic repository for UDS tracings. The DCC is also responsible for network communications and meeting support and provides a secure study Web site and a public Web site. DCC scientists play a leadership role in all network activities, including protocol development, standing committees and work groups, manuscript development, and presentations. Phase II will focus on conduct of the transobturator midurethral sling procedures (TOMUS) trial as well as continuation of the observational followup studies for the SISTEr and BE-DRI studies (i.e., E-SISTEr and E-BE-DRI) of phase I. The Primary Aims of TOMUS are to compare objective and subjective cure rates for stress incontinence at 12 and 24 months between the retropubic and transobturator midurethral sling procedures. Performance of these procedures is increasing rapidly with limited data available on safety and efficacy. Therefore, this study will compare the efficacy and safety of the retropubic and transobturator (inside-out and outside-in) procedures in a two-arm RCT; 588 women with stress UI will be enrolled. The Primary Aim of E-SISTEr is to compare long-term (60 months) effectiveness and durability of the Burch colposuspension and autologous fascial sling for treatment of stress UI in a randomized cohort of 655 women. Primary Aim of E-BE-DRI is to examine long-term (26 months) durability of the addition of behavioral treatment to drug therapy for treatment of urge UI in a randomized cohort of 307 women. The UITN is a multidisciplinary, multicenter group of investigators

dedicated to high-impact clinical research regarding the prevention, evaluation, and management of UI to improve the quality of life for adults. The UITN is conducting three studies of treatments for both stress and urge urinary incontinence.

HIV/AIDS

AIDS International Training and Research Program

Title: **AIDS International Training and Research Program**
P.I.: **Adaora A. Adimora**
Institution: **University of North Carolina, Chapel Hill**
Grant No.: **5-D43-TW-001039-12**
Award: **$20,000**

Fogarty International Center trainees are serving in key leadership positions and are in the center of exciting and critical research activities. Working with their collaborating institutions they have assessed the priority health needs of their partner countries and propose a research training program that addresses the countries' research needs as well as the developmental plans of their collaborating institutions. This is the second competitive renewal application for the University of North Carolina (UNC) AIDS International Training and Research Program (AITRP). They propose to continue to provide training in three countries: The Peoples Republic of China, Malawi, and Cameroon. Investigators at UNC have worked in China since 1979, Malawi since 1989, and Cameroon since 1998. The UNC AITRP has embraced several guiding principles. First, they use training to build strong ties to key in-country organizations. Trainees with guaranteed return jobs in these organizations are preferentially selected. Second, their training opportunities build on funded research projects and bridge many of the strengths of UNC. Wherever possible they combine basic, clinical, and epidemiological training and research in order to build critical mass. Third, they have used the Fogarty training to promote international research, working with many collaborators and funding agencies. Fourth, they have developed south-to-south and international collaborations to facilitate training and ongoing research opportunities. For example, University of the Witwatersrand is a training site for Malawi personnel, and they have developed a strong collaboration with the London School of Hygiene and Tropical Medicine for training of physicians from Malawi (a former British protectorate). Fifth, they have looked for opportunities for evolution and innovation. Such efforts have been particularly important in the development of a new Department of Public Health at the Malawi College of Medicine (which has received dedicated Fogarty support), extensive research ethics and Institutional Review Board training in China, and rapid technology transfer in all three UNC AITRP countries. Sixth, they are committed to in- country leadership and ongoing mentorship after the trainee has completed their program.

Title: **Emory AIDS International Training and Research Program**
P.I.: **Carlos Del Rio**
Institution: **Emory University, Atlanta, GA**
Grant No.: **5-D43-TW-001042-12**
Award: **$20,000**

Located in Atlanta, the Emory AIDS International Training and Research Program (AITRP) has established itself as an interdisciplinary training environment, that is producing highly qualified HIV/AIDS researchers. The collaborating countries of the Emory AITRP proposed for this application are Mexico, Georgia, Vietnam, Rwanda, and Zambia. The Specific Aims of the research training program include: (1) to build academic capacity in partner countries through the support of in-country education and training; (2) to build HIV/AIDS research

human resource capacity through the support of degree-seeking, long-term training; (3) to fill identified gaps in partner country research training capacity through the provision of specialized medium and short-term training; and (4) to build in-country capacity to conduct implementation science research that will allow their trainees to become involved in the evaluation of the impact of a variety of interventions that are currently occurring in their collaborating countries such as PEPFAR.

Title: **AIDS international Training and Research Program**
P.I.: **Lee H. Harrison**
Institution: **University of Pittsburgh**
Grant No.: **5-D43-TW001038-12**
Award: **$20,000**

The proposed Pitt AITRP training will substantially enhance the ability of Brazil, Mozambique, and India to conduct crucial HIV prevention research. They propose to continue the AIDS International Training and Research Program (AITRP) at the University of Pittsburgh. Their mission is to provide Brazilian, Indian, and Mozambican health professionals with the interdisciplinary tools needed to conduct cutting-edge HIV prevention research in their countries. The Director and Co-Director are, respectively, Dr. Lee Harrison, Professor of Epidemiology and Medicine, and Dr. Phalguni Gupta, Professor of Infectious Diseases and Microbiology. An exciting change in their program is the addition of a site in Beira, Mozambique, which has striking training needs and where the University of Pittsburgh has established close collaborations with the Universidade Catolica de Mozambique. The addition of Mozambique and the training of a large cadre of well-trained Brazilian investigators over the past 10 years allows them to dramatically reduce their training efforts in Brazil and shift resources to Mozambique. As a component of their training program, they will leverage the extensive training already provided to Brazil by conducting south-to-south training between these two Portuguese-speaking countries. Ongoing research in Brazil includes HIV vaccine trials, studies of effectiveness of antiretroviral therapy in public clinics, and changes in causes of death among HIV-infected patients. In India, ongoing projects include studies of genetic heterogeneity of Indian HIV strains, CDS suppression of HIV, HIV incidence studies to identify high-risk populations, and development of a novel Clostridium perfringens-based oral HIV vaccine. Research at their new site in Mozambique is currently limited and they will use the training provided by the University of Pittsburgh AITRP to jumpstart a much-needed research agenda there. Trainees from all three countries will have access to the substantial HIV research activities at University of Pittsburgh, including research in epidemiology, behavioral sciences, and laboratory sciences. During the next five years, they propose to establish an extensive training program in Mozambique; provide limited, selected training for Brazil; and provide laboratory and behavioral sciences training for India. Their successful track record during the first 10 years, the excellent training opportunities they propose, and collaboration with key institutions in their three countries assure that their program will continue to be highly productive.

Title: **Vanderbilt University-CIDRZ AIDS International Training and Research Program**
P.I.: **Sten H. Vermund**
Institution: **Vanderbilt University, Nashville, TN**
Grant No.: **5D43TW001035-12**
Award: **$20,000**

The Vanderbilt University Center for Infectious Disease Research in Zambia (VU-CIDRZ) training partnership with their international collaborators is designed to strengthen both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care in developing countries. The VU-CIDRZ AIDS

International Training and Research Program (AITRP), formerly the VU-University of Alabama at Birmingham AITRP, seeks renewal of its grant, now in its 10th year due to an NIH-initiated one-year extension. They contribute research training to both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care. The VU-CIDRZ training partnership with their international collaborators is designed to train foreign scientists and key research support staff to conduct independent research and training in their home countries, as well as perform at an internationally credible level in collaborations with local and foreign scientists. They now seek to renew their AITRP with a continued focus on Zambia (since 1998), Pakistan (since 1994), India (since 2000), China (since 2000), and their newest partnership in Mozambique (VU training partnership since 2006 and developmental AITRP engagement since 2007). They have completed their older training commitments in Mongolia, Jamaica, and Russia and will complete their training commitments for Bangladesh upon the graduation of a current doctoral training (anticipated in 2011). They have restricted their AITRP training partnerships to five focus cities in order not to dilute their impact to where they have funded overseas research and strong research training partners. At the same time, they have leveraged support in each of the five venues such that their AITRP resources will go much further than permitted by the grant's funding alone. They will continue to provide a diverse portfolio of long, medium, and short-term training options. To date 58 trainees have received graduate degrees, 97 percent of whom have returned to work in their home countries, eight are currently in degree programs, and more than 2,000 have been trained through their in-country advanced short courses. They believe VU remains an ideal university partner for this initiative for several significant reasons. The migration of the training program to VU offers the opportunity for trainees to receive the absolute highest quality of graduate training and exposure to innovative HIV/AIDS/STD/TB related research, resources, and faculty mentors. The program is uniquely positioned within the infrastructure of the VU Institute for Global Health (VU IGH), directed by Dr. Vermund with its "center-without-walls" philosophy that nurtures noncompetitive partnerships among and within VU and with partner institutions around the globe. They feel that the innovative features of their renewal and their proven track record address the unmet needs in international AIDS training.

Title: **Women's Interagency HIV Study**
P.I.: **Kathryn Anastos**
Institution: **Montefiore Medical Center, New York, NY**
Grant No.: **5U01AI035004-17**
Award: **$220,869**

Early in the Women's Interagency HIV Study (WIHS), the lower limit of detection for HIV-1 quantification was 4,000 copies/ml. Some of these early timeponts have been requantified with LLD of <80 cps/ml, specifically women who initiated HAART during visits 1–7. However, the high LLD of 4,000 cps/ml (and those few with LLD of 400 cps/ml) for many samples continues to be problematic as WIHS has initiated investigations into new areas. This has been particularly true for studies of elite suppressors and long-term non-progressors (LTNP) and for cardiovascular studies in which quantitative total exposure to virus cannot be calculated. Further, it has been difficult to find controls for the elite suppressors and LTNPs as their true viral load is not known, nor is the viral load of the potential controls. Therefore, they propose here to measure quantitative HIV-1 RNA for all women visits at which the viral load is undetectable at 4,000 or 400 copies/ml. They propose to do this with Taqman, the current platform for viral load measurements in WIHS. This will allow more precise definition of many categories of participants, necessary in several WIHS investigations, now and in the future.

Microbicides Innovation Program (MIP)

In collaboration with the NIH Office of AIDS Research (OAR), National Institute of Allergy and Infectious Diseases (NIAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH), ORWH has funded a number of R21/R33 innovation projects to support exploratory and developmental research on new microbicides and microbicides strategies and technologies in the goal of advancing promising strategies and technologies into the preclinical and clinical development of new agents. RFAs, all using the title Microbicides Innovation Program (MIP), have been issued in recent years to expand the research base in this area. The development of safe, effective, acceptable topical microbicides to prevent the sexual transmission of HIV could play a major role in worldwide reduction of new HIV infections. An effective and acceptable microbicide potentially could save millions of lives. Topical microbicides are agents that can result in inhibition of the transmission of HIV and/or other sexually transmitted infections (STIs), which may be cofactors in HIV transmission. The purpose of the MIP is to support novel and underexplored strategies in the field of topical microbicides.

Title: **Development of Antimicrobial Peptides as Topical Microbicides**
P.I.: **Robert Walter Buckheit**
Institution: **ImQuest BioSciences, Frederick, MD**
Grant No.: **1R21AI082689-01A1**
Award: **$21,428**

They hypothesize that novel anti-HIV and anti-STI topical microbicides based on natural antimicrobial peptides collected in the Antimicrobial Peptide Database developed by the co-principal investigator's laboratory (http://aps.unmc.edu/AP/main.php) can be discovered and improved through peptide engineering technology. During the R21 phase, they will methodically screen peptides from the database and define specific inhibitors of HIV and HSV-2 as well as broad based inhibitory peptides. These active agents will be further developed in order to understand their range and mechanism of anti-HIV action. Superior peptides identified in SA1 will be characterized in SA2 to provide a rationale for continued development in SA3 using various molecular strategies which will result in the improvement of the therapeutic index of the peptide agents, with and without other small molecule microbicides, in order to begin development of an effective microbicide product. This product will be formulated and evaluated in animal models and safety assessment studies in the R33 portion of the project. Their goal is to produce a female controlled preventative agent which can be utilized to prevent the sexual transmission of viral, bacterial and fungal organisms with a focus on inhibiting the transmission of HIV. The research data will be entered into the existing antimicrobial peptide database to facilitate the use by funding agencies, other researchers, students, and the public. Project Narrative: More than 25 million people have died since the first case of AIDS was identified in 1981, and the number of people living with HIV worldwide continues to expand from 35 million in 2001 to an estimated 40 million in 2007. Almost 5 million people worldwide became newly infected with HIV and an estimated 3.8 million human deaths were attributed to AIDS in 2007. They propose to identify HIV-1 and HSV-2 inhibitory antimicrobial peptides which are naturally produced by mammals through evaluation of peptides which are identified in the Antimicrobial Peptide Database developed at The University of Nebraska Medical Center. They intend to discover and develop inhibitors of HIV and other sexually transmitted infectious organisms for use as an effective topical microbicide product.

Title: **Development of a Novel Semen-Activated Prodrug as an Anti-HIV Microbicide**
P.I.: **Robert Walter Buckheit**
Institution: **ImQuest BioSciences, Frederick, MD**
Grant No.: **5R21AI079772-02**
Award: **$37,500**

The S-acyl-2-mercaptobenzamide thioester (SAMT) inhibitors are low molecular weight compounds which target multiple steps in the HIV replication pathway, but primarily function to specifically inactivate cell-free HIV immediately upon exposure to the reactive compounds and to suppress the production of infectious HIV from virus-infected cells. These NCp7-targeted, virus-inactivating compounds act by stripping coordinated zinc ions from the nucleocapsid (NC) protein in the infectious virion or maturing virus particle. In the process, the compounds irreversibly cross-link the nucleocapsid proteins rendering the virion noninfectious and defective. Thus, the NCp7 inhibitors interfere with two potential virus transmission mechanisms required for the infection of target cells in the vaginal environment. In the R21 phase of this proposal they propose to develop new microbicides composed of polymeric pro-drugs for delivery of the SAMTs. This delivery mechanism limits the tissue absorption of the SAMT until it comes in contact with the viral inoculum in semen by attaching it to a high molecular weight biocompatible polymer. They will conjugate the SAMT inhibitors to the polymer carrier through enzyme-cleavable linkages that will release the active drug product in the presence of specific enzymes in semen. This delivery approach offers several advantages in the context of microbicide action since: (1) the NCp7 inhibitors can inactivate cell-free and cell-associated virus in semen, they will target the virus before it can diffuse in an infectious form to or into tissue; (2) they will add moieties to the polymer backbone that will increase the stability of the SAMT inhibitors by decreasing the pH local to the conjugated drug by the Donnan effect; and (3) microbicides will be used by women repeatedly over many years, a polymeric pro-drug approach will allow precise control over the tissue concentrations and exposure to anti-HIV compounds, limiting the chance to develop viral resistance and limiting toxicity. Critical to the development of this pro-drug approach, biological evaluations will be performed to confirm the efficacy of the SAMTs in the presence of seminal plasma and vaginal fluids. Additionally, the enzymatic activation of the compound from its pro-drug form will be evaluated in specially designed in vitro assays to mimic the events which must occur in the vagina and to quantify the kinetics of drug activation and virus inactivation in the presence of semen and other appropriate biological matrices. Finally, the biological properties of both semen and vaginal fluids on the efficiency of transmission of HIV to target cells will be evaluated to define the potential synergies between the antiviral activity of constituents of semen and the biological activity of the thioester inhibitors.

Title: **Targeted siRNA Delivery as an Anti-HIV Microbicide**
P.I.: **Derek Michael Dykxhoorn**
Institution: **University of Miami School of Medicine, FL**
Grant No.: **1-R21-AI-088601-01**
Award: **$21,428**

Human immunodeficiency virus (HIV) is a highly lethal lentivirus which over a protracted course destroys the host's adaptive immune system leaving the host vulnerable to numerous opportunistic infections. Unlike most viruses whose genome replicates independently of the host cell's genome, the HIV-1 genome integrates into and is replicated with the host genetic material. Therefore, even if therapeutic approaches can inhibit new virus production, the viral genome remains intact and competent. Therefore, strategies that can prevent the uptake and integration of the virus would be of tremendous clinical value. The vast majority of HIV

infections occur as a consequence of viral transmission through mucosal surfaces, such as the vaginal mucosa. The delivery of siRNAs that specifically silence host factors required for early events in the HIV lifecycle to lymphocytes in the vaginal mucosa could prove to be an effective means of protecting individuals from HIV infection and serve as a potential microbicide. One of the main challenges facing the clinical application of siRNAs as a genetic therapy is the ability to delivery siRNAs to the cytoplasm of the appropriate target cell types. They have recently developed a novel lipid nanoparticle that is coated with an antibody recognizing the integrin molecule LFA-1 which is broadly expressed on lymphocytes. These immuno-nanoparticles will be used to deliver siRNAs to lymphocytes present in the vaginal mucosa of humanized mouse models of HIV. Given the high level of sequence heterogeneity, the propensity of HIV-1 to mutate and the inability of anti-HIV siRNAs to target the incoming viral RNA genome and prevent integration, alternative therapeutic targets are required to prevent the transmission of HIV. Host factors that are necessary for early events in the HIV lifecycle but are dispensable for cellular functioning could prove to be an effective therapeutic alternative. Using a high-throughput RNA interference-based screening platform, they have identified a large number of potential therapeutic targets that could serve to inhibit HIV integration when silenced. However, these factors require extensive analysis and characterization to ensure their safety and efficacy. They will be combining the LFA-1-mediated cell-type specific vehicle to introduce siRNAs targeting therapeutically relevant host factors as a potential means to inhibit viral infection in humanized mouse models of HIV. These experiments will provide the preclinical groundwork necessary for the development of an effective RNAi-based anti-HIV microbicide. Heterosexual transmission is the leading cause of new HIV infections in the world. A microbicide providing true intracellular immunity would make a significant contribution to controlling the spread of this deadly virus.

Title: **Development of a Novel Nanoparticle Pyrimidinedione Vaginal Polymeric Film as an Anti-HIV Microbicide**
P.I.: **Anthony Sang Won Ham**
Institution: **ImQuest BioSciences, Frederick, MD**
Grant No.: **1R21AI088586-01**
Award: **$21,428**

Pyrimidinediones (PYD) are highly potent small molecule inhibitors that have a dual anti-HIV mechanism of action: viral entry inhibition and non-nucleoside reverse transcriptase inhibition (NNRTI). The PYD compounds have shown in vitro subnanomolar levels of activity as an NNRTI and nanomolar levels of activity as inhibitors of entry occurring prior to chemokine receptor binding and fusion. However, as microbicide compounds are being developed, delivery issues that are part of the formulation of the compound have lagged behind causing a critical delay in product development. Due to low solubility and poor penetration through the mucosa to the target site of action, Pyrimidinediones face significant obstacles as microbicides. Strategic drug delivery design is essential for Pyrimidinediones to advance as viable microbicide products. They propose a combination of innovative drug delivery strategies to enhance PYD anti-HIV efficacy through polymer biochemistry formulations. Specifically, nanoparticle encapsulation has been used to overcome many of the challenges presented when using hydrophobic drug molecules; however, its use as a vaginal drug delivery system has not been investigated. In the R21 phase of this project, they propose to develop nanoparticle encapsulation of PYD as a novel drug delivery method to improve the potency of HIV inhibition activity by increasing long term drug release, protecting against enzymatic degradation, enhancing submucosal tissue penetration and cell localization. Additionally, they propose to further formulate the nanoparticle PYD formulation into a vaginal delivery polymer film dosage form. Such quick-dissolving solid-dosage forms have recently been proposed as a innovative alternative to address several acceptability and compliance issues

observed in more traditional vaginal delivery systems (gels, creams, intra-vaginal rings). Their nanoparticle PYD film delivery approach offers several innovative advantages in microbicide development by suggesting enhanced apparent activity without active pharmaceutical ingredient (API) reformulation, conferring HIV protection over long periods of time through controlled drug release, making such a microbicide coitally-independent, and introducing a novel drug delivery method through vaginal films that addresses many of the acceptability issues with gels and other semi-solid dosage forms. Biological characterization and evaluation will be preformed to confirm the efficacy of PYD nanoparticles in biologically relevant conditions. The encapsulation of PYD into biodegradable nanoparticles will be characterized and evaluated in specifically designed in vitro assays to determine drug targeting and release. Additionally, the anti-HIV efficacy of the nanoparticle PYD will be compared to unformulated PYD in biologically relevant in vitro assays to determine the optimal formulation. Finally, the formulation will be introduced into a solid vaginal film dosage form to evaluate its biological properties in HIV prevention.

Title: **Phosphorothioate Oligonucleotides as Microbicides against HIV Transmission**
P.I.: **Peter D. Katsikis**
Institution: **Drexel University, Philadelphia, PA**
Grant No.: **1-R21-AI-082680-01A1**
Award: **$21,428**

Developing interventions that inhibit the transmission of HIV infection are critical for halting the HIV epidemic. Topical prevention strategies usually termed microbicides have been proposed as one strategy to halt or slow down the HIV epidemic. They have identified novel lead microbicides that potently inhibit HIV and SIV infection/replication in vitro. During their previous submission they reported an oligonucleotide with a phosphorothioate backbone (OPB) that could inhibit HIVBaL or SIVmac251 infection and/or replication in human or simian PBMC, respectively. OPB also inhibited infection/replication in cell-free infections of P4-R5 MAGI cells by HIVBaL and HIVIIIB. OPB exhibited no toxicity against PBMC or P4-R5 MAGI cells after 24-hour continuous exposure. Preliminary data suggested that OPB may also inhibit other viruses as it was also effective against influenza type A virus. Thus, their first generation OPB may be a potent microbicide against HIV that prevents infection at mucosal sites when topically applied. Their preliminary studies were carried out with a 13mer Poly T or Poly A oligonucleotide of OPB and this suggested that the effect was sequence independent and may even be mediated by the phosphorothioate deoxyribose sugar backbone. Indeed in their current resubmission they present data on their next generation compound, a baseless phosphorothioate 2′ deoxyribose backbone (PDB) that has more potent HIV inhibitory activity than OPB. A 14mer PDB they show here has no toxicity, is a potent inhibitor of HIV and has the advantage of being a TLR7/9 antagonist that inhibits HIV-induced IFN-α production. This later property is important as the establishment of HIV infection may depend on HIV-induced mucosal inflammation triggered by TLR. Importantly, they show that PDB is active when formulated in hydroxyethylcellulose (HEC) gel at pH 4.4, survives pH transition to a neutral pH, and retains its activity in HEC for long periods. They hypothesize that PDB binds enveloped viruses and inhibits their infectivity by acting as a "chemical lectin". They further hypothesize that PDB can act as a microbicide against HIV and can prevent SIV vaginal infection of rhesus macaques. The studies planned in the R21 phase will further optimize and characterize the safety and effectiveness of PDB in vitro and its safety in the Swiss Webster mouse vaginal/cervical model of irritation. They will determine the optimal size and composition that remains effective against HIV and exhibits no toxicity. Finally, the mechanism of action of PDB will be investigated, the effect of inclusion into hydroxyethylcellulose gel will be tested and PDB's effect on the growth of commensal lactobacilli will be determined.

Five specific milestones have been set for the progression from the R21 Phase to the R33 Phase. The R33 phase will test the effectiveness of PDB in preventing vaginal SIV infection, investigate the effect of seminal plasma and pH transition on the efficacy of OPB, determine its safety with human genital epithelial tissue, and investigate its effectiveness against HSV-2. The current application will allow for an extensive evaluation of PDB as possible novel microbicide candidates. The studies proposed here address the important public health problem of developing treatments that inhibit the transmission of HIV infection. The current application investigates a novel chemical that may be used to inhibit infection with HIV.

Title: **Microbicide Delivery System to Target Lymphoid Organs**
P.I.: **Mohamed E. Labib**
Institution: **Advanced BioDevices, LLC, Princeton, NJ**
Grant No.: **5R21AI082738-02**
Award: **$37,500**

Sexual transmission of HIV-1 involves complex processes involving exposure of the female genital tract to virus or infected cells and their transport to other sites, including local lymph nodes, where the virus replicates and establishes infection. It has been shown that Langerhans cells (LC) and dendritic cells (DC) capture the virus either from the vaginal surface or from top epithelium layers and transport it to draining and local lymph nodes, where it infects CD4+ T cells. Intense development of topical microbicides is underway with the ultimate goal of decreasing the sexual transmission of HIV-1. Current efforts have been directed to inactivating the virus either at the surface of the vagina before entry, or in the squamous or stroma layers of the vaginal epithelium. Their physical transport modeling predicts that molecular drugs delivered as topical gels cannot reach draining or local lymph nodes. One possible way to deliver drugs to lymphoid sites surrounding the vagina is to use drug-loaded nanoparticles. Their preliminary results provide evidence indicating that nanoparticles can be delivered to local lymph nodes via vaginal application in a mouse model. To further develop this platform for use as a microbicide or prophylactic strategy, they propose the following plans for the R21/R33 application. In the R21 phase, they will study the delivery of quantum dots having different surface chemistry, including conjugation with targeting molecules, to determine the mode of their transport to different lymphoid sites. In the R33 phase, they will use drug-loaded nanoparticles and verify the applicability of this platform to target important sites in the female genital tract. Physical models will be developed to understand the transport processes and to guide the development of the nanoparticle delivery system.

Title: **Small-Molecule Inhibitors of Gp41-Mediated Fusion as HIV-1 Topical Microbicides**
P.I.: **Min Lu**
Institution: **Weill Medical College of Cornell University, New York, NY**
Grant No.: **5R21AI079771-02**
Award: **$37,500**

In the continuing absence of an effective vaccine, topical microbicides offer a credible alternative preventive strategy to reduce sexual transmission of HIV-1. Several viral fusion and entry inhibitors have been shown to prevent SHIV infection of rhesus macaques by the vaginal and/or rectal routes and are in preclinical and early clinical development as microbicide candidates. HIV-1 membrane fusion is mediated by a series of large-scale structural transitions in the gp41 envelope glycoprotein. Evidence indicates that a transient gp41 species known as the prehairpin intermediate is a potential target for drugs that inhibit HIV-1 entry. The long-term goal of this research plan is to use modern molecular and structural methods to identify and develop a novel small-molecule gp41 fusion inhibitor for inclusion in a topical HIV-1

microbicide. To achieve this, they will capitalize on specific surface features revealed by their recent structure determination of an autonomously folded, trimeric coiled-coil subdomain of gp41 that provides an atomic model for the putative prehairpin conformation, as well as small-molecule lead compounds developed by means of an innovative structure-based drug design technology. They propose the following Specific Aim for the R21 component of this project are to identify and optimize two series of novel small-molecule compounds that inhibit HIV-1 membrane fusion by targeting the gp41 prehairpin intermediate. They will design and synthesize two sets of analogs of active triazinone and biphenyl compounds, characterize the equilibrium properties of interactions with the N-trimer coiled coil, and evaluate their anti-HIV-1 activity and mechanism of action. Bound inhibitors will be visualized by x-ray crystallography in order to allow refinement of binding affinity. The Specific Aims of the R33 phase of the project are to characterize the specificity, potency, and toxicity of improved small-molecule compounds with enhanced gp41 inhibitory activity. They will conduct in vitro studies in primary cells and human cervicovaginal tissue explants to determine the virucidal activity of select small-molecule gp41 inhibitory compounds against diverse primary HIV-1 isolates, and their potentially toxic or inflammatory effects. They will also use the rabbit vaginal irritation model to evaluate the irritation potential of the fusion inhibitors, to assess the in vivo potency and breadth of activity of optimized small-molecule fusion inhibitors alone and in combination with entry inhibitors targeting HIV-1 gp120 (BMS-378806) and CCR5 (CMPD167) using the NOD/SCID-hu BLT mouse vaginal transmission model. They will evaluate the protection of humanized BLT mice from vaginal challenge with multiple HIV-1 variants by small-molecule fusion inhibitors alone and in synergistic combination with BMS-378806 and CMPD167. Their emphasis is to identify a new class of potent HIV-1 fusion inhibitors suitable for development as a component of a microbicide formulation.

Title: **Plant-Produced Actinohivin as a Candidate HIV Microbicide**
P.I.: **Nobuyuki Matoba**
Institution: **University of Louisville, Louisville, KY**
Grant No.: **1R21AI088585-01**
Award: **$21,428**

Safe, effective, and inexpensive topical microbicides are urgently needed to curb the global human immunodeficiency virus type-1 (HIV-1) epidemic. Actinohivin (AH) is an actinomycete-derived lectin. This lectin specifically binds to high-mannose clusters uniquely found on the HIV-1 envelope (Env), thereby eliciting nanomolar antiviral activity against multiple HIV strains. Preliminary analyses revealed that AH has a high safety profile in human peripheral blood mononuclear cells (PBMCs) and in the rabbit vaginal irritation assay. Meanwhile, a translational AH-AH fusion protein (recombinant dimer [rd] AH) was suggested to have stronger and broader anti-HIV-1 activity than the original monomer. Given these high potentials, they hypothesize that rAH and/or rdAH (r/rdAH) are excellent HIV-1 microbicide candidates. This project's goal is to reveal the feasibilities of r/rdAH in terms of manufacture, antiviral efficacy, and safety upon use as a vaginal microbicide. In the R21 phase, they will initially focus on developing a highly efficient, scalable production system for r/rdAH that allows for extensive efficacy and safety studies and possible global use. They will utilize recombinant plant virus-based expression systems and various molecular biological approaches for rapid and high-level expression of high-quality r/rdAH. Upon obtaining bulk r/rdAH active pharmaceutical ingredients with high purity standards, they will analyze HIV-1 neutralization effects against selected R5-type viruses in two in vitro HIV neutralization assays based on Env-pseudotyped virus-reporter gene expression and primary isolate-PBMC infection systems. Next, r/rdAH cytotoxic, mitogenic, and inflammatory potentials will be tested in PBMCs and/or human cervicovaginal (CV) epithelial cell lines to establish the minimal safety profile. Their success criteria in the R21 phase are: (1) establishing the bulk

preparation procedure; (2) demonstrating cross-clade antiviral effects to R5 viruses; and (3) demonstrating no apparent in vitro cytotoxicity, mitogenic activity, or inflammatory potential at >100 times above an average anti-HIV IC50, for plant-made r/rdAH. Upon approval of their transition to the R33 phase, they will comprehensively analyze anti-HIV-1 efficacy of r/rdAH for various modes of HIV-1 infection and transmission, using various in vitro assay systems. In addition, they will investigate potential overlap, complementation, synergy, and antagonism of anti-HIV activities between r/rdAH and other inhibitors toward potential microbicide combination strategies. Finally, they will perform extensive evaluations of r/rdAH upon vaginal application in rabbit and mouse models. They will thoroughly evaluate r/rdAH vaginal toxicity, inflammatory potential, and stability. Upon determining the maximal tolerated dose of r/rdAH, they will examine their potential immunogenicity and toxicity after a long-term exposure. Potential toxicity to the symbiotic vaginal commensal bacteria, the Lactobacillus species, will be examined. In summary, the proposed studies should answer the question of whether r/rdAH is justified for advanced next-stage preclinical studies. The proposed studies will analyze the feasibilities of the novel HIV-1-binding lectin Actinohivin and its derivative recombinant dimer, as a candidate vaginal HIV-1 microbicide. The proposed studies should generate a comprehensive data set that will reveal their large-scale producibility, anti-HIV-1 efficacy, and broad toxicity profile upon vaginal application, thereby providing criteria of whether Actinohivin and its derivative are justified for further extensive preclinical and clinical studies.

