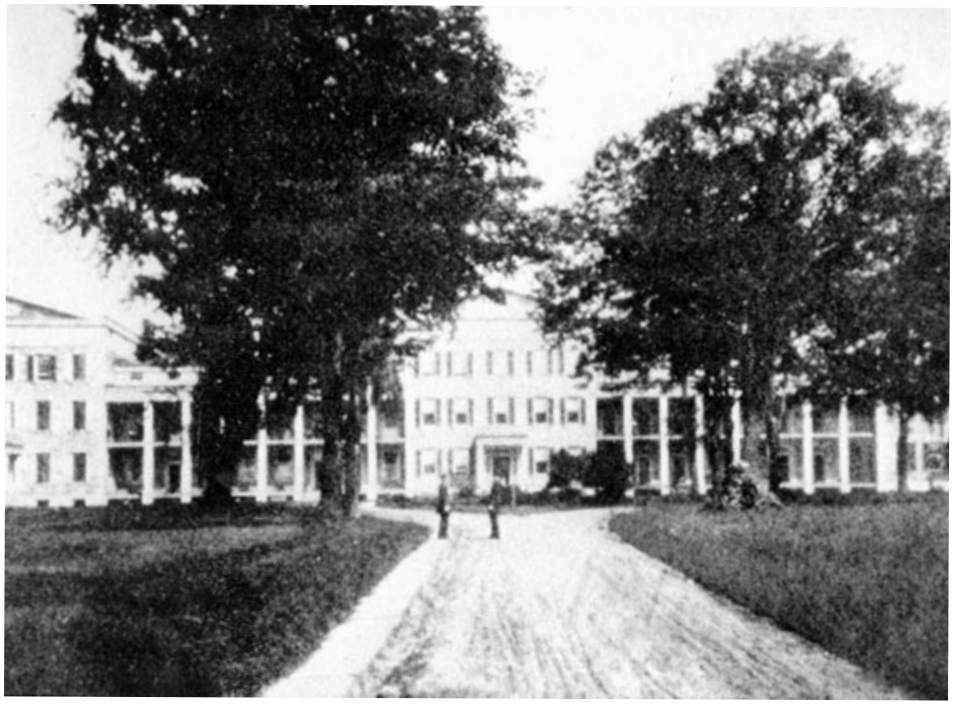
NIH Intramural Research at the Threshold of a New Era

The Mission, Vision and Scope of the National Institutes of Health Intramural Research Program



(above) Humble beginnings. This photograph from the late 1800s shows the Marine Hospital on Staten Island, New York. The National Institutes of Health began here in 1887 as the Hygienic Laboratory, occupying just one room. The Laboratory moved to Washington, D.C., in 1891 and became the National Institute (singular) of Health in 1930.

(cover) An aerial view of part of the NIH Bethesda campus today looking south, prominently featuring the Mark O. Hatfield Clinical Research Center; credit: Duane Lempke, Sisson Studios, Inc.

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The Mission, Vision and Scope of the National Institutes of Health Intramural Research Program September 2009

Preface

The National Institutes of Health is the primary federal agency for conducting and supporting medical research. In practical terms, the NIH is the font of most biomedical research advances in the United States and is the world's most important organization for the advancement of health research. Since World War II, the vast majority of this federal investment has been directed to the extramural research community, where scientists work at universities, institutions and organizations. Slightly less than 10 percent of the NIH budget, however, remains devoted to the distinctive research that takes place within federal laboratories on NIH campuses. This is the intramural program. Of the 27 NIH Institutes and Centers, 23 have an intramural component.

The most important aspect of the Intramural Research Program, as delineated in this document, is its emphasis on high-risk, high-reward research. This takes place in an environment conducive to research that cannot be readily funded or accomplished in traditional academia, made possible through a vast and advanced technology infrastructure of shared resources, a broad range of expertise comprising over 1,000 principal investigators and 4,000 highly selected post-doctoral fellows, and the world's largest clinical hospital to foster the cycle of research from patient studies to laboratory work to bedside cures. Coupled with relatively stable funding and intellectual freedom, this framework enables the pursuit of projects beyond the scope of what is reasonably fundable elsewhere, such as the ability to start long-term research projects or to change directions quickly when the opportunity or need arises.

Intramural research results leading to clinical advances from the past few years alone include the HPV "anti-cancer" vaccine, a treatment for multiple sclerosis, gene therapy to restore salivary gland function, immunotoxins to treat common cancers, and vaccines for Ebola and Marburg viruses. Also within the Intramural Research Program's domain is the National Library of Medicine, a national treasure and, with its database of over 18 million journal citations, a vital entity for researchers and the general public worldwide.

In this era of constrained budgets and its negative impact on the overall biomedical research effort, the NIH Intramural Research Program, with its extensive infrastructure and critical mass of expertise well established, has assumed an ever more crucial role in both maintaining America's research excellence and advancing treatments and cures. The compilation of materials that follows provides an analysis of the Intramural Research Program, detailing achievements as well as elements that need to be improved, with the intention to convey the complexity, scope and importance of the intramural biomedical research enterprise to the nation and to the world.

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NIH INTRAMURAL RESEARCH AT THE THRESHOLD OF A NEW ERA

The NIH Intramural Research Program is widely regarded as the most successful biomedical research program ever assembled in terms of the scope and impact of its basic research accomplishments and the impact of this science and training activities on the practice of medicine and improvements in public health. It has been, and remains, a model for other federal laboratories, for research foundations, and for other governments who seek to establish research laboratories.

By establishing a creative, stably funded environment that remains attractive to the most talented researchers, and by providing research resources and opportunities for interaction that are unprecedented, the NIH Intramural Research Program has fostered an explosion of knowledge and its practical applications. Discoveries that have emerged from the NIH intramural program—such as the use of fluoride to prevent tooth decay, the use of lithium to manage bipolar mental illness, the development of blood tests to detect HIV and hepatitis, the first AIDS drugs, and vaccines against hepatitis, Hemophilus influenza, and human papillomavirus, among others—have repaid many times over in public health savings the total past investment, and any foreseeable future investment, in this program. Many other discoveries, outlined in this document, have improved the quality of healthcare in this country and the world.

The Intramural Research Program represents the nation's investment in resource excellence, a defining element of America's dominance in biomedical research. No other biomedical research organization in the world can match its scope. Yet the very success of the NIH Intramural Research Program—both as a model for effective research activities copied elsewhere and as a training ground for hundreds of investigators who have gone on to establish outstanding extramural research programs—has raised questions about whether it continues to play a critical role in the overall research enterprise.

Some have asked whether the best days of the Intramural Research Program are past and whether its Clinical Center, which has so successfully trained physician-investigators now leading university-based clinical centers nationwide, has outlived its purpose. Others, however, note that the difficulty in conducting truly innovative translational and clinical research in the extramural environment makes the NIH intramural program more critically important than ever before, thus providing opportunities for productive intramural-extramural interactions.

We believe that the facts show that the 23 NIH intramural research programs continues to make critical contributions to the public health despite restricted budgets and that recent new approaches to research at the NIH have adapted to the changing research environment, indicating many more years of innovative and productive science. Our program also continues to complement extramural research in crucial ways, often providing—or, in an intellectual sense, funding—accomplished scientists in academia and the private sector with the basic science and research tools that they need to further our mutual pursuit of treatments and cures. There are, however, some daunting challenges, mentioned below, that must be met to guarantee the future success of this distinctive research facility.

The attached chapters and appendices outline, in some detail, the current status of the NIH Intramural Research Program. As will become obvious, despite five years of flat budgets, which represent a decrease in real buying power of approximately 16 percent, the intramural program continues to be highly productive, especially in areas of research that are difficult to pursue in most extramural environments. The NIH Intramural Research Program is in fact poised at the threshold of discovery in this new era of the genome, nano-scale technologies and advanced computation. The establishment of several new trans-NIH initiatives, for example, leverages the

enormous talent and resources that exist across the NIH and enables many new research initiatives in clinical immunology, new imaging modalities, systems biology, biodefense, HIV, stem cells, biomarkers and epigenetic regulation of gene expression.

Individual intramural programs, in turn, have collaborated to take the lead in new approaches to translational research, such as the NIH Chemical Genomics Center (from NHGRI), the high-throughput RNAi screening program (from NCI and NHGRI), the image probe development center (from NHLBI), and a new cGMP PET facility (from CC and NIBIB). See Appendix D for a detailed list of shared facilities and Appendix F for abbreviations of NIH Institutes and Centers. The Clinical Center, too, remains the foremost clinical research facility in the world. Through its online clinical research training program and coursework on managing a clinical research facility, the Clinical Center is a role model and potential resource for the aspiring Clinical and Translational Science Awards programs established by the NIH Roadmap. Advancing clinical research at the NIH is a major goal of the NIH leadership and a newly established Intramural Clinical Research Steering Committee.

The challenges that have developed in recent years to sustaining the research programs at the NIH are substantial but not insurmountable. Declining budgets have led to new, more efficient ways to support research at the NIH and to a paring of less productive research personnel through outside expert review. But they have also made new recruitments and the development of new research programs more difficult. Federal requirements such as very stringent rules restricting outside activities of research personnel, travel restrictions, salary caps, and other growing administrative requirements have affected the NIH's ability to recruit and retain top researchers. Maintaining the preeminence of the NIH Clinical Center in the face of rapidly rising costs of hospital management and pharmaceuticals is another unique challenge faced by the NIH. For example, while all hospitals face budgetary constraints, the Clinical Center has no reimbursement stream and no private philanthropy.

The solutions to some of these problems lie within the control of the leadership and staff of the NIH; other obstacles to success are controlled by forces such as the economic health of the country and the regulatory environment in the United States, which affect all biomedical researchers.

Notwithstanding these limitations, the NIH Intramural Research Program remains a vital component of the overall U.S. biomedical research effort. With continued support from the American public and their representatives, we will solve these problems and demonstrate, once again, that "the past is prologue."

EXECUTIVE SUMMARY

The NIH Intramural Research Program: Mission, Vision, Guiding Principles, and Distinguishing Features

The NIH leadership has developed the following statements to capture the mission, vision, guiding principles and distinguishing features of the Intramural Research Program. These reflect a consensus and summary of what the Intramural Research Program is and aspires to be.

Mission Statement:
The National Institutes of Health is the steward of medical and behavioral research for the Nation. Its mission is science in pursuit of fundamental knowledge about the nature and behavior of living systems, and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. Within this framework, the mission of the NIH Intramural Research Program is to 1) conduct distinctive, high-impact laboratory, clinical, and population-based research; 2) facilitate new approaches to improve the health though prevention, diagnosis and treatment; 3) respond to public health emergencies; and 4) train the next generation of biomedical researchers.

Vision Statement:
The NIH Intramural Research Program provides an optimal research environment for creative scientists to conduct fundamental research relevant to biomedical knowledge using innovative approaches in humans and non-human model systems. Its scientists efficiently translate this knowledge into new ways to diagnose and to personalize approaches to preempt, treat and reduce suffering from human disease. This research environment also is designed to maximize recruitment, training and mentoring to promote diversity and to create a new cadre of scientists to lead biomedical research in the 21st century.

Guiding Principles:
Reflected in the mission and vision of the Intramural Research Program is a set of principles to guide intramural research and its collaborations with the extramural scientific community:

- To encourage high-risk, high-impact science of unquestionable excellence, the Intramural Research Program recruits the most outstanding researchers and provides them with stable state-of-the-art resources to conduct original and primarily investigator-initiated research that is reviewed regularly by internal and external experts.
- To respond to continuous new research challenges, the Intramural Research Program selects dynamic and forward-thinking leaders; reassigns resources based on a rigorous review and advisory process; and creates new organizational structures and research processes that reflect the changing nature of science and public health needs.
- To enable flexible and rapid response to public health emergencies, emerging new technologies, and new training needs, the control of resources resides at the level of the Institutes and Centers of the NIH.
- To ensure outstanding recruitments and rigorous scientific review, to coordinate responses of the Intramural Research Program as a single unit, and to facilitate sharing of resources and development of collaborations across the NIH for larger-scale efforts, the Office of Intramural Research offers leadership, sets overall policy and provides oversight.
- To facilitate translation of laboratory findings to new approaches to prevent and cure human diseases, the Intramural Research Program promotes interaction among laboratory, population-based and clinical scientists. The NIH Clinical Center is the largest facility in the world devoted purely to clinical research. The work at the Clinical Center emphasizes long-term, natural history studies of human disease, including rare diseases; "first-in-human" interventional clinical research; mechanism-based studies that maximize the scientific benefit of early-phase clinical trials; and studies, unencumbered by any perceived bias, that test existing hypotheses and treatments.

Distinguishing Features:

These distinguishing features were compiled from discussions with senior NIH leadership and NIH's Distinguished Investigators. Although they were prepared recently, there are common themes that extend back several decades to characterize the NIH Intramural Research Program. They form the basis of a case that NIH is a high-risk, high-reward demonstration project, which will be reported to Congress in response to the NIH Reform Act.

1. Highly talented researchers are allocated funds, under their control, to support high-impact, innovative, and where required, long-term research.
2. The ability exists to build and support stable infrastructure, including research facilities and equipment.
3. Although many new projects are potentially risky, the intramural environment mitigates risk by optimizing research support and research strategies.
4. The presence of the NIH Clinical Center fosters the application of basic science to clinical challenges and responses to public health emergencies.
5. Principal investigators can redirect resources and change directions quickly in response to new ideas and research opportunities. Therefore, researchers are not trapped by their successes; pursuing new directions and research areas are common and encouraged.
6. The Intramural Research Program is an environment designed to manage and eliminate financial conflicts of interest.
7. A critical mass of investigators works in close proximity to enable a balanced, rich and diverse portfolio of basic and translational research.
8. Scientific leaders interact directly with investigators.
9. Researchers have the ability to focus completely on research and mentoring of laboratory staff without the requirement to teach or to write grants.
10. Prospective assignment of resources is determined by Scientific Directors who recognize innovative, high-impact projects.
11. Emphasizing rigorous but mainly retrospective peer review permits adjustments of resources over time.
12. Proven NIH scientists, irrespective of seniority, continue to have direct, "hands-on" involvement in research activities, and they interact at the bench and in the clinics.
13. There is a demonstrated commitment to developing a more diverse workforce and a diverse group of trainees.
14. There is a large population of trainees at all levels, but the major emphasis is on postdoctoral rather than graduate training.

CHAPTER 1: Underpinnings of the NIH Intramural Research Program

History and Background

"The National Institutes of Health is not only the largest institution for biomedical science on earth, it is one of this nation's great treasures. As social inventions for human betterment go, this one is a standing proof that, at least once in awhile, government possesses the capacity to do something unique, imaginative, useful and altogether right."