Title: **The Microbial Ecology of Bacterial Vaginosis: A Fine Scale Resolution Metagenomic (The Human Microbiome Project)**
P.I.: **Jacques Ravel**
Institution: **University of Maryland, Baltimore**
Grant No.: **1UH2AI083264-01**
Award: **$125,000**

Bacterial vaginosis (BV) is the most common vaginal disease in women, and yet its cause and effective treatment remain unknown. BV is associated with many adverse health outcomes, such as preterm delivery of low-birthweight babies and increased risk for infection by HIV. This research will contribute valuable information on the causes of BV, help develop improved methods for preventing and treating BV, and may help reduce major reproductive health problems associated with BV. The vaginal microbiota play an important protective role in maintaining the health of women. Disruption of the mutualistic relationship that exists between bacterial communities in the vagina and their hosts can lead to bacterial vaginosis (BV), a condition in which lactic acid producing bacteria are supplanted by a diverse array of strictly anaerobic bacteria. BV has been shown to be an independent risk factor for adverse outcomes including preterm delivery and low infant birth weight, acquisition of sexually transmitted infections and HIV, and development of pelvic inflammatory disease. National surveys indicate the prevalence of BV among U.S. women is 29.2 percent, and yet, despite considerable effort, the etiology of BV remains unknown. Moreover, there are no broadly effective therapies for the treatment of BV, and reoccurrence is common. In the proposed research they will test the overarching hypothesis that vaginal microbial community dynamics and activities are indicators of risk to BV. To do this, they propose to conduct a high resolution prospective study in which samples collected daily from 200 reproductive-age women over two menstrual cycles are used to capture molecular events that take place before, during, and after the spontaneous remission of BV episodes. They will use modern genomic technologies to obtain the data needed to correlate shifts in vaginal microbial community composition and function, metabolomes, and epidemiological and behavioral metadata with the occurrence of BV to better define the syndrome itself and identify patterns that are predictive of BV. The five Specific Aims of the research are: (1) evaluate the association between the dynamics of vaginal microbial communities and risk to BV by characterizing the community composition

of vaginal specimens archived from a vaginal douching cessation study in which 39 women self-collected vaginal swabs twice weekly for 16 weeks; (2) enroll 200 women in a prospective study in which self-collected vaginal swab samples and secretions are collected daily along with data on the occurrence of BV, vaginal pH, and information on time varying habits and practices; (3) determine the gene content (metagenome) of vaginal microbial communities to assess the metabolic potential of representative vaginal communities in women before, during, and after the spontaneous remission of BV; (4) characterize suites of expressed genes (metatranscriptome) in communities representative of vaginal community types in healthy women, as well as before, during, and after the spontaneous remission of BV; and (5) apply model-based statistical clustering and classification approaches to associate the microbial community composition and function with metadata and clinical diagnoses of BV. The large body of information generated will facilitate understanding of vaginal microbial community dynamics, the etiology of BV, and drive the development of better diagnostic tools for BV. Furthermore, the information will enable a more personalized and effective treatment of BV and ultimately, prevent adverse sequelae associated with this highly prevalent disruption of the vaginal microbiome.

Title: **Engineering Antiviral Innate Immunity for Safe and Effective Microbicides**
P.I.: **Hong Shen**
Institution: **University of Washington, Seattle**
Grant No.: **1R21AI088597-01**
Award: **$21,428**

HIV infections afflict millions of people and cause tremendous health and economic burdens. One of the major risk factors for HIV-1 transmission is the pre-existing infections caused by sexually transmitted agents such as herpes simplex virus type 2 (HSV-2). Therefore, a rational prevention strategy to halt HIV spread is to target HSV-2 infection and control its spread. In the absence of vaccines against HSV-2, a more practical and effective intervention for HSV-2 is the utilization of microbicides. A promising microbicidal approach is to potentiate antiviral innate immunity effective against a broad range of viruses at the site of viral encounters. The toll-like receptor (TLR)-based innate immunity have been shown to be crucial in initiating a cascade of antiviral activities mediated by type I interferons (IFNs). Both TLR3 and TLR9 agonists, polyinosinic: polycytidylic acid (poly IC) and CpG oligonucleotides (ODNs) are effective in protection against HSV-2 infections. However, undesirable inflammatory responses and autoimmunity accompanying the non-specific stimulation of TLRs are of major concern, which could severely limit the use of TLR agonists as microbicides. Thus, the key to developing TLR agonists as microbicides is to target them to relevant cell types at the potential sites of viral exposure and to elicit IFN responses in a regulated fashion. They propose to develop localized, controlled-release, and cell-targeted delivery systems to regulate the stimulation of TLR-based innate antiviral immunity. In the R21 Phase, three aims will be accomplished: Aim (1) to design and characterize cell-targeted delivery systems based on poly (lactide-co-glycolide) (PLGA) nanoparticles to specifically and locally target pDCs and epithelial cells with TLR agonists; Aim (2) to evaluate the effectiveness against genital HSV-2 infections by locally and selectively targeting CpG ODNs and/or poly ICs to pDCs and epithelial cells with cell-targeted nanoparticles; Aim (3) to evaluate toxicity by locally and selectively targeting CpG ODNs and/or poly ICs to pDCs and epithelial cells with cell-targeted nanoparticles. Built upon the results from the R21 phase, in the R33 phase, they will: Aim (4) design and characterize delivery systems for sustained release of TLR agonists; Aim (5) evaluate the effectiveness against genital HSV-2 infection and toxicity by localized, sustained-release, and cell-targeted nanoparticles loaded with CpG ODNs and/or poly IC; Aim (6) evaluate the adaptive immunity

against genital HSV-2 infection mediated by localized, sustained-release, and cell-targeted nanoparticles loaded with CpG ODNs and/or poly IC. This application will enable the translation of TLR-based antiviral innate immunity to effective and safe microbicides.

Title: **Exploring the Role of Vif Antagonists in Preventing Sexual HIV Transmission**
P.I.: **Mario Stevenson**
Institution: **University of Massachusetts Medical School, Worcester**
Grant No.: **1R21AI088595-01**
Award: **$21,428**

Since it has proven difficult to develop a vaccine against HIV-1, the major cause of the AIDS pandemic, the research community has shifted some of its focus to the development of topical microbicides. Since both the vaginal and rectal tract are portals of HIV-1 entry, topical microbicides suitable to protect both sites need to be developed. In this grant, they focus on a novel mechanism that has not previously been explored for HIV prevention. In 2002, it was found that the cellular target of the HIV-1 protein Vif is APOBEC3G (A3G). A3G is an enzyme of the AID/APOBEC family, characterized by the targeted deamination of cytosine to generate uracil within DNA. APOBEC3G plays an important role in retroviral defense by acting on viral reverse transcripts and mediates numerous critical immune responses. They believe that A3G is an important innate retroviral defense mechanism in the vaginal and rectal tract. By using inhibitors of the viral protein Vif, the Vif-APOBEC3G interaction is blocked and APOBEC3G is not degraded by the proteosome. As a consequence, fatal hypermutations are introduced into the viral cDNA transcripts and HIV is rendered incompetent for replication. Their grant has four Specific Aims: (1) to explore the role of the restriction factor A3G in mucosal tissues of the vaginal and rectal tract; (2) to examine whether RN18 and its analogs are active in microbicide cell-based assays and ex vivo explant HIV transmission models; (3) vaginal humanized BLT mouse model testing of promising Vif inhibitor candidates; (4) macaque microbicide model testing of promising Vif inhibitor candidates. It is expected that these studies will define the role of A3G in the vaginal and rectal tract and whether inhibitors of the viral Vif protein can prevent sexual transmission of HIV.

Title: **Gp-340 and Syndecan Inhibition-Based Microbicide for HIV**
P.I.: **Drew Weissman**
Institution: **University of Pennsylvania, Philadelphia**
Grant No.: **5R21AI082701-02**
Award: **$37,500**

Education and microbicides active against HIV represent the best approaches to controlling the epidemic worldwide in the absence of a protective vaccine. Their research program studies the earliest events in genital tract transmission. They have identified a protein expressed by genital tract epithelial cells that could serve as a potential target for inhibition of transmission of HIV called gp-340. They have demonstrated that gp-340 is expressed on the cell surface of vaginal and cervical epithelial cells, in vivo, in vitro, and ex vivo and binds HIV envelope. Of significance to genital tract transmission, gp-340 binding of virus leads to an increase in both the infectivity and half-life of the virus. Gp-340 expressed by genital tract tissue and cell lines also mediates transcytosis of HIV, the vesicular transport of macromolecules from one side of a cell to the other. A second molecule called syndecan has been studied and shown to have similar trans-infection and transcytosis properties and is also expressed by genital tract cells. They have identified a peptide inhibitor of envelope binding to gp-340 that blocks both gp-340 mediated trans-infection and transcytosis in both in vitro and ex vivo models of genital tract transmission. This peptide contains a portion of a motif that inhibits syndecan

mediated transinfection, as well, and they will modify this peptide to inhibit envelope binding to both macaque gp-340 and syndecan and develop it into a microbicide. This potential role of gp-340 and syndecan to act at a stage of infection after delivery to the lumen of the genital tract but prior to interaction with and infection of target cells is very attractive and novel in microbicide design. They hypothesize that interfering with this process will inhibit or block genital tract transmission. In the initial R21 portion of this proposal, they will establish in vitro macaque systems of genital tract transmission. If they demonstrate that macaque gp-340 and syndecan mediate trans-infection and transcytosis and V3 loop derived peptides or improved versions block macaque gp-340 and syndecan mediated transinfection and transcytosis, they will proceed with the R33 portion of the grant. The Specific Aims of this are: microbicide development with in vitro testing and to test the effect of blocking gp-340 and syndecan-HIV Env interaction on genital tract SIV transmission in the rhesus macaque vaginal transmission model. Through these Specific Aims, they will develop a new type of microbicide and determine the role of genital tract gp-340 and syndecan in HIV transmission. If successful, these studies will deliver a new microbicide based on host cell interactions with HIV that promote genital tract transmission to preclinical trial studies.

Title: **The Microbial Ecology of Bacterial Vaginosis: A Fine Scale Resolution Metagenomic (The Human Microbiome Project)**
P.I.: **Jacques Ravel**
Institution: **University of Maryland, Baltimore**
Grant No.: **1UH2AI083264-01**
Award: **$125,000**

Bacterial vaginosis (BV) is the most common vaginal disease in women, and yet its cause and effective treatment remain unknown. BV is associated with many adverse health outcomes, such as preterm delivery of low birthweight babies and increased risk for infection by HIV. This research will contribute valuable information on the causes of BV, help develop improved methods for preventing and treating BV, and may help reduce major reproductive health problems associated with BV. The vaginal microbiota play an important protective role in maintaining the health of women. Disruption of the mutualistic relationship that exists between bacterial communities in the vagina and their hosts can lead to bacterial vaginosis (BV), a condition in which lactic acid producing bacteria are supplanted by a diverse array of strictly anaerobic bacteria. BV has been shown to be an independent risk factor for adverse outcomes including preterm delivery and low infant birthweight, acquisition of sexually transmitted infections and HIV, and development of pelvic inflammatory disease. National surveys indicate the prevalence of BV among U.S. women is 29.2 percent, and yet, despite considerable effort, the etiology of BV remains unknown. Moreover, there are no broadly effective therapies for the treatment of BV, and reoccurrence is common. In the proposed research they will test the overarching hypothesis that vaginal microbial community dynamics and activities are indicators of risk to BV. To do this, they propose to conduct a high resolution prospective study in which samples collected daily from 200 reproductive-age women over two menstrual cycles are used to capture molecular events that take place before, during, and after the spontaneous remission of BV episodes. They will use modern genomic technologies to obtain the data needed to correlate shifts in vaginal microbial community composition and function, metabolomes, and epidemiological and behavioral metadata with the occurrence of BV to better define the syndrome itself and identify patterns that are predictive of BV. The five Specific Aims of the research are: (1) evaluate the association between the dynamics of vaginal microbial communities and risk to BV by characterizing the community composition of vaginal specimens archived from a vaginal douching cessation study in which 39 women self-collected vaginal swabs twice weekly for 16 weeks; (2) enroll 200 women in a prospective study in which self-collected vaginal swab samples and secretions are collected daily along

with data on the occurrence of BV, vaginal pH, and information on time varying habits and practices; (3) determine the gene content (metagenome) of vaginal microbial communities to assess the metabolic potential of representative vaginal communities in women before, during, and after the spontaneous remission of BV; (4) characterize suites of expressed genes (metatranscriptome) in communities representative of vaginal community types in healthy women, as well as before, during, and after the spontaneous remission of BV; and (5) apply model-based statistical clustering and classification approaches to associate the microbial community composition and function, with metadata and clinical diagnoses of BV. The large body of information generated will facilitate understanding of vaginal microbial community dynamics, the etiology of BV, and drive the development of better diagnostic tools for BV. Furthermore, the information will enable a more personalized and effective treatment of BV and ultimately, prevent adverse sequelae associated with this highly prevalent disruption of the vaginal microbiome.

Title: **Washington Metropolitan Women's Interagency HIV Study**
P.I.: **Mary A. Young**
Institution: **The George Washington University, Washington, DC**
Grant No.: **5U01AI034994-17**
Award: **$100,000**

The Washington Metropolitan WINS (WMW) Consortium has enrolled and retained a representative cohort of HIV-infected and HIV-uninfected women since 1993 with the purpose of investigating the consequences of HIV infection and its treatment. Although significant progress has been made in both their understanding and treatment of HIV, curative therapy is still not available and the chronically administered complex therapies used to treat HIV are not always successful. Treatment with highly active antiretrovirals (HAART) appears to be associated with a wide range of adverse effects and the impact of other co-pathogens such as HPV and HCV has yet to be fully elucidated. Additionally, the early cohort of infected women is aging, and the effects of age and changes in sex steroids both on the long-term outcomes of HIV, on neurocognition, and the effects of HAART treatment needs investigation. The WMW has joined with centers around the country and with sites across the metropolitan Washington region to develop a scientific plan to address these issues. A successful and flexible infrastructure has been established to allow us to accomplish these scientific aims and to assure ongoing retention of this important cohort. The WMW has successfully participated in all elements of the WIHS protocol, and has actively supported the infrastructure of the national WIHS. WMW investigators have participated in all of the major WIHS scientific initiatives. Additionally, the WMW has established both a local specimen repository and contributes to the national specimen repository. As the study has matured, an increasing number of collaborations have been established with local investigators to allow for broader access to the rich repository of WIHS specimens. Further, the WMW has expanded its local epidemiologic expertise to allow for onsite data analyses. This application will describe both their accomplishments to date and the structure that they have established to (1) advance the scientific agenda as outlined in Part A; (2) to continue to expand their local collaboration in order to better define the status of women with HIV; and (3) to bring to fruition the promises of a sustainable treatment of this devastating disease.

Immunity/Autoimmunity

Title: **Role of Sex Differences in the Expression and Function of Regulatory T Cells in Systemic Lupus Erythematosus**
P.I.: **Ram Pyare Singh**
Institution: **University of California, Los Angeles**
Grant No.: **5R21AI083894-02**
Award: **$231,000**

They propose to study regulatory T cells (CD4 and CD8) (comparing male to female systemic lupus erythematosus [SLE] patients and male to female healthy individuals) for quantities, suppressive capacities and differences in gene expression. The ability of sex hormones to change T regulatory (Treg) numbers, functions, and gene expression will be studied. Regulatory CD4+T cells and CD8+T cells have important roles in suppressing autoimmune disease in the peripheral immune system. Impaired function of regulatory/suppressor T cells contributes to development of autoimmunity. The goal of this project will be to study the quantities and functions of Treg cells in healthy controls and patients with SLE, comparing males to females in both groups (given the fact that lupus disease is much more frequent in females than in males). The first aim is to quantify, immunophenotype, and perform functional analysis of the Treg cell subsets in healthy controls, and in male lupus versus female lupus. The second aim is to compare gene expression profiles of CD4+CD25+hiTreg and CD8+Ts cells in male versus female lupus patients and to compare them with healthy controls. Finally, they will test the effect of testosterone and estradiol in these cells in vitro to see their effects on cell phenotypes, gene expression, signaling, and regulatory functions. The overall purpose is to understand the molecular network of these CD4+T regulatory cells and CD8+ suppressor cells in systemic autoimmunity.

Title: **Molecular Epidemiology of Drug Resistance and Population Genetic Structure of *Plasmodium falciparum* and *Plasmodium vivax***
P.I.: **Fangli Lu**
Institution: **Sun Yat-Sen University, Guangzhou, China**
Grant No.: **5R01TW008151-02**
Award: **$50,000**

This project will be of significant benefit to public health programs aimed at identifying and combating drug-resistant malaria, and have the potential to benefit the health of a substantial proportion of the world's population. The data will provide valuable information for extending the lifespan of individual antimalarial drugs and developing more appropriate malaria control policies in China. Malaria remains a serious public health problem in China. In the subtropical Yunnan Province and the tropical Hainan Island of China, malaria has been the most endemic with high transmission of both *Plasmodium falciparum* and *P. vivax*. However, most of the attention in terms of research and interventions has been focused in Africa and Southeast Asia, while very few studies of malaria in China have been conducted. Because of extensive use, chloroquine (CQ) has now lost its efficacy due to the emergence of resistant strains in most parts of the world. Meanwhile, suspension of the use of CQ has resulted in reappearance of CQ sensitivity. However, there were differences in the evolution of CQ resistance between parasites from Yunnan and Hainan, the exact mechanism needs to be investigated. Sulfadoxine-pyrimethamine (SP) targets the dhfr and dhps genes of *P. falciparum*, and point mutations that confer resistance have been widely reported worldwide. Documenting the identity and extent of SP resistance is also critical for policy decisions regarding antimalarial drugs. In addition, *P. vivax* causes a large burden of morbidity in the world including China but traditionally has been understudied. Based on these, their long-term goal of this proposal is to: (1) identify single-nucleotide polymorphism (SNP) and characterize the geographic distribution of genetic diversity, population structure, and haplotype variability at drug resistant loci of *P. falciparum*

from Yunnan and Hainan, China; (2) examine the geographic population structure and levels of genetic diversity of *P. vivax* using microsatellite and SNP; and (3) yield valuable information for making more effective malaria control policies in China. In the past several years they have developed the molecular methods to study the genetics, population diversity, and evolution of malaria parasites, and have done some preliminary studies on malaria field isolates from Yunnan and Hainan using genetic markers, thus enabling us to study the molecular epidemiology of these important malaria parasites in this proposal. The Specific Aims are to: (1) determine genetic polymorphisms associated with CQ resistance (CQR) in *P. falciparum* field isolates from Yunnan and Hainan provinces in China; (2) determine the point mutation prevalence in the dhfr (pyrimethamine drug resistance) and dhps (sulfadoxine drug resistance) genes associated with SP resistance in *P. falciparum* field isolates from Yunnan and Hainan provinces in China; and (3) assess the changes of *P. vivax* genotypes using pvcsp, pvmsp1, and pvmsp3-1 genes and microsatellite markers and determine the geographic structure and specific epidemiological characteristics of *P. vivax* transmission in Yunnan and Hainan, China.

Title: **Mechanisms of IL-35 Protection Against Arthritis**
P.I.: **David W. Pascual**
Institution: **Montana State University, Bozeman**
Grant No.: **1R21AR058010-01A1**
Award: **$200,000**

The project will evaluate the therapeutic potential of IL-35 to treat rheumatoid arthritis (RA). RA, a chronic inflammatory disease of the joints, manifests as a chronic synovitis and progressive destruction of the joints, leukocyte infiltrates, and cartilage destruction and bone erosion. It is believed this destruction is supported and perpetuated by proinflammatory cytokines contributed by autoreactive T cells. Rodent models have been developed that mimic arthritis, and one such model, collagen-induced arthritis (CIA), requires immunization with heterologous collagen II. Oral tolerance and treatments with regulatory cytokines have been suggested as possible interventions to treat arthritis. One such new therapeutic is the regulatory cytokine, IL-35; however, its mode of action has yet to be determined. IL-35 is a heterodimer cytokine composed of IL-12p35 plus IL-27 EBI3 subunits. They recently expressed IL-35 as a single polypeptide using eukaryotic expression systems. The recombinant mouse IL-35 has the expected molecular weight, and it is recognized with antibodies to IL-12p35 and IL-27-EBI3. Functional analysis reveals that IL-35 can completely block development of clinical symptoms of CIA. This disease suppression does appear to be IL-10-dependent, produced by heterogeneous regulatory T cell subsets, including CD25+ CD4+ T cells, as well as CD39+ CD4+ T cells. Thus, additional studies are warranted to investigate the nature of these regulatory T cells and learn which mononuclear cells are responsive to IL-35's action. Given these findings, the hypothesis to be tested in this application is that IL-35 intervention will reduce disease severity and limit disease progression of CIA by the stimulation of regulatory T cells. To test this hypothesis, two Specific Aims are proposed. Studies in Specific Aim 1 will determine if IL-35 in a paracrine/autocrine fashion stimulates endogenous IL-35 production for treatment of CIA and determine the cell types involved to facilitate IL-35's action. Studies in Specific Aim 2 will define the regulatory T-cell subset induced by IL-35 that is responsible for protection against CIA and determine which inflammatory T-cell subset is diminished. These collective studies will provide the foundation of whether IL-35 can be considered in RA intervention strategies and whether alternative regulatory T-cells can be defined that would facilitate IL-35's therapeutic impact in humans.

Title: **Effects of Malaria on Epstein-Barr Virus Persistence in Children**
P.I.: **Rosemary Rochford**
Institution: **Upstate Medical University, Syracuse, NY**
Grant No.: **2R01CA102667-06A1**
Award: **$167,750**

Endemic Burkitt's lymphoma (BL), the most prevalent childhood cancer in equatorial Africa, is a rapidly growing B-cell malignancy that is ultimately fatal if untreated. The knowledge gained by this study will improve the understanding of the etiology of endemic BL which will ultimately allow for the design of programs aimed at the prevention of BL. While there is a consensus that infection with Epstein-Barr virus (EBV) and repeated infections with *Plasmodium falciparum* malaria in childhood (e.g. holoendemic malaria) are essential components in the etiology of BL, the mechanisms of malaria and EBV interactions that increase the risk for endemic BL remain to be elucidated. The long-term goal of this research is to identify the events that initiate B cell oncogenesis in BL. The overall objective of this proposal is to continue this investigations of EBV and malaria interactions in Kenyan infants at risk for endemic BL. In this current R01 (CA102667), they followed a prospective cohort of children with divergent malaria exposures from 2 months through 36 months of age. They observed that children born in the malaria holoendemic region had a significantly earlier age of primary infection with EBV, with ~35 percent infected by 6 months of age. Importantly, children infected early in life maintained a chronic viral load. These studies support the long-held hypothesis that early age of EBV infection is a risk factor for BL. What they do not know however, is why these infants are infected early in life and how early age of infection limits control of EBV. Based on this data and the data of others, they propose a model whereby susceptibility of infants to infection with EBV by 6 months of age is linked to placental malaria. Infants infected early in life while they have underdeveloped immune responses will have poor immunologic control of the virus. The long term consequences of poor immunologic control is a greater number of latently infected cells which can ultimately exhaust the immune response against EBV and increase the risk for a malignant clone to emerge from the latently infected B cell. This central hypothesis is that placental malaria alters an infant's ability to control primary EBV infection resulting in infection earlier in life and failure to develop effective EBV immunity. They will establish an infant cohort by enrolling pregnant women attending an antenatal clinic at Chulaimbo Hospital in Kisumu District, Kenya where malaria is holoendemic, and follow infants prospectively from birth to their second birthday. To test this hypothesis, they determine the effects of placental malaria on transfer of maternal EBV-specific neutralizing antibodies and in utero sensitization to EBV antigens; determine the factors influencing susceptibility of infants to EBV by 6 months of age; determine the effects of early age of EBV infection on the development of EBV-specific immune responses, the frequency of atypical exhausted memory B cells, and the emergence of pre-malignant B cells. If this model proves valid, the implications are that prevention of BL should focus on delaying the age of EBV infection by focusing on pregnant women with placental malaria, or on blocking transmission to infants.

Title: **Exploring Factors Influencing Gender Disparities in Access to Transplantation**
P.I.: **Dorry Segev**
Institution: **Johns Hopkins University, Baltimore, MD**
Grant No.: **1R21AG034523-01A1**
Award: **$246,000**

Although kidney transplantation is safe, effective, and life-extending for many patients, women have significantly less access to transplantation than their male counterparts, and they have shown that this disparity is widest among older women compared with older men. It is

unknown whether this happens because of patient-level barriers to seeking transplantation or because of provider-level biases against referral of women compared with men. Since more than 50 percent of dialysis patients are over the age of 65, equal access to transplantation for this subgroup is important; the goal of this project is to explore potential sources of the gender disparity in access to transplantation, and access to healthcare in general, so that interventions to minimize this disparity can be designed. In the modern era, kidney transplantation is a safe and effective treatment for many patients with kidney failure. However, choosing the right patients for kidney transplantation is difficult, especially among older patients. Although older patients who receive transplants survive longer than if they had stayed on dialysis, still very few older patients are placed on the transplant waiting list. This is because no tools exist for determining risk in older patients undergoing transplantation, so clinical decisionmaking has to be based on subjective perceptions of a patient's strength and reserve. Misclassification of these factors by the patient or provider likely results in decreased access to transplantation in a population that stands to greatly benefit from this treatment. Although transplant outcomes and survival benefit are similar in men and women, it has been well established that women have significantly less access to transplantation than men. They recently showed that this disparity is strongest in older patients, with older women having 30-60 percent less access than their male counterparts. However, it remains unclear whether patient or provider level factors contribute to this disparity. In this study they will explore differences by gender and age in factors influencing a patient's decision and ability to pursue transplantation. They will then use a new technique to explore the potential role of gender and age biases in a provider's choice to refer a patient for transplantation. Understanding the root causes of this gender/age disparity is crucial to developing interventions to improve access to transplantation, and healthcare in general, for women and older adults.

Title: **Sex Differences in Protective Immunity against Influenza A Viruses**
P.I.: **Sabra Klein**
Institution: **Johns Hopkins University, Baltimore, MD**
Grant No.: **1R21AI090344-01**
Award: **$205,000**

Sex differences in the incidence and severity of influenza A virus infection as well as in response to vaccination have been documented in humans. Small animal models are critical for establishing the mechanisms mediating why males and females respond differently to influenza virus infection and vaccination. They will evaluate whether higher humoral immune responses following sublethal infection confers greater protection from challenge with pathogenic influenza A viruses in females compared with males and the extent to which these differences are mediated sex steroids, which may provide clues into why responses to pandemic influenza A viruses differ between the sexes and during pregnancy. Although exposure rates are often higher in men, fatality following exposure to pathogenic influenza A viruses is reportedly higher in women. Sex differences also are reported in response to influenza virus vaccines, with women consistently mounting higher antibody responses and developing more frequent and severe side effects following vaccination than men. Small animal models are critical for establishing the mechanisms mediating why males and females respond differently to influenza virus infection and vaccination. Following primary inoculation with the mouse-adapted influenza A viruses A/PR/8/34 (PR8; H1N1) or A/HK/68 (HK68; H3N2), female mice mount higher inflammatory and humoral immune responses than males. Their preliminary data further reveal that elevated immunity in females against influenza A viruses represents a delicate balance between immune responses conferring protection or causing pathology. The goal of this proposal is to develop a small animal model to test the hypothesis that protective immunity to heterosubtypic influenza A virus challenge differs between the sexes and is modulated by sex steroid hormones. In Specific Aim 1, they will establish whether

neutralizing antibody responses, virus-specific T cell responses, and protection against lethal influenza A virus challenge is greater among females than males. Whether males and females differentially rely on subsets of adaptive immune cells for protection against lethal influenza A virus infection has not been documented; thus, they also propose to compare heterosubtypic immune responses between male and female mice devoid of specific adaptive immune cell populations. If protective heterosubtypic immunity is elevated in females compared with males, then estrogens and/or progestins may enhance and androgens may suppress adaptive immunity against heterosubtypic influenza A virus challenge. In Specific Aim 2 they will test this hypothesis by manipulating sex steroid concentrations in vivo and establishing the effects on humoral and cell-mediated immunity as well as protection from lethal influenza A virus challenge. These are a series of high risk-high return experiments because there are no data to date assessing the sex-specific induction of heterosubtypic immunity in response to influenza A virus infection. Demonstrating that females mount a broadly protective immune response, however, will have important implications for dealing with annual epidemics of influenza, as this may explain why the attack rates for influenza are higher in men than in women and influenced by pregnancy.

Menopause

Title: **Estrogen: Neuroprotection in the Perimenopause**
P.I.: **Anne M. Etgen**
Institution: **Yeshiva University, Bronx, NY**
Grant No.: **5R01AG027702-05**
Award: **$50,000**

Alterations in the hypothalamic-pituitary-ovarian axis in perimenopausal women are associated with multi- organ risk factors for disease, yet the biological mechanisms underlying this increased disease risk are largely unknown. This proposal addresses unanswered questions regarding the vulnerability of the middle- aged brain to global ischemia. In young female rats, the presence of physiological levels of estradiol before and after global ischemia, as might occur during cardiac arrest, reduces hippocampal CA1 neuron loss and associated cognitive impairments. Whether estradiol retains its neuroprotective actions in middle-aged females, and whether the age-related decline in insulin-like growth factor-l (IGF-I) increases vulnerability to ischemia-induced neurodegeneration and cognitive impairment, are unknown. This proposal examines the roles of age, estrogen, and IGF-I in the survival and function of hippocampal neurons in a rat model of global ischemia. The underlying hypotheses are (1) that the middle-aged brain retains its responsiveness to the neuroprotective actions of estradiol if the duration of estrogen withdrawal is brief (critical period hypothesis) or circulating levels of IGF-I are maintained, and (2) that estrogen acts in the middle-aged brain to activate specific cell survival pathways and thereby intervenes in apoptotic cascades to prevent death of neurons otherwise "destined to die". Specific Aim 1 uses stereological cell counting and behavioral tests to evaluate the outcome of global ischemia in middle-aged female rats that are intact, ovariectomized at various intervals prior to insult, or ovariectomized and treated with estradiol at various intervals after ovariectomy. If estradiol does not preserve neurons and cognitive function in older hormone-deprived animals, they will also determine if IGF-I can reinstate estrogen protection. Specific Aim 2 examines the apoptotic death cascades triggered by global ischemia and identifies the site at which estrogen intervenes in these cascades. They will examine (1) mitogen-activated protein kinase and cAMP response element binding protein at early times after ischemia; (2) the anti-apoptotic gene Bcl-2 and activation of caspase 3 at later times after ischemia; (3) inactivation of Akt and subsequent activation of the forkhead transcription factor FKHRL1 at early times after ischemia. These experiments will provide new information on the potential for hormone therapy instituted during the perimenopausal transition to protect the brain from damage due to global ischemia.

Title: **SWAN: Study of Women's Health across the Nation**
P.I.: **Joel S. Finkelstein**
Institution: **Massachusetts General Hospital, Boston**
Grant No.: **5 U01AG012531-17**
Award: **$75,000**

The Study of Women's Health Across the Nation (SWAN) is a multicenter, multiethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. The goals of the original RFA were to answer the following questions: How do hormones change with the menopausal transition? What factors affect the timing of the transition? What are the symptoms that accompany menopause and who is at risk? How do cardiovascular risk factors change with the transition and is there ethnic variation? What are the rates of bone loss with the transition? When does bone loss begin and what are the risk factors? What are the health consequences of menopause and who is at risk? SWAN is compiling the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. SWAN is now poised to study the effects of these menopause-related changes on subsequent healthy aging and on age-related diseases in the post-reproductive period. SWAN I was first funded in September 1994 by the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the Office of Research on Women's Health (ORWH) in response to RFA AG-94-002, Menopause and Health in Aging Women. The first competing continuation of SWAN (SWAN II) was funded in 1999 and the second (SWAN III) in 2004. SWAN I, II and III have been supported by a cooperative agreement mechanism, with nine funded components: seven clinical centers, a central reproductive hormone laboratory (CLASS), and a coordinating center. A second central laboratory (MRL) was originally funded as a subcontract to the Coordinating Center (CC). In addition, a Core Repository of serum, plasma, and urine specimens and a DNA Repository were established in June 2000 under separate funding (U01 AG 17719, Principal Investigator (PI): Dr. MaryFran Sowers). For non-study-related reasons, site operations at New Jersey Medical School stopped in April 2004. The basis of this action was allegations made by two study employees who resigned abruptly. The SWAN PI and study coordinator were subsequently exonerated from these allegations. Please see Appendix 12 for a more complete report. The grant was transferred to the Albert Einstein College of Medicine in 2005. Since that time, the New Jersey PI and project director have worked tirelessly to overcome the obstacles to re-implement the study. As of June 1, 2008, a total of 155 women have successfully completed their clinic visit and five more visits are scheduled. They project that by the end of SWAN III, data will be available for 250 women. This has been very encouraging and thus Nanette Santoro, PI of the New Jersey SWAN site has been approved by the NIA to prepare a U01 application to cover further contacts for the Hispanic women. Please note that the SWAN IV project applications pertain to the remaining six sites only. Information relative to the New Jersey site is covered in the separate application submitted by Dr. Nanette Santoro. From more than 16,000 women aged 40–55 who were screened during 1995–1997, 3,302 women aged 42–52 years were enrolled in SWAN's longitudinal cohort (approximately 450 at each of seven clinical centers). They completed their baseline clinic visit during 1996–1997. Of the 3,302 women enrolled, 1,550 were Caucasian, 935 African American, 286 Hispanic, 250 Chinese, and 281 Japanese. A subset of 880 menstruating women was enrolled in the Daily Hormone Study (DHS) started in 1997, which is designed to examine cyclical daily hormone and symptom patterns during the menopausal transition.

Title: **Ovarian Hormone-Independent Sex Chromosome Effects in Menopause**
P.I.: **Hong Ji**
Institution: **Georgetown University, Washington, DC**
Grant No.: **1R21AG037832-01**
Award: **$153,500**

This project is designed to make new discoveries into why postmenopausal women are at increased risk for diseases like metabolic syndrome, hypertension and cardiovascular disease compared to premenopausal women. They will make these new discoveries by studying sex chromosome effects independently of the ovarian hormones using a unique animal model in which they can separate, for the first time, sex chromosome differences between males (XY) and females (XX) from the sex hormone differences (e.g., differences in estrogen and testosterone levels). By discovering new genes and pathways responsible for the increased incidence of these diseases in ovarian deficient females, new therapeutic treatments are likely to ensue for postmenopausal women and women with ovarian hormone deficiency. Postmenopausal women have a higher incidence of diseases such as metabolic syndrome, cardiovascular, and renal disease than premenopausal women. To begin to uncover genes and pathways that contribute to these adverse effects of aging in the postmenopausal woman, they propose two distinct strategies for discovering novel genes and pathways that may contribute to the increased risk postmenopausal women face towards these diseases. They will take advantage of the "four core genotypes" mouse model in which sex chromosome effects can be separated from the gonadal sex thus enabling comparisons among XX and XY animals independently of whether they were born with ovaries (e.g., XX- vs. XY-females) or testes (XX- vs. XY-males). While recent microarray studies in mice have demonstrated that thousands of genes are regulated by gonadal hormones, the number of genes regulated by the sex chromosome complement independently of the gonadal hormones is far more limited. Thus, they expect to discover a handful of genes (<10) that are differentially regulated by the sex chromosome complement (SCC) in the ovarian hormone deficient female during overactivity of the renin angiotensin system (RAS). Aim 1 will use a tightly focused microarray approach leveraging their ability to differentiate SCC from gonadal sex to identify genes in the kidney that are differentially regulated by the SCC in the Ang II infused E2-deficient female. Aim 2 will use a candidate gene approach to test the hypothesis that the regulation of the tissue-specific RAS in the kidney by ovariectomy and hypertension is sex chromosome dependent. They hypothesize that the interaction between the XX SCC with the E2-deficient state of ovariectomy tips the vasoconstrictor/vasodilator balance of the renal RAS towards vasoconstriction to a greater extent than in the XY-female by increasing plasma and renal levels of Ang II, the ratio of the Ang II synthetic enzyme, angiotensin converting enzyme (ACE) to the catabolic enzyme, angiotensin converting enzyme 2 (ACE2) and the ratio of the type 1 angiotensin receptor (AT1R) to the vasodilator type 2 angiotensin receptor (AT2R).

Title: **Effects of Estrogen on Brain Morphology and Neuronal Integrity in Early Menopause**
P.I.: **Kejal Kantarci**
Institution: **Mayo Clinic, Rochester, MN**
Grant No.: **1R21NS066147-01A1**
Award: **$213,812**

This study will provide evidence on the neuroprotective effects of estrogens with non-invasive imaging markers of structural and functional neuronal integrity in newly menopausal women, during a hormone treatment trial. This evidence would potentially have a significant impact on women making the decision to use hormone treatments for dementia prevention

as they transition into menopause. Neuroprotective effects of estrogens offer the possibility of preventing or delaying Alzheimer's disease in menopausal women. Estrogen treatment in older women who were late into menopause in the Women's Health Initiative Memory Study, did not prevent dementia. The question remains as to whether or not estrogen can preserve neurological function and decrease the risk of dementia when administered early in menopause from 6-36 months of the last menses. This project is proposed as an ancillary to the Kronos Early Estrogen Prevention Study (KEEPS), which is a nationwide, multicenter, randomized blinded study designed to provide evidence on the benefits and risks of oral and systemic estrogen treatment in recently menopausal women. Their goal is to test the neuroprotective effects of estrogen treatment in early menopause, during the 48 months of the randomized clinical trial. They will determine the rates of hemispheric atrophy on MRI, and the change in neuronal metabolite N-acetylaspartate (NAA) on proton MR spectroscopy (1H MRS) as a surrogate for the neuroprotective effects of estrogen treatment during the early postmenopausal years. In addition to the longitudinal serial measurements of whole brain, hippocampal and ischemic lesion volumes, they will use exploratory 3-dimensional voxel-based analysis of the serial MRI to determine the differences in the change in whole brain morphology in women who are taking estrogens compared to placebo. Their collaboration with the investigators of the KEEPS Cognitive and Affective Study will give us the ability to relate the change in neuronal metabolic integrity and brain morphology with the concurrent change in cognitive function in newly menopausal women. As an outcome of the proposed investigations, they expect to determine whether or not oral and transdermal estrogen treatment preserves brain structure and neuronal function during the immediate years after menopause. Several decades of followup are necessary to determine if estrogen treatment in newly menopausal women prevents Alzheimer's disease. This project will provide the necessary in vivo evidence on the neuroprotective effects of oral and transdermal estrogens in early menopause in the short term, for future large-scale, long term trials. The original contributions of this study to women's health research will include the demonstration of the effects of estrogens on longitudinal change in brain morphology and neuronal integrity, and the relationship between these biological changes and the concurrent change in cognitive function in recently menopausal women.

Title:	**Ultra-Low-Dose Estrogen Gel for Vasomotor Symptoms in Women Failing Placebo or a Behavioral Intervention: A Randomized Trial**
P.I.:	**Andrea Lacroix**
Institution:	**Fred Hutchinson Cancer Research Center, Seattle, WA**
Grant No.:	**U01AG032699-03**
Award:	**$132,000**

The long-term objective of NIA's RFA-AG-08-004 entitled, "New Interventions for Menopausal Symptoms" (U01) is to accelerate progress in identifying effective remedies for vasomotor symptoms (VMS) in women going through the menopausal transition. They have created a network of scientists who are highly knowledgeable about the menopausal transition and experienced in the conduct of women's health trials to fulfill this mission. This data coordinating center (DCC) application is being submitted in conjunction with the network entitled, "The Menopausal Symptoms Initiative-Finding Lasting Answers to Sweats and Hot Flashes (MSI-FLASH)". Their DCC will be jointly led by Andrea LaCroix and Garnet Anderson who have served together as Co-Principal Investigators (PIs) of the Women's Health Initiative Clinical Coordinating Center (Seattle) for more than a decade. The MSI-FLASH network has five clinical sites located in Boston (Lee Cohen and Hadine Joffe, PIs), Indianapolis, IN (Janet Carpenter, PI), Oakland, CA (Barbara Sternfeld and Bette Caan, PIs), Philadelphia (Ellen Freeman, PI) and Seattle (Katherine Newton and Susan Reed, PIs). This interdisciplinary investigator group proposes five randomized controlled trials testing a range

of behavioral, mind-body, hormonal and pharmacologic interventions to treat hot flashes. The specific objectives of the DCC are to: (1) provide and coordinate all necessary leadership activities to facilitate collaboration and productivity among network scientists during all phases in the lifecycle of VMS clinical trials from hypothesis formulation to publication, dissemination, and data sharing; (2) build upon 15 years of experience and well-established human and operational resources to coordinate five or more multisite randomized trials including support of protocol development, recruitment, intervention, data collection and management, and statistical analysis; and (3) Create the infrastructure to involve an expanded network of scientists from the United States and worldwide to facilitate the development and use of common methodologies and measurements for VMS trials inside and outside of this trial network so that emerging new treatments for hot flashes can be rapidly identified and rigorously tested for efficacy and safety with comparable results.

Title: **Menopause: Decreased Response to Increasing Inflammation**
P.I.: **Adriana Caterina Maggi**
Institution: **University of Milan, Italy**
Grant No.: **5R01AG027713-05**
Award: **$50,000**

The long-term goal of their research is to find treatments for the prevention of the disorders associated with menopause which are safer and more efficacious than present hormone replacement therapy (HRT). The failure of present HRT to fulfill medical and women's needs has to be ascribed to an insufficient knowledge of the biology of menopause. The aim of their research is focused on understanding the consequences of cessation of ovarian functions on the physiology of nonreproductive organs such as bone, brain, arteries, and fat. In particular their studies and the studies proposed in the present project will focus on the effects of estrogen decreased production at menopause transition and after in nonreproductive organs. Given recent results demonstrating that in nonreproductive organs of fertile female mice estrogen receptors (ERs) are activated by factors other than estrogens, their Specific Aim 1 will focus on assessing the extent to which ERs are transcriptionally active during menopause transition and after. They will then try to identify the factor(s) involved in ER activation. This part of the project relates to questions which so far could be addressed only partially with the current technology. The generation of a novel model of reporter system, the ERE-Luc mouse, will enable us to precisely quantify ER activity in the organs of interest and facilitate the search of factors involved in ER unliganded activation. Specific Aim 2 will give us the opportunity to test an original hypothesis that would explain the widespread protective effects provided by the estrogen-ER system. This hypothesis is based on numerous very recent observations made in their group and several other groups showing that estrogens and cognate receptors may exert a strong anti-inflammatory action by inhibiting the immune response of cells of the monocyte lineage. They here propose that menopause consists of a decreased response to increased inflammation. They will test this hypothesis by the direct assessment of ER relevance on macrophage activity through the generation of a novel conditional ERalpha knockout mouse. Furthermore, using brain as a paradigmatic non-reproductive organ, they will measure basal and induced activity of brain inflammatory cells. Finally, the specific involvement of ER anti-inflammatory activity in the development of menopause-associated diseases will be tested with the study of the activity in menopause of another class of intracellular receptors devoted to the control of inflammation, the PPARs.

Title: **Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO**
P.I.: **Puliyur S. Mohankumar**
Institution: **Michigan State University, East Lansing, MI**
Grant No.: **5R01AG027697-05**
Award: **$50,000**

Perimenopause is one of the most complex and least understood states of a woman's life. Many of the health risks associated with this state were believed to be due to decreases in estrogen levels and that estrogen could protect against health risks faced by perimenopausal women. However, estrogen fluctuates during perimenopause and if at all increases during the premenstrual and follicular phases. Recent clinical trials have shown that chronic administration of estrogenic compounds in postmenopausal women may increase the risk for several diseases. Therefore, it is important to investigate the effects of estrogen exposure on various organ systems. Studies so far indicate that estrogen's effects in the brain are beneficial. These reported effects, however, deal with non-hypothalamic regions of the brain. The effects of chronic estrogen exposure on the hypothalamus which regulates several key body functions have not been investigated. This is critical because women use estrogenic preparations on a prolonged basis and are exposed to endogenous estrogen throughout their adulthood. This proposal focuses on the effects of chronic estrogen exposure on one of the estrogen sensitive neuronal systems of the hypothalamus, namely, the tuberoinfundibular dopaminergic (TIDA) system. Dopamine (DA) released from TIDA neurons inhibits prolactin (PRL) secretion from the anterior pituitary. Age-related reductions in TIDA activity is associated with hyperprolactinemia and appearance of mammary and pitutiary tumors in animal models. The mechanisms behind the loss of TIDA neuronal function is not clear. In this application, they are proposing a novel hypothesis and an interesting model to study how estrogen could affect TIDA neurons and increase PRL levels. This series of studies is important because women not only use estrogen on a long-term basis in HRT but are also exposed to environmental estrogens. Prolonged exposure to estrogen and elevated levels of PRL may promote the risk for breast cancer.

Title: **Biological Mechanisms of Arterial Stiffening with Age and Estrogen Deficiency**
P.I.: **Kerrie Moreau**
Institution: **University of Colorado, Denver, CO**
Grant No.: **5R01AG027678-05**
Award: **$47,579**

The purpose of this R01 proposal is to determine the key functional mechanisms by which the loss of female sex hormones, particularly estradiol (E2), contribute to the age-related decrease in large artery compliance. The overall hypothesis is that basal large artery compliance will decrease in response to acute sex hormone suppression in pre- and perimenopausal women due in part to a decrease in vascular endothelial-dependent vasodilatory tone mediated, in part, to the development of vascular oxidative stress. However, E2 administration during sex hormone suppression will decrease vascular oxidative stress, improve endothelial vasodilatory tone and restore arterial compliance to basal levels. Secondary and tertiary hypotheses are that the changes in arterial compliance and vasodilatory function with sex hormone suppression and E2 will be related to unfavorable, and favorable, respectively, changes in vascular endothelial cell protein expression including oxidant (e.g., NADPH) and antioxidant (e.g., glutathione peroxidase) enzymes, vasoconstrictors (endothelin-1), and estrogen receptor alpha (ERalpha). To test these hypotheses, healthy pre-, peri-, and postmenopausal women will be studied at, before, and following acute sex hormone suppression (gonadotropin releasing hormone antagonist [GnRHant]) with or without E2 add-back therapy. The GnRHant

intervention will enable us to study the direct mechanisms associated with sex hormone deficiency and the E2 add-back intervention will enable us to isolate the independent effects of E2. Insight into the molecular mechanisms mediating the decrease in large artery compliance will be obtained using a novel translational research technique to determine changes in vascular endothelial cell protein expression of genes involved in the regulation of cellular and systemic adaptations to aging and sex hormone deficiency including oxidative stress, nitric oxide bioavailability, and the potent transcription factor ERalpha proteins. The results should provide new insight into the integrative biological mechanisms by which sex hormone deficiency modulates the age-related reduction in large artery compliance in women as they transition through the menopause.

Title: **Study of Women's Health Across the Nation Repository III**
P.I.: **MaryFran Sowers**
Institution: **University of Michigan, Ann Arbor**
Grant No.: **2 U01AG017719-11A2**
Award: **$100,000**

This competing renewal application is to provide for continued maintenance of and activities associated with the Study of Women's Health Across the Nation (SWAN) repositories of serum, plasma, urine, DNA, and transformed cells generated from a 10-year study of a population of 3,302 women from five ethnic groups who have been evaluated annually prior to, during, and following the menopausal transition. These repositories, an arm of SWAN, are meant to support, facilitate, and extend the Core SWAN; additionally, the repositories provide a mechanism for opening the resources of SWAN to the greater scientific community. Implementing activities associated with three proposed Specific Aims of this competing renewal will (1) provide for the continued management of the current 1.7 million repository specimens and the additional specimens that will accrue as a result of fielding SWAN IV in 2009 to 2014; (2) expand the DNA repository, the most frequently requested specimen type that is uniquely renewable because of their investment in cell immortalization; (3) promote effective information interchange about the SWAN Study, its data, and the repository resources through development of a two-level Web-based "data warehouse"; (4) provide for continued administration of the application review process for specimen utilization and administrative management of specimen distribution including Material Transfer Agreements; (5) engage in strategies to promote utilization of specimens; and (6) expand the scope of the genetics studies associated with the SWAN study and its Repository.

Title: **Study of Women's Health Across the Nation III**
P.I.: **Kim Sutton Tyrrell**
Institution: **University of Pittsburgh, PA**
Grant No.: **5U01AG012553-16**
Award: **$125,000**

Study of Women's Health Across the Nation (SWAN) has compiled the most comprehensive characterization to date of the health and the physiological and psychosocial changes of women from pre- to postmenopause in community based samples. Of particular public health importance is that the continuation of SWAN will permit the study to increase understanding of the effects of these menopause-related changes on subsequent health and risk factors for age-related diseases. The SWAN is a seven-center multiethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition. SWAN has amassed 10 years of data about endocrinology of the transition and other factors relevant to midlife health and aging. As SWAN requests its fourth competing renewal, the study itself proposes to transition from a study of the menopause to

a study of aging in women. The average age of participants at the beginning of the SWAN IV project will be 59 years (54 to 65) and SWAN IV will follow these women through the age range of 59 to 70. SWAN has the unprecedented capability to link the expansive biological, medical, social, behavioral, and demographic data it has collected during midlife and the menopausal transition to the development of both positive and adverse health states in early old age. The primary objectives of SWAN IV are to: (1) characterize the endocrinology and symptomotology of the post-menopause (2–12 years after final menses); (2) ascertain additional health outcomes (such as measured physical performance) that are relevant to the early old age range and that may be affected by the factors that they have studied in mid-life; and (3) understand the relations between the midlife and menopausal transition experience of women and subsequent positive and negative health outcomes. To accomplish this, the investigators propose annual phone contact to closely track menopausal status, menopausal symptoms, and selected health events. In addition, two in-person clinic visits are proposed to accomplish detailed physical measures of early disease. The major thematic areas of SWAN IV include (1) physical Functioning, (2) bone/osteoporosis, (3) cognitive function/ symptoms/ mental health, and (4) cardiovascular. New areas for SWAN include physical performance and osteoarthritis, history of major depression, and carotid wall thickness. SWAN will continue to monitor symptoms, cognition, cardiovascular risk factors, endocrinology, bone density, and fractures. SWAN IV will advance their understanding of how modifiable risk factors related to the menopause transition are linked to subclinical disease measures and hard outcomes. This may lead to improved strategies for the primary prevention of disease in women.

Title: **Menopause Symptom Clusters: Refocusing Therapeutics**
P.I.: **Nancy Fugate Woods**
Institution: **University of Washington, Seattle**
Grant No.: **1R21NR012218-01**
Award: **$200,000**

The results of this study will help clinicians and women themselves identify symptoms that cluster together and that may have different causes. Knowing which cluster of symptoms a woman has may help her clinician recommend the treatment or treatments that are most likely to work best for her. Using some of the genetic and hormone tests, as well as information about the woman's history, such as stressful experiences she has had, may help understand what causes some of her symptoms and may help her and her clinician decide on the best treatment available for her. Although women experience clusters of symptoms during the menopausal transition, most research focuses on individual symptoms such as hot flashes. The proposed study shifts the paradigm from focusing on individual symptoms to symptom clusters (SCs). Reanalyzing data on symptoms and genetic polymorphisms, endocrine biomarkers, symptom vulnerability factors and sociobehavioral risk factors from more than 500 participants in the Seattle Midlife Women's Health Study (P50 NR02323, R01 NR04141, P30 NR04001, P30 ES07033) with longitudinal followup spanning up to 19 years will allow us to achieve these aims: (1) identify prevalent symptom clusters during the late reproductive stage, early and late menopausal transition stages, and early postmenopause using latent class analysis; (2) determine the consistency of symptom clusters as women change from one menopausal transition stage to the next; (3) test models linking genetic polymorphisms, endocrine biomarkers, symptom vulnerability factors, social-behavioral risk factors, and menopause-related factors to symptom clusters, and outcomes of well-being and symptom interference; 4) conduct a systematic review of controlled clinical trials to identify symptoms as secondary treatment effects and adverse effects that will inform us about therapies for symptom clusters; and (5) synthesize results of the empirical analyses and systematic review to develop novel symptom cluster management protocols to be tested in future feasibility studies. An interdisciplinary scientific advisory board including National Institute on Aging-funded

MS-FLASH clinical trials investigators will provide their research team an opportunity for immediate sharing of their results in order to inform design of symptom cluster management approaches as well as their ongoing studies, including the generation of ancillary studies of symptom clusters and related mechanisms.

Mental Health

Title: **Novel Approaches to Understanding Mental Disorder, Substance Abuse and HIV-Risk Among Homeless Women**
P.I.: **Leslie B. Whitbeck**
Institution: **University of Nebraska, Lincoln**
Grant No.: **5R21HD058989-02**
Award: **$255,535**

This R21 developmental application will set the stage for the first multistate longitudinal diagnostic study of homeless women. It builds on more than a decade of work with hard-to-access homeless populations and a prior 3-year longitudinal diagnostic study of homeless adolescents. This application will fund the development of innovative measures and sampling techniques specifically for this understudied population and for the piloting of measures with a sample of 200 homeless women in two Midwestern cities. This revised R21 application seeks two years of support to develop state-of-the-science methodologies to address four important needs in existing research with homeless women: (1) capture the diversity of circumstances among a fluid and hard-to-access population; (2) increase their understanding of mental and substance use disorders (particularly personality disorders) across the diversity of homeless women; (3) improve their understanding of trajectories to homelessness through development of an innovative event history calendar approach; and (4) advance knowledge of homeless women's health and HIV-risk by circumstance and trajectories to homelessness. This research will provide measurement development and preliminary studies for a multistate longitudinal R01 designed to advance their understanding of mental and substance use disorders among homeless women, their movement into and out of homelessness, the consequences of homelessness for women and minor children in their custody, and women's health, HIV-risk, and HIV-testing behaviors. The planned longitudinal research will focus on a growing but poorly understood population of the nation's most vulnerable women. The Specific Aims of this R21 developmental application are to (1) develop and pilot a sampling plan that will better reflect the diversity of homeless women; (2) develop and pilot an innovative events history calendar for use with homeless women; (3) program and pilot Axis 1 (UM-CIDI) and Axis II (DIPD-IV) diagnostic interview schedules for computer-assisted personal interviews with homeless women; (4) develop and program women's health and HIV-risk measures; and (5) pilot the measures with 200 homeless women in two Midwestern cities.

Title: **Race and HIV Risk: Contextual and Neurocognitive Influences on Sex Partnerships**
P.I.: **Leah Floyd**
Institution: **Johns Hopkins University, Baltimore, MD**
Grant No.: **5R21DA025543-02**
Award: **$246,574**

Currently, there is a hidden HIV epidemic among young adult African-American females with no history of substance abuse. These women are at increased risk for contracting HIV by virtue of their social/sexual networks. If successful, the proposed research project: (1) should provide insight into why African-American females have higher rates of HIV than their white counterparts; (2) highlight the importance of considering the contextual influences of drugs,

that is how drug markets change social structures and alter sexual norms and behaviors of entire communities; and (3) increase understanding of the processes through which neighborhood factors influence HIV risk. The primary aim of this R21 application in response to NIDA's ANSWHR Initiative (PAS-07-381) is to address gaps in literature focused on HIV risk and disparities among females. In the United States, as rates have increased among females, the rate of HIV/AIDS diagnoses for African-American females approaches 25 times the rate for white females. Despite the broad base of findings documenting health disparities in HIV, extant studies cannot explain why African Americans continue to be disproportionately affected. The proposed study requests two years of support for a cross-sectional epidemiologic examination of racial/ethnic differences in sexual partnerships among 220 females (110 Black and 110 White) residing in low socioeconomic status (SES) neighborhoods. Guided by ecosocial theory, they seek to explain why these differences exist across race/ethnicity. They will consider the extent to which neighborhood social and economic factors (e.g., drug markets) interact with race/ethnicity to produce different levels of HIV risk. They will expand drug abuse and HIV prevention research by, in addition to considering individual differences, examining the influences of neighborhood drug markets on the sexual behaviors, sexual partnerships, and rates of a sexually transmitted disease among young adult females residing in disadvantaged neighborhoods. Finally, the proposed study will move beyond descriptive social epidemiology and into identifying neurocognitive processes that mediate/moderate relationships between neighborhood factors and individual behavior. As a small-yet-growing base of research suggests, to the extent that individuals are able to make decisions, solve problems and control impulses, neurocognitive functions may serve as protective factors or pathways through which external social factors influence individual behavior. Identifying social factors that influence partner selection and individual level factors that may serve to reduce the adverse effects of living in disadvantaged neighborhoods will inform HIV prevention interventions for African-American and underserved women. If successful, the proposed research project: (1) should provide insight into why African-American females have higher rates of HIV than their white counterparts; (2) highlight the importance of considering the contextual influences of drugs, that is the influence of drug markets on social structures and sexual norms and behaviors; and (3) identify modifiable individual level factors linking neighborhood social and economic factors to individual HIV risk behaviors.

Title: **Emotions are Emergent Events Constrained by Affective and Conceptual Processes**
P.I.: **Lisa Barrett**
Institution: **Northeastern University, Boston, MA**
Grant No.: **5DP1OD003312-04**
Award: **$391,250**

Emotional states are central to mental and physical health. NIH invests tremendous resources in research on emotion, much of it devoted to animal models. Ironically, this research is guided by a scientific paradigm that is grounded in human experience. People experience fear and see it in others, so scientists assume there must be a literal (modular) neural circuit for fear in the mammalian brain. Rats freeze when they hear a tone paired with a foot shock, so they are presumed to be in a state of fear (versus surprise, anger, or even a general state of alarm) and undergoing "fear learning." Scientists also presume that a map of the neural circuitry of freezing behavior will yield a neural mechanism for fear that is largely preserved in humans, and a decade of neuroimaging studies have focused on locating a homologous neural circuit in the human brain. In the last 5 years, the researcher has traced the roots of this "natural kind" model, conducted a comprehensive review of the literature to examine its veracity, and found it wanting. In response, the researcher has fashioned a new systems-level model, called the Conceptual Act Model, grounded in the neuroanatomy of the human brain. This model

parsimoniously incorporates neuroscience findings from rats, primates, and humans, and explains the mechanisms that produce the range and variety of behavioral and introspective instances that they call "emotion". The Conceptual Act Model asks different—and perhaps better—questions about what emotions are and how they function in mental and physical health. The NIH Director's Pioneer Award will allow me the intellectual freedom and resources to continue building evidence for the Conceptual Act Model of emotion, thereby shaping a new paradigm to guide the scientific study of emotion.

Musculoskeletal Systems

Title: **A Link between Parity, Trunk Muscle Function, and Degenerative Spondylolisthesis**
P.I.: **Jacek Cholewicki**
Institution: **Michigan State University, East Lansing, MI**
Grant No.: **1R21AR056404-01A2**
Award: **$199,929**

The Study of Women's Health Across the Nation (SWAN) has compiled the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community-based samples. Of particular public health importance is that the continuation of SWAN will permit the study to increase understanding of the effects of these menopause-related changes on subsequent health and risk factors for age-related diseases. This study will examine relationships between pregnancy, cesarean section (CS) and other abdominal surgery, trunk and abdominal muscle deficiency, and degenerative spondylolisthesis (DS) in older females. The key question is whether pregnancy and/or CS mediated trunk muscle deficiency could be a precipitating factor in the development of DS later in life. Three Specific Aims are to determine whether: (1) parity/CS/other abdominal surgeries are associated with DS; (2) trunk muscle deficiency is associated with DS; and (3) parity/CS/other abdominal surgeries are associated with trunk muscle deficiency. The costs associated with the treatment of degenerative low-back disease make it one of the top 5 most expensive conditions in the American healthcare economy. DS is considered one of the major causes of low-back pain among the older population. Women suffer from DS at a rate of three to nine times higher than men, as yet, without a clear explanation. Previous studies documented relationships between pregnancy and low-back pain, and suggested abdominal muscle deficiency as an underlying cause. Of special concern is the effect of CS. The rates of CS rose three-fold over the last three decades and may cause significant public health problems regarding DS in coming years. They propose to conduct a case-control study of 200 DS patients and 200 age-matched (in 5-year age groups) controls, including a more detailed assessment of trunk-muscle function in 80 DS and 80 matched control subjects. Group designation will be based on a DS diagnosis from a sagittal view x-ray. The 400 subjects will be administered a detailed questionnaire regarding their parity, CS, previous surgeries, and other potential covariates. A subset of 80 subjects from each group will in addition undergo a physical examination of their abdominal and trunk muscle function and quantitative assessment of motor control. Physical exam will include abdominal muscle and hip extension tests. These tests examine the ability of the abdominal and paraspinal muscles to stabilize pelvis and the lumbar spine during simple hip flexion and extension maneuvers. Motor control tests will quantify muscle reflex latencies in response to sudden trunk perturbations, and postural control while balancing on an unstable seat. Both delayed muscle reflex responses and poor postural control are associated with low back pain and constitute predisposing risk factors to future low-back problems. Poor motor control could lead to spine instability, chronic problems and degenerative changes in the spine over time. All measures will be quantified (continuous or categorized) and used in the regression and chi-square analyses to test the

hypotheses. Innovative aspects of this proposal include quantifying muscle function objectively and documenting variables related to parity in women with and without DS, which gives a better chance of finding any relationships that might exist.

The Osteoarthritis Initiative

ORWH-supported Clinical Centers in the Osteoarthritis Initiative include the following:

Title: **Clinical Centers for The Osteoarthritis Initiative**
PI: **Charles B. Eaton**
Institution: **Memorial Hospital of Rhode Island, Pawtucket, RI**
Grant No.: **N01AR22262-12-0-1**

Title: **Clinical Centers For The Osteoarthritis Initiative**
PI: **Marc Hochberg**
Institution: **University of Maryland Baltimore, Baltimore, MD**
Grant No.: **N01AR22259-12-0-1**

Title: **Clinical Centers For The Osteoarthritis Initiative**
PI: **Rebecca Jackson**
Institution: **Ohio State University, Columbus, OH**
Grant No.: **N01AR22261-13-0-1**

Title: **Clinical Centers For The Osteoarthritis Initiative**
PI: **Kent Kwoh**
Institution: **University of Pittsburgh, Pittsburgh, PA**
Grant No.: **N01AR22260-13-0-1**

Award: **$650,000**

Knee osteoarthritis (OA) is the most common cause of disability in adults. The Osteoarthritis Initiative (OAI): A Knee Health Study is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA. Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury, or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and follow participants who have knee OA or are at high risk for developing knee OA for at least a 4-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and x-rays will be completed at each of four annual followup visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee OA. Levels of knee pain and physical disability will be assessed at study start and at each of the followup visits by questionnaire and examination.