Lewis Thomas, then President Emeritus at Memorial Sloan-Kettering Cancer Center in New York, wrote these words in his foreword to a 1984 book by NIH luminary DeWitt Stetten titled "NIH: An Account of Research in Its Laboratories and Clinics." Dr. Thomas, a renowned essayist on biological issues and an expert on leukemic cells, spoke in general of the expansion of the NIH following World War II but in focusing on the NIH Intramural Research Program, added:

"[A]t the center of the NIH scientific effort, driving the whole vast enterprise along, is the research conducted on the Bethesda campus itself—the so-called Intramural Research Program. Although this represents only a minor portion of the total NIH budget, around 10 percent, for sheer excellence and abundant productivity the institution cannot be matched by any other scientific enterprise anywhere."

In the early days of the National Institutes of Health, all its research was "intramural," performed in federal laboratories. The NIH traces its roots to 1887, when a one-room laboratory on Staten Island was created within the Marine Hospital Service, a predecessor agency to the U.S. Public Health Service. This lab evolved into the Hygienic Laboratory, which moved to Washington, D.C., in 1891 and, with the Ransdell Act of 1930, became the National Institute of Health. This was the start of something grand. Several institutes were established over the next two decades. Then, with the golden era of expansion beginning after World War II, the primary focus of the NIH turned to a rigorous grants program to bolster research in U.S. colleges and universities.

Remaining at the heart of the NIH mission, however, is this intramural program, the expanse of federal laboratories that "are something for the Government to boast about, to dine out on, and to be immensely proud of," as Thomas wrote in that foreword. This has included the NIH training program, where for over five decades, "the youngest and brightest candidates for careers in biomedical research have competed for the opportunity to learn how to do science" and where "a high percentage of these alumni turned into the country's leaders in academic science," wrote Thomas.

The Underpinnings of Success

Nearly a quarter of a century after Lewis Thomas' laudatory words, we describe here the continuing story of the Intramural Research Program and offer a recipe for its ongoing success, as guided by its current Deputy Director for Intramural Research, Michael Gottesman, M.D., one of DeWitt Stetten's successors. Several distinctive features of the Intramural Research Program, as compared particularly to academia, have been essential for its success. These are the special ways the program funds, reviews, staffs and organizes its assemblage of technology, talent and tolerance, what we call the underpinnings of success. Detailed in the next chapter, this includes long-term and relatively stable funding for projects; rigorous but primarily retrospective external reviews; a critical mass of expertise across institutes and centers; the physical and intellectual proximity of basic research and a hospital for clinical research; encouragement of trans-NIH collaborations; and an emphasis on training and mentoring to stimulate the ideas.

Not resting on our laurels—our program has produced numerous Nobel Prize winners, more than all other federal agencies combined—the NIH Intramural Research Program has undergone repeated reviews by outside experts. These reviews have strengthened the program and have led to new features, such as a carefully articulated tenure system, more rigorous scientific reviews of NIH scientists by outside experts, a renewed emphasis on clinical research at the NIH, a focus on training and mentoring, and attention to scientific misconduct and risk management, among other initiatives. We highlight four of these reviews in the next section.

Major External Reviews, 1988-2008

Institute of Medicine Report: A Healthy Intramural Program (1988)

The Office of Management and Budget requested a review by the National Academy of Sciences' Institute of Medicine to evaluate strategies to promote the continued excellence of the NIH intramural laboratories, including consideration of privatizing the NIH. The report's description of the mission of the Intramural Research Program has many of the elements found in the mission today. The following is an excerpt of that report.

Mission of the Intramural Program: "As a government laboratory, the intramural program has multiple roles in support of the NIH mission of improving the health of the nation through biomedical research. The program's activities include basic research, clinical research, training scientists, communicating research findings, developing policies on biomedical research priorities, and translating research findings into more effective medical care. It has the capacity to respond to national health emergencies. The Clinical Center is one of the important features that differentiate the intramural program from other research settings.

"No single element of the intramural program is literally unique. But the aggregation of elements—for example, research laboratories, a clinical center, freedom from competitive grant renewals, disease-related institutes—forms a distinctive environment. Further, the intramural program is a visible focus and rallying point for the nation's overall biomedical research effort… Moreover, the NIH intramural program has created an atmosphere that many researchers believe is unparalleled."

The IOM Committee recommended several changes that led to improved personnel systems with higher salaries for scientists, the creation of the Foundation for the NIH, and improved review of intramural research including regular reviews of NIH Scientific Directors. The committee reached various conclusions, including that a high-quality intramural program is a distinctive and valuable component of the nation's overall biomedical research effort and that privatization, in the sense of making the intramural program free-standing and self-supporting, is undesirable and impractical.

Report of the External Advisory Committee of the NIH Director's Advisory Committee (1994)

An External Advisory Committee mandated by Congress issued a report on the NIH Intramural Research Program to the NIH Director. The committee recognized that the Intramural Research Program possesses several special characteristics that set it apart from the extramural research program. These include relatively long-term and stable funding of research programs, the availability of the Clinical Center's patient investigational facilities, few or no distractions from research for scientists, and a primarily retrospective rather than prospective review process for determining scientific quality and the funding of research.

The overall recommendations included strengthened reviews of senior scientists and Scientific Directors, improved procedures for selecting outside reviewers of intramural research, the creation of a Central Tenure Committee, and renewal of the Clinical Center. These recommendations have remained guiding principles for intramural research.

Institute of Medicine Report: Enhancing the Vitality of the National Institutes of Health (2003)

The Institute of Medicine undertook a review of the NIH organizational structure at the request of Congress, which expressed concern whether the NIH's organizational structure was right for the times. The following two recommendations in that 2003 report cite the NIH Intramural Research Program. They have served to stimulate and encourage the direction and work of the Program, and their influence is evident in this document.

Strengthen Clinical Research: "NIH should pursue a new organizational strategy to better integrate leadership, funding, and management of its clinical research enterprise. The strategy should build on but not replace existing organizational units and activities in the individual ICs' [Institutes and Centers] intramural and extramural research programs. It should also include partnerships with the nonprofit and private sectors. Specifically, the Committee recommends that several intramural and extramural programs be combined in a new entity to subsume and replace the National Center

for Research Resources, to be called the National Center for Clinical Research and Research Resources (NCCRRR). In addition, a deputy director for clinical research should be appointed in the Office of the Director to serve as deputy director and head of the new entity."

Promote Innovation and Risk Taking in Intramural Research: "The intramural research program should consist of research and training programs that complement and are distinguished from those in the extramural community and the private sector. The intramural program's special status obligates it to take risks and be innovative. Regular in-depth review of each component of the intramural program should occur to ensure continuing excellence. Allocation of resources to the intramural program should be closely tied to accomplishments and opportunities. Inter-institute and intramural-extramural collaborations should be supported and enhanced."

OMB's Performance Assessment and Rating Tool (2005)

This review was not carried out by scientists, as the other reviews listed above were, yet it demonstrated that the Intramural Research Program passed muster with the standardized Office of Management and Budget's Performance Assessment and Rating Tool (PART) and achieved a high score of 90, which exceeds that of any federal laboratory reviewed to date. The review assessed the program, purpose and management of resources allocated to the Intramural Research Program.

Blue Ribbon Panel reviews of the Intramural Research Programs

As specified in the Report of the External Advisory Committee of the NIH Director's Advisory Committee (1994), almost all of the NIH intramural research programs have undergone a detailed external review with important recommendations and program changes resulting from these reviews. Several programs have undergone two reviews (NIDCR, NIMH, NIEHS) and others have reviews in the planning stage (NCCAM, NINDS). In addition, Nobel laureate Joseph Goldstein and cancer expert Edward Benz co-chaired a Blue Ribbon review of clinical research at the NIH in 2004, which is discussed in more detail in Chapter 4. An outside panel under the supervision of each of the NIH Institutes' and Centers' National Advisory Councils reviews the intramural Scientific Director every four to six years.

The NIH Intramural Research Sourcebook

In the mid-1990s, the Office of Intramural Research developed an electronic compilation of procedures, practices and guidance for the intramural community. It is useful at all levels, from trainees to tenured Senior Investigators and from administrators to scientific leaders. Yet more than a tool for our researchers, this Sourcebook catalogs all that the Intramural Research Program comprises and aspires to, far too extensive to include in this document. The URL for this valuable reference is http://www1.od.nih.gov/oir/sourcebook.

The chapters in this document mirror the Sourcebook in an attempt to capture the essence of Intramural Research Program. And this document itself was a trans-NIH effort, incorporating the feedback of scientists in each of the Institute and Center intramural programs. This begins with an essay by Michael Gottesman, Deputy Director for Intramural Research, followed by a dialogue in subsequent chapters to provide insights into the Intramural Research Program's workings, demographics and other characteristics.

CHAPTER 2: Fostering Creativity and Innovation in Biomedical Research — Lessons from the NIH Intramural Research Program

An essay by Michael M. Gottesman, M.D., Deputy Director for Intramural Research, NIH
November 2008

In science, as in all human endeavors, creativity is a fragile flower that must be nurtured in an appropriate environment. Research on basic biology and its applications to the understanding and treatment of human disease—an endeavor called biomedical research—is no exception. Although some might argue that producing practical applications from biomedical research is a relatively rote exercise, this is not the case. Appropriate ingredients must come together to facilitate landmark advances in finding cures and to enhance our understanding of health and disease.

We are fortunate to live in a time when enormous amounts of data about the biological world are becoming available. But the synthesis of these data into a coherent view of biology and its application to real medical problems requires extraordinary creativity. In this essay, I will describe how the NIH Intramural Research Program has created a culture that fosters highly innovative approaches to medical research and draw lessons from this analysis about how best to encourage creativity in biomedical research in the future, both at the NIH and elsewhere. We believe that NIH research provides much of the foundation of biomedical investigations for the United States and for our international colleagues.

Historical Ingredients in a Creative Culture: The Three T's

In his 2002 book "The Rise of the Creative Class," urban studies theorist Richard Florida identified three major elements that must come together for the establishment of a creative enclave. He calls these the Three T's: Technology, Talent and Tolerance. This is an excellent description of what happened for the NIH intramural program during the 1950s and 1960s under the leadership of James Shannon and what we hope to augment today.

Before and during Shannon's tenure, the NIH gradually developed a physical and organizational infrastructure in which to perform state-of-the-art research. This included the establishment of the Bethesda campus and incorporation of the Rocky Mountain Laboratories in Hamilton, Montana; the relocation of the Library of Medicine; the formation of many of the Institutes and Centers that define the research direction of the NIH; and the creation of the NIH Clinical Center. The heart of intramural research, the Clinical Center placed basic scientists, physician-scientists and clinicians in close physical and intellectual proximity, providing a fertile environment for translational and clinical research, with all patient treatment costs covered by the intramural budget.

Stable research funding for NIH intramural scientists and the availability of funds and facilities to purchase and build the most sophisticated instrumentation (that is, Technology) set the stage for an incredible burst of creative energy from the individuals that Shannon and later directors recruited. Many of their contributions represented major advances and, in some instances, groundbreaking approaches to medical science. Indeed, four of NIH's five Nobel laureates performed their research all within a few floors from each other in the Clinical Center. And 12 others who trained at the NIH have gone on to win Nobel Prizes.

Shannon had a legendary eye for scientific talent and a genius for recruiting, as one chronicler of NIH history put it, but he needed to convince the most outstanding scientists of the time that it was sensible to come to work for a government agency. Talented researchers came to the NIH for diverse reasons: Women scientists and minority scientists recognized opportunities at the NIH sometimes denied to them at universities and in industry. For example, Ida Bengtson, the first woman Ph.D. at the NIH, was recruited to the Hygienic Laboratory in 1916; and David Johnson, the first African-American senior scientist at the NIH, was appointed in 1952. Scientist couples, such as Earl and Thressa Stadtman and Herb and Celia Tabor, could pursue careers not accommodated elsewhere because spouses were not permitted to have

independent positions at the same institution. Many of our most senior scientists today, as well as our scientist emeriti, came to the NIH in the 1950s and 1960s, as perceptive government officials recognized that the doctors' drafts during and between the Korean and Vietnam wars offered an opportunity to recruit young physicians to work on a variety of public health and research priorities. Also, the NIH research environment proved attractive to outstanding U.S. and foreign scientists, including individuals who preferred not to embrace the responsibilities and conventions of academe.

These talented individuals contributed in major ways to biomedical research and have been recognized by numerous awards, including five shared Nobel Prizes, 23 Lasker Awards, nearly 100 elections to the National Academy of Sciences, and over 60 to the Institute of Medicine—and counting. Fellows trained at the NIH became the leaders of academic medical centers and industry in the United States and abroad and were in turn afforded similar recognition.

Richard Florida's last T stands for Tolerance. Tolerance conveys both the intellectual freedom that was afforded NIH scientists and the personal tolerance that has sustained a diverse, international family of scientists at the NIH. The NIH melting pot has facilitated integration of eccentric, brilliant and culturally diverse individuals in an atmosphere that encourages free exchange of ideas, irrespective of their source. The NIH strives to be an intellectual meritocracy. Julius Axelrod, winner of the 1970 Nobel Prize in Physiology or Medicine, had only recently received his Ph.D. when he did his Nobel-winning work on synaptic transmission, for example.

When we asked contemporary NIH scientists about the aspects of NIH culture that facilitate their work, they said they highly prize their intellectual freedom—the ability to test and adapt or discard new ideas quickly and to range freely in a variety of research areas, with world-class collaborators close at hand in almost any direction their research may go.

The Intramural Recipe

Several distinctive aspects of the way the intramural research program funds, reviews, staffs and organizes its assemblage of technology, talent, and tolerance stand out as being essential for its success:

- Long-term, stable research funding makes possible economies of scale, the assembly of major infrastructure and high-tech instrumentation, and the initiation of very long-term or even open-ended clinical investigations, such as analyses of families with extremely rare heritable diseases and epidemiological studies such as the Baltimore Longitudinal Study on Aging.
- Rigorous, primarily retrospective review by senior investigators from outside NIH provides the freedom to pursue high-risk, high-impact undertakings.
- A critical mass of people with wide-ranging skills permits speedy assembly and re-assembly of complementary talents into teams to solve an evolving array of complex problems, as exemplified by NIH's rapid identification of the cause, pathophysiology and first treatment of HIV-AIDS.
- The physical and intellectual proximity of basic research and the world's largest hospital devoted exclusively to clinical research creates a fertile and rapid movement of ideas between bedside and bench, leading to many of the discoveries described in this document.
- Trans-NIH collaborations and communication lead to sharing of ideas, techniques and approaches among researchers.
- Emphasis on training and mentoring of Ph.D. and M.D. researchers provides a constant, stimulating influx and exchange of knowledge and a stream of emerging leaders for the biomedical research enterprise (that is, the NIH intramural program as an "incubator" for future leadership).

Renovating for Innovation

To sustain high-risk, high-impact biomedical research in the NIH Intramural Research Program, NIH leaders have continued to update and rethink the three T's. Under NIH Directors Harold Varmus (1993–1999) and Elias Zerhouni (2002–2008) there was a vigorous upsurge in this renewal.