Title: **Sexual Dimorphism of Skeletal Muscle**
P.I.: **Virginia H. Huxley**
Institution: **University of Missouri-Columbia**
Grant No.: **1R21HL093068-01A2**
Award: **$209,109**

This project is to develop and validate a skeletal-muscle model for the study of the primary functions of the smallest blood vessels in age-matched male and female animals of the same species, the mouse. The two primary functions of the microcirculation (1) blood flow to metabolizing tissue, and (2) the movement of nutrients from blood to tissue as well as the removal of wastes from tissue to blood, appear to differ between males and females in health and cardiovascular disease including hypertension and secondary to type 2 diabetes. As materials distribute themselves between blood and tissue, so too will fluids move between compartments; thus if exchange regulation differs between males and females it is likely that volume distribution will also differ. Therefore it is imperative to have access to a model to learn the differences and similarities between the sexes as the data from males, disease incidence and severity, and subsequent treatment strategies will not apply equally to females. Skeletal muscle (SKM) microvasculature has been studied extensively with respect to respiratory gas and nutrient exchange, volume distribution, and blood flow control, into and within the organ, in health and disease. This R21 is in response to a RFA requesting development of models for the study of function in males and females. This is terribly important as most studies of SKM have been conducted in males (animals and humans) with the presumption that the data apply equally to both sexes. Evidence from multiple studies accumulated over the last decade is making it clear that this assumption is in error. One model used widely for in vivo study is the rodent cremaster, a thin muscle derived from the abdominal wall that raises and lowers the testes. Surprisingly, no microvascular skeletal muscle preparation of equivalent metabolic and fiber type substitutes presently for the cremaster that facilitates study of both males and females. This proposal aims to rectify this lack by validating the abdominal wall skeletal muscle preparation in male and female rodents. The hypothesis is that microvascular skeletal muscle functions do not differ between age-matched males and females of the same species. Accordingly, three aims will be carried out in in situ and isolated abdominal muscle microvessels from age- and strain-matched female and male mice. Aim 1 will assess whether sexual dimorphism exists with respect to blood flow regulation from measures from microvascular diameter to selected endothelium-dependent and -independent agents. Given recent data they expect to reject their hypothesis as they anticipate that: (a) arterioles from males will develop greater basal tone; and (b) the dose-response relationship for the endothelium-dependent dilation will differ between males and females. Aim 2 will assess whether sexual dimorphism exists with respect to exchange regulation from measures from measures of microvessel solute permeability (Ps). Given their data, they expect to reject their hypothesis as they anticipate that: (a) venules from males will be leakier than those from females; (b) basal arteriole and capillary barrier properties will not differ by sex; and (c) the vasoactive agents will produce a variety of exchange responses reflecting differences in sex-specific mechanisms regulating solute distribution between the vascular and tissue compartments of males and females. Aim 3 will compare the sex, age, organ, and species matched diameter (Aim 1) and exchange data (Aim 2) from microvessels as they lay in the living tissue and following isolation from the tissue. This is an incredible opportunity to make these comparisons as not all tissues are amenable to study in situ and it is assumed that the data from the isolated vessels reflect the behavior in the tissue. Data from this project will form the foundation for future genetic, biochemical, and physiological studies of microvascular function in males and females. It is imperative to develop a validated model for study of microvascular function in both sexes to understand intelligently the sex-dependent

mechanisms regulating vascular function in health and dysfunction in disease. With this knowledge as the foundation it may be possible to provide a rational means to prevent and treat vascular disease specific to the needs of males and females.

Title: **Structural, Molecular, and Functional Specialization in Osteocyte Mechanosensing**
P.I.: **Sheldon Weinbaum**
Institution: **City College of New York**
Grant No.: **1R01AR057139-01A2**
Award: **$200,000**

Osteocytes are the cells in bone that sense mechanical loading and translate mechanical strain into biochemical signals that initiate modeling and remodeling through which bone adapts its structure to its mechanical loading environment. This ability is key to skeletal health; failure to adapt results in bone in fragility. Increases and decreases in osteocyte mechanosensitivity have been implicated in regulating the bone response to anabolic agents, and conversely the bone loss resulting from estrogen loss, respectively. Thus understanding how osteocytes "perceive" and transduce mechanical signals may provide key new insights into bone physiology leading to the identification of novel therapeutic targets against bone loss due to aging and disease. Osteocytes, the cells that reside within bone matrix, are the most abundant bone cells. They function as the mechanical sensors in bone, and are critical to activation and coordination of osteoclastic and osteoblastic activities by which bone adapts to mechanical usage, maintains its health and prevents fractures. The mechanisms underlying osteocyte mechanotransduction are not well understood, though changes in osteocyte mechanosensitivity have been implicated in regulating the effect of both bone anabolic agents and sex hormones. The investigators have developed engineering models which show that small whole bone strains can be amplified locally around osteocyte processes by focal attachments to the canalicular wall. Osteocyte cell bodies cannot see similar high strains as they are too compliant and lack the cellular attachments needed for local strain amplification. These mathematical models argue that the osteocyte cell process may be uniquely designed to function as a detector of small tissue strains. To test this hypothesis, they developed a broad-based multiple-PI program that combines expertise in ion channel physiology, in vivo osteocyte structure/biomechanics and bioengineering/modeling to understand how osteocytes perceive and transduce their local mechanical environment. This program will: (Aim 1) examine the functional polarity of osteocyte mechano-responsiveness using electrophysiological approaches on cultured osteocytes; (Aim 2) identify the molecular components of mechanotransduction complexes in osteocytes; (Aim 3) characterize the structure of the mechanotransduction complex in osteocytes in vivo; and (Aim 4) build integrative mathematical models relating local hydrodynamic forces and membrane strains at osteocyte processes and cell bodies to cellular responses in vitro and in vivo.. They have also developed a novel technology (Stokesian Fluid Stimulus probe) that allows us to hydrodynamically load osteocyte processes versus cell bodies at extremely low forces (<10pN) typical of what bone cells actually experience in vivo. Expansion of this technology to interrogate mechano-responsiveness in a broad range of cell types is a developmental goal of this grant. The significance of the study is that understanding how osteocytes "perceive" and transduce mechanical signals may provide key new insights into bone physiology leading to the identification of novel therapeutic targets against bone loss due to aging and disease.

Title: **Delayed Pubertal Development on the Mechanism of Bone Loss at Maturity**
P.I.: **Vanessa R. Yingling**
Institution: **Temple University, Philadelphia, PA**
Grant No.: **1R03AR057518-01A1**
Award: **$75,000**

Fracture risk in the elderly has its origins during growth and development. A delay in the onset of puberty results in both low bone mass and an increased incidence of stress fracture in young women. Therefore, the failure to accrue peak bone mass during the adolescent years represents a missed opportunity to optimize bone mass during one's life. Osteoporosis is "a pediatric disease with geriatric consequences." Simply stated, suboptimal skeletal development in childhood and adolescence may result in decreased bone strength and an increase in lifetime fracture incidence. A delay in the onset of puberty (primary amenorrhea) correlates with both low bone mass and an increased incidence of stress fracture. Suboptimal bone accrual may have long term consequences. Even with current treatment options as studies that treated amenorrheic dancers for 2 years with hormone replacement therapy found no difference in bone mineral density between treated and placebo groups. The most significant factors during development may be nutritional and lifestyle factors. Therefore, their overall goal is to ascertain the affect of delayed pubertal development on the mechanism of bone loss at maturity. Density measures alone, although widely used clinically, cannot identify osteoporotic subjects who will sustain fractures, due to the large overlap in bone mass measures in individuals with fractures and those without fractures. Other factors including bone size, architecture and material properties must be considered. They have recently developed a texture analysis approach using Gabor filters, which is capable of providing insight into bone structure from localized texture information on a pixel level. The texture approach is therefore a potentially powerful tool in analyzing trabecular bone texture where orientation, shape, and architecture as well as density are the fundamental components. Their previous work was analyzing 2-D images but they propose to transfers this approach to 3-D images. This novel approach will indicate not only bone mass changes but changes in orientation which may be very significant later in life. In Aim 1, they will test the hypothesis that the mechanism and magnitude of bone loss in a mature animal is dependent on bone development. Specifically, delayed pubertal onset will alter the architecture of bone that will affect the mechanism of bone loss at maturity. Pubertal delay will be completed by gonadotropin releasing hormone antagonist (GnRH-antagonist) injections. At 50 days of age changes in bone morphology will be evaluated using a novel 3-D texture analysis. The following biomarkers will be measured to assess the response of pubertal delay on systemic changes in bone metabolism osteocalcin (a marker of bone formation) and N-telopeptide of collagen type I (NTx) (a marker of bone resorption). Serum estradiol and IGF-1 will also be assayed to confirm the hormonal response to the protocol. Flourescent histomorphometry will assess bone formation rates on trabecular bone. At maturity (150 days of age) the experimental rats will undergo ovariectomy surgery to model post menopausal bone loss. Changes in bone morphology will be evaluated using static and dynamic histomorphometry, micro-CT and texture analysis. By using a systems approach relating environmentally induced delayed puberty to bone growth, they propose to gain a new understanding of the important relationship between growth and its variability and the bone structure they become heir to during the aging process.

Neurology/Neurosciences

Title: Identification and Validation of Human Hypothalamic Nuclei In Vivo and Ex Vivo Using 7 Tesla MRI
P.I.: Nikolaos Makris
Institution: Massachusetts General Hospital, Boston
Grant No.: 5R21MH084041-02
Award: $221,250

Hypothalamic nuclei will be identified in living humans using high field magnetic resonance imaging (MRI) (i.e., a 7 Tesla scanner) and in ex vivo human hypothalamic tissue. The MRI results will be compared with postmortem human tissue to assure methodological validation. These hypothalamic nuclei are key regulators of autonomic and endocrine functions implicated in numerous psychiatric and medical disorders with known sex differences such as depression and schizophrenia. Understanding sex differences and the hypothalamic involvement in relation to neurological, psychiatric, cardiovascular, endocrine and sleep disorders is very relevant for public health in general and women's health in particular. There is increasing evidence regarding the importance of the hypothalamus for understanding women's health and sex differences in relation to neurological, psychiatric, endocrine and sleep disorders. In fact, hypothalamic nuclei, key regulators of autonomic and endocrine functions, are some of the most highly sexually dimorphic nuclei in the brain and implicated in psychiatric and medical disorders with known sex differences. They would argue that an understanding of hormonal effects on the brain and the regulation of other organs and/or systems, such as the cardiovascular and reproductive systems, are critical as downstream effects of hypothalamic activity. Thus an understanding of the neuroanatomy of hypothalamic nuclei and how they are differentially disrupted in men and women in specific disorders will contribute to elucidating sex differences in clinical medicine. However, the identification of hypothalamic nuclei in vivo in humans has not been realized. This is important since studies have shown the association of the hypothalamus, endocrine dysfunction and sex differences in psychiatric disorders. In fact, the paraventricular hypothalamic nucleus (PVN) is enlarged in patients with major depressive disorder (MDD), in PVN neurons that are dense in corticotropin releasing hormone (CRH) and estrogen receptor (ER)1. In their recent work in schizophrenia (SCZ) they identified structural abnormalities using MRI in the hypothalamus particularly in the PVN in women. Furthermore, in healthy women they showed, using functional MRI, regulation of brain activity in hypothalamic nuclei such as the PVN, dependent on gonadal hormone changes over the menstrual cycle. The principal focus of this study is to use a new in vivo methodology for the assessment of the hypothalamus comparing neuroimaging data using 7 Tesla magnetic resonance imaging (MRI) and human postmortem validation. The proposed study aims to identify the PVN in vivo and ex vivo in the human hypothalamus using high field MRI, to investigate the relationship of the MRI methodology and the histological technique, and to establish the correlates of the histological structures with the MRI representations. In addition to the PVN, which is critical for its role within the hypothalamic-pituitary-adrenal (HPA) axis and its dysfunction in MDD and SCZ, they will identify the supraoptic nucleus (SON), which will be used as a control region. High-resolution 7 Tesla MRI will be carried out in thirty healthy subjects, and four ex vivo human hypothalamic samples. Their overarching goal is an innovative methodological one: to identify the PVN of the human hypothalamus in healthy adult women and men in vivo. They expect this method, once defined, to be applied clinically in subjects with MDD and SCZ.

Title: **Cellular and Molecular Basis of Hippocampal Atrophy in Depressed Female Monkeys**
P.I.: **Carol A. Shively**
Institution: **Wake Forest University Health Sciences, Winston-Salem, NC**
Grant No.: **5R21MH086731-02**
Award: **$185,000**

Depression is a significant health problem in the United States, particularly in women, as 20 percent of reproductive-aged women experience clinically significant depression. Unfortunately, very little research has been conducted in female animal models of depression. The use of the first primate model of adult depression in females proposed here, which has greater similarity to human neurobiology and depression than rodent models, will advance their understanding of the neurobiology of depression especially in women. Clinical and experimental studies suggest that hippocampal volumes may be smaller in individuals with depression, although the cellular mechanisms underlying this relationship are unclear. Stressful life events are associated with an increased risk of depression and animal models exposed to chronic stress have been used previously to investigate hippocampal shrinkage in depression. Although the data from preclinical stress models are compelling, the degree to which stress responses in animal models are relevant to human depression remains controversial, particularly since women are at two-fold greater risk of depression and the animal models are mostly male rodents. Evaluation of the causes of reduced hippocampal volume in an experimental model that more closely resembles human depression would be valuable. They have developed a primate model of depression in adult female cynomolgus monkeys which closely resembles human depression, and recently observed that depressed monkeys have relatively small anterior hippocampi (HC). The overall goal of this proposal is to evaluate hippocampal morphologic, cellular, and molecular characteristics in depressed and nondepressed female monkeys to determine whether the smaller hippocampi of depressed female monkeys are accompanied by reductions in neutrophils and synaptic, spinous, and dendritic integrity. They have a unique and valuable collection of fixed, frozen hippocampi derived from the population of adult female monkeys in which the behavioral and physiological characteristics of depression were studied premortem for 4 years. Using the tissue from eight depressed and eight nondepressed monkeys they will determine astrocyte, pyramidal, and granule neuron size and number, and protein and mRNA levels of markers of synaptic, spinous, and dendritic integrity in the cornu ammonis (CA) CA1, CA2, CA3, and dentate gyrus of the anterior and posterior HC of behaviorally depressed and nondepressed monkeys. The results of this study will establish the use of the model in future investigations of the mechanisms of depression and the efficacy of interventions for depression. The research is particularly responsive to the FOA entitled "Advancing Novel Science in Women's Health Research" (PAS-07-381). The results of the proposed study will be used in support of a competitive NIH application.

Title: **Sex-Specific Gene Regulation of Neuronal Chloride Co-Transporter Kcc2**
P.I.: **Wolfgang B. Liedtke**
Institution: **Duke University, Durham, NC**
Grant No.: **5R21NS066307-02**
Award: **$195,000**

Neuronal chloride dictates nerve cells' excitability, and is reduced in chronic pathological pain as well as in certain forms of epilepsy, diseases characterized by therapeutic refractoriness and strong female preponderance. Experiments are described that will elucidate the regulation of the dominant electroneutral chloride transporter of mature neurons, Kcc2. Estrogen and xenobiotic estrogen-mimetics will be used for stimulation of primary cortical neurons in

culture, which will be maintained strictly separate for male versus female, based on a novel methodology platform described here. Neurons derived from late-pregnancy embryos of rats and mice, the latter genetically encoded to lack functional estrogen-receptors, will be subjected to assays probing function and regulation of the kcc2 gene, namely reporter gene assays and measurement of neuronal chloride. Chronic pathological pain and certain epileptic syndromes are neuropsychiatric disorders that share an increased female prevalence and refractoriness to treatment. The latter feature is considered to be linked to pathologically increased neuronal excitability caused by increased neuronal chloride (Cl-), which in turn is rooted in downregulation of the dominant neuronal Cl--transporter, Kcc2, which extrudes Cl-. Here they propose experiments to elucidate sex-specific regulation of the kcc2 gene by estrogens, based on a hypothesis that neuronal Cl- is dysregulated in response to neuronal injury in a sexually dimorphic manner, with the consequence of rendering women more susceptible to the above diseases. They have obtained exciting preliminary results (1) showing that kcc2 transcription is regulated by the repressor REST/NRSF which binds to a novel RE1/NRSE DNA binding site in kcc2 regulatory regions, (2) demonstrating this regulation to underlie the early developmental transformation of GABAergic transmission from excitatory to inhibitory, (3) developing a novel method to culture cortical primary neurons from individual rat E17 embryos which are being sex-typed by X- and Y-chromosome-specific DNA markers. The latter method, straightforward yet possibly a groundbreaking novelty, permits strictly separate female versus male primary cortical neuronal culture. They intend to elaborate molecular mechanisms how neuronal Cl- and Kcc2 are regulated sex-specifically by exposing male versus female neurons to 17-estradiol and xenobiotic estrogen-mimetics. For this, they will electroporate kcc2 reporter gene constructs, wildtype and mutated for binding sites, driving a secreted luciferase reporter, which will facilitate establishment of a time-course of kcc2 transcription. For direct determination of Cl-, the fluorescent Cl--indicator clomeleon will be co-transfected. Cultures will be exposed to physiologically relevant concentrations of estradiol and practically relevant concentrations of xeno-estrogens (coumestrol, bisphenol-A, dieldrin). Use of the latter compounds will allow us to address modulation of estrogen responses by these ubiquitous compounds. Any sex-specific regulation will be confirmed in primary cultures derived from gene-targeted mice (estrogen-receptor (ER)-a, - and non-classical-ER-knockin). These experiments will be conducted in a highly collaborative environment at Duke University, involving molecular and physiology neuroscience labs, in addition to molecular endocrinology and environmental toxicology input. Results can be expected to shed new light on a fundamental matter, neuronal Cl--regulation, which very likely has sex-specific regulation as a basis for increased female prevalence in therapy-refractory neuropsychiatric diseases.

Title: **Sex Differences in the Central Nervous System During Disease**
P.I.: **Rhonda R. Voskuhl**
Institution: **University of California, Los Angeles**
Grant No.: **1R21NS071210-01**
Award: **$231,000**

This is an exploratory (R21) grant to determine the effect of sex chromosomes and sex hormones on the central nervous system's (CNS's) response to an immune attack using the multiple sclerosis model, experimental autoimmune encephalomyelitis. This proposal will establish a model system to determine the effect of sex chromosomes and sex hormones on a variety of neurological diseases characterized by a sex difference. Numerous neurological diseases are characterized by a sex difference. The neuropathology often includes infiltration of immune cells, with this immune infiltration potentially contributing to disease pathogenesis. Since it is known that sex differences exist in the immune system, this confounds investigations into sex differences in the CNS. Thus, they will use bone marrow chimeras to investigate sex differences in the CNS. By varying sex chromosomes or sex hormones in hosts reconstituted

with a common immune system, one can ascertain the role of sex chromosomes and sex hormones on the brain response to injury. They will use one of the most inflammatory of all CNS disease models, the multiple sclerosis model, experimental autoimmune encephalomyelitis (EAE), to show applicability of this approach to a variety of neurological diseases. They will employ mice which differ in the complement of sex chromosomes (XX vs. XY), while having the same gonadal type, to determine the effect of sex chromosomes in the absence of confounding effects of exposure to different types of sex hormones. Specifically, in Aim 1 they will determine whether the greater severity of EAE in XX, as compared to XY mice is due to sex chromosome effects in the CNS. In Aim 2, they will determine if the sex chromosome effect in the CNS during EAE is due to the dose of X or Y genes. Finally in Aim 3, they will use mice which differ in gonadal type, female versus male, while having the same sex chromosome complement (XX vs. XX Sry) to determine whether the greater severity of EAE in female, as compared to male, mice is due to sex hormone effects in the CNS.

Nutrition

Title: **National Food and Nutrient Analysis Program (NFNAP)**
Institution: **National Cancer Institute/U.S. Department of Agriculture, Bethesda, MD**
Grant No.: **Y1-CN-501054**
Award: **$50,000**

The NFNAP is a research program that seeks to achieve sound estimates of dietary components and thus, improvements in nutrient values with particular focus on components with possible roles in human health. The project, directed by the Nutrient Data Laboratory (NDL), Agricultural Research Service, USDA, was initiated in 1997 and recently renewed in collaboration with the NIH National Cancer Institute and the Office of Dietary Supplements, ORWH, and other supporting NIH Offices, Institutes, and the FDA. The primary outcome of the program will be a body of nutrient data representative of the U.S. population intake and consumption patterns with unprecedented analytical quality. This is a collaborative, interdisciplinary project with the NFNAP. Specifically, the two leading causes of death in women in the U.S. are: (1) cardiovascular disease; and, (2) cancer. The NFNAP may prove particularly relevant to these women's health issues because the food consumption and composition databases target those foods that are major contributors of public health significance in the U.S. Specifically, the five objectives of the NFNAP are to: (1) sample and analyze selected key foods; (2) institute a monitoring program for key foods; (3) develop databases for foods consumed by U.S. ethnic subpopulations; (4) develop and update databases for bioactive food components; and (5) develop and validate databases for dietary supplement composition. Moreover, the NFNAP may be significant to research on women's health on several different levels. Better estimates of the mean nutrient content of foods and variance indicators will permit more accurate assessment of nutrient intakes by individuals. This will improve the ability to detect etiologic relationships, delineate biologic mechanisms, assess time trends in nutrient intake, and define populations at nutritional risk. Further, the NFNAP may provide background data supporting nutritional guidance and communications focused specifically on women.

Obesity/Overweight

Title: Intervening on Spontaneous Physical Activity to Prevent Weight Regain in Women
P.I.: Barbara J. Nicklas
Institution: Wake Forest University Health Sciences, Winston-Salem, NC
Grant No.: 5R21HL097252-02
Award: $156,894

Weight loss programs using caloric restriction and regular, structured exercise can lead to a reduction in physical activity performed outside of the planned exercise sessions. This study will test whether or not women reduce their spontaneous daily physical activity more than men with weight loss, and whether this reduction can be prevented by using self-monitoring, thereby slowing or preventing weight regain. Since reductions in spontaneous physical activity could potentially negate the intent of a structured exercise program for weight loss therapy, it would be important to know whether recommendations for weight loss maintenance in women should include promotion of spontaneous physical activity, rather than structured exercise, during and following a period of intensive weight loss. Recommendations for more effective long-term weight loss strategies may need to consider the role of gender differences. If, as shown in female versus male animal models, negative energy balance resulting in weight loss results in greater compensatory reductions in energy expenditure in women compared to men, obesity treatments may need to be tailored in women to override these reductions in total energy expenditure. Their approach focuses on a behavioral strategy (self-monitoring) to eliminate the compensatory reduction in non-exercise 'spontaneous' physical activity (SPA) seen in women who lose weight by means of a hypocaloric diet and structured exercise training. Their long-term research goal is to establish empirical evidence for innovative treatment options that are more effective in producing weight loss and preventing weight regain in women. The main goal of this pilot is to provide preliminary data and effect estimates to begin to test their overall hypothesis that prevention of weight loss-induced reductions in SPA will be more beneficial for long-term maintenance of weight loss in women than in men. They propose to conduct a pilot study using a two-arm, 10-month design in 72 obese, older (55–70 yrs) men and women (n=36 per group). Participants will be randomized to a 5-month standardized weight loss intervention involving a hypocaloric diet and aerobic exercise (DIET+EX) or to the same weight-loss intervention with addition of a behavioral component that targets self-monitoring (SM) of SPA (SM+DIET+EX), and then followed for another 5 months after weight loss. The primary Specific Aims of this R21 exploratory/developmental application are to examine whether SPA self-monitoring results in less body weight regain in the followup phase in both men and women. The secondary Specific Aims are to examine whether: (1) women regain more weight than men in the followup phase; (2) SPA self-monitoring and gender have an effect on change in weight in the intensive weight loss phase; (3) SPA self-monitoring and gender have an effect on change in SPA in the intensive weight loss phase; (4) there is an association between SPA changes in the weight loss phase and weight regain in the followup phase. They anticipate that the results will lead to a larger and longer trial to definitively test their hypothesis, which could potentially provide evidence against the current standard of care (i.e., exclusive prescription of structured moderate-intensity exercise) for obesity therapy in women and may lead to sex-specific treatment guidelines.

Pain

Title: Sex Differences in Acute Pain and Analgesic Responses
P.I.: Barbara A. Hastie
Institution: University of Florida, Gainesville
Grant No.: 5R21DE019267-02
Award: $181,294

Pain is one of the most costly and pervasive public health problems in the United States, and women are at increased risk for under-treatment of pain. This study will use a common acute clinical pain model to identify and characterize psychosocial, physiological and genetic factors that contribute to sex differences in pain perception, analgesia and side effects. The ultimate goal is to develop translational research that will reduce the increased burden of clinical pain in women through the development of tailored interventions designed to enhance the quality of life for women, consistent with priorities of the NIH Office of Research on Women's Health. Pain is one of the most costly and pervasive public health problems, with women and minorities facing increased risk for under-treated and mismanaged pain. Women, compared to men, report more frequent and intense pain and have increased prevalence of debilitating pain across a multitude of conditions. Women also represent the majority of the 40 million outpatient and ambulatory surgeries conducted each year. Acute postoperative pain and under-treatment of pain are well documented and lead to prolonged recovery and potentially to development of chronic long-term pain conditions. Despite incongruent findings of sex differences in analgesic efficacy, consistent reports show that women experience between 30 percent and 75 percent more adverse drug reactions (ADRs) compared to men. ADRs can lead to life-threatening complications, discontinuation of pain treatment, prolonged recovery, and noncompliance. Recent pharmacogenomic studies have demonstrated that genotype may contribute to sex differences in pharmacokinetic (PK) and pharmacodynamic (PD) responses to certain drugs. Genetic and nongenetic contributions to sex differences in opioid analgesia, related side effects and treatment outcome have received limited attention in the field of pain research. This study will use a common acute clinical pain model to identify and characterize psychosocial, physiological and genetic factors that contribute to sex differences in pain perception, analgesia and side effects. Aim 1 will determine sex differences in perceptual and physiological responses to acute post-operative pain and will examine how those are related to genetic, pre-operative psychophysical and psychosocial factors. Aim 2 will determine sex differences in opioid analgesia and side effects and will examine genetic, PK, PD, and psychosocial factors that explain group differences in analgesic responses. One hundred and forty male and female patients (age range 16–45) who undergo third molar extraction will be included in this study. Preoperatively, they will assess experimental pain responses and psychosocial measures. They will monitor postoperative pain levels along with PK/PD responses to the opioid fentanyl. They will examine sex differences in postoperative pain, analgesic responses, and side effects immediately and for several hours post-surgery and for 3 days post-procedure. The study is designed to build a foundation for an R01 grant proposal supporting an independent line of clinically-relevant experimental pain research. This project will enhance understanding of translational research in pain as well as biopsychosocial factors that contribute to health disparities in pain and its treatment, particularly for women. Additionally, this study will provide insight into the complex genetic, PK/PD processes involved in postoperative pain and analgesic responses and will elucidate biopsychosocial contributions to sex differences in pain and side effects. The ultimate goal is to develop translational research that will reduce the increased burden of clinical pain in women through the development of tailored interventions designed to enhance the quality of life for women, consistent with priorities of the NIH Office of Research on Women's Health.

Title: **Epidemiology of Patellofemoral Pain Syndrome: Identifying Gender-Specific Risk Factors**
P.I.: **Michelle Clara Boling**
Institution: **University of North Florida, Jacksonville**
Grant No.: **1R03AR057489-01A1**
Award: **$72,866**

Patellofemoral pain syndrome (PFP) is one of the most common chronic knee conditions affecting young adults, with an increased occurrence in females. Individuals suffering from this condition may experience symptoms lasting multiple decades, limiting their participation in physical activity, and predisposing them to chronic diseases associated with inactivity such as obesity, arthritis, coronary artery disease, diabetes, and cancer. The results from this investigation may be used to identify those at greatest risk to PFP and develop appropriate prevention programs to decrease the occurrence of this condition, particularly in females. Patellofemoral pain syndrome (PFP) is one of the most common causes of knee pain, affecting approximately 25 percent of the physically active population, with females being 2-3 times more likely to develop PFP compared to their male counterparts. The overall objective of this proposal is to determine the mechanical (structural and biomechanical) and non-mechanical (demographic and psychosocial) risk factors that are associated with PFP and identify the risk factors specific to females and males. The approach will be to use a prospective cohort design to identify risk factors that are associated with incident PFP. The central hypothesis is that individuals who develop PFP will have altered movement patterns, abnormal lower extremity anatomical alignments, decreased lower extremity strength, previous history of knee injury, previous participation in a low number of athletic activities, decreased levels of hardiness, and increased number of healthcare visits. A secondary hypothesis is that females and males will have different risk factor profiles. They will utilize baseline risk factor data that has been collected on 5,690 freshman (males=3,482, females= 2,208) during the summers of 2005−2008 at the United States Naval Academy, the United States Military Academy, and the United States Air Force Academy. Baseline risk factor data was collected through a current NIH funded project (R01-AR054061001), entitled JUMP-ACL. Participants will contribute followup time for incident PFP until they graduate from their respective academies. Medical record reviews will be performed to identify those participants who developed PFP during their followup times. Based on the 2 years for the proposed investigation, followup time will be 4 years for all participants enrolled in the JUMP-ACL investigation from 2005−2008. Poisson regression analyses will be performed to determine the risk factors for PFP. Additionally, males and females will be analyzed separately to determine gender-specific risk-factor profiles. The proposed project is making an efficient use of already collected risk-factor data by adding analysis of a new outcome (PFP) that would not otherwise be investigated by the JUMP-ACL project. Additionally, the proposed investigation is cost effective due to no funds being required for baseline data collection. Their rationale for the proposed investigation is that there is a crucial need for prospective studies that identify the risk factors for PFP so that more focused prevention strategies can be developed that are appropriately gender specific.

Title: **Pain and Endometriosis: Effects on Ectopic Cyst Innervation and Axons**
P.I.: **Geoffrey M. Bove**
Institution: **University of New England, Biddeford, ME**
Grant No.: **5R21HD053510-03**
Award: **$171,069**

In these studies they plan to develop their recently developed model of sciatic endometriosis to make novel inquiries regarding the etiology of endometriosis-related pain. The information that this study will yield stands to improve diagnostic awareness and mechanistic

understanding, and thus therapeutic approaches, of the treatment of the symptoms of endometriosis. As a result of this research, consideration and specific examination of nerves within the pelvis during ablative laparoscopic techniques may become an important additional diagnostic procedure for women with endometriosis. Women with endometriosis often have significant pain. Modern studies have implicated the neo-innervation of endometrial cysts as a primary source of this pain. However, the presence of nerve fibers does not necessarily specify their function and cannot determine whether, or in which situations, they are active. There has been no investigation to functionally characterize the effect of endometrial lesions on nerves or on axons. Their laboratory has focused on the effects of inflammation on axons. They have shown that nerve inflammation induces ectopic mechanical sensitivity of nociceptor axons, which are not normally sensitive. Their data also indicate that nerve inflammation induces ongoing activity that arises from both the inflamed site and/or the cell body, and that sympathetic neuronal activity is decreased during nerve inflammation. Recently they adapted the model of rat endometriosis to involve the sciatic nerve. This model is very similar to the rat endometriosis model where a section of uterus is transplanted to an intraperitoneal site. In preliminary data, a uterine section was transplanted to the sciatic nerve. Three complimentary electrophysiological methods are proposed to determine the characteristics of the effect of uterus, endometrium, and myometrium on the sciatic nerve. First, the proportion of through-conducting axons will be determined. Then, teased fiber recordings will be made from the dorsal roots in some experiments and from the distal end of peripheral nerves in other experiments. This combination of methods offers the advantage that sensory and sympathetic axons that pass through the cyst, as well as those innervating the cyst, can be studied. They will determine if the axons passing in close proximity to the cyst or directly innervating the cyst develop ongoing activity and/or mechanical sensitivity. Recordings will be made 3 months post surgically, after the cysts become stable, and the results compared to myometrium or fat transplant, and unoperated nerves. Because preliminary results revealed the presence of intraneural immune cells, they will determine whether the lesions of endometriosis damage axons. Importantly, they will use not only full thickness uterus, but also isolated endometrium and myometrium, and evaluate the viability of these specific tissues to form cysts. Using immunohistological methods, they will determine the extent of neutrophil and macrophage invasion of the nerve-uterus complex. They will also determine if axons are damaged using ninjurin and fluoro-jade, assessing the presence in both axons and dorsal root ganglion cells. These studies will determine the function and thus the importance of the ectopic innervation of endometrial cysts, as well as the effects of the lesions on through-conducting axons. The results of this study will impact the understanding of endometriosis pain and seed further research into the pain mechanisms of endometriosis.