The rejuvenation of infrastructure has included construction of more than 333,000 square feet of versatile, multidisciplinary lab and animal space, including the Porter Neuroscience Research Center and the Dale and

Betty Bumpers Vaccine Research Center. Patients were relocated to the new Mark O. Hatfield Clinical Research Center, a 240-bed, state-of-the-art Clinical Research Center, in 2005. In 2006 NIH researchers moved into the C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases (Building 33), conceived during the era of grief and resolve following the September 11 attacks and subsequent anthrax mailings to government buildings and media outlets. The National Institute of Allergy and Infectious Diseases remains committed to two BSL-3/BSL-4 facilities at Fort Detrick and Rocky Mountain Laboratories. Construction is underway on the Fort Detrick Integrated Research Facility, a 100,000-gross-square-foot building to house laboratory space for animal research, radiology equipment, mechanical space and a waste-handling area. Construction is complete on the 47,000-net-square-foot BSL2, 3, 4 Integrated Research Facility at Rocky Mountain Laboratories. In addition, completion of the second phase of the Porter Neuroscience Research Center, the Center for Human Immunology and the Center for the Biology of Disease will provide clustered, collaborative labs devoted to the development and use of animal models and innovative technology, including systems biology and other approaches, to pursue integrated studies of disease.

Upgrading technology also has meant the development of sophisticated core facilities with instruments for genomics, proteomics, imaging, structural biology and clinical research support. The National Center for Biotechnology Information, a part of the National Library of Medicine, which houses GenBank and PubMed, remains a major information resource for both intramural and extramural scientists. Extramural scientists also use the Center for Inherited Disease Research (positional cloning of disease genes) and the NIH Chemical Genomics Center, the first such facility in the country supported with NIH Roadmap funds, which screens a large library of small molecules for candidate compounds that affect specific cellular targets or functions.

Key to current and future recruitment is cultivating some of our own talent through intramural training programs. Efforts to recruit and develop underrepresented minority scientists include loan repayment programs and the NIH Undergraduate Scholarship Program, which provide a research experience along with loan repayment or tuition and expenses for disadvantaged students. Another program that attracts students who have not traditionally pursued research careers is the NIH Academy, which trains recent college graduates who are highly motivated to learn about and address health disparities in our society.

We are especially hopeful about recruiting underrepresented minority scientists, women scientists, married couples, scientists from abroad, early career investigators, idealistic scientists interested in public service, and scientists who want to contribute to versatile teams addressing important public health problems and some of the most exciting and difficult questions in biomedical research. Our distinctive culture provides training opportunities for diverse alternative careers in science that allow broad leadership opportunities over and above traditional principal-investigator roles in academia.

Partnerships with the Howard Hughes Medical Institute (the HHMI-NIH Research Scholars program) and with the Pfizer Corporation and Foundation for the NIH (the Clinical Research Training Program) prepare medical students for careers at the productive interface of laboratory and clinical research. "Demystifying Medicine," a course taught primarily for Ph.D.s, is designed to lure basic scientists in this direction. We also continue to develop and improve training programs to support new interdisciplinary fields at the cutting edge of biomedical research as part of our graduate partnerships and post-doctoral training programs.

Closely linked to tolerance and cultivation of new talent is our special attention to protecting the intellectual freedom and resources of early-career investigators. In the last decade, the intramural program formalized its tenure-track policies to nurture scientists in what should be a very creative part of their career. Our aim is to permit them to "get in the game" easily, to have access to the wealth of intramural resources, to take chances and to make innovative contributions during an extended period of committed and stable resource support.

The Future of the NIH Intramural Research Program: Challenges and Opportunities

Great focus in recent years has been placed on maintaining the extraordinary pace of pioneering research originating from the laboratories of the National Institutes of Health. Cures, therapies and groundbreaking

basic research results continue to spring forth despite five years of a flat intramural research budget and the need to assimilate dramatic changes in research tools for biomedical research.

In the face of austere fiscal realities for the coming years, however, the NIH Intramural Research Program needs to take stock of its assets should it hope to uphold its reputation as one of the world's most distinctive and productive research organizations. Key to this endeavor will be to preserve strong, unwavering support for its core principle of providing a laboratory and clinical environment that enables creative opportunities to address critical biomedical and public health challenges, all within the context of budgetary limitations and encroaching barriers to research. My personal prescription for future success includes the following:

1. Enhance the translational continuum

More emphasis must be placed on the continuum of approaches that allow the pursuit in the laboratory of important clinical and epidemiological observations and that translate basic science into new treatments or preventative strategies for human disease (bedside to bench to bedside). The NIH Intramural Research Program should be able to bring laboratory innovations to clinical practice in months rather than years. Our basic investment in talent and new technology at the laboratory level must be matched by investments in transferring technologies, such as the existing Roadmap-initiated NIH Chemical Genomic Center and Image Probe Development Center. These trans-NIH centers enable high-throughput analysis of small molecules (chemicals and RNA) that target well-credentialed disease-related genes and gene products and provide chemical modification to develop higher-affinity reagents, drugs and image probes. We must invest also in animal research facilities that are state-of-the–art, as proposed for the NIH Center for Biology of Human Disease, so that new ideas can be tested in novel animal models of human disease. And we must be sure that the existing Clinical Research Center and other institute-originated clinical research activities have sufficient funding to keep pace with inflation in pharmaceuticals and medical personnel costs.

Many of these investments are beyond the capacity of a single NIH institute and necessitate the creation of trans-NIH initiatives, supported at the highest levels by NIH leadership and funded through improved buildings and facilities allocations from Congress and from shared NIH resources.

If budgets remain flat, how can NIH manage? Some saving can be realized, as they have been in recent years, by prudent downsizing of less competitive research activities. Administrative infrastructure costs can be reduced by partnerships among existing institutes and centers, so that the overhead of maintaining 23 separate intramural research programs (housed in 23 of our 27 institutes and centers) is reduced. Also, a change in the demographics of the NIH research pool can provide some help to meet inflationary pressures, as explained in further detail below.

2. Revitalize Clinical Research

The combination of increasing bureaucratic restrictions on clinical research, restricted funding and a declining pool of talent threatens the preeminence of clinical research at the NIH. The NIH Intramural Research Program has created a new governance structure to take forceful action to reduce the impact of these negative forces. A new Deputy Director for Intramural Clinical Research, within the Office of Intramural Research, will chair a senior-level group of clinical directors, scientific directors, institutes directors and human subject research professionals to take on these challenges. We plan to dramatically reduce the time needed for review and approval of clinical protocols, to provide administrative stewardship for these protocols through complex bureaucratic hurdles, and to further develop electronic tools to simplify the process of writing and managing protocols. We will encourage investments in career development of talented clinical researchers by using a more seamless set of opportunities that provide training and mentoring in the early years and stable clinical research support for the most creative and productive researchers. Trans-NIH approaches including shared Institutional Review Boards and a clinical research service center can provide more uniform and efficient clinical research support.

3. Change the Demographics of Scientists at the NIH

The entire NIH-supported pool of biomedical researchers nationwide is aging, and this includes researchers in the NIH intramural program. About 75

percent of our research faculty are tenured senior investigators, and 25 percent are tenure-track investigators, with an overall median age of 58. It is more expensive to support senior investigators and, although many continue to be highly creative and productive and bring a wealth of experience and wisdom to the biomedical research enterprise, the most innovative and transforming science is likely to come from earlier-career investigators. The 12 NIH trainees who ultimately went on to win Nobel Prizes is evidence of this.

As our senior scientists depart, due to retirement, being attracted by outside employers, or as the result of a stringent review process, we must bring new talent and earlier-career investigators to the NIH with the goal of having a more equal mix of senior and tenure-track investigators. We also should create a mechanism to bring a broader group of talented scientists to the NIH, many of whom need not be committed to a lifetime career in federal service. One proposal is for a "research package" of 10 years of research support for clinical investigators, which would include six years of intramural funding to conduct independent research at the NIH followed by four years of extramural support for those who are attracted by extramural academic positions. This award would highlight the advantages of beginning a research career at the NIH, increase the pool of talented NIH investigators without occupying permanent slots, and encourage interactions between the intramural and extramural communities.

We have made notable progress on each of the elements outlined in this essay. For example, my office has led efforts in the last two years to define and develop grassroots scientific projects that could draw resources and talent from all of the NIH Institutes and Centers. This has brought forth several trans-NIH initiatives now in their early stages but with extraordinary potential, such as the Center for Human Immunology, initiatives in systems biology and in imaging, and so-called "Manhattan Projects" to quickly concentrate resources and talents to create cures in our "war" against human disease and suffering, such as the Bone Marrow Stromal Cell Transplantation Center.

These efforts are coupled with the clinical element of the NIH mission, from the digital—advanced software to write clinical protocols, destined to become an "industry" standard nationwide—to the physical, our roll-up-the-sleeves reconstruction of the clinical research enterprise. Similarly, recruitment and funding improvements are in place or well under development.

Relevance of the NIH Intramural Experience to Extramural NIH-Supported Research

The NIH intramural experience indicates that innovative science requires resources, talent and an environment of tolerance to encourage creativity. Budgetary pressures and restricted research goals and research tools throughout the academic world and industry could militate against the nurture of creative endeavors.

Under the leadership of Elias Zerhouni, the NIH Director from 2002 to 2008, the NIH came to recognize these potential limitations. Through the NIH Roadmap, the NIH has sought to provide for all biomedical researchers some of the tools that have made the intramural research program so effective, including access to the latest technological advances. The Roadmap's "New Pathways to Discovery" has channeled investments to eliminate roadblocks delaying progress in areas such as nanotechnology, structural biology of membrane proteins, and characterization of small molecules in metabolism and as targeted agents to dissect cell function. Intramural-extramural collaborations are an important way to expand access to the resources and tools available in the intramural program, and Dr. Zerhouni advocated for them.

In addition, the need to support talented individuals willing to take on high-risk projects has been highlighted by the creation of the NIH Pioneer Awards. This is a relatively small investment considering the size of the NIH grant portfolio, but it has served as a pilot experiment for further efforts designed to facilitate a grant review process that recognizes scientific excellence and innovation and that does not penalize high-risk endeavors. The recent reorganization of study sections and efforts to encourage seasoned investigators to serve as grant reviewers should be a step in the right direction.

Conclusions

Innovation in biomedical research has been and will continue to be dependent on updating technology and infrastructure and on finding approaches to recruiting

talent and supporting programs that are creative and not risk-averse. The intramural program's approach to the Three T's is distinctive, especially in its emphasis on the tight integration of basic, translational, and clinical research.

Extramural programs in academia and industry have pursued other approaches, but likewise must continue to rethink how best to encourage the creative endeavors as budget pressures and narrowly focused review mechanisms can lead to incremental research goals. Although talent and technology are essential elements of successful research, it still falls to those of us who manage large research programs to keep sight of the importance of creating and protecting a free intellectual environment that encourages the flowering of creative research.

I believe the best years are ahead of us. Considering our remarkable past, this is no small statement about the United States' continued contribution to biomedical knowledge and indeed the very health of humankind.

CHAPTER 3: Quality and Scope of Science in the NIH Intramural Research Program

Boards of Scientific Counselors (BSCs) have assessed the quality of intramural science with increasingly greater rigor since their creation in 1956. Improvements in the process have been recommended from within and by outside reviews, most recently by the Director's Advisory Committee Report on the Intramural Research Program. BSC reviews rely on expert outside peer review of scientific performance to advise on the quality of research, the resources that should be allocated to scientists, and the promise of tenure-track investigators for future success in their careers. The BSC evaluations are based mainly on scientists' past accomplishments and objectives met but also on future plans.

The review criteria in many ways mirror those used by extramural peer review with the addition of considering whether the investigator is taking advantage of the special features of the NIH intramural scientific environment and employing useful collaborative arrangements. Each NIH principal investigator (Senior Investigator and Tenure-Track Investigator) in every NIH laboratory or branch must be reviewed at least once every four years by a BSC. All BSCs are chartered under the Federal Advisory Committee Act. This assures the proper composition of the Boards based on racial, ethnic, gender and geographical diversity. As a result of these reviews, recommendations for altering allocated resources are made to the Scientific Director, the Institute or Center Director, the NIH Deputy Director for Intramural Research, and the Institute or Center National Advisory Council or Board. These Advisory Councils or Boards have an informed, broad perspective that allows them to advise on alternative programs, if they determine that there is a need for more effective or cost-efficient approaches.

In spite of a thorough, effective review process, there are improvements that would make the application of this process more consistent across NIH Institutes and Centers. The areas of consideration for improvement include:

- more explicit attention to the encouragement of innovative, high-risk, high-impact research that is difficult to perform in an academic setting;
- development of data systems that benchmark the accomplishments of intramural scientists;
- more frank recommendations by BSCs that include explicit recommendations for resource adjustment; and
- more accurate analysis of the research budgets of intramural scientists to allow BSCs to compare funding with scientists outside the Intramural Research Program and an accurate estimate of the indirect costs of conducting intramural research.

Characteristics of the Intramural Research Program: Innovative, high-risk, high-reward and original

The mission of the NIH Intramural Research Program is by definition to conduct original laboratory, clinical and population-based research that is innovative, distinctive, high-risk, high-reward and high-impact. Intramural research is carried out in a fertile environment, where mentors train a diverse population of outstanding future researchers to conduct high-impact peer-reviewed research. Core ingredients in the "intramural recipe" necessary for success are the freedom and time to conduct independent investigator-initiated research; the capability of flexible and rapid research responses to public health emergencies, emerging new technologies and new training needs; and the creative leadership of science by scientists. The recipe is sweetened by elements mentioned in the previous chapter: stable funding, retrospective reviews, critical mass of expertise, collaborations, and the physical and intellectual proximity of basic and clinical research.

Special Challenges Intramural Scientists Face

There remains much room for improvement in the NIH Intramural Research Program. These include improvements that can be made internally as well as externally, with the latter referring to federal regulation. Top challenges faced by intramural scientists include:

- *Allocation of resources* — This includes space, budget and personnel to operate laboratory and clinical research programs; the concerns are reduced budgets for supplies and equipment since the flattening of the

NIH budget, the challenge of maintaining a research hospital, and the escalating contractual costs for various services.

- *Recruitment and retention* — This pertains particularly to specialists and underrepresented minorities, who are in high demand among all leading research organizations.
- *Replacement of capital equipment* — This pertains to the replacement at a sufficient pace to maintain a state-of-the-art infrastructure.
- *Transaction costs* — This pertains to the increasing time and energy associated with satisfying regulations for the proper conduct of research, such as animal care and use and human subjects research.
- *Federal restrictions* — These include implicit restrictions associated with federal employment, such as limitations on higher-level salaries, especially for clinical investigators, limits on staff/FTE, travel restrictions, highly-restrictive conflict-of-interest rules, high levels of computer and physical security, and hiring impediments.

Also, each NIH Institute and Center must determine the appropriate balance among laboratory-based, population-based and clinical research based on the opportunities and challenges reflected in its mission. Thus, the balance varies. But approximately one third of the overall intramural budget is devoted to clinical research, including population-based or epidemiological research.