Title: **Functional Networks in Migraine**
P.I.: **Todd Schwedt**
Institution: **Washington University in St. Louis, MO**
Grant No.: **1K23NS070891-01**
Award: **$163,523**

Migraine is an exceedingly common disease, affecting 12 percent of the population. Migraine results in substantial disability due to headache pain, hypersensitivities to environmental stimuli, and skin sensitization. Unfortunately, migraine is poorly understood and can be difficult to treat. This study will employ advanced neuroimaging techniques to investigate functional networks in the brain that may explain the relationship between migraine headache and hypersensitivities, as well as how environmental stimuli trigger a migraine attack. Description of these functional networks will allow for future investigations into methods to normalize or block activation of these networks, methods that may reduce migraine symptoms and improve the lives of millions of migraine sufferers. Migraine attacks are characterized by

moderate to severe pain, nausea, vomiting, increased sensitivity to lights, sounds, and odors, and cutaneous allodynia. Migraine, which afflicts 36 million Americans, causes substantial individual and societal burden. Although individual migraine attacks last for several hours to a few days, there is often persistence of hypersensitivities such as photophobia, phonophobia, and osmophobia and cutaneous sensitization between migraine attacks. Furthermore, migraine attacks can be triggered by light, noise, and odors. The mechanisms for interictal persistence of these symptoms and the mechanisms by which environmental stimuli trigger migraine attacks are unknown. In this set of experiments they address these associations by using functional magnetic resonance imaging to investigate functional networks in episodic and chronic migraine subjects. The Specific Aims will test the following hypotheses: (1) stimulus-induced deactivation of the default mode network is less in migraine subjects compared to non-migraine controls; (2) migraineurs have stronger functional connectivity among regions of the brain responsible for pain processing and between these pain processing regions and those responsible for processing of auditory, visual, and olfactory stimuli; (3) abnormal default mode network deactivation and stronger functional connectivity among pain regions and between pain regions and regions of the auditory, visual, and olfactory networks are positively associated with greater migraine burden. It is necessary to establish and assess functional networks in migraine so that future studies can investigate methods to normalize potentially aberrant networks and block activation of these networks, actions that may prevent and alleviate migraine symptoms. The candidate is an Assistant Professor of Neurology and Anesthesiology and Director of the Washington University Headache Center in St. Louis. The candidate's short-term goal is to enhance his functional neuroimaging skills so that he can transition from mentored to independent patient-oriented research employing functional imaging to investigate the pain and associated symptoms (hypersensitivities to and triggering of migraine by sound, light, and odors and cutaneous sensitization) of migraine. Once the relationships between migraine headache and these associated symptoms are described, the longer-term goal is to explore mechanisms by which to normalize these relationships or block activation of functional networks that lead to migraine symptoms. The interdisciplinary team of world-class mentors and the extensive intellectual and physical resources available at Washington University will optimize the candidate's training experience and likelihood for successful transition to independent research.

Reproductive Health/Developmental Biology

Title: **Advancing Research on the Sexually Transmitted Female "Nuisance" Pathogen *Trichomonas vaginalis***
P.I.: **Jane Carlton**
Institution: **New York University School of Medicine**
Grant No.: **5R21AI083954-02**
Award: **$211,250**

Trichomoniasis, caused by the eukaryotic parasite *Trichomonas vaginalis*, is the most common nonviral, sexually transmitted infection worldwide. It has been long considered a female "nuisance" disease. The goal of this project is to determine the genetic diversity of the parasite in women attending sexually-transmitted disease (STD) clinics in New York City, and to use these extant isolates in the development of a model system for the study of colonization of the vagina. Trichomoniasis is the most common nonviral STD, estimated to cause ~174 million infections worldwide each year. The *Trichomonas vaginalis* parasite resides in the urogenital tract of both sexes and can cause vaginitis in women and urethritis and prostatitis in men. However, the disease is known more as a female "nuisance" condition, which has resulted in a lack of scientific and medical attention and scant interest by public health officials in developing trichomoniasis control programs. Acute infections among women are associated with pelvic inflammatory disease and adverse pregnancy outcomes. Most alarming is the

recognition that *T. vaginalis* infection appears to increase women's susceptibility to HIV-1 infection. Because of the association between *T. vaginalis* and risk for HIV-1 acquisition, interventions to reduce *T. vaginalis* infection and transmission would likely result in fewer HIV-1 infections. Completion of the *T. vaginalis* genome sequence in 2007 has significantly increased their knowledge concerning the biology and mechanisms of pathogenesis of the parasite, but significant gaps remain. In particular, the genetic diversity of the parasite is not known, i.e., whether the parasite is maintained as a clonal population, or whether genetic exchange occurs between parasites in the urogenital tract. The extent of genetic diversity has implications for the control of the disease, for example it determines how virulent parasites spread or how they may evade a vaccine. The focus of this R21 proposal is to examine the genetic diversity of *T. vaginalis* infecting women attending eight New York City Bureau of STD clinics in inner city areas, and to use some of these isolates to develop a standardized and accessible in vitro model system for the study of colonization of the vagina by the parasite. A panel of polymorphic genetic markers - microsatellites and single copy genes - will be developed using the *T. vaginalis* genome sequence, and used to genotype *T. vaginalis* isolates identified in vaginal swabs taken from women attending the clinics. Knowledge of the genetic diversity and colonization characteristics of the parasite will provide important data points for subsequent studies, for example determining associations between *T. vaginalis* genotypes and the commensal microbes that make up the vaginal "microbiome".

Title: **The Role of GPR54 Signaling in Pubertal Disorders**
P.I.: **Suzy Drumond-Carvalho Bianco**
Institution: **University of Miami School of Medicine, FL**
Grant No.: **3R21HD059015-02S1**
Award: **$65,912**

The long-term goal of this project is to identify factors that regulate the timing of pubertal onset and reproductive maturation. The identification of GPR54, a G-protein coupled receptor, and its ligand, kisspeptin, as upstream regulators of GnRH secretion has led to intense research to elucidate their roles in the regulation of the reproductive axis. Inactivating mutations in GPR54 cause failure to undergo puberty and infertility. In contrast, early stimulation of this receptor triggers precocious puberty in mice. Their preliminary results indicate that GPR54 is desensitized and internalized in response to continuous kisspeptin stimulation, and that a GPR54 amino acid substitution identified in a female patient with central precocious puberty (a disorder with disproportionately high female incidence) increases GPR54 responsiveness by delaying the desensitization of the receptor. Thus, they hypothesize that the timing of signaling and desensitization of GPR54 is critical for its role in controlling puberty and reproduction, and that amino acid substitutions in GPR54 may affect its responsiveness by interfering with signaling or desensitization, thereby contributing to the clinical presentation. Although G-protein coupled receptor desensitization is generally strongly regulated, no data have been published on GPR54 desensitization. The short term goal of this project is to define the mechanisms underlying GPR54 desensitization, in order to understand how genetic mutations of this receptor affect these mechanisms and hence the timing of pubertal onset and sexual maturation. Specifically, the aims of this proposal are to define: (1) the mechanisms of GPR54 desensitization, focusing on the roles of phosphorylation and arrestin recruitment; (2) the mechanisms of GPR54 internalization, focusing on the roles of arrestin, dynamin, and clathrin; and (3) the fate of the internalized GPR54, to determine whether the receptor is directed to lysosomal degradation or recycled back to the plasma membrane. In each case, the effects of two mutations in GPR54, one identified in a patient with precocious puberty, and the other in a patient with hypogonadotropic hypogonadism, on these pathways will be determined. A thorough understanding of the mechanisms underlying GPR54 signaling may uncover the basis of gender differences in normal and abnormal pubertal development, as well as

reveal a new array of potential targets of pharmacological manipulation for the treatment and prevention of abnormal pubertal development and possibly other reproductive disorders. The goal of this project is to define the mechanisms underlying the regulation of GPR54 receptor signaling and desensitization, in order to understand how genetic mutations of this receptor affect these mechanisms and hence the timing of pubertal onset and sexual maturation. These studies are expected to offer important contributions to their understanding of the mechanisms underlying the reproductive disorders in the patients carrying the mutations. These insights, in turn, may contribute to future development of therapies designed to modulate the timing of puberty by manipulating the kisspeptin-GPR54 signaling system.

Title: **Physiological Reactivity to Acute Stress During Pregnancy**
P.I.: **Lisa Michelle Christian**
Institution: **Ohio State University, Columbus**
Grant No.: **5R21HD061644-02**
Award: **$221,012**

This study will fill important gaps in their knowledge regarding physiological adaption during pregnancy and effects of race on such adaptation. Information gained from this study will provide the groundwork for the following: (1) identifying women at greater risk of negative perinatal outcomes; (2) describing physiological mechanisms underlying the link between stress and risk of preterm delivery; and (3) providing interventions designed to reduce the effects of stress and promote healthy pregnancy and fetal development. Preterm delivery, an increasingly frequent occurrence in the United States, is associated with significant family burden and an estimated societal cost of at least $26 billion per year. In the United States, the preterm birth rate is 12–13 percent as compared to 5–9 percent in other developed countries. Persistent racial disparities contribute to this discrepancy. Psychosocial stress and related physiological sequelae may contribute to preterm birth overall, as well as to racial disparities in preterm birth. The experience of chronic stress, such as that conferred by racial minority status, may sensitize physiological stress responses. Indeed, as compared to Caucasians, African-Americans exhibit greater cardiovascular reactivity to a variety of acute stressors. Importantly, blood pressure, glucocorticoid, and catecholamine responses to acute stress are attenuated during healthy pregnancy as compared to nonpregnancy. This adaptation may protect the mother and fetus from potentially detrimental effects of maternal physiological activation. Thus, women who exhibit greater and more extended physiological reactions to everyday stressors may be at increased risk for negative perinatal outcomes. Notably, no studies of acute stress during pregnancy have examined inflammatory immune responses or mechanisms underlying blood pressure change (i.e., cardiac output, total peripheral resistance). Moreover, limited information is available regarding effects of race on physiological adaptation to pregnancy. The current study will address important gaps in the literature by examining cardiovascular, endocrine, and immune reactivity to acute stress among 40 healthy pregnant women (20 Caucasian, 20 African-American) and 40 demographically matched nonpregnant control women. This research is designed to ultimately lead to the identification of women at greater risk for negative perinatal outcomes and elucidation of mechanisms underlying increased risk, providing a basis for individualized health care services. The study's Specific Aim 1 is to utilize more comprehensive and advanced methodology to assess physiological reactivity during pregnancy versus nonpregnancy, including measures of inflammation, impedance cardiography, and glucocorticoid receptor function. Hypothesis 1: pregnant women will show attenuated physiological responses to acute stress as compared to nonpregnant women. Specific Aim 2 is to examine racial differences in physiological reactivity during pregnancy versus nonpregnancy. Hypothesis 2: as compared to Caucasian women, African-American women will exhibit greater physiological reactivity to stress during pregnancy and nonpregnancy. Specific Aim 3 is to examine psychosocial correlates of physiological reactivity during pregnancy and

nonpregnancy. Hypothesis 3: women reporting greater distress will exhibit greater physiological reactivity during pregnancy and nonpregnancy. Specific Aim 4 is to examine associations between physiological reactivity and length of gestation. Hypothesis 4: greater physiological reactivity to acute stress will predict shorter gestational length.

Title: **Upstream Regulation of Kiss1 Cells**
P.I.: **Horacio O. de la Iglesia**
Institution: **University Of Washington, Seattle**
Grant No.: **1R03HD061853-01A1**
Award: **$78,000**

Ovulation depends on a surge in the release of luteinizing hormone (LH), which in turn depends on a surge of gonadotropin-releasing hormone (GnRH). In recent years, kisspeptin (KISS) has emerged as the most potent stimulator of GnRH and a key regulator of reproductive development and health in vertebrates, including humans. In females, KISS signaling to GnRH cells is critical for the induction of the LH surge. Despite the central role of KISS in reproduction and specifically in female reproductive development and fertility, little is known about the upstream regulators of neurons expressing Kiss1, the gene coding for KISS. Here they present preliminary results that indicate that Kiss1 expression and the expression of c-fos within Kiss1 neurons in female mice is under circadian regulation, and this regulation is dependent on the presence of high ovarian estrogen levels. The overall goal of this proposal is to determine the pathways by which the circadian system may regulate the activity of Kiss1 neurons. Their laboratory has developed a rat model of circadian desynchronization in which independent circadian outputs are associated with the desynchronized activity of anatomically identifiable subregions of the hypothalamic suprachiasmatic nucleus(SCN), the site of the mammalian master circadian pacemaker. Their preliminary data on this forced desynchronized rat model indicates that the gating of the luteinizing hormone (LH) surge is associated with the activity of the dorsomedial (dm) SCN irrespective of the activity of the ventrolateral (vl) SCN. Because the dmSCN is the main source of vasopressinergic efferent fibers, their hypothesis is that vasopressin (VP) release is a critical SCN signal to induce the LH surge and therefore to activate Kiss1 neurons in a circadianpattern. They propose experiments that test specific predictions of this hypothesis. They will test the prediction that SCN vasopressinergic fibers innervate Kiss1-expressing cells and that innervation of the Kiss1 neuronal network by SCN efferent fibers is critical to sustain the circadian regulation of Kiss1 and of c-fos expression within Kiss1 neurons, which are concomitant with the LH surge. They will use unilateral lesions of the SCN to ipsilaterally deplete the anteroventral periventricular nucleus of SCN efferent fibers. In these animals they will assess the level of asymmetric VP innervation of Kiss1neurons as well as the asymmetry in the circadian regulation of Kiss1 expression and c-fos expression within Kiss1 cells. Their proposed studies will characterize the pathways and mechanisms by which the activity of theKiss1 neuronal network is regulated. Specifically, they will determine how a critical component of the mechanisms leading to ovulation such as the circadian system regulates gene expression within Kiss1 cells. Because the activity of these neurons and the release of KISS are essential for normal ovulation, understanding the upstream regulators of Kiss1 neurons will be key to developing therapies to treat disorders of the hypothalamo-pituitary-ovarian axis.

Title: **A Study of the Factors Influencing Women's Decisions about Childbirth**
P.I.: **Mary J. Regan**
Institution: **University Of Maryland, Baltimore**
Grant No.: **5R21HD059074-02**
Award: **$187,063**

This project in focused on building knowledge about what women want from their birthing experience and what informs their choices about mode of birth. This knowledge is essential if they are to understand the role of maternal demand in use of CS. Their data will inform public health policy concerned with both supporting maternal choice and ensuring long term maternal-child health by reducing the risks associated with childbirth. This study is part of a systematic program of research dedicated to improving women's health and satisfaction with their birthing experience. Cesarean section (CS) is currently used at over twice the rate recommended by the World Health Organization (CDC, 2006); use of the procedure has almost doubled in the last two decades for reasons that are as yet poorly understood. Overutilization results in avoidable morbidity and mortality and higher health costs related to childbirth. Many causes for the increased use of CS have been suggested, including growth in the number of 'maternal requests,' that is, healthy women asking for CS in the absence of medical indications. An NIH expert panel explored maternal request CS and concluded that at this time there is insufficient evidence to warrant CS on maternal demand without medical indications and recommended "increased research devoted to strategies to predict and influence the likelihood of successful vaginal birth" (NIH, 2006, p. 20). Using the same data, the American College of Obstetrics and Gynecologists (ACOG) concluded that there is no reason to deny a surgical birth to a healthy mother as long as she is well-informed (ACOG, 2003). The divergence between these positions points to a critical gap in knowledge about the factors that drive CS rates, including the influence of maternal demand on the use of CS. Despite this recent focus on maternal demand, there is scant research on what women want from their birthing experience, including their reasons for choosing one mode of childbirth over another. The purpose of their proposed research is to answer the question: what factors influence women's decisions about how their babies will be born? Women's hopes and desires for their first birth experience are influenced by what they know - both consciously and unconsciously. Because people are only partly aware of the attitudes and beliefs that inform their hopes and desires, this proposal will use three methods of data collection. The first is a projective method commonly used in the social sciences to access knowledge that exists outside of consciousness. The second is a focus group method that provides a venue for birthing women to articulate the conscious basis for their ideas about childbirth and allow participants to compare their ideas with others. Third, all women will be interviewed after the baby is born to build understanding about how their experiences influence future birthing choices the women make. Participants will be 50 primigravid women with uncomplicated pregnancies aged 21 or older. This proposal builds on the researchers' previous work related to the use of CS. It is one step in a defined program of research directed towards improving the health of mothers and their children by optimizing care during pregnancy, labor, and birth.

Title: **Modulation of Polycyclic Aromatic Hydrocarbons Ovarian Toxicity by Biotransformation Enzyme Polymorphisms**
P.I.: **Ulrike Luderer**
Institution: **University of California, Irvine**
Grant No.: **5R21ES016846-02**
Award: **$189,823**

The primary and long-term goal of this research is to understand how toxicants cause ovarian dysfunction so that they can prevent it. These studies will provide insights that will help to understand why some women are more sensitive to ovarian toxicants than other women. In so doing, they will also lay the groundwork for possible interventions to protect against ovarian dysfunction. Infertility or impaired fecundity affects 12 percent of American women. Ovarian dysfunction, including premature ovarian failure is a major cause of infertility. It is likely that exposure to environmental toxicants is responsible for many more cases of impaired ovarian function than is currently appreciated. Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants, which are known to impair ovarian function and cause ovarian failure in rodents and are probable ovarian toxicants in women. Tobacco smoke, foods, and air pollution are among the sources of exposure to PAHs. The mechanistic basis for interindividual variation in susceptibility to PAH ovarian toxicity is not understood, but polymorphisms in enzymes that metabolize PAHs likely play an important role. The work outlined in this proposal will demonstrate the feasibility of a larger study to test the hypothesis that genetic variations in Phase 1 and Phase 2 biotransformation enzymes involved in metabolizing PAHs modulate the ovarian toxicity of PAHs in women. Specific Aim 1: to test the feasibility of prospectively measuring time to pregnancy and PAH exposure and of using genomewide genotyping methods to determine PAH biotransformation enzyme polymorphisms for a study analyzing the associations between PAH exposure and biotransformation enzyme polymorphisms and fecundability (time to pregnancy). Specific Aim 2: to test the feasibility of using microelectronic dipstick monitors to measure daily urinary reproductive hormone concentrations over multiple menstrual cycles for study of the associations between PAH metabolizing enzyme polymorphisms and PAH exposure and menstrual cycle abnormalities. Specific Aim 3: to pilot test serum anti-Müllerian hormone, follicle stimulating hormone, and inhibin B concentrations as markers of ovarian reserve for study of the associations between PAH exposure and diminished ovarian reserve.

Title: **Neuroactive Steroids and Seizure Control During Pregnancy in Women with Epilepsy**
P.I.: **Page Buckhannan Pennell**
Institution: **Brigham And Women's Hospital, Boston, MA**
Grant No.: **5R03NS063233-02**
Award: **$101,800**

Treating women with epilepsy during pregnancy requires a precarious balance of controlling the mother's seizures without exposing the developing fetus to more anticonvulsant medication than necessary. During pregnancy, the rising sex steroid hormones and their metabolic byproducts may directly influence seizure control; this study will analyze blood samples already obtained in women with epilepsy during pregnancy to examine whether women with increased seizures have alterations in neuroactive steroid levels. These findings could lead to the development of novel treatment strategies for women with epilepsy during pregnancy, such as use of supplemental progesterone, to improve mother and child health outcomes. Epilepsy is a common disorder, affecting approximately 1.3 million women of childbearing age in the United States. Seizures during pregnancy can cause increased risks to both the mother and fetus. These risks have to be balanced against the known teratogenic

effects of antiepileptic drugs (AEDs). During pregnancy, the sex steroid hormones estradiol and progesterone increase dramatically. Sex steroid hormones and the metabolic byproducts that are capable of modifying neural activity are classified as neuroactive steroids (NAS). Animal models demonstrate modulation of seizure activity by the NAS 17β-estradiol (EST), progesterone (PROG), and allopregnanolone (ALLO). In women, fluctuations in these NAS have been implicated in seizure control in the non-pregnant state, with worsening seizures at certain times of the menstrual cycle (catamenial epilepsy). Human studies have demonstrated an increase in seizure frequency with elevated EST/PROG ratios and with declining or low PROG levels. This has not been studied during pregnancy in women with epilepsy. This proposed study will utilize serum samples (n=810 samples) already collected from 135 women with epilepsy during different stages of pregnancy during a Specialized Center of Research in Women and Gender Issues program project grant. These women were enrolled prospectively with tracking of seizures and medications. Collection of plasma samples occurred at multiple points in each trimester. Based on variable points of enrollment (< 20 weeks gestation), they have increased observations/samples in the later trimesters of pregnancy. Seizure frequency will be analyzed during the second and third trimesters of pregnancy and compared to the nonpregnant baseline for each subject. Consistent with the R03 mechanism, the current application will extend the analysis of these existing data/samples via measurement of the neuroactive steroids EST, PROG, and ALLO. The working hypotheses are: (1) during pregnancy, changing concentrations of EST and PROG influence seizure control; and (2) the progesterone metabolite, ALLO, mediates the seizure-reducing effect of PROG. The following will be analyzed in relationship to change in seizure frequency during pregnancy: EST/PROG ratio, the rate of rise of PROG, and the rate of rise of ALLO. Additionally, given that labor and delivery is a particularly vulnerable time for increased seizures, ALLO and PROG levels will be compared between women who had peripartum seizures and those who did not. This study can ultimately lead to a better understanding of the NAS regulation of seizure control during pregnancy. Insights gained from this study could provide the impetus for further development of NAS analogs, with treatment benefits extending to both genders and across all ages. During pregnancy, treatment with supplemental progesterone could allow for decreased levels of fetal exposure to AEDs in utero, with improved seizure control and reduced anatomical and neurodevelopmental teratogenicity.

Title: **Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women**
P.I.: **Brahim Aissani**
Institution: **University of Alabama, Birmingham**
Grant No.: **1R01HD064398-01**
Award: **$83,333**

Currently, the only effective and non-invasive therapy to treat uterine fibroids is a hormone-based (gonadotropin releasing hormone) therapy with serious side effects. The knowledge to be gained from this study could, at some point in the near future, lead to the development of the first genetic counseling protocol for fibroids and ultimately to a more appropriate therapy. Uterine leiomyomas (ULs) are the most common pelvic tumors in women of reproductive age, accounting for more than 600,000 hysterectomies annually in the United States. Several lines of evidence support a genetic liability in the pathogenesis of ULs, yet no susceptibility gene is known. Advances in research on the genetics of ULs (fibroids) have so far been limited by the paucity of genetic epidemiologic studies and infrastructure to conduct them. The goal of this epidemiologic study is to evaluate the contribution of a region of Chr.1q43 that predisposes to uterine fibroids but remains inadequately investigated. Genetic predisposition to ULs has been studied primarily in the context of two rare inherited autosomal-dominant conditions, the hereditary leiomyomatosis and renal cell cancer (HLRCC) and the multiple cutaneous

and uterine leiomyomatosis (MCUL1) syndromes, where germline mutations were found in the gene on Chr. 1q43 encoding the tricaboxylic acid cycle (Krebs cycle) fumarate hydratase (FH) enzyme. However, a direct role of this important metabolic housekeeping gene in tumorigenesis remains to be proven. Inactivating FH mutations have rarely (< 1-2 percent of the tumors analyzed) been observed in nonsyndromic (common) ULs; however, loss of FH appears to be a significant event in the pathogenesis of a subset of these tumors. Furthermore, several observations support the existence of an alternative or additional candidate gene on Chr.1q43 acting alone or interacting with FH to increase the risk of ULs in susceptible individuals: (1) the absence of FH genotype-phenotype correlations, (2) the marked genetic heterogeneity in ULs, and (3) the failure to observe ULs or multiple leiomyomatosis in siblings or parents of cases with fumarase deficiency, a severe recessive disorder. Taken together, these observations underscore the importance of exploring an extended FH region in a population-based study of ULs. To this end, they will generate a high-density single nucleotide polymorphism genotyping data across a 2-Mb region spanning FH in subsets of African American (n=582) and Caucasian (n=455) women enrolled in the NIEHS-Uterine Fibroids Study. This is a well-designed cross-sectional study of ULs that includes data on most potential confounders. Their study is not intended to shift any paradigm about the origins of ULs; rather it will extensively investigate the role of FH in nonsyndromic ULs, dissect the intricate genetic correlates of Chr.1q43 markers in the expression of the disease phenotype and evaluate their effects in two populations with a marked difference in disease risk. Recent updates in the genome databases have revealed new potential candidate genes for tumor growth and important structural variations including a large (~308 Kb) copy number variation in the vicinity of FH; these new findings further justify a study with the proposed depth and extent of genetic coverage. This study will likely open new avenues for research and may ultimately redirect current preventive and therapeutic approaches or enhance their efficacy.

Title: **Midcareer Investigator Award in Patient-Oriented Research**
P.I.: **Kurt T. Barnhart**
Institution: **University of Pennsylvania, Philadelphia**
Grant No.: **5K24HD060687-02**
Award: **$187,466**

The recruitment and retention of productive junior investigators is one of the more critical priorities of academic medical institutions and the research community in general. The purpose of this Midcareer Investigator Award in Patient-Oriented Research is to provide support for Kurt Barnhart M.D., M.S.C.E., a reproductive endocrinologist and epidemiologist at the University of Pennsylvania. Dr. Barnhart is an accomplished clinical investigator with continuous NIH support since he joined the faculty at Penn in 1996. He has also been recognized as an outstanding mentor. The candidate's immediate and long-term career goals center on his desire and intention to continue to evolve and mature as a patient-oriented researcher, teacher, and mentor. In doing so, he needs to be able to enhance and focus his efforts on conducting patient-oriented research (POR), and building a clear training and mentoring path for those interested in POR in women's health. This award will be essential to allow him to achieve these goals by protecting 50 percent of his time by reducing his clinical and administrative duties. He will also reduce effort on some of his funded projects while concomitantly increasing the effort of junior faculty he currently mentors. Mentoring: Dr. Barnhart will focus his mentoring on scholars enrolled in the Masters of Science in Clinical Epidemiology (M.S.C.E.) via the NIH supported T32 Reproductive Epidemiology training grant. Candidates for this program include fellows in subspecialties in women's health, family medicine, and/or pediatrics. Other mentees will include junior faculty, and fellows in Reproductive Endocrinology and Infertility. He plans to serve as primary thesis mentor for some, a research mentor for others, and will transition to become PI of the T32 training grant. Research Plan: new science proposed in this

application will evaluate the short-term and long-term consequences of assisted reproductive technology (ART), a priority area of research for the NIH. In a series of three Specific Aims he will investigate the association of ART with short-term perinatal morbidity and childhood development. These three aims were chosen for the ability to adequately design and conduct the study in a reasonable period of time, each with a specific hypothesis that would lead to important information. Complementary, diverse, and sophisticated research methods have been proposed to address this important research area, with focus on overcoming inherent limitations in imperfect datasets and potential bias in nonrandomized studies. Specific Aim 1 will use the national SART database to test if a fresh embryo transfer is associated with increased adverse outcome compared to frozen embryo transfer. Specific Aim 2 will use a three-arm cohort study assessing childhood development in children conceived with IVF, superovulation, or without medical assistance. Specific Aim 3 will use a large administrative dataset to link mothers and children and assess for autistic spectrum disorder in true population setting. These aims are designed to advance the skills of the principal investigator, enhance interdisciplinary research and provide optimal opportunity for mentorship. Finally these aims will likely provide evidence to be used to design larger trials, hopefully using the growing cadre of reproductive epidemiologists and POR researchers in women's health nationwide, many of whom will have been mentored by Dr Barnhart.

Title: **Uterine Leiomyoma Research Center**
P.I.: **Serdar E. Bulun**
Institution: **Northwestern University, Chicago, IL**
Grant No.: **5P01HD057877-02**
Award: **$250,000**

Symptomatic uterine leiomyomata affect millions of U.S. women and causes irregular uterine bleeding, anemia, recurrent pregnancy loss leading to more than 200,000 hysterectomies per year. Available treatments are limited due in large part to the fact that the mechanisms regulating the development and growth of these tumors are unclear. They propose integrated molecular, cellular, and translational studies that should lead to a better understanding and future development of novel therapeutics for uterine leiomyomata. Uterine leiomyomata (fibroids) represent the most prevalent benign gynecologic disorder in the United States. The cellular and molecular mechanisms regulating the development and growth of leiomyoma are not well understood. Their interdisciplinary team has designed three well-integrated projects focusing on interactions between biologically critical hormonal pathways in uterine leiomyoma involving the transcription factors progesterone receptor (PR) and FOXO, the signaling pathway PI3K/AKT and the pro-fibrotic factor TGF-beta. Project I (Bulun) will be pursued to understand the mechanisms as to how anti-progestins such as RU486 reduce tumor size. They hypothesize that progesterone regulates a number of critical genes that favor increased proliferation and decreased apoptosis of leiomyoma smooth muscle cells, whereas anti-progestins reverse this effect by enhancing apoptosis and decreasing proliferation. Project II (Kim/Chakravarti) will determine the role of the PI3K/AKT/F0X0 signaling pathway regulating leiomyoma cell growth and survival in response to progesterone. They hypothesize that progesterone induces proliferation of leiomyoma cells through activation of the PI3K/AKT/F0X0 signaling pathway and that inhibitors of the AKT pathway should override the proliferative effects of progesterone and promote apoptosis. Project III (Nowak) will define the mechanisms as to how antifibrotic drugs regulate leiomyoma growth. They hypothesize that the increased proliferation exhibited by leiomyoma smooth muscle cells is due to a major shift in the extracellular matrix environment caused by increased synthesis of new, monomeric collagen type I by these cells. They will determine whether antifibrotic drugs may be an effective new treatment for leiomyomas. These projects are supported by an Administrative Core (Bulun) and Tissue Procurement and Cell Culture Core (Kurita). Overall, as part of their long-range

goal, all projects investigate local hormonal signaling regulating apoptosis and proliferation as biologic endpoints and test existing and upcoming pharmaceutical compounds that target these pathways in uterine leiomyomata

Title: **Identification of Genes Predisposing to Pelvic Floor Disorders**
P.I.: **Lisa A. Cannon Albright**
Institution: **University of Utah, Salt Lake City**
Grant No.: **5R01HD061821-02**
Award: **$66,667**

This research has a major potential to affect public health in the prevention of PFDs: they may be able to identify high risk populations who can be identified at a young age, studied and possibly targeted for prevention; and at a later stage in the development of PFDs, special interventions can be studied and possibly implemented in women at risk for recurrence of their condition. Someday, identification of these high risk populations may be as general as familial risk, or as specific as specific gene screening. The investigators propose a unique and powerful collaboration between basic and clinical scientists in Utah to identify genes affecting predisposition to pelvic organ prolapse (POP). The co-principal investigators both have significant experience, Dr. Norton in Pelvic Floor Disorder (PFD) genetics and Dr. Cannon-Albright in predisposition gene identification. The investigators will access the Utah Population Database, a computerized genealogy of Utah combined with decades of medical data from the two largest healthcare systems in Utah (serving 90 percent of the state), to identify and recruit surgically treated cases of POP (1,250 cases in 5 years). All POP cases sampled will be genotyped with the Illumina 610Q SNP marker set. The PIs will apply multiple different genetic analyses to this resource of genotyped POP cases to aid in the identification of predisposition genes. The record linkage of medical procedure codes (identifying surgeries performed on each patient) to individual genealogy data allows us to identify all genetic relationships among the POP cases. They will perform genomewide association analysis, using software they have developed which allows inclusion of both independent and related cases. They will identify all genetic relationships between the sampled POP cases and perform linkage analysis in informative, high-risk POP pedigrees. They will identify chromosomal regions shared Identical by Descent (IBD) in very distantly related cases in these pedigrees, and they will identify IBD sharing within the small subset of POP cases (2 percent) who are inbred. Initial collaborative analysis of data obtained by Dr. Norton's NIH funded study of affected PFD sib-ships has already provided significant evidence for a predisposition gene localization on chromosome arm 9q, and suggestive evidence for at least one other locus on chromosome 1. In summary, they will create a population-based resource of surgically treated POP cases, they will pursue established and new methods to identify and localize predisposition genes affecting POP, and they will begin a detailed search for the chromosome 9 gene they have localized.

Title: **Cellular Mechanisms of Amniotic Fluid Volume Regulation**
P.I.: **Cecelia Cheung**
Institution: **Oregon Health and Science University, Portland**
Grant No.: **1R01HD061541-01A1**
Award: **$200,000**

The proposed studies will generate a new level of understanding for the mechanisms of amniotic fluid volume regulation. This knowledge is crucial in the development of therapies for the treatment of pregnancy complications due to abnormalities in amniotic fluid volume. The studies will ultimately lead to improvement in the clinical management of oligohydramnios and polyhydramnios, thereby reducing perinatal and neonatal morbidity. A normal volume of amniotic fluid (AF) is essential for normal fetal development with favorable perinatal

outcome. However the mechanisms that regulate AF volume and the factors that maintain the volume within the physiological range are not well understood. The current understanding suggests that the transfer of AF water and solutes across the fetal membranes into fetal blood vessels that vascularize the surface of the placenta is the pathway where regulation occurs. This intramembranous (IM) pathway for AF absorption is constituted by an active bulk transport component and a passive diffusional component. In addition, the active process is regulated by stimulatory and inhibitory factors in the AF and amniotic membrane. Although the existence of these regulatory factors has been proposed, their identity and mechanisms of action are not known. In this application, they propose to elucidate the cellular pathways of IM transport and decipher the factors that regulate these pathways. These studies will be carried out in ovine amnion cells in vitro and chronically catheterized ovine fetuses in vivo. In Specific Aim 1, they will identify the cellular pathway for transport of solutes across amnion cells and test the hypothesis that AF transport is a vesicular transcytotic process via caveolae. They will investigate the role of VEGF165 as a stimulator and VEGF165b as an inhibitor of caveolar transport, as well as the effect of the soluble VEGF receptor 1 (sVEGFR-1) in antagonizing VEGF bioactivity. Specific Aim 2 will determine VEGF165 and VEGF165b mRNA and protein levels in amnion cells and amniotic membranes under conditions of normal, increased, or decreased IM absorption rates. The correlation of VEGF165 levels with sVEGFR-1 will be determined. In Specific Aim 3, they will examine the VEGF165 activation of caveolar transcytosis by induction of VEGF receptor 2 to initiate a c-Src signaling pathway leading to downstream activation of cavoelin-1 and dynamin-2 as required for caveolar endocytosis and transcytosis. The involvement of other signaling proteins including protein kinase C and phosphatidylinositol 3-kinase will be explored. Specific Aim 4 will investigate the expression of the water channel proteins aquaporin 1, 3 and 9 in amnion cells and determine their effects on passive and active transport across amnion cells. In Specific Aim 5, they will evaluate the in vivo function of the stimulator VEGF165 and the inhibitors VEGF165b and sVEGFR-1 in modulating IM absorption rate in ovine fetuses under conditions of normal, increased, or decreased AF volume. They anticipate the in vivo results to support the in vitro findings that VEGF165 is an important determinant of IM absorption and that its stimulatory effect is antagonized by VEGF165b and sVEGFR-1. Overall these studies will elucidate the transcellular vesicular pathway for AF transport and determine the stimulatory and inhibitory regulatory factors that modulate this pathway in amnion cells. Further, the signal transduction cascades that mediate these transport events will be investigated. The findings will lead to an improved understanding of the etiology of amniotic fluid volume abnormalities.

Title: **Oklahoma Native American Research Centers for Health**
P.I.: **Gloria Ann Grim**
Institution: **Cherokee Nation, Tahlequah, OK**
Grant No.: **1S06GM092238-01**
Award: **$100,000**

The purposes of this project are: to encourage competitive research linked to reducing health disparities; to increase the capacity of the tribes and University of Oklahoma to work in partnership to reduce distrust by the Native American communities and peoples toward research; and to develop a cadre of Native American scientists and health professionals engaged in biomedical, clinical and behavioral research that is competitive for NIH funding. The sixth Oklahoma Native American Research Center for Health (ONARCH6) continues the productive research and training partnership with the University of Oklahoma Health Sciences Center (OUHSC) by the tribes, especially the Chickasaw, Creek, Choctaw, and Cherokee nations. Population served consists of 42,749 Chickasaws, 121,680 Cherokees, 49,714 Choctaws, and 30,181 Creeks for a total of 244,324 in North, East, and South Central Oklahoma. The research will include: (1) the impact of infections on maternal and child health in Native Americans; (2)

research to develop better diagnostic and prognostic tests for rheumatic disease in Oklahoma tribal members and to examine the potential roles of environmental triggers for autoimmunity focusing on vitamin D levels, tobacco smoke exposure (through serum cotinine levels), and abnormal immune responses to common viruses; (3) research to prevent excessive gestational weight gain in otherwise healthy but overweight Native American women and to consequently decrease the proportion of women who gain in excess of the guidelines,potentially decreasing the risk and costs of obstetric complications associated with excessive weight gain; and (4) development of methods to understand attitudes, beliefs, and perceived barriers or motivators to organ/tissue donation among American Indians living off-reservation.

Title: **Research to Improve Preconception Health of Adolescent Women**
P.I.: **Sara Jumping Eagle**
Institution: **Oglala Lakota Oyate, Pine Ridge, SD**
Grant No.: **5S06GM087165-02**
Award: **$128,436**

The Oglala Sioux Tribe, in partnership with Stanford Research/University of South Dakota School of Medicine and the Oglala Lakota College, will address priority health issues identified by the tribe and will support and expand the research capacity and infrastructure that will build on the research foundation that has been developed within the tribe over the past decade.

Title: **Xenograft Study on Growth-Control of Human Uterine Leiomyomata**
P.I.: **Takeshi Kurita**
Institution: **Northwestern University, Chicago, IL**
Grant No.: **1R01HD064402-01**
Award: **$83,333**

A better understanding of how uterine leiomyomata grow is essential to developing novel therapies for this tumor. While the dependency of uterine leiomyoma on ovarian steroids is well established, the relative importance and function of 172-estradiol versus progesterone are yet to be clarified. Recently, they developed a method of growing human uterine leiomyoma tumors in immunodeficient mice. The xenografts of human uterine leiomyoma faithfully preserved the phenotype and hormone responsiveness of original human tumors in situ, and their growth was totally dependent on progesterone and 172-estradiol. Using this novel xenograft model in combination with viral gene transduction, they will elucidate the cellular and molecular mechanisms of human uterine leiomyoma growth. The ultimate goal of this study is to elucidate the molecular mechanisms of uterine leiomyoma (UL) formation and growth, and identify potential targets for novel therapeutic and preventive treatments of this disease. UL is a benign tumor of the myometrium that affects millions of reproductive-age women. Surgical removal of the entire uterus (hysterectomy) is the primary treatment option, and management of UL puts an enormous burden on the health care system. Therefore, finding a new therapeutic treatment replacing surgery is of great interest to the public. Due to the absence of a proper research model system reflecting characteristics of the original tumors, the biological nature and the causes of UL are poorly understood. Although growth dependency of UL on ovarian steroids (172-estradiol and progesterone) is well established, the relative importance and function of 172-estradiol and progesterone are yet to be clarified. In spite of accumulating evidence for the essential role of progesterone in UL growth, no research model has clearly demonstrated a growth-promoting effect of progesterone on UL. To elucidate the function of ovarian steroids in UL, they have established a novel xenograft model in which tissue fragments of human leiomyoma were grafted beneath the renal capsule of immunodeficient mice. The size of the leiomyoma xenografts increased in response to 172-estradiol and progesterone as demonstrated by cell proliferation and accumulation of

extracellular matrix. In contrast, xenograft growth induced by 172-estradiol and progesterone was blocked by the anti-progestin RU486, indicating the essential role of progesterone and progesterone receptor (PR) in leiomyoma tumor growth. Previously, 172-estradiol has been thought to be the primary stimulus for UL growth. Surprisingly, 172-estradiol by itself neither increased nor maintained tumor size. Likewise, progesterone alone did not affect UL growth in this model. Although not mitogenic, 172-estradiol was required for expression of PR, and was essential for progesterone to act on UL xenografts. Their study clearly demonstrates the pivotal role of progesterone in growth and maintenance of UL. The results of their xenograft model agree with clinical observations, yet radically change the paradigm of steroid hormone-regulated human UL growth by emphasizing the importance of progesterone instead of 172-estradiol. Using the novel xenograft model, they will elucidate the cellular and molecular mechanisms of human UL tumor growth controlled by 172-estradiol and progesterone.

Title: **Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team**
P.I.: **Pamela A. Moalli**
Institution: **Magee-Womens Research Institute, Pittsburgh, PA**
Grant No.: **5R01HD061811-02**
Award: **$66,667**

Prolapse (i.e., abnormal descent) of the pelvic organs is a common costly condition that negatively impacts the lives of millions of women worldwide. Biologic and synthetic meshes are often used in the surgical repair of prolapse due to improved anatomical outcomes over native tissue repairs; but with little scientific data on which to base the selection of a particular product. Unfortunately, the complications associated with certain meshes cause unacceptably high rates of morbidity including infection, tissue contraction, vaginal discharge, and pain. In this proposal, they aim to establish a comprehensive mesh testing center in which previously or newly marketed prolapse meshes can be objectively tested and the next generation of prolapse meshes can be developed based on specific scientific criteria. Each year roughly 200,000 U.S. women undergo a surgery to repair pelvic organ prolapse. Biologic and synthetic meshes are widely used in prolapse repairs to improve anatomical outcomes over native tissue repairs which currently have a failure rate of more than 30 percent. To date, however, there is little scientific data to guide surgeons in the selection of a particular product. As a result, meshes are used based on the recommendations of a local vendor and consequently, are placed in women on a trial-and-error basis. There is growing evidence, however, that the complications associated with prolapse meshes cause unacceptably high rates of morbidity including infection, mesh shrinkage, mesh erosion, mesh exposure, pelvic, rectal and bladder pain, and dyspareunia. Such complications have become significant enough for the FDA to recently release a warning about mesh use, especially when it is placed transvaginally. In this proposal, they therefore aim to establish an interdisciplinary team of scientists dedicated to the comprehensive testing of previously or newly marketed prolapse meshes and for the development of the next generation of graft materials based on specific scientific criteria. In the first phase of the study, they determine how biochemical and structural changes in the prolapsed vagina impact passive and active mechanical behavior so as to develop a mesh in which these deficiencies are repaired or compensated for, allowing us to restore the prolapsed vagina to the nonprolapsed condition. In the second phase, they hypothesize that the shortcoming of current prolapse meshes is that they are too stiff. While this results in a repair with increased tensile strength, it occurs at the expense of tissue function with accelerated tissue contraction, decreased elasticity and compliance, and deterioration of smooth muscle function. To test their hypothesis, they implant commonly used synthetic prolapse meshes into the vagina of nonhuman primates with prolapse using the gold standard surgical procedure (the abdominal sacrocolpopexy) and then define the cellular, biochemical, and biomechanical

impact on the vagina at 6 months post implantation. Eventually, they will implant meshes transvaginally to characterize the distinct host response to this surgical approach. In the third phase, they explore the development of future grafts for prolapse surgery. They hypothesize that because of its bioinductive effects, a combined biologic/synthetic mesh will be superior to a synthetic mesh alone in restoring vaginal structure and function. They propose that a key yet poorly developed component of prolapse repairs is the re-establishment of smooth muscle reactivity and therefore, test the use of a temporary biologically active scaffold in achieving this process. In this way, this grant proposal provides a mechanism to establish the first team of scientists dedicated to the comprehensive unbiased evaluation of prolapse meshes as a means of educating both current and future prolapse surgeons, and the public regarding potential problems associated with certain materials. Indeed, the development of such a group is imperative for protecting the health of women.

Title: **Genetic Studies of Uterine Leiomyomata**
P.I.: **Cynthia Casson Morton**
Institution: **Brigham and Women's Hospital, Boston, MA**
Grant No.: **1R01HD060530-01A1**
Award: **$83,333**

The importance of this research is to further their understanding of the biology of uterine leiomyomata. Uterine leiomyomata, or fibroids, are the most common pelvic tumors in females and occur in a minimum of 20–25 percent of women of reproductive age. Uterine leiomyomata may serve as an important model system to study the genetic events that distinguish benign and malignant neoplasms. A more complete understanding of the genes involved in the pathogenesis and pathobiology of uterine leiomyomata will provide a foundation for future diagnosis, management, and treatment of uterine fibroids. Uterine leiomyomata, or fibroids, are the most common pelvic tumors in females and occur in a minimum of 20– 25 percent of women of reproductive age. Although benign neoplasms, they constitute a major public health problem as 25–50 percent of affected women experience debilitating symptoms including excessive menstrual bleeding and pelvic discomfort as well as reproductive failure. Fibroids are the major indication for hysterectomy accounting for over 200,000 procedures annually in the United States. It is highly likely that there is a genetic liability to develop fibroids; they are at least three times more frequent in African-American than Caucasian women (representing a serious health disparity) and twin-pair correlations for hysterectomy in monozygotic twins are about twice that observed in dizygous twins. Despite these findings and enhanced research in this area in recent years, much remains to be known about this racial predisposition and specific genes involved in the pathogenesis of fibroids. Also of particular interest and of unknown molecular mechanism, fibroids rarely proceed to their malignant counterpart, uterine leiomyosarcoma. Thus, it follows that uterine leiomyomata may serve as an important model system to study the genetic events that distinguish benign and malignant neoplasms. Consistent chromosome aberrations have been observed in fibroids indicating the location of genes involved in these tumors. A number of cytogenetic subgroups have been identified and they have been successful in using positional candidate gene approaches in determining that two high mobility protein genes, HMGA2 and HMGA1, located on chromosomes 12 and 6, respectively, participate in the pathobiology of uterine leiomyomata, in addition to MYST4, located on chromosome 10. The major goal of this proposed application is to further their understanding of the biology of uterine leiomyomata. Experiments are focused on continuing to develop and use a uterine leiomyomata tissue bank and database for gene discovery, gene expression studies, and genotype-phenotype correlations. A variety of molecular and cytogenetic approaches will be used in the identification, isolation and characterization of genes involved in the pathogenesis and pathobiology of uterine leiomyomata. Chromosomal rearrangements

in tumor cells will provide biological landmarks for positional cloning experiments. Transcriptional profiling offers a powerful approach to discriminate genes that differentiate fibroids of different cytogenetic subgroups as well as fibroids of variant histologies from their normal smooth muscle counterpart, the myometrium, or their malignant counterpart, uterine leiomyosarcoma. Lastly, the potential role of sequence variants in HMGA2 will be explored by a variety of mechanistic experiments to assess their role in uterine leiomyomata.

Title: **Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and Its Association With Incidence, Progression, and Recurrence of Pelvic Floor Disorders**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah, Salt Lake City**
Grant No.: **5R01HD061787-02**
Award: **$66,667**

The effect of strenuous physical activity on new or recurrent pelvic floor disorders is unknown. They developed an intravaginal pressure sensor to measure intra-abdominal pressure. They will perfect the wireless technology needed to use the sensor remotely so that they can understand how different activities done during real world settings affect intra-abdominal pressures and pelvic floor disorders. Pelvic floor disorders affect one in four American women. Few modifiable risk factors have been identified that might reduce the incidence or progression of pelvic floor disorders. Popular wisdom and scant clinical data suggest that strenuous activity causes or promotes pelvic floor disorders. Given the health benefits of activity, women should be encouraged to be maximally active unless there is scientific evidence to the contrary. Existing physical activity instruments are largely designed to assess cardiovascular exertion and are validated using activity diaries, accelerometers, and step counters. Such measures may not accurately measure activities that increase loading on the pelvic floor (such as lifting). After researching available technologies, they concluded that a tool to understand how physical activities impact abdominal pressure in the real world does not exist. Over the past 18 months, their interdisciplinary team of bioengineers, urogynecologists, electrical engineers, and exercise scientists developed and validated the performance of a prototype for an intravaginal abdominal pressure sensor that accurately measures pressure in the upper vagina, an easily accessible space that records pressures similar to the true intra-abdominal pressure. In this proposal, they plan first to further develop an integrated system (the "WRAPS", Wireless Remote Abdominal Pressure System) to monitor intra-abdominal pressure outside of the clinical setting. This system will consist of three key elements: an intravaginal pressure sensor with wireless data transmission capability, a small portable data monitoring and storage unit, and computer based data translation software for downloading and managing the pressure data. In a controlled exercise laboratory setting, they will then use intra-abdominal pressure data generated by the WRAPS to determine the reproducibility of intra-abdominal pressures measured during specific types of physical activity and will finalize development of a valid questionnaire that categorizes the magnitude of intra-abdominal pressures during activities. Finally, in a real-world setting in which participants wear the intravaginal sensor during waking hours for four 1-week periods over the course of a year, they will characterize intra-abdominal pressures experienced by women of varying degrees of habitual physical activity and, using WRAPS data as the gold standard, determine whether activity can be appropriately categorized in terms of pelvic loading by means of self-administered questionnaires, the current standard. Obtaining future evidence about the impact of physical stressors on pelvic floor disorders relies on their ability to measure the risk factor in question. This innovative translational collaboration will remove a critical barrier to progress in understanding the etiology of pelvic floor disorders in women.

Title: **Racial Disparity in Adverse Pregnancy Outcomes: Ancillary Study to Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-To-Be (NuMoM2b)**
P.I.: **Corette B. Parker**
Institution: **Research Triangle Institute, Research Triangle Park, NC**
Grant No.: **1U01HD063036-01**
Award: **$100,000**

The incidence of preterm birth is unequally distributed among races and ethnic groups. For example, African Americans have the highest rate of preterm birth, followed by Mexican-Americans, Asians, and Caucasians. Strikingly, a substantial health disparity exists between African Americans and Caucasians, with African Americans being 1.6 times more likely to deliver preterm infants than Caucasians. In addition, the United States' high infant mortality rate compared to that of Europe is mainly due to the higher frequency of preterm births in the United States. The NuMoM2b project is a prospective cohort study of a racially/ethnically/geographically diverse population of 10,000 nulliparous women with singleton gestations. The women will undergo intensive research assessments during the course of their pregnancies to study the mechanisms for and prediction of adverse pregnancy outcomes such as preterm birth, preeclampsia, and fetal growth restriction in their first pregnancy. With funding from ORWH, biomarkers reflecting the maternal-placental-fetal endocrine milieu related to stress will be analyzed from the bio-specimens being collected from 10,000 women. As part of the parent study, various questionnaires assessing psychosocial status during pregnancy are being administered during pregnancy. The combination of race/ethnic-specific profiles of genetic variation, perceived stress, and resilience factors (psychosocial environment) as well as biomarker differences will likely account, in part, for racial/ethnic disparities in the risk of preterm birth.

Title: **The Role of Maternal Nutrition in Adverse Pregnancy Outcomes: Ancillary Study to Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-To-Be (NuMoM2b)**
P.I.: **Corette B. Parker**
Institution: **Research Triangle Institute, Research Triangle Park, NC**
Grant No.: **1U01HD063036-01**
Award: **$100,000**

Preterm birth affects one in eight women in the United States, with half a million preterm births each year. Excluding congenital malformations, preterm birth accounts for approximately 70 percent of all neonatal deaths and nearly 50 percent of long-term neurological problems. Despite decades of research, there has been little progress in developing effective interventions to prevent preterm birth in the first pregnancy. The NuMoM2b project is a prospective cohort study of a racially/ethnically/geographically diverse population of 10,000 nulliparous women with singleton gestations. Nutrition is an understudied area with relation to preterm birth, although several nutritional factors have been related to preterm birth. There is biologic plausibility for the relationship of folate and vitamin B12 with preterm birth, as both may be important regulators of proinflammatory cytokine and DNA synthesis. Vitamin D is another example of a nutritional factor that, if deficient, has been linked to adverse pregnancy outcomes, including preterm birth, preeclampsia, and fetal growth restriction. With funding from ORWH, the role of nutrition in adverse pregnancy outcomes will be studied by administering the Modified Block 2005 Food Frequency Questionnaire in all 10,000 women in the cohort. A full assessment of usual intake of more than 51 nutrients and seven food groups in the 3 months before conception will be conducted by 14 weeks of gestation using a semi-

quantitative modified Block 2005 food frequency questionnaire. The findings will be correlated to clinical data and biospecimen collection as part of the parent study to determine the role of maternal nutrient status in adverse pregnancy outcomes.

Title: **ORWH-NICHD Leiomyoma Tissue Bank**
P.I.: **James Segars**
Institution: **NICHD Intramural Program, Bethesda, MD**
Grant No.: **Z01HD008737-10**
Award: **$50,000**

The health of 30–50 percent of women in the United States is adversely affected by uterine leiomyoma (fibroids). Uterine fibroids are a health disparity issue that disproportionately affect African-American women. Research into causes and treatment has lagged behind other disciplines, in part due to lack of available tissues, since surgical samples are often not made available to scientists. To address the problem of tissue availability, and promote research on this condition, this project proposes to establish a fibroid tissue bank as an initiative in the intramural program of NICHD. This tissue bank will provide samples to NIH-funded investigators and DoD-funded investigators to support work on this condition. The Leiomyoma Tissue Bank (LTB) will be physically located in space assigned to Dr. Segars of NICHD. The LTB will be structured after RStaR-banks for endometrium and ovary established by the Specialized Cooperative Program in Reproductive Research. Computerization of sample inventory will be performed with software provided by NICHD.

Title: **Adrenal Hyperplasia among Adolescent Patients Polycystic Ovarian Syndrome (Bench-to-Bedside Program)**
P.I.: **Constantine A. Stratakis**
Institution: **NICHD Intramural Program, Bethesda, MD**
Award: **$200,000**

Adolescent and young women of reproductive age and clinical picture of polycystic ovarian syndrome (PCOS) have increased adrenal androgens. Anecdotal reports from patients and animal studies have also suggested that this phenotype is associated with adrenal hyperplasia. Finally, certain minority populations (i.e. Hispanics and African Americans) are particularly susceptible to PCOS and related complications (e.g. diabetes, infertility). The common link between the adrenal and ovarian pathology has been postulated to be insulin resistance, but this remains unclear. Dr. Ten runs a large clinic in downtown New York where a lot of these patients are being seen. In this proposal, they plan to bring a subset of these patients, those that have elevated adrenal steroid hormones, to the NIH Clinical Research Center (NIH-CRC) and study their metabolic profile, adrenal imaging, genetic parameters, and steroidogenesis before and after treatment with metformin, an insulin sensitizer. This study will clearly lead to a new clinical protocol and offer the opportunity to study a new disorder for the pediatric endocrine clinic and program.

Title: **The Genetics of Polycystic Ovary Syndrome**
P.I.: **Corrine Welt**
Institution: **Massachusetts General Hospital, Boston**
Grant No.: **1R01HD65029-01A1**
Award: **$200,000**

Polycystic ovary syndrome (PCOS) is a disorder of irregular menses and elevated androgens that carries a high risk for diabetes, hypertension, and elevated lipids. The investigators have now discovered a genetic variant that is associated with PCOS in a genomewide association

study and will try to determine the causal variant and gene it marks. Discovering the variants and/or gene(s) that predispose to PCOS will determine an etiology and will provide a novel target to develop new treatments for the 1 in 10 reproductive age women it affects. PCOS is the most common endocrine disorder in reproductive age women, yet its etiology is poorly understood. The disorder is defined by its cardinal features: irregular menstrual cycles, hyperandrogenism and a polycystic ovary pattern on ultrasound. In addition, women with PCOS have increased risk for infertility, endometrial cancer, type 2 diabetes, and cardiovascular risk factors. They completed a genomewide association study in collaboration with deCODE in Iceland. The study identified a variant on chromosome 4 reaching genomewide significance in an Icelandic case control cohort and replicating in an identically phenotyped Boston cohort. The broad goal of this proposal is to identify the causal variant that this risk variant marks through fine mapping. They will also examine the functional effects of the causal variant using expression studies and/or assays of protein function. Finally, they will examine the phenotypic features defined by the genotype. Specific Aim 1 will examine the region around the chromosome 4 variant to identify the causal variant that affects protein production or gene expression. Fine mapping will be performed using common single nucleotide polymorphisms (SNPs) in the HapMap and 1,000 genomes projects. In addition, the exons and promoter regions of genes in linkage disequilibrium with the associated variant will be sequenced in large numbers to identify rare variants that may affect protein production or gene expression. Specific Aim 2 will dissect the phenotype conferred by the genotype in PCOS, controls, males, and postmenopausal women using an extensive database assembled by the principal investigator over the past 6 years. Specific Aim 3 will examine expression of two candidate genes in LD with the chromosome 4 variant in carriers and noncarriers to determine the gene of interest. When a causal variant is identified, expression will also be examined to identify a functional effect of variant(s) in a lymphoblastoid cell line database and in adipose, theca, and peripheral white blood cells in vitro using quantitative PCR. Coding sequence causal variants and rare variants will be assessed using signaling assays and overexpression or knock-down of the variants in cell systems and animal models. These studies will uncover the causal variant and gene that is marked by the first known variant identified in a genomewide case control association study of PCOS. The proposal has the potential to illuminate the etiology of PCOS. Such information has been long in coming and is essential to provide better diagnostic and treatment information for this very common disorder with its adverse health consequences.

Pelvic Floor Disorders Network

Title: **The Cleveland Clinic Clinical Site**
P.I.: **Matthew Barber**
Institution: **Cleveland Clinic, Cleveland**
Grant No.: **5U10HD054215-05**
Award: **$25,000**

Pelvic floor disorders (PFD) including urinary incontinence, pelvic organ prolapse (POP), and fecal incontinence affect a substantial proportion of women in the United States. PFDs result in significant psychosocial costs to an individual and their aggregate social and economic costs to society are enormous. Despite their substantial health impact, the quality of the evidence supporting most of the commonly used treatments, especially surgical interventions, is limited by the lack of standardization of diagnostic and therapeutic interventions, use of non-standardized and non-validated outcome measures, poor quality research designs, and inadequate power to detect clinically meaningful differences. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with PFD using the highest quality research methods available. The Specific Aims of this application are: (1) to demonstrate that the Cleveland Clinic Foundation (CCF) possesses the personnel, patient, clinical, and administrative resources needed for

successful participation as a Clinical Site in the PFDN and that their participation would be advantageous to the successful attainment of the Network's scientific goals; and (2) to present a concept application for potential conduct by the PFDN. The broad, long-term objectives of their concept application are: (1) to compare sacrospinous ligament fixation (SSLF) to uterosacral vaginal vault fixation (USWS); and (2) to assess the role of perioperative pelvic floor physiotherapy (PFPT) in women undergoing transvaginal surgery for apical or uterine POP. Their Specific Aims are to: (1) compare the anatomic outcomes of SSLF to USWS in women undergoing transvaginal surgery for Stage 2–4 POP involving the vaginal apex or uterus 3 years after surgery; (2) compare functional, sexual, and health-related quality of life (HRQOL) outcomes of SSLF to USWS in the same women 3 years after surgery; (3) assess whether short-term functional, sexual, and HRQOL outcomes improve in women receiving PFPT perioperatively compared to those who receive surgery alone; (4) assess whether perioperative PFPT improves anatomic, functional, sexual and HRQOL outcomes 3 years after surgery (long-term) compared to surgery alone; and (5) determine the incremental cost-effectiveness of perioperative PFPT at the time of transvaginal surgery for POP. They present a collaborative multicentered randomized trial comparing SSLF to USSVS with or without perioperative PFPT using a 2x2 factorial study design. A standardized common protocol for enrollment, treatment and data collection will be employed by 6–8 Clinical Sites within the PFDN coordinated by the data coordinating center.

Title: **The Pelvic Floor Disorders Network**
P.I.: **Linda Brubaker**
Institution: **Loyola University, Chicago, IL**
Grant No.: **5U10HD041250-10**
Award: **$25,000**

Loyola is a productive, innovative, clinical research institution that has contributed to the first cycle of the Pelvic Floor Disorders Network and they are eager to build on the PFDN's excellent start. Their application documents: the qualifications and commitment of institution and key personnel at Loyola; a qualified and committed institution with an interdisciplinary faculty with experience in clinical trials design and conduct; a highly qualified and committed research team lead by the same principal investigator, Dr. Brubaker, this research team contains urogynecologists and urologists. Two of the faculty members received master's degrees in clinical research design and statistical analysis and one is currently in this degree program. A cadre of study coordinators are cross-trained to meet the needs of the PFDN study roster. The team has excellent collaborations within the Loyola faculty. Their application also documents Loyola's high quality participation in PFDN protocols with excellent and consistent recruitment. They also demonstrate their consistent contributions in PFDN work, including dissemination of PFDN scientific findings. Loyola has been productive and has worked well with the PFDN team. Their first cycle application proposed the essence of the CARE trial, which was completed ahead of schedule and is under consideration for publication. Their application further documents a feasible, scientifically relevant concept protocol (randomized surgical trial). They believe they have demonstrated their ability to design and conduct high-quality clinical trials. This application also describes a randomized surgical trial for women who select vaginal apical reconstruction. A comparison of the two most common techniques may inform a future study which seeks to determine which route of surgery (abdominal vs. vaginal) is best suited for an individual woman. This trial is a feasible, scientifically relevant randomized surgical trial. The draft protocol is suitable for PFDN Steering Committee discussion and revision, prior to implementation.

Title: **Pelvic Floor Disorders Network**
P.I.: **Charles William Nager**
Institution: **University of California San Diego**
Grant No.: **5U10HD054214-05**
Award: **$25,000**

The objectives and aims of this application are for San Diego to become the first western United States clinical site in the Pelvic Floor Disorders Network (PFDN). The San Diego Clinical Site is a collaboration of three medical centers: (1) the University of California, San Diego (UCSD); (2) Kaiser Permanente, San Diego (Kaiser); and (3) the Naval Medical Center, San Diego (NMCSD). This same collaboration in the Urinary Incontinence Treatment Network (UITN) led all sites in patient recruitment for the UITN SISTEr (Stress Incontinence Surgery Treatment Efficacy) trial. The efficiency of the San Diego Clinical Site's efforts was recognized by the PFDN and we were asked to become a subcontract site for the University of Alabama for the Colpopexy and Reduction Efforts (CARE) study. In the brief nine months available before the CARE study ended, San Diego (UCSD and Kaiser only) recruited 19 patients to CARE. This total was more than all but one center during those nine months. We were the third UITN site to reach recruitment goals in the UlTN's BE-DRI (Behavior Enhances Drug Reduction Incontinence) study. Additionally in the UITN, our site has led efforts in the design, protocol development, and workgroup leadership for the UlTN's current study, TOMUS (Trial of Mid-Urethral Slings). Urodynamic studies are commonly performed in the United States at an annual cost of approximately 400 million dollars. These urodynamic studies are routine preoperative investigations in most centers that have urodynamic capability, yet we do not have evidence that these tests improve outcomes. Our concept proposal is a randomized trial of preoperative urodynamic studies in women with predominant stress urinary incontinence. The primary aim is to determine if preoperative urodynamic studies improve treatment success rates in all women considered candidates for SUI surgery after an office evaluation. We believe that this proposed urodynamics study requires a multi-center randomized clinical trial and has significant relevance to the appropriate evaluation and care of women with pelvic floor disorders, namely urinary incontinence. The proposed study also has potential significant importance for national health care resource allocation and expenditures. The work that the San Diego investigators have done for the UITN in the last 5 years to develop standardized, quality urodynamic studies make them the ideal investigators to lead this effort. We believe that the PFDN will benefit greatly by the proven ability of the San Diego Clinical Site's demonstrated energy, skills, and leadership.

Title: **Utah Pelvic Floor Disorders Network**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah, Salt Lake City**
Grant No.: **5U10HD054136-05**
Award: **$25,000**

Pelvic floor disorders are common, bothersome, and inadequately treated. The overarching aim of the investigators from the proposed University of Utah Pelvic Floor Disorders Clinical Site is to improve women's health in the area of pelvic floor dysfunction. To this end, site Specific Aims include: (1) identifying priority areas of research, (2) developing assessment tools, (3) developing and implementing PFDN protocols, (4) recruiting and enrolling subjects in PFDN protocols, (5) achieving on-target recruitment goals and high subject retention, (6) ensuring high-quality data, (7) transmitting data accurately to the data coordinating center, (8) participating in data analysis, (9) disseminating results to the research community, and (10) producing high-quality publications. The broad scientific aim for the randomized clinical trial outlined in this proposal is to evaluate whether postoperative pelvic floor muscle training

following surgery for pelvic organ prolapse and/or stress urinary incontinence improves postoperative outcomes (anatomic, symptomatic, and quality-of-life outcomes) at 3 months, 1 year and 2 years postoperatively.