Measuring the Impact of Intramural Scientists and Their Work

Before meeting, each Board reviewer receives data about the person or entity up for review. Each laboratory or branch being reviewed provides: a description of the overall past accomplishments of all PIs in the laboratory or branch (or independent section) since the last review; a summary of the organizational structure of the laboratory being reviewed; a listing of all personnel, including their position, type of appointment and grade, including contract service workers; space usage; operating budget, though budget allocation procedures vary considerably among the Institutes and Centers; outside contracts, if any; and Cooperative Research and Development Agreements (CRADAs), if any.

Each scientist being reviewed provides: a current CV and bibliography; copies of up to three important recent manuscripts or publications; a progress report on current research, including descriptions of each project and accomplishments since the last review and a description of future plans (usually, a concise, well-articulated progress report of 2,500 words and a description of future plans of 1,000 words); a summary of the amount of support staff and space that the scientist uses, in addition to information about budget, contracts and CRADAs; a listing of former fellows and their current positions; and a copy of their most recent prior Board of Scientific Counselors report.

Recent Examples of Distinctive Research That Could Not Be Done Easily Outside the Intramural Program

The National Institutes of Health comprises 27 institutes and centers, of which 23 have intramural research programs. The aforementioned intramural recipe provides an environment that enables innovative high-risk, high-reward research, which in a traditional academic setting would take many years to yield tangible benefits or, often, would not be undertaken at all. In this regard, the Intramural Research Program excels in the type of basic research needed to advance biomedical knowledge, providing the very foundation for health research worldwide, as well as the type of clinical research that culminates in cures and therapies, as evidenced by the its role in HIV and cancer therapies.

The following pages highlight some of the major research advances reported in the past five years, both clinical and basic, which have taken full advantage of the special character of the Intramural Research Program. Appendix C lists additional major advances. In some cases, funding would have been difficult to obtain in an extramural setting because the research concept was so nascent that no scientific literature existed to support a grant application. In other cases, the advances arose from years of basic research, sometimes serendipitously, utilizing a combination of equipment, expertise and research freedom only available in the Intramural Research Program. Many of these examples below earned the praise of the Board of Scientific Coun-

selors reviewers, who noted that the research could not have been performed elsewhere. In many cases, several NIH Institutes and Centers either collaborated to produce these results or built upon the success of previous NIH research. Refer to Appendix F for a list of Institutes and Centers and their abbreviations.

MAJOR RESEARCH HIGHLIGHTS

The HPV "anti-cancer" vaccine — The NCI CCR has developed a novel vaccine technology involving virus-like-particles, which has led to the first FDA-approved vaccine against cancer. This research involves the human papillomavirus, or HPV, the primary cause of nearly all cases of cervical cancer. Studies indicate that upwards of 90 percent of adult woman are infected by HPV, leading to over 10,000 cases of cervical cancer each year. The NCI CCR partnered with private industry to create two vaccines against certain cancerous strains of HPV, which could help to prevent most cases of cervical cancer, as well as genital warts and other types of genital cancer. The NCI DCEG continues this work with a Phase III trial in Costa Rica testing the safety and efficacy of one of these vaccines against specific deadly strains of HPV. The vaccine likely will have its major impact on the prevention of cervical cancer in developing nations, where medically underserved women are especially vulnerable to this devastating disease, as well as in underserved populations within the United States. (NCI CCR, DCEG) [Hildesheim et al., JAMA. 2007 298:743-753]

Immunotoxins for treatment of solid tumors: assassin proteins that kill cancer — Immunotoxins are bioengineered proteins with ninja-like instincts, able to stealthily target cancer cells, enter inside and deliver toxins. NCI has helped to pioneer the development of immunotoxins, which were expensive and tricky to make two decades ago. NCI has since streamlined the process and has made more efficient immunotoxins better able to target cancer cells, particularly blood cancers such as leukemia. By 2005, clinical studies were showing cancer remission or stabilization in over half the patients treated. A breakthrough has been made recently, however, with immunotoxins targeting solid tumors, such as breast and organ cancers. Phase II clinical trials are in the works. (NCI CCR) [Onda et al., Proc Natl Acad Sci USA. 2008 Aug 12;105(32):11311-6]

Parkinson's Disease — NIH researchers have an unparalleled record in Parkinson's disease basic research, particularly in understanding the genetic basis of this disorder. NIH scientists found mutations at three of the six known genetic regions associated with Parkinson's disease, including the identification of mutations in a gene called LRRK2, which underlie approximately 20,000 to 40,000 cases of Parkinson's disease in the United States. This work has been possible with agile and stable funding, which enabled scientists to quickly mobilize resources and collaborators for rapid identification of these mutations. As the mutations were identified, researchers were able to work easily across institutes bringing together experts to jointly solve complex problems and then provide data to the entire scientific community studying neurodegenerative diseases. These findings have revolutionized our understanding of Parkinson's disease, previously thought of as a non-genetic disease, and has offered insights into the disease process, leading to improved screening and animal models and highlighting potential points of therapeutic intervention. (NIA, NINDS, NHGRI) [Hardy et al., Ann Neurol. 2006 Oct;60(4):389-98]

Multiple Sclerosis: treatment and new insights — Over the past eight years, the Neuroimmunology Branch (NIB) in NINDS has conducted a series of clinical and basic studies of daclizumab in the treatment of multiple sclerosis (MS). The studies represent an example of the type of translational research that is possible at few places outside of NIH, particularly because NCI developed daclizumab as a treatment for a rare type of leukemia. The initial study examined the effect of daclizumab on disease activity as measured by MRI in a cohort of patients already on approved therapy but with breakthrough of disease activity. The results demonstrated an impressive and significant reduction in new disease activity, with each of the subsequent studies demonstrating a significant treatment effect. Combined with the clinical studies were detailed examinations of the immunological events associated with treatment, which uncovered how da-

clizumab works at the cellular level. Efforts are now underway to explore other treatments for autoimmune disease. Studies of daclizumab have depended on special resources at NIH, such as the Clinical Center and the NIH In Vivo NMR Center for frequent and advanced MRI studies. The immunology element was made possible by the support of a strong basic science component of a clinical branch and was facilitated by being able to obtain large amounts of lymphocytes by lymphocytophoresis performed in the Clinical Center. (NINDS, NCI, CC) [Bielekova et al., Proc Natl Acad Sci USA. 2006 Apr 11;103(15):5941-6]

Microscopy breakthrough: PALM — NICHD researchers and their colleagues have developed a new and relatively inexpensive microscopy technique called Photoactivation Localization Microscopy, or PALM, which allows one to visual single molecules in tissue with a light microscope. PALM allows researchers to image intracellular proteins at nanometer spatial resolution, greatly expanding the horizon of cell biology research. In a conventional optical microscope, objects less than about 200 nanometers apart cannot be distinguished from one another. The trick of the new technique is to control the light to activate only a few molecules at a time, so that they are statistically likely to be well separated. Repeating this process thousands of times, a computer image is eventually created in which the positions of all the molecules are determined with near-molecular precision. The NICHD Cell Biology and Metabolism Branch, Section on Organelle Biology, developed the technique and will use PALM for quantitative studies, making "movies" to visualize how protein and organelle move about in living cells. What researchers learn from the new microscopy technique will provide a broad foundation for understanding the complexity of how proteins, the building blocks of cells, interact in health and disease. This is a research tool available to researchers worldwide. (NICHD) [Betzig et al., Science. 2006 Sep 15;313(5793):1642-5]

Biodefense: Ebola and Marburg — Researchers at the VRC have accelerated progress in the development of vaccines against Ebola and Marburg hemorrhagic fevers. The VRC has developed a DNA prime, rAd boost vaccine approach that protects monkeys from lethal Ebola virus infection. A Phase I trial of the DNA vaccine component has been completed. This vaccine, composed of three DNA plasmids, was well tolerated and elicited both humoral and cellular immune responses at all doses. The VRC also has developed an accelerated rAd vaccine for Ebola that is being tested in humans; a single shot of this fast-acting, experimental Ebola vaccine successfully protected monkeys after only one month. This finding suggests that it might be possible to quickly contain Ebola outbreaks with ring vaccination. In parallel, non-human primate challenge studies continue to refine the design of final Ebola/Marburg vaccine products. (NIAID) [Sullivan et al. Nature 2003. 424: 681-684]

Molecular profiling of lymphomas: cancer's fingerprints — Understanding the enemy is the first step towards conquering it. The same is true in cancer treatment, where the cure is dependent on knowing the type and stage of the cancer. NCI CCR has developed a new molecular profiling technique that improves the classification of lymphomas, which are cancers of the lymph nodes, such as Hodgkin's disease. The precise molecular fingerprinting of these cancers can lead to effective new drug therapies, as well as inform the best course of treatment. (NCI CCR) [Lenz et al., Proc Natl Acad Sci USA. 2008 Sep 9;105(36):13520-5]

Gene therapy to restore salivary gland function — The treatment of most head and neck cancer patients includes ionizing radiation. Salivary glands ultimately suffer irreversible damage, and there has been no conventional treatment available to correct this condition. This leads to dry mouth (xerostomia), difficulty in swallowing (dysphagia), and severe oral infections. The NIDCR Molecular Physiology and Therapeutics Branch has developed a gene transfer strategy to treat this condition. Researchers developed a recombinant serotype 5 adenoviral (AdhAQP1) vector to transfer the human aquaporin-1 (hAQP1) cDNA to parotid glands. Animal studies showed that the AdhAQP1 strategy for restoring salivary flow to radiation-damaged salivary glands was effective and that AdhAQP1 gene therapy was without significant untoward effects after salivary gland delivery. NIDCR has begun testing in adult patients with radiation-induced salivary hypofunction

with the goal of an elevated salivary output. The FDA has given full approval to a clinical protocol to test the safety and efficacy of AdhAQP1 in adult patients with established radiation-induced parotid gland hypofunction, and this clinical trial is underway at the NIH Clinical Center. (NIDCR, CC) [Zheng et al. Hum. Gene Therapy 2006. 17: 1122-1133]

Origins of taste: molecular and behavioral discoveries — Researchers in the NIDCR Laboratory of Sensory Biology and extramural colleagues have systematically analyzed four of five taste modalities in the mouse; largely solved the major questions in sweet, umami and bitter taste; and are well on their way to pinning down sour taste. Still on the horizon lies salt taste, which has been an elusive and confusing taste quality. NIDCR employed a clever experimental strategy over the course of four years to get at these as yet uncharacterized cells and molecules. By engineering mice to express different receptors in cells that typically underlie one or another taste quality (e.g. opiate or bitter receptors in sweet cells), or selectively eliminating classes of receptor cells (e.g. sour-sensitive cells) the work provides elegant evidence for the specificity of taste receptor cells. The researchers' publications have set the standards for much of the field. (NIDCD) [Chandrashekar et al., Nature. 2006 Nov 16;444(7117):288-94]

Immune system gone haywire: ALPS — Autoimmune lymphoproliferative syndrome, or ALPS, is at the heart of how the immune system works. For people with ALPS, the immune system is efficient at fighting infections, but the lymphocyte "soldiers" never get the message that the war is over. Apoptosis, or programmed cell death, doesn't work well, and as a result, excess T cells and B cells gather in the lymph nodes, liver and spleen, causing them to become enlarged. The NIH identified the disease in the mid-1990s and has since studied and treated more than 250 ALPS patients. There is no cure yet. But based on extensive ALPS research done almost exclusively at the NIH, researchers have begun several clinical studies, such as one study evaluating the usefulness of PET scans to better understand the nature of lymph node and spleen enlargement in ALPS patients and to explore experimental treatments against the disorder. Cell death and apoptotic cell clearance affect the finely tuned balance between peripheral immune tolerance and autoimmunity, and work on ALPS—such as its association with Hodgkin and non-Hodgkin lymphoma—may have broad significance. (NIAMS, NIAID, CC) [Rao VK and Straus SE, Hematology. 2006 Feb;11(1):15-23]

Inherited Periodic Fever syndromes: autoinflammatory disorders — Inherited Periodic Fever syndromes are a family of diseases causing episodic fevers with no trigger of an infection from a virus or bacterium. NIH researchers have made broad gains finding the cause and developing therapies for these rare diseases, which ultimately have led to a deeper understanding of the immune response. NIAMS researchers and their NIH colleagues found the single gene responsible for Familial Mediterranean Fever, called the MEFV gene. From this platform they moved on to tackling other periodic fever syndromes. They next demonstrated that mutations of the tumor necrosis factor cytokine receptor cause a disease called Tumor Necrosis Factor Receptor Associated Periodic Syndrome, or TRAPS, and that mutations of the gene CIAS1 cause a spectrum of diseases now referred to as cryopyrinopathies (familial cold autoinflammatory syndrome, Muckle-Wells syndrome and Neonatal Onset Multisystem Inflammatory Disease, or NOMID). NIAMS discovered that antagonizing interleukin-1 is effective treatment for NOMID, a previously untreatable, devastating disease. More therapies for other syndromes are anticipated soon from this work. (NIAMS, NIAID, NHGRI) [Farasat et al., Arch Dermatol. 2008 Mar;144(3):392-402.]

Prestigious Awards and Recognitions

NIH Intramural researchers have won hundreds of significant professional awards in the last five years alone—many among the highest in their fields or the highest in their professional societies, far too many to list here. Among these prestigious awards or memberships are:

- Presidential Medal of Freedom (Francis Collins, Anthony Fauci)
- Lasker Award (Anthony Fauci)
- National Medal of Science (Anthony Fauci)

- National Medal of Technology and Innovation (Roscoe Brady)
- National Academy of Science (49 current members)
- Institute of Medicine (57 current members)

The NIH Intramural Research Program has also produced or trained 18 Nobel Prize winners, who either did the bulk of their award-winning research at NIH or trained in one of our labs. These include: Arthur Kornberg (1959), Marshall Nirenberg (1968), Julius Axelrod (1970), Christian Anfinsen (1972), D. Carleton Gajdusek (1976) and Martin Rodbell (1994), all NIH researchers; plus Baruch Blumberg (1976), Baruj Benacerraf (1980), Michael Brown and Joseph Goldstein (1985), Michael Bishop (1989), Alfred Gilman (1994), Stanley Prusiner (1997), Ferid Murad (1998), Arvid Carlsson, Paul Greengard and Eric Kandel (2000), and Richard Axel (2004). Harold Varmus (1989) was the NIH Director from 1993 to 1999. Considering the fact that the NIH competes primarily for only two of the six prize categories, this list of Nobel laureates rivals that from any university-based biomedical program.

External Review: Outside bodies that ensure the quality and compliance of NIH programs with applicable laws and policies through a recognized accreditation processes

As mentioned previously, NIH Intramural Research Program invites regular and periodic review by outside bodies. The following is a complete list of the source of such regular independent evaluations of intramural research and critical support functions:

- Federally-chartered NIH Boards of Scientific Counselors that are overseen by National Advisory Councils/Boards
- External Blue Ribbon Panels appointed by the NIH Director to review intramural research programs in the Institutes and Centers as well as component parts such as intramural clinical research
- U.S. Congress and its committees; General Accountability Office
- National Academies of Sciences, Institute of Medicine
- Office of Inspector General
- Office of Management and Budget (e.g., Program Assessment Rating Tool)
- American Association for Accreditation of Laboratory Animal Care International*
- Joint Commissioned for Accreditation of Hospital Organizations*
- Accreditation Council for Graduate Medical Education*
- Accreditation Council for Continuing Medical Education*
- Nuclear Regulatory Commission*,
- Occupational Safety & Health Administration
- Association for Accreditation of Human Research Protection Programs (pending)

These and other reviews confirm and assure that the NIH meets the documented accreditation standards. The reviews provide assurance that the NIH intramural programs are of high quality and effective in the conduct of NIH research that relates to the program/questions reviewed. The reviews marked by an asterisk (*) above resulted in a certification or letter of compliance that indicated an effective rating from the external evaluation.

CHAPTER 4: The Clinical Research Enterprise in the NIH Intramural Research Program

Since the NIH Clinical Center opened in 1953, clinical research has been a key feature of the NIH Intramural Research Program. The intramural program not only conducts clinical research but has a long-standing commitment to train physician-scientists for future careers in clinical research. Vast numbers of academic leaders in medicine and research were trained at the NIH beginning in the 1960s and 1970s.

Today, maintenance of an appropriate clinical research portfolio at the NIH and around the country is threatened by the rising costs of patient care and operating hospital facilities, by the numbers and quality of physicians entering the field, and by a focus on exciting progress in laboratory research—for example, through the understanding of the human genome. In contrast, the opportunities to apply new basic knowledge to clinical problems, the burgeoning interest in translational research by laboratory scientists, the availability of new technologies to accelerate clinical applications, and the expectations of the funders of research for advances in clinical medicine are challenges for our time and for the Intramural Research Program.

Facilities and Programs

Outside experts who reviewed the NIH Intramural Research Program in 1994 noted that "a central goal of the work of intramural clinical investigators is the application of basic laboratory advances to clinical application." These experts thus recommended renewal of the Clinical Center that included construction of a new hospital, but not at the expense of the NIH extramural research program (Report to the External Advisory Committee of the Director's Advisory Committee, 1994, co-chaired by Gail A. Cassell, Ph.D., and Paul A. Marx, M.D.). The new hospital subsequently opened in 2005 as the Mark O. Hatfield Clinical Research Center. In 2008 there were 1450 clinical protocols underway in the Clinical Center that operated at an approximate 64-percent capacity. Approximately 24 percent of NIH principal investigators conduct these research protocols (202 tenured principal investigators among 857 tenured scientists.)

New programs at the Clinical Center, such as the NIH Bench-to-Bedside Program, encourage the application of new findings in patients, often with the participation of investigators from outside institutions. Many of the key advances in NIH research are clinical in nature (see Chapter 3 and Appendix C for annotated examples). Recently, the Undiagnosed Diseases Program was initiated with the National Human Genome Research Institute as lead institute to bring selected, difficult-to-diagnose cases to the NIH Clinical Center for evaluation and possible treatment with the potential outcome of developing new research protocols. This program places renewed emphasis on a long-standing practice at the NIH of studying new, frequently rare, diseases; in fact, approximately 50 percent of NIH clinical protocols are created as "natural history" protocols to study the underlying causes of rare diseases. In addition, novel treatments for both rare and more common diseases that have never been tested before in humans are a goal of the Clinical Center.

As a result of the 632 treatment protocols at NIH, 90 percent are Phase I or II, a percentage much higher than is typical at academic medical centers. The work of NIH investigators on rare diseases and to test new therapies has been recognized nationally and internationally and continues to lead to important public health advances.

Careers in Clinical Research

In follow-up to the 1994 report of Cassell and Marx cited above, NIH examined internally the recruitment and career development of its own intramural clinical investigators (Report of the NIH Committee on the Recruitment and Career Development of Clinical Investigators, 1997, chaired by Stephen E. Straus, M.D.). This study was prompted by the recognition that the morale of NIH clinical investigators had waned, leaving them often feeling "undervalued and unsupported." Some solutions followed, including:

- improvements in pay and personnel systems, such as the new Clinical Research pay track and the initiation of a new position description for early career clinical

researchers (the Assistant Clinical Investigator) that is analogous to a mentored K23 in an academic center;
- a lengthening of the tenure track for clinical investigators and population scientists to eight years;
- improved training in clinical research exemplified by the Clinical Center's internationally-recognized course in clinical research; and
- improvements in evaluating clinical researchers for tenure, including (a) revision of criteria for tenure at the NIH and (b) the pre-review and advocacy of clinical researchers by an intramural Investigator Review Panel that advises the NIH Central Tenure Committee.

Other issues persist, including the aging of the clinical research workforce, the funding of increasingly costly clinical research studies in the face of flat budgets for the past five years, capital equipment needs, and preserving the overall quality of clinical services in the NIH Clinical Center with decreased buying power each year and increasing pharmaceutical and personnel costs.

Future Directions

In 2003, NIH Director Dr. Elias Zerhouni called for a review by both outside and internal experts in clinical research, mainly to find ways to energize the NIH clinical research enterprise (NIH Director's Blue Ribbon Panel on the Future of Intramural Clinical Research, 2004, co-chaired by Edward J. Benz, Jr., M.D., and Joseph L. Goldstein, M.D.). The Director's NIH Roadmap had already identified clinical research as "the linchpin of the nation's biomedical research enterprise." The panel concluded that "as academic institutions strive to maximize their impact, the NIH intramural program, with its unique resources and professional groups, also must refocus and enhance it efforts in clinical research."

The panel spoke of vision, leadership, the need for novel programs, and defining a distinctive role that would complement the extramural community—all to elevate the status of clinical research at the NIH. Among its many recommendations, foremost was a call to revise the NIH intramural clinical research oversight structure. As a result, the Advisory Board for Clinical Research was created to "provide advice and guidance to integrate the vision, planning and operations of the intramural clinical research programs of the National Institutes of Health, including the clinical research conducted at the NIH Clinical Center."

Further steps are being taken to preserve and enhance the fragile flower that is innovative clinical research. Prompted further by a clear call from NIH principal clinical research investigators to streamline clinical research, and supported by leadership at the highest levels at NIH, there is now a high-level NIH Intramural Clinical Research Steering Committee (ISRSC) under the leadership of a Deputy Director for Intramural Clinical Research that is addressing the following issues, with an initial focus on reducing barriers to clinical research:

- standards and strategies for the development, review and implementation of human subjects protocols, including IRB operations, support, accountability, and ethical interactions with the pharmaceutical industry (including technology transfer);
- standards and strategies for the development, review and implementation of human subjects research more broadly, including the scientific review of protocols and the BSC review of clinical programs;
- oversight of the global portfolio of NIH intramural clinical research, including the coordination of Institute- and Center-specific programs and trans-NIH initiatives;
- recruitment, salaries, career paths and organizational structure of clinical and translational research in the IRP, including the roles of the Institute and Center leadership in clinical research; and
- policies governing the conduct of clinical research.

In summary, the priorities are clear for enhancing clinical research that is both supported and conducted by the NIH. The NIH Intramural Research Program has led and is prepared to continue to lead in this endeavor using its breadth and depth of expertise to streamline and energize clinical research.

CHAPTER 5: Trans-NIH Initiatives

The NIH Intramural Research Program has a long history of interactions and has shared resources among its investigators. (Refer to Appendix D). These include core facilities that support crucial research activities, such as a sequencing center, a magnetic resonance imaging facility, a mass spectroscopy service and a protein expression service. The Warren Grant Magnuson Clinical center is the nation's largest hospital devoted entirely to clinical research. It provides comprehensive services and facilities in support of clinical research sponsored by the Institutes and Centers. In addition, there are over 125 active Scientific Interest Groups (SIGs) that focus on specific scientific or research-related topics.

Both intramural and extramural researchers participate in the SIGs, which sponsor symposia, lectures, and poster sessions, and offer mentoring and career guidance for junior scientists. Finally, the NIH Office of Intramural Training and Education organizes and sponsors a variety of training and career development activities for the entire intramural community. Several mechanisms are used to support the activities described above, including contributions from participating NIH Institutes and Centers, such as the management funds, user fees and program support from the Office of Intramural Research.

Formal trans-NIH initiatives

In the past few years, we have been identifying new and creative ways to take advantage of the special features of the NIH intramural research program. Over 100 intramural scientists, representing all the NIH Institutes and Centers, met in focus groups to identify scientific projects of broad interest. Extramural scientific leaders helped set the priorities for the initiatives discussed. This led to the start of the Trans-NIH Initiative Program as one response to the challenge. The Trans-NIH Initiative Program aims to take advantage of unexploited research opportunities. It encourages trans-NIH and intramural-extramural scientific interactions, and taps the creativity and talent of the intramural investigators. The program currently emphasizes three fields of research.

One of the strengths of the program is its multidisciplinary, cooperative approach to solving challenging biomedical problems. Another strength is the potential to provide unparalleled services to both the intramural and extramural scientific community. A limitation, though, is obtaining the needed resources, particularly finances and space.

The Center for Human Immunology

The first Trans-NIH Initiative to be established is the Center for Human Immunology, Autoimmunity and Inflammation (CHI). The CHI aims to pioneer a new, integrated approach that combines the expertise of basic immunologists, clinicians and epidemiologists. A successful program would jointly improve clinical therapies and fundamental knowledge of immune-mediated diseases.

We anticipate several notable components to the CHI translational center. One set of research projects would focus on rigorously characterizing similarities and differences in pathophysiologies, with a major objective being the determination of common mechanisms of inflammation or immunologically-based diseases. Other projects would be more speculative in nature, and may include the application of emerging technologies to disease. In both cases, the projects are expected to include highly collaborative interactions that utilize the vast resources of the NIH Clinical Research Center. Core facilities and renovated space will be provided to support these activities. Another component of the CHI is the expansion of current training programs towards the development of a true and unique clinical immunology specialty.

The spectrum of possible diseases that can be included in this initiative is wide and diverse. The following fields and diseases have been identified as scientifically and clinically justified targets: organ-specific auto-immune diseases like inflammatory bowel disease, multiple sclerosis and type I diabetes; multi-organ pathologies like systemic lupus erythematosus and rheumatoid arthritis; congenital and acquired immunodeficiency syndromes and immune suppression in transplant and cancer patients; processes in which inflammation, the immune system or altered immunity

have pathophysiologic roles; and malignant diseases in which the immune system has a role in fostering or controlling genomic instability.

The Systems Biology Initiative

Systems biology is a relatively new, multi-disciplinary field of biomedical research that studies complex interactions at a systems-wide level. This emerging discipline is a response to the post-genomic, information-intensive biology of today, in which computation and modeling are critically important tools. The goal of the NIH program is to advance and utilize these tools to elucidate the large-scale cellular and molecular networks that regulate cell activation and differentiation.

One component of the initiative is to recruit tenured and tenure-track investigators to an intramural program in systems biology. The initial recruitment would focus on investigators with expertise in computational analysis, modeling and simulation in order to complement the current intramural strengths in bioinformatics and molecular modeling. Then, the initiative will provide financial support for investigator-initiated projects in systems biology. The projects will involve multiple principal investigators, of whom at least one must be a computational scientist. Another component will focus on developing new tools and resources for researchers. This includes a focused effort in data collection and data analysis and in assembling and maintaining public databases. Several intramural programs have agreed to contribute newly recruited investigators to this effort.

The Imaging Initiative

This initiative aims to create novel opportunities for the development of cutting-edge technologies for imaging and image analysis. Notably, the initiative will concentrate on bridging the gap between imaging at the atomic, cellular and tissue levels of resolution. The intramural program could contribute advances to several areas, including high-resolution light and electron microscopy, magnetic resonance imaging at molecular and cellular resolution, and secondary ion mass spectrometry for the characterization of cells and tissues. The improved technologies should contribute to discoveries of fundamental molecular mechanisms underlying disease, as well as to new technologies with unprecedented resolution for non-invasive clinical imaging and diagnosis.

One component of the initiative is the formation of an advanced imaging center under direction of the National Institute of Biomedical Imaging and Bioengineering intramural program, which will provide a physical focus on campus. A second, complementary component is the creation of a competitive intramural grant mechanism to support multi-institute, interdisciplinary research. Successful proposals will seek to provide integrated and quantitative understanding of cell structure and function.

The Intramural Bone Marrow Stromal Cell Transplantation Center

This is a production facility with NIDCR as the lead institute to prepare GMP-quality (clinical-grade) mesenchymal stromal bone marrow stem cells for clinical studies at the NIH. Investigators from multiple Institutes and Centers are planning clinical trials using these cells to treat a variety of diseases of the immune and skeletal systems. Bone marrow harbors within its stroma a population of cells that have been shown to have a beneficial effect when administered directly to an injured tissue or via the circulation in preclinical and clinical studies of a human diseases and disorders. These bone marrow stromal cells are reported to be immunosuppressive and immunomodulatory, and the positive effects of these cells are most likely due to the repertoire of cytokines and growth factors that they secrete, which may encourage local stem/progenitor cells to initiate repair.