Title: **Perioperative Pelvic Floor Rehab: A Randomized Trial**
P.I.: **Holly E. Richter**
Institution: **University of Alabama, Birmingham**
Grant No.: **5U10HD041261-10**
Award: **$25,000**

Surgical techniques for the treatment of stress incontinence (SUI) have significantly evolved over the last 100 years. The gold standard Burch urethropexy and pubovaginal sling procedures are now being performed less frequently, with the increased use of the newer minimally invasive mid-urethral sling procedures, the most common being the tension-free vaginal tape procedure (TVT). The TVT procedure is comparable in efficacy to the open Burch procedure with low morbidity and fewer complications. Because the sling is placed at the level of the mid-urethra under no tension, it was thought that the TVT would yield fewer postoperative lower urinary tract symptoms. However, a review of the literature has not borne this out, with postoperative storage symptoms reported in up to 42 percent of women. The primary purpose of the proposed randomized clinical trial is to test whether a perioperative behavioral/pelvic floor muscle training program can reduce the occurrence of these postoperative storage symptoms and voiding dysfunction in women undergoing a TVT procedure for SUI. Behavioral interventions are known to be effective for treating urge incontinence and voiding dysfunction unrelated to surgery, but have not been tested as a preventive adjunctive strategy. Approximately 400 subjects will be randomized to a perioperative behavioral program or usual care. The intervention will be implemented 2 weeks preoperatively, and reinforced before leaving the hospital and two weeks postoperatively. The primary outcome will be complaints of urgency, frequency, nocturia and urge incontinence using the overactive bladder questionnaire (OABq). Evaluations will be performed at 2 and 6 weeks, 3, 6, and 12 months postoperatively, and will include the OABq, questionnaire for urinary diagnosis (QUID), urogenital distress inventory (UDI), pelvic organ prolapse/urinary incontinence sexual function questionnaire (PISQ), patient global impression of severity (PGI-S) and SF-36. Subjects will also complete a 7-day bladder diary to assess frequency of storage symptoms. Secondary aims are to determine whether this intervention reduces time to voiding and symptoms of voiding dysfunction, whether it impacts on patient satisfaction and quality of life, and to identify predictors of postoperative storage symptoms and voiding dysfunction symptoms. This type of information will allow physicians to more effectively counsel and treat their incontinent female patients to further enhance long-term quality of life.

Title: **NICHD Pelvic Floor Disorders Network**
P.I.: **Joseph I. Schaffer**
Institution: **University of Texas Southwest Medical Center, Dallas**
Grant No.: **5U10HD054241-05**
Award: **$25,000**

This application describes the qualifications and experience of the urogynecology and urology faculty and research teams at the University of Texas Southwestern (UT Southwestern) Medical Center and Parkland Hospital and the facilities and patient population available to carry out clinical protocols sponsored by the Pelvic Floor Disorders Network. In 2004, there were more than 2,100 women with pelvic floor disorders seen in their clinics and 617 women underwent surgical procedures for correction of pelvic floor disorders. The Departments of Obstetrics and Gynecology and Urology have increasingly collaborated since 1997 to offer

comprehensive care of women with pelvic floor disorders. In addition to urogynecology and urology, collaboration includes faculty from colorectal surgery, radiology, physical therapy, and maternal-fetal medicine. The clinical research teams described in this application have successful prior as well as on-going experience in NIH sponsored national multicenter trials. Centerpieces in this application are two existing research clinics, one targeted at private patients (operated by the Urology Department) and the other focused on medically indigent patients (operated by the Obstetrics and Gynecology Department). Also included in this application is a concept application for a randomized trial designed to assess the efficacy of end-to-end versus overlapping repair of the external anal sphincter lacerated during childbirth. The primary outcome is anal incontinence which is a significant consequence of such lacerations. This trial would permit accurate evaluation of the outcome of specific surgical procedures which is one of the prime areas of interest leading to creation of the Pelvic Floor Disorders Network. They are of the view that along with strategies for prevention of anal sphincter laceration during childbirth, optimal management of the torn sphincter should also be studied since more than 200,000 women sustain such pelvic floor injuries each year in the United States.

Title: **Pelvic Floor Disorders Network—Data Coordinating Center**
P.I.: **Catherine A. Spino**
Institution: **University of Michigan, Ann Arbor**
Grant No.: **5U01HD041249-10**
Award: **$25,000**

Pelvic floor disorders such as urinary incontinence, pelvic organ prolapse, and fecal incontinence are common and significant health-related problems for women in the United States. Outcomes following surgical and non-surgical intervention for pelvic floor disorders have not been adequately evaluated. As a result, data necessary to fully inform patients and to make important policy decisions are unavailable. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to systematically evaluate these outcomes. This application to be the data coordinating center (DCC) for the pelvic floor disorders network brings together experienced investigators from biostatistics, urogynecology, urology, quality of life and health services research to prospectively assess the outcomes from various surgical interventions for female pelvic floor disorders. The Specific Aims of the DCC are to: (1) assist in protocol development by providing expertise in the design, conduct, and analysis of clinical trials conducted by the PFDN; (2) provide expertise in measurement of quality of life and in the selection of the appropriate instruments to assess treatment outcomes and, when appropriate, to perform the interviews; (3) coordinate the implementation of the study protocols approved by the steering committee, including design of the case report forms and interviewing protocols, development of a manual of operations, centralized database management with either centralized or remote data entry, submission of an IND to the FDA when necessary, and by organizing training and certification sessions, as needed; (4) establish a database for each study conducted by the PFDN; (5) implement either centralized or web-based data entry and verification; (6) monitor the clinical sites with respect to data quality; (7) provide infrastructure for monitoring adverse events and regulatory oversight for the network; (8) provide logistical support for the steering committee, advisory board and DSMB, for both face-to-face meetings and teleconferences; (9) maintain a website for the PFDN that includes web pages with content for the public and a password-protected site with all study documentation and databases; (10) manage and distribute protocol funds to the Clinical Centers. To illustrate the work of the DCC, a randomized clinical trial is proposed to compare surgical procedures for pelvic organ prolapse using a vaginal approach.

Title: **Pelvic Floor Disorders Network**
P.I.: **Anthony G. Visco**
Institution: **Duke University, Durham, NC**
Grant No.: **5U10HD041267-11**
Award: **$25,000**

Women's health research at the University of North Carolina (UNC) is sophisticated and widespread with many committed investigators addressing issues of fundamental importance to women. UNC has a tradition of excellence in clinical care, training and research in pelvic floor disorders and includes one of the nation's first accredited fellowship programs in the Division of Urogynecology and Reconstructive Pelvic Surgery. They offer comprehensive evaluation and treatment options in a high-volume care setting that serves as a tertiary referral center for women from across the state. Women sought consultation or treatment for more than 2,700 pelvic floor disorders by urogynecologists at UNC in the previous two years. Seventy-eight percent of the women were Caucasian and 15 percent were African American, predominantly from rural and suburban communities with stable care and followup patterns. Approximately 427 women had multi-channel urodynamic studies annually. UNC providers have extensive expertise in both surgical and nonsurgical management of urinary incontinence, pelvic organ prolapse and defecatory dysfunction. The Division of Urogynecology performs an average of 106 surgical procedures for the primary indication of urinary incontinence, 300 for prolapse and provides medical management for over 1,464 women with these conditions each year. The UNC Pelvic Floor Disorders Research Collaborative, led by the Division of Urogynecology is an interdisciplinary team of outstanding investigators in urogynecology, urology, gastroenterology, radiology, maternal-fetal medicine and clinical research methodology. They have a history of strong clinical ties and dedication to interdisciplinary research. Diagnostic resources include multichannel urodynamic testing, cystoscopy, defecography, pelvic MRI, 360-degree endoanal ultrasound, anal manometry, and needle electromyography. Clinical services include surgical treatment of complex pelvic floor disorders and a wide range of non-surgical options. As an active PFDN clinical network site, UNC has an established research infrastructure with the proven ability to support large-scale, multicentered clinical research. The collaborative is well-equiped and uniquely qualified to continue as a valuable member of the Pelvic Floor Disorders Network. Given the exceptional quality of the research opportunities and resources available at UNC, the stable and diverse patient population, the strength of the investigator pool, their proven high-level recruitment and the commitment of the institution to the stated goals of this RFA, they look forward to continuing to make substantial contributions to advancing women's health related to pelvic floor disorders.

APPENDIX D

ORWH-Cofunded Research Conferences and Workshops

ORWH provides funding for research projects and research dissemination through conferences and workshops held at NIH and nationwide. Through partnerships with NIH ICs and Offices, other Federal agencies, and extramural organizations, ORWH seeks to bring together researchers investigating women's health and sex differences to exchange ideas, foster collaborations, and explore emerging concepts and technologies. A description of ORWH-cofunded conferences and workshops occurring during this reporting period is provided below.

Annual Interdisciplinary Women's Health Research Symposia

The Interdisciplinary Women's Health Research Symposium is held annually in November in conjunction with the annual meeting for principal investigators from two signature ORWH programs: the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health and the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program. The BIRCWH scholar meeting is also held at this time and provides the scholars an opportunity to showcase scientific research from these programs. (For more information on the SCOR and BIRCWH programs, see Section III.

The Sixth Annual Interdisciplinary Women's Health Research Symposium on November 17, 2009 included a keynote address from Thomas Insel, M.D. Director of NIMH, and featured 16 oral presentations from scholars from the BIRCWH program and SCOR principal investigators. In addition, 62 BIRCWH and 10 SCOR abstracts were selected for poster presentations. The symposium was attended by more than 200 people.

The Seventh Annual Interdisciplinary Women's Health Research Symposium on November 9, 2010 featured a keynote address by Alan Guttmacher, M.D., Director of NICHD, titled "Advances in Women's Health Research: Where We've Been, Where We're Going." The 2010 symposium featured 16 oral presentations and 60 poster presentations from BIRCWH scholars and 12 presentations from SCOR principal investigators on a wide range of topics related to women's health and sex/gender factors.

U.S. Bone and Joint Decade Global Network Conference

ORWH cosponsored, with NIAMS, the U.S. Bone and Joint Decade Global Network Conference in October 2009 in Washington, DC. This meeting was also cosponsored by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), NICHD, NIDCR, NIDDK, and NIA. The Bone and Joint Decade is an international movement sanctioned by the United Nations/World Health Organization from 2002 to 2011. The goal of this meeting was to improve bone and joint health by enhancing collaborative efforts among individuals and organizations to raise awareness of the growing burden of musculoskeletal disorders on society, to promote wellness and prevent musculoskeletal disease, and to advance research that will lead to improvements in prevention, diagnosis, and treatment.

Second Annual Trauma Spectrum Disorders Conference

The second annual trauma spectrum disorders conference, titled "A Scientific Conference on the Impact of Military Service on Family and Caregivers," was held on the NIH campus in December 2009 and examined the needs of families and caregivers in support of military and veterans with trauma spectrum disorders. The term "trauma spectrum disorders" refers to the injuries and illnesses that occur as a result of combat or an unexpected traumatic event and covers a broad range of traumatic brain injury and psychological health issues. The conference convened researchers and practitioners from DoD, VA, and several NIH ICs and HHS offices and agencies. The goal was to provide a forum to examine evidence-based science relative to family functioning, caregiving, and child and adolescent development in the context of trauma.

Fourth Global Summit on International Breast Health

The Breast Health Global Initiative (BHGI) and the Latin American and Caribbean Society of Medical Oncology convened the biennial global summit in June 2010 in Chicago, bringing together collaborating national and international organizations to address the optimization of breast health care delivery in limited resource countries. In association with the BHGI summit, Susan G. Komen for the Cure, a global leader in advocacy and the fight against breast cancer, held a global summit on international breast cancer advocacy.

Workshop: Challenges in Infant Immunity

The objectives of the "Challenges in Infant Immunity" workshop held in June 2010 were to understand and assess the scientific knowledge base on infant immunity, including maternal-fetal interactions, as they relate to vaccines and responses to infections; to identify gaps and key issues in immune mechanisms in the mother and infant that would inform the design of improved vaccines; and to foster collaborations among investigators studying infectious disease pathogenesis, vaccine design and development, and immune mechanisms.

Add Health Users Conference

The ninth National Longitudinal Study of Adolescent Health (Add Health) Users Conference took place in Bethesda, Maryland, on the NIH campus on July 22–23, 2010. Over 100 researchers who are working with Add Health data assembled to share research goals, experiences and results. The conference agenda included over 50 presentations by investigators who are using Add Health data to conduct research in substantive areas spanning the social, behavioral and biological sciences. Focus areas for these researchers include deviance, depression, violence victimization, relationship values, educational attainment, obesity, and the factors—including genetic factors—that contribute to these domains. In addition, methodology sessions provided in-depth information on the Add Health study design and the unique biomarker, genetic, geographic and relationship data that enhance this rich data set. Conference materials and methodology presentations are available online at http://www.cpc.unc.edu/projects/addhealth/news/.

Genetics 2010: Model Organisms to Human Biology

The Genetics Society of America meeting, "Genetics 2010: Model Organisms to Human Biology," held in June 2010, addressed the value of model organisms for understanding diverse aspects of human biology. This was the third biennial meeting in this area that brought together investigators who study model organisms with investigators who study human biology and disease. The goal of the meeting was to provide a dynamic forum for the exchange of results and ideas between scientists who do not normally interact. Attendees were able to participate in broad subject area sessions to stimulate new ideas that could be brought back to their labs and applied to their organism research and network with potential collaborators. Plenary sessions at the meeting included topics such as sex and gene expression, personal genomics, cancer as a genetic disease, and models of disease, among others. The keynote address was delivered by Nobel Laureate Carol Greider, Ph.D., of The Johns Hopkins University.

17th Ovarian Workshop: A Global Perspective of Ovarian Function

The 17th Ovarian Workshop, held in July 2010, provided a forum for clinicians, scientists, and students to exchange ideas and current concepts on the development, regulation, and maintenance of the ovary without regard to disciplinary boundaries. The workshop promoted the presentation and exchange of ideas at the frontiers of research in female reproductive biology. The scientific program has evolved into an internationally respected conference attracting scientists from diverse backgrounds who share a common interest in understanding the function of cells in the ovary.

The goal of the workshop was to advance understanding of ovarian function so that this basic knowledge can be translated to clinical and environmental applications to enhance or control fertility and to treat, reduce, and/or eliminate ovarian dysfunctions and cancer. The format of the workshop expanded on the theme of translational research that reaches from bench to bedside by incorporating new basic science together with clinically and environmentally relevant issues and presentations by clinical scientists and toxicologists.

The theme of the workshop was ovarian function in a format that incorporated international speakers, new investigators, and established experts, and topics ranging from oogenesis to luteal function at the basic and applied levels. The program included a keynote address and poster sessions related to the theme of the workshop. New investigators were invited to submit expanded abstracts to be evaluated for scientific merit and competition for travel awards and the Cornelia P. Channing New Investigator Award.

Workshop on Virtual Reality Technologies for Research and Education in Obesity and Diabetes

This workshop, held on the NIH campus in July 2010, explored the research potential of virtual reality (VR) technologies as tools for behavioral and neuroscience studies in diabetes and obesity and the practical potential of VR technology in fostering more effective utilization of diabetes- and obesity-related nutrition and lifestyle information. A significant portion of the U.S. population has difficulty assimilating and implementing public health or therapeutic guidance on optimal diet and physical activity. Even if individuals are willing to make behavioral changes, it is difficult to navigate the environmental choices and opportunity cost issues that present themselves at the point of decision. This difficulty is the cause of failure for many approaches seeking to promote positive behavioral changes, which is of particular concern for individuals with obesity and diabetes.

Sixth International Symposium on Hormonal Oncogenesis

The Sixth International Symposium on Hormonal Oncogenesis (ISHO), held in September 2010, was a joint venture with the Universities and Pharmaceutical Consortium of Japan. The format of the symposium consisted of a symposium address, state-of-the-art lectures, speaker presentations, and two poster sessions. The symposium emphasized translational studies in epidemiology and clinical and basic research. More than 50 percent of the presentations by speakers involved studies in breast and ovarian cancer. The goal of the sixth ISHO was to focus on major developments in the rapidly expanding field of hormonal oncogenesis and hormonal cancers. A novel format for these symposia was used to integrate different disciplines and approaches in each of the sessions, whenever possible, to include basic science, epidemiology, and clinical research. Each session focused on a specific aspect of a hormone-related cancer. Information gathered from cell-free systems, cell cultures, animal models, and human studies provided important insights to understanding hormonal cancer causation, development, and prevention, which was the primary objective of the symposia. A special emphasis will continue to be placed on the two major endocrine-related cancers: breast and prostate. Other highly relevant cancers to be addressed are ovarian and endometrial. Emerging fields to be examined are colon, thyroid, pituitary, and lung cancers in relation to hormones.

APPENDIX E

Select BIRCWH Scholar Publications
(June 2009–June 2010)

2007 Sites

Boston University

Tracy Battaglia

Battaglia, T.A., Santana, M.C., Bak, S., Gokhale, M., Lash, T.L., Ash, A.S., ... Freund, K.M. (2010). Predictors of timely follow-up after abnormal cancer screening among women seeking care at urban community health centers. *Cancer*, 116(4), 913–21.

Renee Boynton-Jarrett

Boynton-Jarrett, R., Fargnoli, J., Suglia, S.F., Zuckerman, B., & Wright, R.J. (in press). The impact of maternal intimate partner violence on incidence of obesity in preschool children: Findings from the fragile families and child wellbeing study, *Archives of Pediatric and Adolescent Medicine*.

Harville, E.W., **Boynton-Jarrett, R.**, Hypponen, E., & Power, C. (in press). Effects of childhood hardships on pregnancy outcomes. *Archives of Pediatric and Adolescent Medicine*.

Andrea Coviello

Coviello, A.D. (2009). Polycystic ovary syndrome: multiple pathways to a common phenotype? *Endocrinology Practice,* 15(4), 387–389.

Lynette Craft

Perna, F.M., **Craft, L.,** Freund, K.M., Skrinar, G., Stone, M., Kachnic, L., ... Battaglia, T. (2010). The effect of a cognitive behavioral exercise intervention on clinical depression in a multi-ethnic sample of women with breast cancer. *International Journal of Exercise and Sport Psychology*, 8(1), 36–47.

Michelle David

Mostow, C., Crosson, J., Gordon, S., Chapman, S., Gonzalez, P., Hardt, E., ... **David, M.** (2010). Treating and precepting with RESPECT: A relational model addressing race, ethnicity, and culture in medical training. *Journal of General Internal Medicine,* Suppl(2), S146–S154.

Eve Davison

Rowe, E. L, Gradus, J. L., Pineles, S. L., Batten, S.V., & **Davison, E. H.** (2009). Military sexual trauma in treatment-seeking women veterans. *Military Psychology, 21*(3), 387–395.

Terry Ellis

Tickle-Degnen, L., **Ellis, T.,** Saint-Hilaire, M.H., Thomas, C., & Wagenaar, R.C. (2010). Self-management rehabilitation improves quality of life outcomes in Parkinson's disease: A randomized controlled trial. *Movement Disorders,* 25(2), 194–204.

White, D., Wagenaar, R.C., Tickle-Degnen, L., & **Ellis, T.** (2009). Changes in home and community activity following self-management rehabilitation in individuals with Parkinson's disease. *Archives of Physical Medicine and Rehabilitation,* 90(1), 43–50.

Angela Jefferson

Jefferson, A.L., Massaro, J.M., Larson, M.G., Wolf, P.A., Au, R., D'Agostino, R.B., ... DeCarli, C. (2007). Inflammatory biomarkers are associated with total brain volume: The Framingham Heart Study. *Neurology*, 68, 1032–1038.

Andrea Kronman

Kronman, A.C., Freund, K.M., Hanchate, A., Emanuel, E.J. & Ash, A.S. (2010). Nursing home residence confounds gender differences in Medicare utilization an example of Simpson's paradox. *Women's Health Issues*, 20(2), 105–113.

Rebecca Perkins

Perkins, R.B., Pierre-Joseph, N., Marquez, C., Iloka, S., & Clark, J.A. (2010). Why do low-income, minority parents choose HPV vaccination for their daughters? *The Journal of Pediatrics,* 157(4), 617–622.

Natalie Pierre Joseph

Perkins, R.B., **Pierre-Joseph, N.**, Marquez, C., Iloka, S., & Clark, J.A. (2010). Why do low-income, minority parents choose HPV vaccination for their daughters? *The Journal of Pediatrics,* 157(4), 617–622.

Oregon Health Sciences University

CURRENT SCHOLARS

Sonnet Jonker

Jonker, S.S., Giraud, M.K., Giraud, G.D., Chattergoon, N.N., Louey, S., Davis, L.E., ... Thornburg, K.L. (2010). Cardiomyocyte enlargement, proliferation and maturation during chronic fetal anemia in sheep. *Experimental Physiology,* 95(1), 131–139.

Jonker, S., & Roselli, C. (2010). Early-gestation exposure to excess testosterone reduces cardiomyocyte proliferation and maturation in near-term female fetal sheep. *The Physiologist,* 52(6), 19.

Jonker, S.S., & Segar, J.L. (2009). Cardiac consequences of transfusion following fetal anemia during ovine pregnancy. *Journal of Women's Health,* 18(10), 1507.

Beth Darnall

Darnall, B.D., Aickin, M., & Zwickey, H. A. (2010). Pilot study of inflammatory responses following a negative imaginal focus in persons with chronic pain: Analysis by gender. *Gender Medicine,* 7(3), 247–260.

Darnall, B.D. & Suarez, E.C. (2009). Sex and gender in psychoneuroimmunology research: Past, present and future. *Brain, Behavior and Immunity,* 23(5), 595–604.

Darnall, B.D. (2009). Self-delivered home-based mirror therapy for lower limb phantom pain. *American Journal of Physical Medicine & Rehabilitation,* 88(1), 78–81.

Darnall, B.D. (2009). Hysterectomy is associated with opioid use in women with chronic pain. *Journal of Women's H*ealth, 18(10), 1496.

BIRCWH ALUMNI

Karen Eden and Nancy Glass

Glass, N., Eden, K.B., Bloom, T., & Perrin, N. (2009). Computerized aid improves safety decision process for survivors of intimate partner violence. *Journal of Interpersonal Violence*, 25(11), 1947–1964. PubMed: 20040709

Tanja Pejovic

Pejovic, T., Pande, N.T., Mori, M., Mhawech-Fauceglia, P., Harrington, C., Mongoue-Tchokote, S., ... Odunsi, K.O. (2009). Expression profiling of the ovarian surface kinome reveals candidate genes for early neoplastic changes. *Translational Oncology,* 2(4), 341–349. PubMed: 19956396

Medical University of South Carolina

Ananda Amstadter

Amstadter, A.B., Koenen, K.C., Ruggiero, K.J., Acierno, R., Galea, S., Kilpatrick, D.G., & Gelernter, J. (2009). Variation in RGS2 is associated with suicidal ideation in an epidemiological study of adults exposed to the 2004 Florida hurricanes. *Archives of Suicide Research*, 13(4), 349–357. PMC2760049

Amstadter, A.B., Nugent, N.R., Koenen, K.C., Ruggiero, K.J., Acierno, R., Galea, S., ... Gelernter, J. (2009). Association between COMT, PTSD, and increased smoking following hurricane exposure in an epidemiologic sample. *Psychiatry*, 72(4), 360–369. PMC2808117

Amstadter, A.B., Koenen, K.C., Ruggiero, K.J., Acierno, R., Galea, S., Kilpatrick, D.G., & Gelernter, J. (2010). NPY moderates the relation between hurricane exposure and generalized anxiety disorder in an epidemiologic sample of hurricane-exposed adults. *Depression and Anxiety*, 27(3), 270–275.

Koenen, K.C., **Amstadter, A.B.**, & Nugent, N.R. (2009). Gene-environment interaction in posttraumatic stress disorder: An update. *Journal of Traumatic Stress,* 22(5), 416–426. NIHMS135393

Koenen, K.C, Uddin, M., **Amstadter, A.B.**, & Galea, S. (2010). Incorporating the social environment in genotype environment interaction studies of mental disorders. *International Journal of Clinical Practice,* 64(11), 1489–1492.

Mona Buhusi

Granholm, A.C., Lockrow, J., Boger, H., & **Buhusi, M.** (2010). A common role for locus coeruleus neurons in Parkinson's and Alzheimer's disease. In K. Kompoliti & L. Verhagen (Eds.) *Encyclopedia of Movement Disorders,* Oxford, UK: Elsevier.

Buhusi, M., & Buhusi, C.V. (2010). *Aging alters responses in a fear conditioning paradigm.* (Manuscript in progress).

Buhusi, M., & Granholm, A.C. (2010). *BDNF processing and signaling in the aged mouse hippocampus.* (Submitted for publication)

Buhusi M., & Granholm, A.C. (2010). Impact of estrogen on memory: a matter of timing. (Manuscript in progress).

Fortress, A.M., **Buhusi, M.**, Helke, K.L., & Granholm, A.C.. Cholinergic degeneration and p75 receptor up-regulation following pro-NGF injection into aged rats. *Journal of Neuroscience.*

Karen Hartwell

Back, S.E., **Hartwell, K.**, DeSantis, S.M., Saladin, M.E., McRae-Clark, A.L., Price, K.L., ... Brady, K.T. (2010). Reactivity to laboratory stress provocation predicts relapse to cocaine. *Drug and Alcohol Dependence*, 106:, 21-–27. PMC2815094

Hartwell, K.J., Tolliver, B.K., & Brady, K.T. (2009). Biologic commonalities between mental illness and addiction. *Primary Psychiatry*, 16(8), 33–39.

Hartwell, K., Back, S., Waldrop, A., Saladin, M., Yeatts, S., Simpson, A., ... Brady, K.T. (2009, April). Effects of gender and cigarette smoking on reactivity to psychological and pharmacological stress provocation. In L. Zawertailo & H. De Wit (Chairs), *The relationship between stress and smoking,* Session conducted at the annual meeting of the Society of Research on Nicotine and Tobacco, Dublin, Ireland.

Hartwell, K., Back, S., Saladin, M., McRae-Clark, A., Price, K., Moran-Santa Maria, M., ... Brady, K.T. (2009, June). *Reactivity to laboratory stress provocation predicts relapse to cocaine.* Poster presented at The College on Problems with Drug Dependence, Reno, Nevada.

Hartwell, K., Johnson, K., Li, X., White, K., Myrick, H., & Brady, K. (2009, November). *Regional areas of brain activation during attempts to resist craving in nicotine dependent smokers: Preliminary findings.* Poster presentation at Sixth Annual Interdisciplinary Women's Health Research Symposium, Bethesda, MD.

Hartwell, K.J., Johnson, K.A., LeMatty, T.A., Myrick, H., George, M.S., & Brady, K.T. (2010, February). *Identification of brain activation patterns utilized to resist cue-induced craving in treatment-seeking smokers.* Oral presentation at 16th Annual Meeting of Society for Research on Nicotine and Tobacco, Baltimore, MD.

Johnson, K., Govindarajan, K., Borckardt, J., Morgan, P., **Hartwell, K.,** Brady, K., & George, M.S. (in press). Modulation of brain activation during an imagined movement task using true and false real-time fMRI feedback. *Journal of Neuroimaging*.

Payne, R., Back, S.E., Wright, T., **Hartwell, K.,** & Brady, K.T. (2009). Alcohol dependence in women: Comorbidities can complicate treatment. *Current Psychiatry*, 8(6), 52–59.

Brady, K.T., **Hartwell, K.** (in press). Aftercare: A review. *UpToDate*.

McRae, A.L., Brady, K.T., **Hartwell, K.,** White, K., & Carter, R.E. (Submitted). Methylphenidate transdermal system in adults with past stimulant misuse. *Journal of Attention Disorders*.

Mathew Feltenstein

Buffalari, D.M., **Feltenstein, M.W.,** & See, R.E. (2009). *Stress and cue interactions in the reinstatement of cocaine-seeking in female rats.* Presented at the 70th Annual Meeting of the College on Problems of Drug Dependence, Reno, NV.

Feltenstein, M.W. & See, R.E. (2008). The neurocircuitry of addiction: an overview. *British Journal of Pharmacology*, 154(2), 261–274. PMC2442446.

Feltenstein, M.W., Byrd, E., Henderson, A., & See, R.E. (2009). Attenuation of cocaine-seeking by progesterone treatment in female rats. *Psychoneuroendocrinology*, 34(3), 343–352. PMC2675282

Feltenstein, M.W., & See, R.E. (2009, June). *Sex differences in nicotine self-administration and reinstatement in rats.* Presented at the 70th Annual Meeting of the College on Problems of Drug Dependence, Reno, NV.

Feltenstein, M.W., Do, P.H., Boatwright, S.W., & See, R.E. (2009, October). *Sex differences in nicotine self-administration and reinstatement in rats.* Presented at the 39th Annual Meeting of the Society for Neuroscience, Chicago, IL.

Feltenstein, M.W., Smalls, B., Boatwright, S.W., Ghee, S.M., & See, R.E. (2009, November). *Sex differences in nicotine self-administration and reinstatement in rats.* Presented at the Sixth Annual Interdisciplinary Women's Health Research Symposium, Bethesda, MD.

Feltenstein, M.W., Shippenberg, T.S., Zapata, A., See, R.E,, & Riegel, A.C. (2010, June). *Pain during heroin self-administration enhances relapse of heroin-seeking in rats.* Presented at the 71st Annual Meeting of the College on Problems of Drug Dependence, Scottsdale, AZ.

Feltenstein, M.W., Henderson, A.R., & See, RE. (in progress). Potentiation of cue-induced reinstatement of cocaine seeking in female rats by yohimbine.

Crystal Flynn Longmire

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University of Pittsburgh

Steven Abramowitch

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Julie K. Schwarz

Shokeen, M., **Schwarz, J.K.**, & Zheleznyak, A. (2009, November). *Imaging sites of metastasis before they happen: Targeting the premetastatic niche.* Poster presented at the Building Interdisciplinary Research Careers in Women's Health Annual Scholar's Meeting, Bethesda, MD.

Shokeen, M., **Schwarz, J.K.,** Zheleznyak, M., Wilson, J.M., Nguyen, K., Liu, R., ... Anderson, C. J. (2009, October). *Predicting sites of metastasis: Molecular imaging of the pre-metastatic niche.* Presented at the IX International Meeting on Cancer Induced Bone Disease, Arlington, VA.

Shokeen, M., Zheleznyak, A., **Schwarz, J.K.**, Wilson, J.M., Nguyen, K., Liu, R., ... Anderson, C.J. (2009, September). *PET imaging of the pre-metastatic niche with ^{64}Cu-CB-TE2A-LLP2A, a high affinity ligand for integrin $\alpha_4\beta_1$.* World Molecular Imaging Congress, Montreal, Canada.

Shokeen, M., **Schwarz, J.K.**, Zheleznyak, A., Wilson, J.M., Nguyen, K., Liu, R., ... Anderson, C.J. (in preparation). PET imaging of the pre-metastatic niche with ^{64}Cu-CB-TE2A-LLP2A, a high affinity ligand for integrin $\alpha_4\beta_1$.

Reina Villareal

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Consuelo Wilkins

Sheline, Y.I., Pieper, C.F., Barch, D.M., Welsh-Boehmer, K., McKinstry, R.C., **Wilkins, C.,** ... Doraiswamy, P.M. (2010). Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Archives of General Psychiatry*, 67(3), 277–285. PMC2838210

APPENDIX F

Select SCOR Publications That Include Sex and Gender Analyses, Arranged by Program

Northwestern University

Abbott, D. H., Bruns, C. R., Barnett, D. K., Dunaif, A., Goodfriend, T. L., Dumesic, D. A., & Tarantal, A. F. (2010). Experimentally induced gestational androgen excess disrupts glucoregulation in rhesus monkey dams and their female offspring. *American Journal of Physiology-Endocrinology and Metabolism, 299*(5), 741–751.

Ackerman, C. M., Lowe, L. P., Lee, H., Chen, F., Hughes, E., Cholod, P., Dyer, A. R., Hayes, M. G., Metzger, B. E., Lowe, W. L., &,Urbanek, M. (2010). The role of the polycystic ovary syndrome susceptibility locus D19S884 allele 8 in maternal glycemia and fetal size. *Journal of Clinical Endocrinology & Metabolism, 95*, 3242–3250.