The Director's Innovation Awards and other new trans-NIH concepts

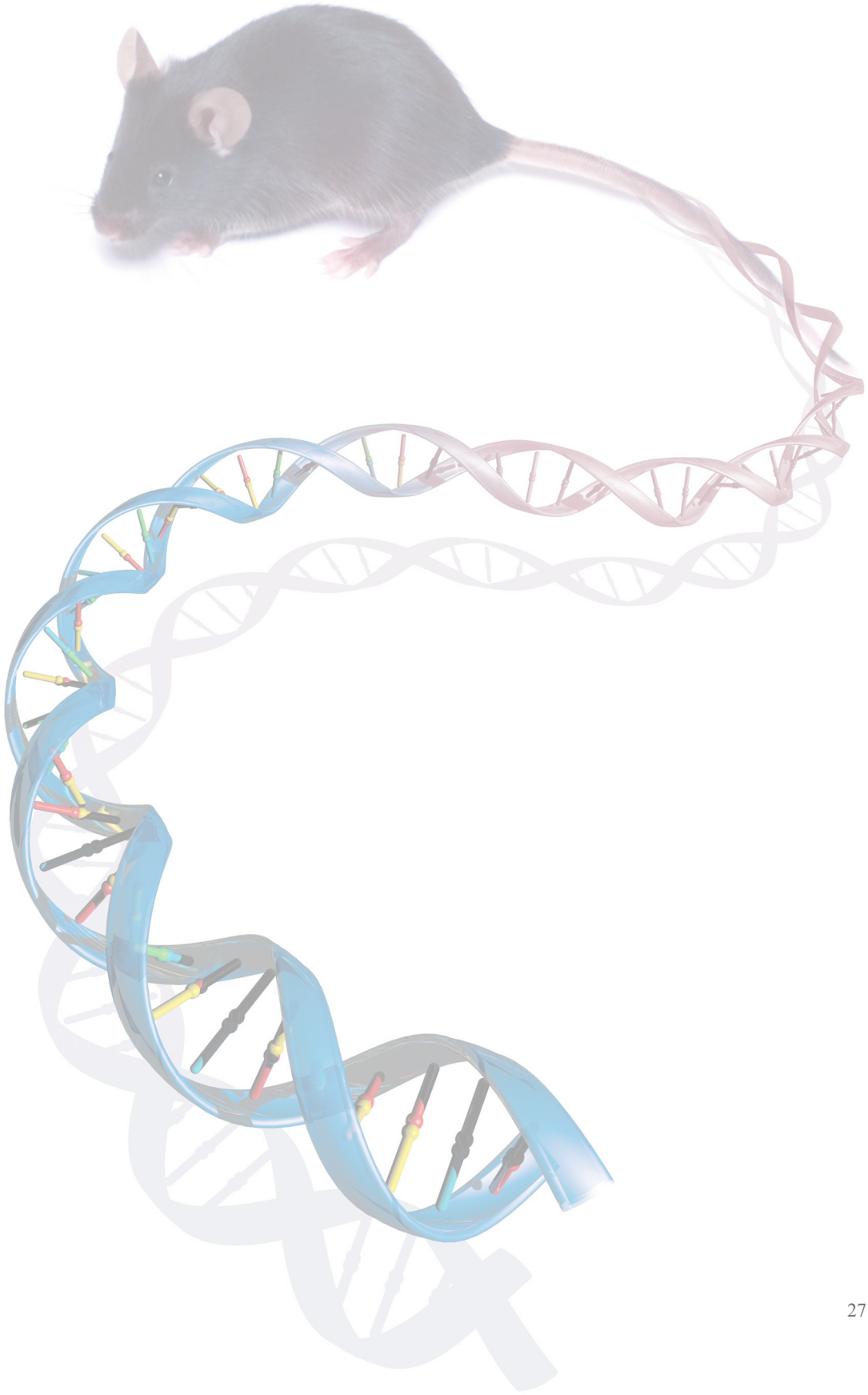
The NIH Director has provided intramural funds to stimulate innovative, high-impact research. These NIH Director's Challenge Awards seek to bring together researchers from multiple Institutes and Centers in order to take advantage of the strengths and unique as-

pects of the intramural program. Projects can include clinical, basic or population-based research. Research teams can receive two years of funding for equipment, supplies and personnel. Projects are selected by the Institute and Center scientific directors, in conjunction with the Office for Intramural Research. Each project can receive up to $250,000 per year with a total of $1.5 million awarded per year.

Management and organizational changes to stimulate trans-NIH initiatives

The organization of the Intramural Research Program contributes positively to investigator productivity and accountability. However, by emphasizing the contributions of individual researchers, it may simultaneously create a barrier to collaborative, trans-NIH efforts. The following changes might enhance interactivity among NIH researchers:

- Restructure the intramural program to facilitate collaboration and resource sharing across the campus.
- Provide substantial funding for intramural investigators by competitive program-project type mechanisms through OD offices.
- Affiliate investigators with multiple ICs, similar to extramural joint appointments.



CHAPTER 6: Training

The NIH Intramural Research Program has approximately 3,800 post-doctoral fellows, 450 graduate students, 600 post-baccalaureates and 1,000 summer students in any given year. The distinctive interdisciplinary culture of the Intramural Research Program has and continues to provide a venue to prepare scientists to take on diverse important scientific challenges and leadership roles from tenure-track positions to numerous alternative careers that are critical for the overall scientific enterprise to move forward.

The Office of Intramural Training & Education (OITE) coordinates training and mentoring and is responsible for ensuring that the biomedical research experiences of trainees in the Intramural Research Program are as rewarding as possible. There are programs for high school and college students, recent college graduates, graduate students, professional students, and postdoctoral and clinical fellows. OITE staff members recruit trainees to the various programs, both in person—by attending professional conferences and other events—and via the OITE website at www.training.nih.gov, which facilitates communication between potential trainees around the world and the NIH.

To ensure we are getting the best possible candidates, we sponsor numerous recruitment initiatives, such as the Graduate Partnerships Program recruitment event and the National Graduate Student Research Festival. We also place ads on bannered pages in Science, Nature and the New England Journal of Medicine and maintain many Web sites. We have several programs that are effective in enhancing diversity, as well. These include the NIH Academy, which is for health disparities research; the Undergraduate Scholarship Program (UGSP), which reaches students from disadvantaged backgrounds; Intramural Fellowships to Promote Diversity; and the ORWH-FAES-NIH High School Summer Program. We ensure that recruitment efforts are targeted to appropriate schools and that selection committees are committed to the initiative.

Postdoctoral opportunities include the Intramural Research Training Award (IRTA), the Cancer Research Training Award (CRTA), and the Postdoctoral Visiting Fellowship (VF), among others. Graduate programs include the NIH Oxford/Cambridge Scholars Program and similar opportunities to earn an advanced degree studying at the NIH. The Clinical Center is accredited by the Accreditation Council for Graduate Medical Education. Other successful programs include the Clinical Research Training Program (CRTP) for Medical and Dental Students, a 12-month program designed to attract the most creative, research-oriented medical and dental students to the intramural campus; and the HHMI-NIH Research Scholars Program, also known as the Cloister Program, established in 1985 to give outstanding students at U.S. medical schools the opportunity to receive research training at the NIH.

Research is the highest priority for NIH trainees. OITE aims to ensure that trainees also take part in relevant career development activities, learn all they can possibly learn from the scientific staff at the NIH and from their fellow trainees, and have an enjoyable experience. Trainees benefit from numerous courses ranging from bioinformatics and genetics to clinical pharmacology and translational research. Training activities in place to ensure that our trainees are prepared to move on to the next stage of their careers, regardless of what it might be, include OITE workshops on topics such as written communication skills, oral communication skills, grant preparation, improving English skills, and CV and resume preparation.

Other opportunities are the OITE seminar series on career opportunities and the OITE career counseling center. OITE staff members also are available to help trainees resolve any problems that might arise during their time at the NIH.

To measure the quality of mentoring provided by principal investigators to their trainees, we coordinate BSC reviews quadrennially, analyze positions to which trainees move, and rely on Scientific Directors' reviews of mentor performance through yearly performance plan review. To measure the success of our trainees while they are here, we conduct Annual Progress Reviews to determine productivity (for example, publications and presentations) and appropriate career development goals and advancement. A second measure of success is an assessment of the positions they

attain when leaving the NIH. To measure the success of our trainees once they have left the NIH, we gather information from their mentor or principal investigator. When principal investigators are reviewed by the Board of Scientific Counselors once every four years, they must report on the status of former fellows.

CHAPTER 7: Budget Formation

NIH Institutes and Centers (ICs) vary in how they formulate their intramural budgets, but they all evaluate the needs for resources within their program areas and various projects prioritizing the funds available. Items are evaluated such as capital equipment needs, animal program needs, personnel costs, and requests from Board of Scientific Counselors (BSC) evaluations of Principal Investigators; and the Scientific Director generally decides on the final level of funding for each requested budget. The intramural formulation is on a different time frame than the congressional budget formulation process.

Generally the intramural budgets are formulated during the fourth quarter of the preceding year. Since the actual budgets are not available, the budgets are estimates until the appropriation is finalized sometime during the fiscal year.

Who has final decision on budget distributions within Institutes and Centers: The IC Director has the final decision on budget distributions within the IC. The ICs are generally given a percentage cap for increasing the intramural program. If the requests are higher than the Office of Director (OD) recommended percentage, the IC budget officer will have to negotiate any requests with the OD Budget Director for reprogramming to the requested budget level. This would be very uncommon to do.

Types of unit assigned an intramural budget: Each principal investigator is generally given a Common Accounting Number (CAN) or in newer terminology, project numbers, to track the principal investigator budget during execution of the budget. For the purpose of this discussion, a CAN will be used to describe the tracking number. Other units or services or functions that are required to be tracked within the intramural program generally are given their own CAN. Service cores, special projects, capital equipment budgets, animal programs, rent costs, NIH central service costs, contracts and renovations are examples of these units, services or functions.

How budgets are executed: Execution of budgets is the process of spending and managing the annual, individual budget assigned to various units, services and functions within the intramural program. The appropriation is broken down into individual CANs assigned within the IC budget office in coordination with the intramural administrative office. Once the budgets are formulated and approved, the execution process begins within the intramural programs at the start of the new fiscal year on October 1. The majority of budgets are one-year appropriated funds and must be spent by September 30 of that fiscal year. Royalties (three-year) and Gift Funds (no-year) are exceptions to this rule in the intramural programs. Scientific Directors and Principal Administrative Officers monitor the entire intramural budget as a whole so they can address budgets that are over budget or under budget.

How principal investigators track their budgets: Generally, budget reports are generated within the intramural administrative offices or intramural budget offices and forwarded either electronically or in hard-copy to the "owner" of the CAN/budget. Reports vary by IC, but usually each principal investigator receives reports in a time frame determined by the Scientific Director and Principal Administrative Officer. The timeframes may vary according to the period within the fiscal year. The budget reports may be distributed more often in the fourth quarter so principal investigators may monitor their spending more closely. The principal investigators work with their administrative officer where problems may arise with incorrect charges or other errors shown in the budget reports. More detailed reports can be run to answer any questions that may show up on the original report and the administrative officer works with the Office of Financial Management or other relevant NIH offices to correct the errors.

How intramural programs track and administer their budgets: Most intramural programs have central funds or CANs to track non-laboratory expenses, such as renovations, NIH central services, and Clinical Center costs, in addition to monitoring the laboratory

budgets. The Principal Administrative Officer and the Scientific Director usually review these reports within the intramural programs and make management decisions based on these reports. Either an intramural budget person or an Administrative Officer assigned to run the reports distributes the reports to the Principal Administrative Officer and the Scientific Director.

How outside funds are accepted: Outside funds are accepted by intramural programs. These generally are in the form of PI-generated grant awards from outside organizations approved by the IC Director for acceptance as a conditional gift. It is an honor to be awarded these grants from outside organizations, and the grants are generally very difficult to obtain. The grant applications are reviewed within the IC before the applications can be forwarded to the organization. All administrative issues are resolved before the application is approved within the IC so when the funds become available, the PI generally is able to spend the funds according to the terms within the grant and as soon as the funds arrive and are accepted within the budget process. Other Gift Fund monies may be donated by individuals for specific research and assigned to a PI. Other funds accepted by intramural programs are incorporated in Cooperative Research and Development Agreements (CRADAs) negotiated through the Technology Transfer Offices of the ICs and the outside companies. The terms of the CRADA determines how the funds may be spent.

Central budget tracking systems: The NIH uses data from the NIH Enterprise Business System (NBS) downloaded into the Data Warehouse. Within the Data Warehouse resides a budget-tracking module for tracking the assigned budgets. Some ICs also use the Data Warehouse system for their day-to-day reporting. The ICs enter their allocations into the Data Warehouse and generate reports from the system for day-to-day management of their budgets.

How outside systems are used: Most ICs use a commercial product called Status of Funds Internet Edition (SoFIE), a web-based reporting tool developed by Netcomm, Inc. SoFIE is a reporting system using the IC-specific data downloaded from the Data Warehouse onto IC servers and used by all administrative and budget people within the IC. Other ICs may use their IC-developed reporting tool to track their funds, but these also use the Data Warehouse information.

Types of taps paid out of intramural budgets: There are various taps and central services charges assigned to each IC. From that, each IC then decides how much is to be paid out of the intramural budgets. Some of these include the costs of the Clinical Center Operating Budget, a share of the Management Fund and Service and Supply Fund taps, enterprise computer systems, and other central costs for NIH and DHHS.

How Clinical Center tap is calculated: The largest tap to the intramural budgets is the cost of operating the Clinical Center. The funds are collected based on a "school tax" formula. The formula is calculated on the percentage of each IC intramural budget over the total of all NIH intramural budgets. The funds are transferred each quarter to the Clinical Center.

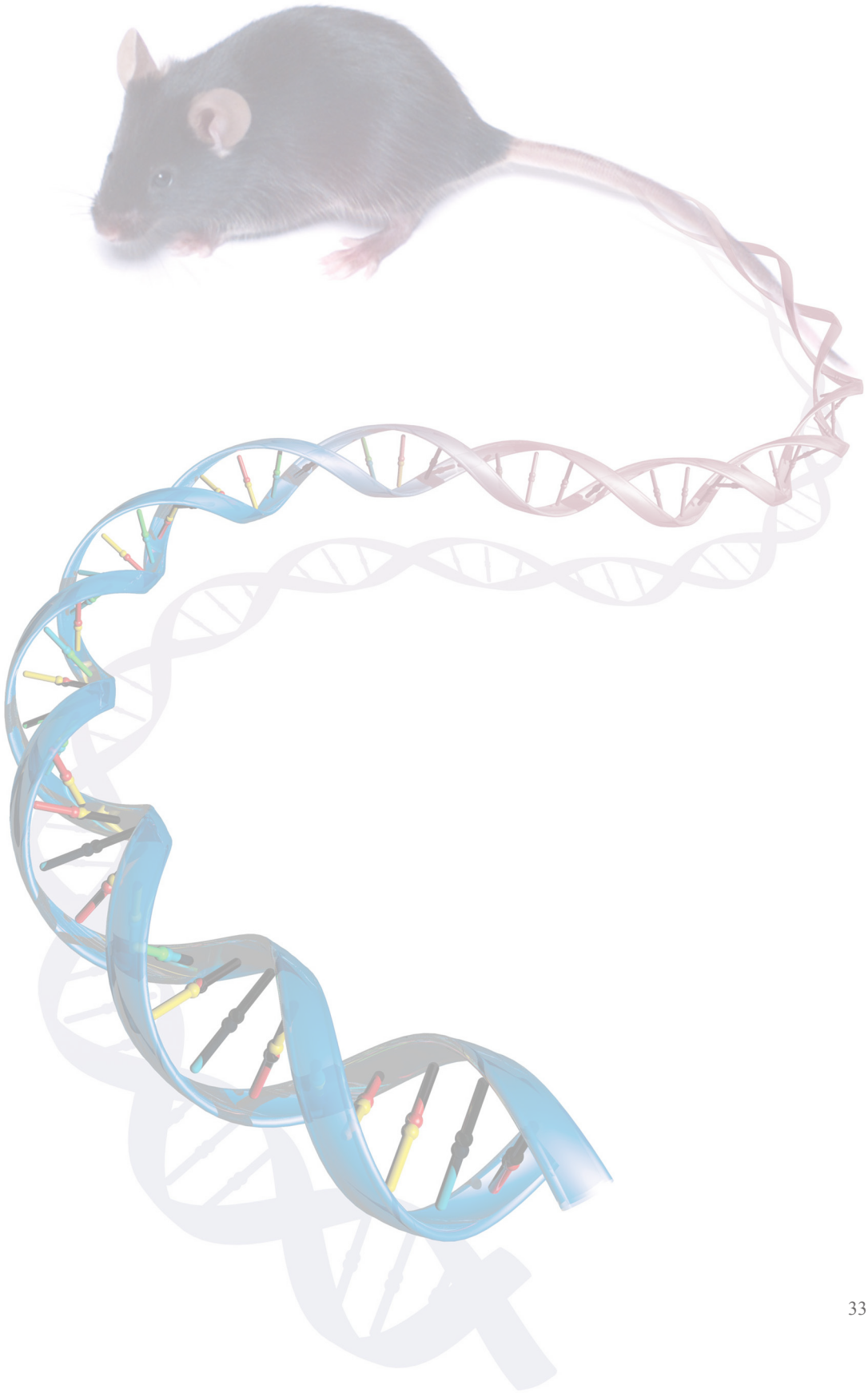
The Consolidated Services Statement: The Consolidated Services Statement (CSS) is the Office of Research Services (ORS) and Office of Research Facilities (ORF) budgeting system used to charge the ICs for rent of the IC assigned space and ORS central services. The charges are measured by unit costs based on either census data, square footage of assigned space, or usage. Each item has unit costs and is multiplied by these units of measure. It is up to the IC to assign CANs to cover the costs of services within the CSS. The IC can split the costs of various charges between organizational units. Intramural programs use their CANs to identify their portions of the charges and are billed either monthly or quarterly depending on the type of charge. The IC verifies their assigned charges and space each quarter and discrepancies are evaluated and corrected within the system once agreement has been reached between ORS/ORF and the IC. The system documents all adjustments so there is an historical accounting of both the IC charges and any changes.

How rent is calculated: Within the CSS, each IC has access to their space data. The data is summarized in a spreadsheet showing how each building and room is charged and the unit cost of each type of space. Detailed square footage charges are also included. Space is charged differently by usage. The various types of space are administrative, clinical, laboratory, storage, and leased. Each space allocation is identified as Intramural, Office of the Director or Extramural. Leased space costs are determined by terms of the lease, but the square footage is also totaled in the CSS and charged through this system.

Types of projects covered in various trans-intramural funds: Intramural programs often form core facilities to service intramural laboratories. They form agreements on how to pay for these projects if they are a trans-intramural facility. The NIH Intramural Sequencing Center is an excellent example of a trans-intramural initiative. Other examples would be a microarray core used by three ICs. The funding of these projects is documented by Memoranda of Understanding (MOUs) detailing what IC will pay for what portion of the costs and which intramural administrative office will manage and administer the program. Besides MOUs, often equipment is purchased jointly by using Direct CAN Citations giving the authority of one intramural program to cite the other intramural programs' CAN to share the cost of the equipment.

Sharing charges on various items among Institutes and Centers: Many pieces of large and costly equipment are shared among intramural laboratories within an IC. They cooperate on the acquisition and maintenance costs. They generally request shared equipment during the intramural budget formulation process and share both the requested procurement funds as well as the maintenance costs in the execution of the budgets.

How intramural programs budget centrally: The intramural programs pay for items centrally based on their needs. If the intramural program has a very large animal program, it may be paid centrally, but other intramural programs may charge their PIs directly for animal costs. Renovations are generally costly and controlled by the Scientific Director and paid out of central funds. Rent charges, Clinical Center tap, and other ORS charges are generally paid centrally. Most of these are considered indirect charges and not charged directly to PI budgets.



CHAPTER 8: Ethics

The NIH intramural researchers are held to the highest standards of scientific ethics and are required to disclose financial information and, indeed at times, to decline opportunities or awards to an extent unheard of in academia or private practice. We understand the importance of vigorous ethical standards. As government employees and as stewards of medical and behavioral research for the Nation, entrusted with generous U.S. tax dollars, we expect to be held to high standards. Certain federal ethics regulations, however, particularly in the realm of awards and service as professional society officers, are so burdensome that they have restricted the ability of the NIH to recruit and retain the most outstanding investigators. Below are a few examples of NIH ethic rules and their restrictions.

Restrictions on outside activities by NIH employees

As a result of regulations promulgated by the Department of Health and Human Services in August 2005, all NIH intramural scientists have severe restrictions on outside activities and financial holdings that might present the appearance of a conflict of interest. The NIH Ethics Advisory Committee, comprising senior NIH leadership, and the NIH Ethics Office oversee these restrictions. Restrictions include:

- No consulting for compensation with any significantly affected organization (SAO)—that is, an organization whose business could reasonably be expected to be affected by NIH activities. (This includes the biotech and pharmaceutical industries, the health care industry, universities and professional organizations. Exceptions are made for course lecturing, writing that is not directly related to the research subject of the federal employee, and continuing medical education coursework. In these cases payment can be received from a non-industry SAO as part of an outside activity.)
- No ownership of stocks in SAOs that are not publicly traded, and less than minimum amounts of stock in publicly traded stocks ($15,000) or mutual funds ($50,000).
- Restricted service on professional society boards and boards of not-for-profit organizations with no compensation allowed.
- Restricted service on science advisory board memberships.

The effect of restrictions on the ability of NIH to recruit and retain the most outstanding investigators

Many intramural programs report a loss of a senior investigator or the failure to hire an extraordinary candidate because of dissatisfaction with NIH ethics policy. These numerous examples include the resignation of some senior scientists, who were leaders in their fields, over the prohibition on consulting for companies or the restrictive nature of dealing with the private sector. Elsewhere, dozens of job offers have been declined with the stated reason being ethics concerns. From throughout the intramural program we have received reports of low morale over the inability to participate on the boards or as officers of many of professional societies, as well as low morale and a loss of researchers over the extensive process of financial disclosure for themselves and their spouses (such as the SF278 form), including the forfeit of stocks and opportunities perceived to be unrelated to their field of research. Similarly, many researchers have expressed frustration over the inability to accept money associated with numerous scientific awards, as well as the long process of seeking permission to accept an award while the awarding society waits for an answer (delineated in a following section). Another difficulty has been recruiting BSC reviewers who must fill out federal financial disclosure forms, which many find to be burdensome and intrusive.

Ways in which intramural scientists can work with industrial partners

The inability to consult with pharmaceutical companies can hamper access to state-of-the-art drug discovery and development, as historically drug companies do not publish their best work in a timely fashion, if at all. As a result of the moratorium on paid consultan-

cies with drug companies, some NIH researchers find it difficult to form collaborations that may lead to technology transfer or CRADA agreements to enhance and accelerate the basic research conducted in the Intramural Research Program toward medication development. Some researchers also believe this decreases opportunities for intramural scientists to interact with drug company scientists to share information, strategy and critical scientific information for future research. However, official-duty activities (not compensated) with industry continue as a rich source of productive collaborations, such as CRADAs. After a two-year dip in CRADAs following the implementation of the NIH conflict-of-interest rules, they are back now to historic levels.

Government regulations affecting the ability to serve on professional society boards

Holding office or membership on the board of a professional society is an important measure of success and stature in one's field. NIH scientists are restricted from holding voting positions on such boards. The reason is that some boards are associated with fiduciary matters on behalf of the particularly society. This restriction is considered by many researchers to be a deterrent to working at the NIH, as well as a hindrance to career advancement due to the lack of peer recognition and networking opportunities. Many researchers also consider the position of government liaison to be ineffective and isolating, both on the individual level and for the voice of government research in general. Some researchers need to pay their own way to board meetings to stay involved as much as possible.

Exceptions to this rule exist, but some researchers consider the process of clearance to be so cumbersome that they prefer not to try. Dissatisfaction with this ethics ruling is widespread at the NIH. A top concern is the need to switch from or decline the offer of full membership on the board of a professional society, resulting instead in non-voting federal liaison status. There have been cases of the need to decline offers to be President or Vice President of influential professional societies, resulting in professional embarrassment for the NIH researcher, as well as denial of request to serve on a board despite a letter from the society stating the board members would not have any fiduciary responsibility. Another concern is the requirement to pay one's own way to attend meetings and use one's annual leave.

How current ethics regulations affect the ability of intramural scientists to accept awards for their scientific work

The inability of intramural scientists to accept certain awards has been a source of individual embarrassment. Intramural programs have reported dozens of situations in the last few years in which their scientists have had to decline an award or wait as long as seven months for clearance. This results from the restructure of government regulations and the complexity of the review and approval process at the NIH. A prominent example was the embarrassment of an awarding organization that needed to disclose the value of its gold medal on a public government ethics form. Other serious concerns for the future of the intramural program include examples such as: a researcher needing to forfeit a $1,500 award five months after acceptance, prompting the awarding organization to state they would no longer consider NIH researchers for future awards; numerous situations in which NIH researchers performed the primary work yet needed to refuse acceptance of the award which their non-NIH colleagues could accept; and numerous situations in which the approval process took many months, to the embarrassment of the researcher and the frustration of the awarding society needing to make a decision about whether the award must go to someone else.

CHAPTER 9: Technology Transfer

The NIH has few peers when viewed in terms of numbers of biomedical patents and licenses, commercialized products resulting from this activity, or the amount of royalties collected. The NIH Intramural Research Program accounts for the majority of the royalties collected by all U.S. federal government agencies. We support $6 billion in sales annually from our licensed projects, which would place us in the Fortune 500 if we were a company.

The Program is guided by several statutory authorities to conduct technology transfer, and these include:

- 15 USC 3710 (Stevenson-Wydler Technology Innovation Act of 1980 [Public Law 96-480]) and, as amended by,
- Federal Technology Transfer Act of 1986 (FTTA) (Public Law 99-502), in part establishing the authority for Cooperative Research and Development Agreements (CRADAs) and the authority to distribute royalties to inventors and retain the remaining portion within the laboratory,
- National Technology Transfer and Advancement Act of 1995 (NTTAA) (Public Law 104-113),
- Technology Transfer Commercialization Act of 2000 (TTCA) (Public Law 106-404).

How Technology Transfer Is Organized and Encouraged

The NIH technology transfer effort is supported by Technology Development Coordinators (TDCs) in each Institute and Center and in the central NIH Office of Technology Transfer (OTT) located in the Office of Intramural Research, Office of the Director. The offices work closely to carry out NIH's goals and priorities for technology transfer.

In general, the TDCs responsibilities include, but are not limited to, providing information and guidance to Institute and Center staff on matters associated with ongoing research programs. These activities include invention reporting and the negotiation of research agreements, including CRADAs, material transfer agreements, clinical trial agreements, confidential disclosure agreements, and drug screening agreements, among others.

OTT is responsible for facilitating the transfer of NIH inventions to the commercial sector for further research and commercial development into products that benefit the public health. To this end, OTT evaluates, patents, markets, licenses, and monitors NIH inventions. Most research tools are not patented but licensed to industry for internal use or sale as reagents, whereas technologies are more likely to be patented if they require commercial development to benefit the public, such as drugs, vaccines, diagnostics, and devices. The OTT Royalties Administration Unit and the NIH Office of Financial Management work closely to manage NIH royalties. Additionally, OTT has the lead responsibility for NIH intramural and extramural technology transfer policy matters. With respect to extramural recipients of funding, OTT evaluates and approves requests for invention waivers of title to inventors and third parties as well as waiver of the U.S. manufacturing requirement for licensed inventions.

Mechanisms for Partnering with Industry

- Material Transfer Agreements
- Non-disclosure Agreements
- Drug Screening Agreements
- Clinical Trial Agreements
- Biological Material Licenses and Patent Licenses
- CRADAs

NIH scientists collaborate informally in the exchange of scientific information with scientific colleagues outside NIH including those in industry. Some mechanisms may be used with a variety of outside collaborators, such as Clinical Trial Agreements, but others such as CRADAs and licenses are used primarily with industry. CRADAs establish research collaborations between the NIH and industry in which personnel, equipment and materials may be shared. In addition, CRADAs allow NIH to offer the industry collaborator the option to take an exclusive or non-exclusive license to inventions made under the joint research project and permit NIH to receive funding for the project by the industry collaborator. NIH cannot provide funding to industry under any of these mechanisms.

Number of FDA-Approved Products: There are 25 FDA-approved products that include technologies li-

censed from the NIH: 6 vaccines, 14 therapeutics, 1 device, and 4 diagnostics. There are two USDA-approved veterinary products, both of which are vaccines.

Number of Invention Disclosures Since 2003: NIH scientists reported a total of 2,379 invention disclosures from FY 2003 through FY 2008. In FY 2008 alone, there were a total of 402 invention disclosures.

Total U.S. Patent Applications Filed Since 2003: The NIH had a total of 1,788 U.S. Patent Applications filed from FY 2003 through FY 2008 and a total of 343 U.S. Patent Applications in FY 2008 alone. The total portfolio of pending and issued U.S. patents managed by OTT is about 3,500. There are often international patent application and equivalents filed in various foreign countries for these inventions.

U.S. Patents Issued Since 2003: The NIH had a total of 572 U.S. patents issued from FY 2003 through FY 2008. There were a total of 88 U.S. patents issued in FY 2008 alone.

FY	NIH Royalty	Inventor Awards	Net Remaining to ICs
FY 2003	$ 46,335,818	$ 8,802,778	$ 37,533,039
FY 2004	$ 52,321,229	$ 8,891,394	$ 43,429,835
FY 2005	$ 95,844,231	$ 10,161,976	$ 85,682,255
FY 2006	$ 81,795,031	$ 9,773,072	$ 72,021,959
FY 2007	$ 82,410,716	$ 10,040,452	$ 72,370,263
FY 2008	$ 91,182,999	$ 9,763,387	$ 81,419,612
Total	$ 449, 890,024	$ 57, 433,059	$ 392,456,963

NIH Royalties since 2003: *Starting in FY07, the NIH royalty amount reported does not include the royalties administered by OTT that were distributed to other institutions under Inter-Institutional Agreements. OTT also administers royalties for the FDA that are not included above. For example, in FY08 the total amount managed by OTT was $97,241,944; however, from that total $782,047 was distributed to FDA, $5,276,897 to other institutions, and $91,182,999 to NIH inventors and ICs.*

Fully Executed Licenses Since 2003: NIH entered into a total of 1,575 licenses from FY 2003 through FY 2008. There were a total of 259 licenses in FY 2008 alone.

How Royalty Income Is Distributed Between Inventors and the NIH: Inventors under a given license receive annually the first $2,000 received by the NIH; 15 percent of royalties above $2,000 and up to $50,000; and 25 percent of royalties in excess of the first $50,000. No inventor can receive more than $150,000 in royalty payments for a calendar year. Any remaining royalties are distributed to the appropriate NIH Institute or Center, which uses the income to pay technology transfer expenses and support its research and training programs. Inventors continue to receive royalty income after they leave NIH.

From FY2003 to FY2008, 419 CRADAs have been executed. This includes 44 in FY2007 and 72 in FY2008.

MTAs Executed by NIH in FY07: The NIH executed over 3,400 Material Transfer Agreements in FY2007. Many are delegated to the principal investigator level and are not recorded centrally. The following table summarizes by Institute or Center those MTAs that were recorded centrally.