Anderson, H., Fogel, N., Grebe, S. K., Singh, R. J., Taylor, R. L., & Dunaif, A. (2010). Infants of women with polycystic ovary syndrome have lower cord blood androstenedione and estradiol levels. *Journal of Clinical Endocrinology & Metabolism, 95*, 2180–2186.

Ciofi, P., Garret, M., Lapirot, O., Lafon, P., Loyens, A., Prévot, V., & Levine, J. E. (2009). Brain-endocrine interactions: A microvascular route in the mediobasal hypothalamus. *Endocrinology*, 150, 5509–5519.

Coviello, A. D., Sam, S., Legro, R. S., & Dunaif, A. (2009). High prevalence of metabolic syndrome in first-degree male relatives of women with polycystic ovary syndrome is related to high rates of obesity. *Journal of Clinical Endocrinology & Metabolism, 94*, 4361–4366.

Ewens, K. G., Stewart, D. R., Ankener, W., Urbanek, M., McAllister, J. M., Chen, C., Spielman, R. S. (2010). Family-based analysis of candidate genes for polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism, 95*, 2306–2315.

Gottsch, M. L., Navarro, V. M., Zhao, Z., Glidewell-Kenney, C., Weiss, J., Jameson, J. L., Clifton, D. K., Levine, J. E., Steiner, R. A. (2009). Regulation of Kiss1 and dynorphin gene expression in the murine brain by classical and nonclassical estrogen receptor pathways. *Journal of Neuroscience, 29*, 9390–9395.

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Liu, S., Le May, C., Wong, W. P., Ward, R. D., Clegg, D. J., Marcelli, M., Korach, K. S., Mauvais-Jarvis, F. (2009). Importance of extranuclear estrogen receptor-alpha and membrane G protein-coupled estrogen receptor in pancreatic islet survival. *Diabetes, 58*, 2292–2302.

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Liu, S., Navarro, G., & Mauvais-Jarvis F. (2010). Androgen excess produces systemic oxidative stress and predisposes to beta-cell failure in female mice. *PloS One, 5*, e11302.

Wong, P. S., Tiano, J., Liu, S., Hewitt, S. C., Le May, C., Dalle, S., Katzenellenbogen, J. A., Katzenellenbogen, B. S., Korach, K.S., & Mauvais-Jarvis, F. (2010). The extranuclear estrogen receptor-α stimulates NeuroD1 binding to the insulin promoter and favors insulin synthesis. *Proceedings of the National Academy of Sciences of the United States of America, 107,* 13057–13062.

Medical University of South Carolina

Project 1, Ron See, Principal Investigator (PI)

Buffalari, D. M., & See, R. E. (2009). Footshock stress potentiates cue-induced cocaine-seeking in an animal model of relapse. *Physiology and Behavior, 98*(5), 614–617.

Feltenstein, M. W., Byrd, E. A., Henderson, A. R., & See, R.E. (2009). Attenuation of cocaine-seeking by progesterone treatment in female rats. *Psychoneuroendocrinology, 34*(3), 343–352.

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Yahyavi-Firouz-Abadi, N., & See, R. E. (2009). Anti-relapse medications: Preclinical models for drug addiction treatment. *Pharmacology & Therapeutics, 124*(2), 235–247.

Project 2, Kathleen Brady, PI

Back, S. E., Hartwell, K., DeSantis, S. M., Saladin, M., McRae-Clark, A. L., Price, K .L., & Brady, K. T. (2010). Reactivity to laboratory stress provocation predicts relapse to cocaine. *Drug and Alcohol Dependence, 107,* 21–27.

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Moran-Santa Maria, M. M., Baker, N. L., Feltenstein, M. W., McRae-Clark, A. L., DeSantis, S. M., & Brady, K. T. (under review). Endogenous progesterone and the subjective response to CRH in cocaine-dependent women. *American Journal of Drug and Alcohol Dependence*.

Moran-Santa Maria, M. M., McRae-Clark, A. L., Back, S. E., DeSantis, S. M., Baker, N. L, Spratt, E. G. Simpson, A. N., & Brady, K. T. (2010). Influence of cocaine dependence and early life stress on pituitary-adrenal axis responses to CRH and the Trier social stressor. *Psychoneuroendocrinology, 35*(10), 1492–1500.

Spratt, E. G., Back, S. E., Yeatts, S. D., Simpson, A. N., McRae-Clark, A. Moran-Santa Maria M. M., Price, K. L., Hartwell, K. T., & Brady, K. T. (2009). Relationship between child abuse and adult smoking. *International Journal of Psychiatry in Medicine, 39*(4), 417–426.

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Project 3, Michael Saladin and Kevin Gray, Co-PIs

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University of Miami

Accornero, V. H., Anthony, J. C., Morrow, C. E., Xue, L., McCoy, C. B., & Bandstra, E. S. (2011). Estimated effect of prenatal cocaine exposure on examiner-rated behavior at age 7 years. *Neurotoxicology and Teratology, 33*(3), 370–378.

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Messiah, S. E., Lipshultz, S. E., Miller, T. L., & Bandstra, E. (2011). Potential latent effects of prenatal cocaine exposure on growth and the risk of cardiovascular and metabolic disease in childhood. *Progress in Pediatric Cardiology, 31*(1), 59–65.

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University of Missouri, Kansas City

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Washington University in St. Louis

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APPENDIX G

Ad Hoc Trans-NIH Working Group for Research on Chronic Fatigue Syndrome

FY 2009

Eleanor Hanna, Ph.D., *Chair*	ORWH/OD
Joyce Rudick	ORWH/OD
J. Terrell Hoffeld, D.D.S., Ph.D.	CSR
Richard Nahin, Ph.D.	NCCAM
John Harding, Ph.D.	NCRR
Cheryl McDonald, M.D.	NHLBI
Michael Twery, Ph.D.	NHLBI
Laurie Foudin, Ph.D.	NIAAA
Thomas Esch, Ph.D.	NIAID
David Morens, M.D.	NIAID
Suzanna Serrate-Sztein, Ph.D.	NIAMS
Lynne Haverkos, M.D.	NICHD
John Kusiak, Ph.D.	NIDCR
Annette Kirshner, Ph.D.	NIEHS
Matthew Rudorfer, M.D.	NIMH
Peter Muehrer, Ph.D.	NIMH
Linda Porter, Ph.D.	NINDS
Kathy Mann Koepke, Ph.D.	NINR
Jerry Flanzer, D.S.W.	OBSSR
Rebecca Costello, Ph.D.	ODS/OD

FY 2010

Eleanor Hanna, Ph.D., *Co-Chair*	ORWH/OD
Dennis Mangan, Ph.D., *Co-Chair*	ORWH/OD
Janine Clayton, M.D.	ORWH/OD
Cheryl Kitt, Ph.D.	CSR
Donald Blair, Ph.D.	NCI
John Harding, Ph.D.	NCRR
Cheryl McDonald, M.D.	NHLBI
Simone Glynn, M.D.	NHLBI
Basil Eldadah, M.D., Ph.D.	NIA
M. Katherine Jung, Ph.D.	NIAAA
Timothy Gondré-Lewis, Ph.D.	NIAID
Catherine Laughlin, Ph.D.	NIAID
Eun Chung Park, Ph.D.	NIAID
Yan Wang, M.D., Ph.D.	NIAMS
John Kusiak, Ph.D.	NIDCR
Christopher Mullins, Ph.D.	NIDDK
Annette Kirshner, Ph.D.	NIEHS
Matthew Rudorfer, M.D.	NIMH
May Wong, Ph.D.	NINDS
Xenia Tigno, Ph.D.	NINR
Maureen Boyle, Ph.D.	OBSSR
Rebecca Costello, Ph.D.	ODS/OD

APPENDIX H

NIH Working Group on Women in Biomedical Careers

FY 2009

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Vivian W. Pinn, M.D., Associate Director for Research on Women's Health; Director, ORWH

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Barbara Alving, M.D., Director, NCRR
Jeremy Berg, Ph.D., Director, NIGMS
Patricia Grady, Ph.D., R.N., F.A.A.N., Director, NINR
Story Landis, Ph.D., Director, NINDS
Donald Lindberg, M.D., Director, NLM

Office of the Director
Lawrence Tabak, D.D.S., Ph.D., Acting Deputy Director, NIH
Janine Austin Clayton, M.D., Deputy Director, ORWH
Joyce Rudick, Director, Programs and Management, ORWH
Lawrence Self, Director, OEODM (*Ex-Officio member*)

Intramural Research
Michael Gottesman, M.D., NIH Deputy Director for Intramural Research
Joan Schwartz, Ph.D., Assistant Director, OIR
Edward Giniger, Ph.D., Investigator, NINDS
Elaine Ostrander, Ph.D., Chief & Senior Investigator, Cancer Genetics Branch, NHGRI
Kathryn Zoon, Ph.D., Scientific Director, NIAID

Extramural Research
Sally Rockey, Ph.D., Acting NIH Deputy Director for Extramural Research
Walter Schaffer, Ph.D., Senior Scientific Advisor for Extramural Research, OER
J. Taylor Harden, Ph.D., Assistant to the Director for Special Populations, NIA
Pamela Marino, Ph.D., Program Director, Pharmacology, Physiology, and Biological Chemistry Division; Co-Director, Pharmacology Research Associate Program, NIGMS
Belinda Seto, Ph.D., Deputy Director, NIBIB

Staff to Working Group
Joslyn Yudenfreund Kravitz, Ph.D., AAAS Science and Technology Policy Fellow, ORWH

FY 2010

Co-chairs
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Vivian W. Pinn, M.D., Associate Director for Research on Women's Health; Director, ORWH

Institute and Center Directors
Barbara Alving, M.D., Director, NCRR
Jeremy Berg, Ph.D., Director, NIGMS
Patricia Grady, Ph.D., R.N., F.A.A.N., Director, NINR
Story Landis, Ph.D., Director, NINDS
Donald Lindberg, M.D., Director, NLM

Office of the Director
Lawrence Tabak, D.D.S., Ph.D., Deputy Director, NIH
Janine Austin Clayton, M.D., Deputy Director, ORWH
Joyce Rudick, Director, Programs and Management, ORWH
Lawrence Self, Director, OEODM (*Ex-Officio member*)

Intramural Research
Michael Gottesman, M.D., NIH Deputy Director for Intramural Research
Joan Schwartz, Ph.D., Assistant Director, OIR
Edward Giniger, Ph.D., Investigator, NINDS
Elaine Ostrander, Ph.D., Chief & Senior Investigator, Cancer Genetics Branch, NHGRI
Kathryn Zoon, Ph.D., Scientific Director, NIAID

Extramural Research
Sally Rockey, Ph.D., NIH Deputy Director for Extramural Research
Walter Schaffer, Ph.D., Senior Scientific Advisor for Extramural Research, OER
J. Taylor Harden, Ph.D., Assistant to the Director for Special Populations, NIA
Pamela Marino, Ph.D., Program Director, Pharmacology, Physiology, and Biological Chemistry Division; Co-Director, Pharmacology Research Associate Program, NIGMS
Belinda Seto, Ph.D., Deputy Director, NIBIB

Staff to Working Group
Joslyn Yudenfreund Kravitz, Ph.D., Special Assistant to the Director, ORWH

APPENDIX I

Intramural Program on Research on Women's Health Steering Committee

FY 2009

Esther Sternberg, M.D., NIMH, *Co-Chair*
Barbara Vonderhaar, Ph.D., NCI, *Co-Chair*
Ms. Joyce Rudick, OD/ORWH
Rosemarie Filart, M.D., M.P.H., NCRR, *WHSIG Coordinator*
Lawrence Brody, Ph.D., NHGRI
Giovanni Cizza, M.D., Ph.D., NIDDK
Janine Austin Clayton, M.D., OD/ORWH
Wendy Fibison, Ph.D., NIAID
Kenneth Korach, Ph.D., NIEHS
Joslyn Kravitz, Ph.D., OD/ORWH
James Lacey, Ph.D., NCI
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Maria Morasso, Ph.D., NIAMS
Lawrence Nelson, M.D., NICHD
Pamela Robey, Ph.D., NIDCR
Joan Schwartz, Ph.D., OD/OIR
Monica Skarulis, M.D., NIDDK
Cathy Wolkow, Ph.D., NIA
Marian Young, Ph.D., NIDCR

FY 2010

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Esther Sternberg, M.D., NIMH, *Co-Chair*
Ms. Joyce Rudick, OD/ORWH
Rosemarie Filart, M.D., M.P.H., NCRR, *WHSIG Coordinator*
Lawrence Brody, Ph.D., NHGRI
Cherié Butts, Ph.D., FDA
Janine Austin Clayton, M.D., OD/ORWH
Wendy Fibison, Ph.D., NIAID
Gretchen Gierach, Ph.D., M.P.H., NCI
Kenneth Korach, Ph.D., NIEHS
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Lawrence Nelson, M.D., NICHD
Pamela Robey, Ph.D., NIDCR
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Marian Young, Ph.D., NIDCR

Ex Officio Members, FY 2009 & FY 2010

Michael Gottesman, M.D., OD/OIR
Vivian Pinn, M.D., OD/ORWH
Richard Wyatt, M.D., OD/OIR

APPENDIX J

Comparison of Old and New Minority Enrollment Reporting Forms

OLD FORM: Combined 1977 OMB Race/Ethnicity Categories

Race/Ethnicity Category	Minority Total (Old Form)	Minority Total (New Form)
American Indian/Alaska Native	X	
Asian/Pacific Islander	X	
Black or African-American	X	
Hispanic, Not White	X	
White		
Unknown/Other		

NEW FORM: Separate 1997 OMB Race/Ethnicity Categories

Race/Ethnicity Category Part A: Total Enrollment Report Ethnic Category	**Minority Total (Old Form)**	**Minority Total (New Form)**
Hispanic or Latino*		
Not Hispanic or Latino		
Unknown (ethnicity not reported)		
Ethnic Category Total of All Subjects**		
Racial Categories		
American Indian/Alaska Native		X
Asian		X
Black or African-American		X
Hawaiian/Pacific Islander		X
White		
More Than One Race		X
Unknown/Other		
Racial Categories: Total of All Subjects**		
Race/Ethnicity Category Part B: Hispanic Enrollment by Race	**Minority Total (Old Form)**	**Minority Total (New Form)**
American Indian/Alaska Native		
Asian		
Black or African-American		
Hawaiian/Pacific Islander		
White (Hispanic)		X
More Than One Race		
Unknown/Other (Hispanic)		X
Racial Categories: Total of Hispanics or Latinos*		

* The "Hispanic or Latino" (Part A) must be equal to "Racial Categories: Total of Hispanics or Latinos" (Part B).
** The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects"

Acronyms and Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes lipid trial
ACE	Autoimmunity Center of Excellence
ACRWH	Advisory Committee on Research on Women's Health
ACTG	AIDS Clinical Trials Group
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
Add Health	National Longitudinal Study of Adolescent Health
ADEAR Center	Alzheimer's Disease Education and Referral Center
ADH	atypical ductal hyperplasia
ADSC	adipose tissue-derived stem cell
AED	antiepileptic drug
AEP	alcohol-exposed pregnancy
AF	atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program
AL	allostatic load
AMD	age-related macular degeneration
ANSWHR	Advancing Novel Science in Women's Health Research
A NULIFE	African-American Nutrition for Life study
AREDS	Age-Related Eye Disease Study
ARRA	American Recovery and Reinvestment Act
ARV	antiretroviral
ASA	American Stroke Association
ASM	airway smooth muscle
AVP	arginine vasopressin
BAFF	B cell activating factor belonging to the TNF family
BASIC	Brain Attack Surveillance in Corpus Christi
BCCP	Breast and Cervical Cancer Program
BCERC	Breast Cancer and the Environment Research Center

BCERP	Breast Cancer and the Environment Research Program
BCSC	Breast Cancer Surveillance Consortium
BDNF	brain-derived neurotrophic factor
BHGI	Breast Health Global Initiative
BIRCWH	Building Interdisciplinary Research Careers in Women's Health
BMD	bone mineral density
BMI	body mass index
BMP-2	bone morphogenic protein 2
BMSC	bone marrow stromal cell
BN	bulimia nervosa
BNST	bed nucleus of the stria terminalis
BOLD	blood-oxygenation level dependent
BPD	borderline personality disorder
BRDG-SPAN	Biomedical Research, Development, Growth to Spur Acceleration of New Technology
BRIC	Building Research Infrastructure and Capacity
BRONJ	bisphosphonate-related osteonecrosis of the jaw
BUFS	breast ultrasound fluoroscopy system
BV	bacterial vaginosis
caBIG	cancer Biomedical Informatics Grid program
CaD	calcium plus vitamin D
CAM	complementary and alternative medicine
CAPRISA	Center for the AIDS Program of Research in South Africa
CARDS	Computer Access to Research on Dietary Supplements
CAREDS	Carotenoids and Age-Related Eye Disease Study
CBI	Combined Behavioral Intervention
CBPR	Community Based Participatory Research
CCRWH	Coordinating Committee on Research on Women's Health
CDC	Centers for Disease Control and Prevention
CDE	continuing dental education
CDK	cyclin-dependent kinase

CEE	conjugated equine estrogen
CERED	Comparative Effective Research for Eliminating Health Disparities
CFAR	Centers for AIDS Research
CFS	chronic fatigue syndrome, also known as myalgic encephalomyelitis (ME/CFS)
CFSAC	Chronic Fatigue Syndrome Advisory Committee
CGEMS	Cancer Genetic Markers of Susceptibility
CHD	coronary heart disease
CIDRZ	Center for Infectious Disease Research in Zambia
CIN	cervical intraepithelial neoplasia
CLEK	Collaborative Longitudinal Evaluation of Keratoconus study
CLHNS	Cebu Longitudinal Health and Nutrition Survey
CMV	cytomegalovirus
CNRU	Clinical Nutrition Research Unit
COE	Centers of Excellence
COPD	chronic obstructive pulmonary disease
COPE	Creating Opportunities for Parental Empowerment
Co-STAR	Cognition in the Study of Tamoxifen and Raloxifene
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
CPDD	College on Problems of Drug Dependence
CR	cardiac rehabilitation
CR	computed radiography
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial
CRF	corticotropin-releasing factor
CSA	childhood sexual abuse
CT	computed tomography
CTN	Clinical Trials Network
CTP	community treatment provider
CVD	cardiovascular disease
dbGaP	Database of Genotypes and Phenotypes
DBT	digital breast tomosynthesis

DCE-MRI	dynamic contrast–enhanced MRI
DCIS	ductal carcinoma in situ
DcoE	DoD Centers of Excellence in Psychological Health and Traumatic Brain Injury
DED	dry-eye disease
DERT	Division of Extramural Research and Training
DETS	Diabetes Education in Tribal Schools
DHP	dihydropyridines
DOT	diffuse optical tomography
DP	developmental programming
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcomes Study
DREAM	Disparities Research and Education Advancing Mission awards
DSHEA	Dietary Supplement Health and Education Act
DSM-IV	*Diagnostic and Statistical Manual of the American Psychological Association,* Fourth Edition
DW-MRI	diffusion weighted MRI
E+P	estrogen plus progestin
EAE	experimental autoimmune encephalomyelitis
EBMT	European Group for Blood and Marrow Transplantation
ECM	extracellular matrix
EDRN	Early Detection Research Network
EEMS	Etiologic and Early Markers Program
EFA	essential fatty acid
EGFR	epidermal growth factor receptor
EHDIC	Exploring Health Disparities in Integrated Communities
ELP	elastin-like polypeptide nanoparticles
EMS	Environmental Mutagen Society
EMS	eosinophilia-myalgia syndrome
EPDS	Edinburgh Postnatal Depression Scale
ER-positive	estrogen receptor-positive

ERR-alpha	estrogen-related receptor-alpha
ESRD	end-stage renal disease
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorders
FDG-PET	fluorodeoxyglucose positron emission tomography
f-fMR	fetal functional MRI
FHS	Framingham Heart Study
FIC	Fogarty International Center
FICRS	Fogarty International Clinical Research Scholars program
fMRI	functional magnetic resonance imaging
FMRP	fragile X mental retardation protein
FOA	funding opportunity announcement
FSH	follicle-stimulating hormone
GAO	U.S. Government Accountability Office
GDC	group drug counseling
GDM	gestational diabetes mellitus
GEP study	Genetic Etiology of POAG
GFR	glomerular filtration rate
GFWC	General Federation of Women's Clubs
GID	Global Infectious Disease research training program
GITMO	Gruppo Italiano Trapianto di Midollo Osseo
GLAUGEN	Glaucoma Genes and Environment Initiative
GRIP	Global Research Initiative Program
GWAS	genomewide association study
HAART	highly active antiretroviral therapy
HAD	HIV-associated dementia
HANDLS	Healthy Aging in Neighborhoods of Diversity across the Life Span
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes study
HDL	high-density lipoprotein
HER2	tyrosine kinase receptor
HIV	human immunodeficiency virus

HMP	Human Microbiome Project
HOW	Health of Women study
HPA	hypothalamic-pituitary-adrenal
HPFS	Health Professionals Follow-up Study
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HSV	herpes simplex virus
HUCM	human umbilical cord matrix
HVTN	HIV Vaccine Trials Network
HWs	Hispanic Whites
IAS	internal anal sphincter
IBC	intracellular bacterial community
IBIDS	International Bibliographic Information on Dietary Supplements
ICs	Institutes and Centers
IDU	injection drug use
IED	intermittent explosive disorder
IER	intermittent energy restriction
I-FSCBT	Individual Female Specific Cognitive Behavioral Therapy
IGFBP-3	IGF-binding protein-3
IGF-I	insulin-like growth factor-I
IIH	idiopathic intracranial hypertension
IL-17	interleukin-17
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IPCP-HTM	Integrated Preclinical/Clinical Program for HIV Topical Microbicides
IPV	intimate partner violence
IRSDA	International Research Scientist Development Award
ISIS	Women's HIV SeroIncidence Study
ITREOH	International Training and Research in Environmental and Occupational Health

IUGR	intrauterine growth restriction
JIA	juvenile idiopathic arthritis
KEEPS	Kronos Early Estrogen Prevention Study
LABS	Longitudinal Assessment of Bariatric Surgery
LAM	lymphangioleiomyomatosis
LBW	low birth weight
LGBT	lesbian, gay, bisexual, and transgendered
LIPS	luciferase immunoprecipitation system
LMIC	low- and middle-income country
LMN	lupus membranous nephropathy
LMW	low molecular weight
LONS	Longitudinal Optic Neuritis Study
LPS	lipopolysaccharide
LRP	Loan Repayment Program
LRP-ECR	Loan Repayment Program—Extramural Clinical Research
LRP-HDR	Loan Repayment Program—Health Disparities Research
LT	L-tryptophan
LUTS	lower urinary tract symptom
MAOI	monoamine oxidase inhibitor
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MCI	mild cognitive impairment
MDD	major depressive disorder
MDSC	muscle-derived stem cell
ME/CFS	myalgic encephalomyelitis, also known as chronic fatigue syndrome (CFS)
MEBS	Minnesota Eating Behavior Survey
MeCP2	methyl-CpG-binding protein 2
MEPI	Medical Education Partnership Initiative
MFMU	Maternal-Fetal Medicine Units
MHIRT	Minority Health and Health Disparities International Research Training
MHT	menopausal hormone therapy

MILES	Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus trial
MIP	Microbicide Innovation Program
miRNA, miR	microRNAs
MLV	mouse leukemia virus
MMG	magnetomyographic
MNR	maternal nutrient reduction
MONEAD	Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs
MOTHER	Maternal Opioid Treatment: Human Experimental Research
MOTOR	Maternal Oral Therapy to Reduce Obstetric Risk trial
MP3	Methods for Prevention Packages Program
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRSI	magnetic resonance spectroscopic imaging
MS	multiple sclerosis
MSC	mesenchymal stem cell
MsFLASH	Menopause Strategies: Finding Lasting Answers for Symptoms and Health
MSM	men who have sex with men
MSTP	Medical Scientist Training Program
MTN	Microbicides Trials Network
MV	matrix vesicle
MYCY	mother-to-child-transmission
NAEC	National Advisory Eye Council
NAS	neonatal abstinence
NCCAM	National Center for Complementary and Alternative Medicine
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCDD	National Commission on Digestive Diseases
NCI	National Cancer Institute
NCI-MMHCC	NCI Mouse Models of Human Cancers Consortium
NCLR	National Council of La Raza
NCMHEP	National Children and Maternal Health Education Program

NCoD	Noncommunicable Chronic Diseases research training program
NCRR	National Center for Research Resources
NDEP	National Diabetes Education Program
NEI	National Eye Institute
NEIGHBOR	NEI Glaucoma Human Genetics Collaboration
NHGRI	National Human Genome Research Institute
NHIS	National Health Interview Surveys
NHOPI	Native Hawaiians and Other Pacific Islanders
NHS	Nurses' Health Study
NHWs	non-Hispanic Whites
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NICU	neonatal intensive care unit
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NKDEP	National Kidney Disease Education Program
NLST	National Lung Screening Trial
NMR	nuclear magnetic resonance
NMRI	Network of Minority Health Research Investigators

NORDIC	Neuro-Ophthalmology Research Disease Investigator Consortium
NRSA	National Research Service Award
NRTI	nucleoside reverse transcriptase inhibitor
NSA	National Stroke Association
NSAID	nonsteroidal anti-inflammatory drug
NSDUH	National Survey on Drug Use and Health
NSES	neighborhood socioeconomic status
NSHLEW	National Study of Health and Life Experiences of Women
NTD	neural tube defect
NTP	National Toxicology Program
NURSA	Nuclear Receptor Signaling Atlas
OAI	Osteoarthritis Initiative
OAR	Office of AIDS Research
OBSSR	Office of Behavioral and Social Sciences Research
OCD	obsessive-compulsive disorder
OCI-R	Obsessive-Compulsive Inventory-Revised
OCS	obsessive-compulsive symptom
OCT	optical coherence tomography
ODS	Office of Dietary Supplements
OGAC	Office of the U.S. Global AIDS Coordinator
OHARA	Oral HIV/AIDS Research Alliance
OMHRC	NIDDK Office of Minority Health Research Coordination
ONJ	osteonecrosis of the jaw
ONRC	Obesity/Nutrition Research Center
ONTT	Optic Neuritis Treatment Trial
OPPERA	Orofacial Pain: Prospective Evaluation and Risk Assessment
OPT	Obstetrics and Periodontal Therapy trial
ORWH	Office of Research on Women's Health
OSA	obstructive sleep apnea
OSC	Office of Strategic Coordination
PA	program announcement

PAD	peripheral arterial disease
PAH	pulmonary arterial hypertension
PASS	Prenatal Alcohol in SIDS and Stillbirth
PBC	primary biliary cirrhosis
PBRN	Practice-Based Research Network
PCG	primary caregiver
PCOS	polycystic ovary syndrome
PD	purging disorder
PEPFAR	President's Emergency Plan for AIDS Relief
PET	positron emission tomography
PHS II	Physicians' Health Study II
PI	protease inhibitor
PID	pelvic inflammatory disease
PILI	Partnerships for Improving Lifestyle Interventions
PLCO	Prostate, Lung, Colorectal, and Ovarian cancer screening trial
PMDD	premenstrual dysphoric disorder
PMH	postmenopausal hormone
PMTCT	prevention of mother-to-child transmission
POAG	primary open angle glaucoma
POC	point of care
POI	primary ovarian insufficiency
POP	Global Research Training in Population Health
POP-Q	pelvic organ prolapse quantification
PPD	postpartum depression
PrEP	preexposure prophylaxis
PREVENT III	Project of Ex Vivo Vein Graft Engineering via Transfection III
PROMISE	Promoting Maternal-Infant Survival Everywhere
PROWESS	Program Regarding Older Women's Education for Sexual Safety
PTB	preterm birth
PTH	parathyroid hormone
PTHrP	PTH-related protein

QOL	quality of life
RA	rheumatoid arthritis
RBC	red blood cell
RCT	randomized clinical trial
RDC/TMD	Research Diagnostic Criteria for Temporomandibular Disorders
REACH	Racial and Ethnic Approaches to Community Health Across the United States
REAP	Research Enhancement Awards Program
REMAS	Real Men Are Safe
RFA	radiofrequency ablation
RFA	request for applications
ROC	receiver operating characteristic
RUTI	recurrent urinary tract infection
RWEH	Researching Women's Environmental Health
SAHIV	susceptibility for acquiring HIV
SAVVY	Sex Differences in Vascular Markers of Stroke Risk
SBC	small business concern
SBIR	Small Business Innovation Research program
SCCPIR	Specialized Cooperative Centers Program in Reproduction and Infertility Research
SCD	sudden cardiac death
SCOT	Scleroderma Cyclophosphamide or Transplantation study
SD NVP	single-dose nevirapine
SEER	Surveillance, Epidemiology, and End Results
SERM	selective estrogen receptor modulator
SES	socioeconomic status
SET	structural ecosystems therapy
SGMAP	Salivary Gland Molecular Anatomy Project
SHARE	Supporting Healthy Activity and Eating Right Everyday trial
SHARe	SNP Health Association Resource
SHBG	sex-hormone binding globulin
SIDS	sudden infant death syndrome

SISTEr	Stress Incontinence Surgical Treatment Efficacy Trial
SLE	systemic lupus erythematosus (lupus)
SNA	social network analysis
SNHL	sensorineural hearing loss
SNP	single nucleotide polymorphism
SNR	signal-to-noise ratio
SoF	Study of Osteoporotic Fractures
SPORE	Specialized Programs of Research Excellence
SRC-3/AIB-1	steroid receptor coactivator-3/amplified in breast cancer-1
SS	Sjögren's syndrome
SSRI	selective serotonin reuptake inhibitor
STD	sexually transmitted disease
STEMM	science, technology, engineering, math, and medicine
STI	sexually transmitted infection
STTR	Small Business Technology Transfer program
SUD	substance use disorder
SUI	stress urinary incontinence
SWA	slow-wave activity
SWAN	Study of Women's Health Across the Nation
SWS	slow-wave sleep
TAILORx	Trial Assigning Individualized Options for Treatment
TCGA	The Cancer Genome Atlas program
TFV	tenofovir
TGF	transforming growth factor
Th17	T-helper-producing interleukin 17
TMD	temporomandibular disorders
TMJD	temporomandibular joint disorders
TNF	tumor necrosis factor
Tobacco	International Tobacco and Health Research and Capacity Building Program
TODAY	Treatment Options for type 2 Diabetes in Adolescents and Youth
TOMUS	Trial Of Mid-Urethral Slings

TORI	Translational Oncology Research International network
TReND	Tobacco Research Network on Disparities
TRPV-1	vanilloid receptor 1
TV	*Trichomonas vaginalis*
TZV	Trizivir
UDA	Urologic Diseases in America project
UI	urinary incontinence
UNAIDS	United Nations Joint Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UPEC	uropathogenic *Escherichia coli*
URMC	University of Rochester Medical Center
UTI	urinary tract infection
VIRGO	Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients
VLBW	very low birth weight
VM	ventriculomegaly
VMN	ventromedial
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VTE	venous thromboembolism
VUR	vesicoureteral reflux
WEMS	Women in the Environmental Mutagen Society
WGRG	Women and Sex/Gender Research Group
WHEEL	Women's Health and the Environment over the Entire Lifespan
WHI	Women's Health Initiative
WHIMS	Women's Health Initiative Memory Study
WHISCA	Women's Health Initiative Study of Cognitive Aging
WHO	World Health Organization
WHPN	Interdisciplinary Network for Pathogenesis Research in Women
WHS	Women's Health Study
WIC	Women, Infants, and Children's program
WIHS	Women's Interagency HIV Study
WIN	Weight-control Information Network

WISP-1	Wnt-induced secreted protein 1
WRG	women's recovery group
WSM	women who have sex with men
WWP	Well Woman Program
XMRV	xenotropic murine leukemia virus-related retrovirus
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

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