Institute/Center	Number of MTAs
CC	17
CIT	0
NCCAM	5
NCI	1,002
NHGRI	101
NHLBI	294
NIA	97
NIAAA	61
NIAID	309
NIAID-VRC	75
NICHD	144
NIBIB	0
NIDA	28
NIDCD	35
NIDCR	242
NIDDK	413
NIEHS	270
NIMH	105
NINDS	103

Appendix A: Personnel and Recruitment

The Intramural Research Program maintains numerous professional designations and personnel mechanisms used by NIH Institutes and Centers. Designations include: Senior Investigator, an employee who has been granted tenure by the Deputy Director for Intramural Research after review and recommendation by the NIH Central Tenure Committee or the Senior Biomedical Research Service Policy Board; Investigator, an employee who is a tenure-track scientist on a time-limited appointment, selected by a competitive national search; Senior Scientist/Senior Clinician, a scientist in a time-limited, renewable appointment, such as a manager of a large Institute or Center program or department with responsibility for substantial resources (category 1) or a senior scientist or clinician spending a limited period of time at the NIH (category 2); Assistant Clinical Investigator, an employee on a time-limited appointment selected by a competitive national search and whose abilities and focus in research make them candidates for tenure-track positions at the NIH; Staff Scientist/Staff Clinician, an employee appointed to a time-limited, renewable position, usually someone with a doctoral degree selected by the Institute or Center to support the long-term research of a Senior Investigator, or a physician or dentist who provides critical patient care services; Research Fellow/Clinical Fellow, a scientist with a doctoral degree providing service relevant to an Institute's or Center's program needs or a doctoral-level health professional with interest in biomedical research relevant to NIH program needs, employed on a time-limited appointment renewable subject to the five-year/eight-year rule; Postdoctoral Fellow, a trainee who participates in laboratory-based or population-based biomedical research for the purpose of obtaining advanced training under the direction of a senior member of the scientific staff; Senior Research Assistant/Research Assistant, an employee appointed under the General Schedule serving in a scientific or technical support capacity at GS-12 or GS-13; Adjunct Investigator, a scientist who works full-time or part-time in an intramural setting, whose primary career appointment is elsewhere (e.g., medical school, university faculty, or at NIH outside of an Institute's or Center's intramural program); and Student in high school through graduate, medical or dental school.

The following table summarizes the distribution by gender and minority status of scientists in various categories at the NIH. The under-representation of women and minority scientists is similar to that at academic research and medical centers, but efforts continue through improved recruitment and retention practices to make progress in creating a more diverse scientific staff.

The subsequent tables provide an overview of personnel and recruitment efforts. Also note that from 1974 to 2007, there have been 128 NIH Scientist Emeritus appointments made. Of these, 48 are still at the NIH.

Number and Categories of Scientific Employees (FTEs) in the Intramural Program

IPD	Total	Female	Male	Af.Am.	As./PI	Hisp.	Nat.Am.	White
SI	901	166	735	9	106	22	1	763
I	237	71	166	5	61	11	0	160
Sr.Cl. Cat.1	14	4	10	0	2	1	0	11
Sr.Sc. Cat.1	41	7	34	1	7	0	0	33
St.Cl.	258	115	143	5	26	4	0	223
St.Sc.	1197	438	759	10	357	31	2	797
CF/SCF	280	122	158	17	85	6	0	172
RF/SRF	710	294	416	13	410	9	2	276

Subdivided by Intramural Professional Designation (IPD): Senior Investigator (SI), Investigator (I), Senior Clinician Cat.1 (Sr.Cl.), Senior Scientist Cat. 1 (Sr.Sc.), Staff Scientist (St.Sc.), Staff Clinician (St.Cl.), Clinical Fellows/Sr.Clinical Fellow (CF/SCF), and Research Fellow/Sr.Res.Fellow (RF/SRF). Principal investigators (first four rows) are intramural scientists who have been given resources to conduct their investigator-initiated research.

Investigators and Assistant Clinical Investigators are recruited through national and international searches. The number of searches varies year to year, but the trend in recent years has been a decline. There also has been a decline in the number of PIs at the NIH over the last 10 years. Particularly worrisome is the decline in the number of new tenured clinical investigators, a national phenomenon reflecting the dwindling pool of young physician scientists interested in translational research. This information is captured in the tables below, culminating with a table showing the PI turnover trend.

Number of National and International Searches for Investigators

Year	Number of Searches
2003	63
2004	47
2005	58
2006	55
2007	53

Number Hired in the Last Five Years

Year	Number Hired
2003	41 (8 SI, 33 I)
2004	35 (3 SI, 32 I)
2005	22 (3 SI, 19 I)
2006	45 (13 SI, 32 I)
2007	35 (7 SI, 28 I)

Number Tenured in the Last Five Years

Year	Total Tenured	From Outside	From the Tenure Track
2003	28	8	20
2004	26	3	23
2005	31	3	28
2006	46	15	31
2007	34	7	27

Number of Tenured Clinical Investigators

Year	Total Clinical Tenured	From Outside	From the TT
2003	8 (29% of total tenured)	2	6
2004	8 (31%)	0	8
2005	6 (19%)	1	5
2006	12 (26%)	4	8
2007	3 (9%)	1	2

Source of Researchers Hired to Tenure Track

Year	Total Tenure Track Hired	Inside (from same Lab or IC)	Outside (from another IC or from outside NIH)
2003	33	14	19 (58%)
2004	32	8	24 (75%)
2005	19	5	14 (74%)
2006	32	11	21 (66%)
2007	28	12	16 (57%)

Average Length of the Tenure Track

Years, Total Average	Male	Female
5.5	5.4	6

There does appear to be a gender difference. The overall average is skewed because there are many more men than women investigators (see first table in this section).

Tenured Investigators Decade by Decade

Time Period	Still Senior Investigators
1950 – 1955	0
1956 – 1960	3
1961 – 1965	2
1966 – 1970	10
1971 – 1975	50
1976 – 1980	78
1981 – 1985	129
1986 – 1990	156
1991 – 1995	103
1996 – 2000	139
2001 – 2005	148

NIH Intramural Research Program (IRP) PI Turnover Trends

Year	Total PIs	Net change in total PI during this period	Replaced by New PI hires during same period	No longer PI during same period	Calculated PI turnover/yr during same period
1990	~1584	**	**	**	**
1995	1301	-283 [1990-1995]	-160	-443	-89/yr
2000	1206	-95 [1995-2000]	-353	-448	-90/yr
2002	1263	+57 [2000-2002]	-112	-55	-28/yr
2007	1138	-125 [2002-2007]	-178	-303	-61/yr

The table above demonstrates that there is substantial turnover of tenured and tenure-track Principal Investigators at the NIH. For example, in the past five years, despite a net loss of 303 PIs from retirement resulting from normal attrition or from stringent reviews and budget restrictions, 178 new PIs were hired.

The total loss captured in column 5 is 1,249 PIs from 1990 to 2007. Note: 1990 includes about 300 tenure-track-equivalent; no formal NIH-wide tenure track until 1994. "Total PIs" includes new PI hires during that period. The period from 1994 to 2000 saw implementation of recommendations for the IRP of the "Report of the External Advisory Committee of the Director's Advisory Committee" of November 17, 1994. The period from 2000 to 2002 represents the peak of the NIH Intramural Research Program budget. The period from 2003 to 2007 represents the era of flat budgets.

Number of Scientists Recruited or Appointed Each Year

<u>Recruited</u>

Senior Investigators	approximately 7 per year
Tenure-Track Investigators	approximately 29 per year

<u>Appointed</u>

Staff Scientists	approximately 300 per year
Staff Clinicians	approximately 100 per year

<u>Senior Leadership</u>

Scientific Directors	1-2/year
Clinical Directors	1-2/year
Lab/Branch Chiefs	27/year*

* There were 244 in 2004 and 214 in 2007 with 81 new Lab/Branch Chiefs appointed in this period.

Approximately 50 percent of Scientific Directors and Clinical Directors come from outside of NIH. Of the 81 new lab chiefs appointed between 2004 and 2007, 21 were recruited from outside the NIH; the average number of total appointments is 27 per year.

To ensure the best possible candidates, the Intramural Research Program places ads and conducts searches nationally. A search committee is thoughtfully formed to include researchers from various important and appropriate scientific disciplines. And the DDIR reviews and approves searches and those selected for the position. To enhance the diversity of the applicant pool, an Assistant Director in the Office of Intramural Research works with each search committee and provides a list of addresses and Web sites to send or post recruitment ads in order to target underrepresented groups.

The characteristic of recruits is important for the vitality and innovation of the Intramural Research Program, so search committees are charged with identifying well-trained and innovative investigators interested in high-risk, high-impact research. These decisions on recruitment mesh with the NIH vision, for searches focus on the Institute's or Center's needs for future scientific directions. Each Institute and Center strives to maintain a balanced portfolio of basic, translational and clinical research.

Appendix B: Space

Space Assigned for Laboratory Research, Clinical Research, Animal Facilities and Administration

The Intramural Research Program has about 5.1 million net assignable square feet (nasf) of leased and owned space (laboratory, animal, clinical and administrative) in leased and owned research buildings. This includes NIH's leased and owned research facilities in the Bethesda-Washington area; in Frederick and Baltimore, Md.; Rocky Mountain Laboratories in Hamilton, Mont., Research Triangle Park, N.C.; Phoenix, Ariz.; and Detroit, Mich.

In addition there is approximately 400,000 nasf of space supporting the Intramural Research Program, including about 250,000 nasf in administrative buildings (offices for administration, bioinformatics and research staff) and about 190,000 nasf in NIH research buildings for conferences, cafeterias and storage.

Intramural Research Program space is summarized in the table below.

How Space Assignments Have Changed Since 1990

Since 1990, most of the changes in the Intramural Research Program space have been in the local Bethesda area. Total Intramural Research Program space in research facilities has gone from about 2 million nasf to about 3.3 million nasf during this period. The biggest change has been in the amount of leased research space, which has quintupled (from about 64,000 to 326,000 nasf).

Space per Principal Investigator has not been tracked and there is no standard across the Institutes and Centers. Nevertheless, it does not seem to have changed dramatically. There is, however, a trend toward multiple Principal Investigators being within a single architectural "neighborhood" with a lab, lab support and lab office modules, so as to encourage greater collaboration between groups and among Institutes and Centers.

Percentage of Research Space Not in Need of Renovation

Based on the criteria discussed below, about 40 percent of the total nasf of NIH research space can support up-to-date research. About 60 percent of NIH's research portfolio may require major systems renovations to be able to support up-to-date research.

The important evaluation criterion is whether a facility has sufficiently modern utility systems to support renovations needed for up-to-date science. NIH constantly renovates the layout of specific labs, if the type of science changes and requires renovation. NIH builds its government-owned research facilities with utility systems designed to last up to 30 years. Therefore, research facilities that were built or totally renovated with new systems in 1990 or after are likely capable of supporting up-to-date research. That rule of thumb does

Bldg. and Space Type	Owned Facilities (nasf x 1,000)	Leased Facilities (nasf x 1,000)	Sub Total: IRP Space by Type (nasf x 1,000)
Research Bldgs: Lab, Lab Support, Lab Office, and Animal	4,100	1,000	5,100
Admin Bldg: Program Offices	110	140	250
Research Bldgs: Support Space	190	<1	190
Sub Totals: Owned vs. Leased	4,400	1,140	
Grand Total Intramural Research Program Space			5,540

not, however, consider partial renovations or additions or facilities with weaker initial systems or demanding new scientific requirements. Therefore, the true ability of a given facility to support modern research must be analyzed on a building-by-building basis considering a specific scientific requirement.

Examples of buildings built or totally renovated in 1990 or after capable of supporting up-to-date research include buildings 5, 35, 37, 40, 49 and 50 on the Bethesda campus; Building 104 at Poolesville; Building 25 at Rocky Mountain Laboratories; and Building 321 at Frederick. Examples of facilities built before 1990 that likely need major renovation before they can support up-to-date research include buildings 7, 8 and 10 on the Bethesda campus.

Plans for Developing New Space

The NIH plans to renovate or replace the 60 percent of the NIH research space portfolio that cannot support up-to-date research. The central focus for those plans is the renovation of Building 10 and the Ambulatory Care Research Facility (ACRF) over the next 20 years to adequately support translational research and clinical services, which are core to NIH's research mission. These plans will provide utilities to about 300,000 nasf of vacant space in Buildings 10 and 3, converting the currently unusable space into modern research and support facilities for the Intramural Research Program.

In addition, the NIH plans to build the second phase of the Porter Neuroscience Research Center and to replace the outdated Building 14/28 complex with a new Center for the Biology of Diseases, which will include a modern vivarium. The NIH also has plans to renovate other out-dated facilities on the Bethesda, Frederick, Baltimore and Rocky Mountain campuses.

At present, the NIH does not plan to lease more research space because of the higher costs and greater difficulties associated with constructing leased labs. Instead the NIH plans to move the Bethesda area leased facilities back to the Bethesda campus as part of the renovations described above as the leases expire. If new research leases are needed in the interim, acquisitions will be made with plans to relocate them eventually back to NIH campuses. In this planning, NIH intends to renovate and occupy the current FDA facilities on the Bethesda campus, when the FDA Center for Biologics Evaluation and Research moves to White Oak. That will provide about 145,000 nasf of additional research space for the Intramural Research Program.

If funding allows, these projects could be accomplished in parallel. Currently, however, NIH only has sufficient building and facilities funds to barely maintain the existing facilities. Multiple fold increase in building and facilities funds will be needed to support the construction efforts described above. The above plans provide little new, expansion space for the Intramural Research Program. That will require additional funds to build new facilities.

Relative Cost of Campus and Off-Campus Space

In the Bethesda area, leased research space is almost twice the cost of government-owned research space. Rent on the Bethesda campus is about $39 per rentable square foot for research space. Rent for leased research space in the Bethesda area is about $65 per rentable square foot. Additionally, off-campus research requires more space per person, because there is less opportunity for sharing equipment and services in scattered leased facilities than on the campus.

Appendix C: Research Highlights

The following research highlights from the past five years, sorted by disease category, complements the 11 top research advances listed in Chapter 3.

CANCER THERAPIES

Adoptive cell transfer therapy: halting the spread of cancer — Cancers can spread from one part of the body to another, a process called metastatis. The NCI CCR has developed a potent and effective treatment for patients with metastatic melanoma, a highly fatal cancer of the pigment-forming cells of the skin. The treatment is called adoptive cell transfer therapy, or ACT. The treatment involves (1) identifying cancer-killing T cells produced by a patient in response to cancer; (2) removing a sample and creating tumor-infiltrating lymphocytes from these in the lab; (3) selecting the most aggressive among these and multiplying them; and (4) placing them back in the patient's body to fight the cancer. Studies have shown the therapy to be successful in over 40 percent of patients with solid tumors resistant to other treatments. New advances enable effective treatment of metastatic melanoma by vaccinating patients with antigens from their cancers. (NCI CCR)

Kidney cancer genes — Genes and genetic mutations often play a primary role in the development of cancers. The NCI CCR has discovered two important kidney cancer genes, for von Hippel-Lindau (VHL) tumors and hereditary papillary renal cell carcinoma (HPRC). Their discovery is leading to ways to suppress cancer gene expression in general and to develop strategies for early detection, prevention and treatment. (NCI CCR)

Kepivance: a drug to reduce cancer pain — In most cancer treatment, about 10 percent of the patients develop mucositis, a painful inflammation and ulceration of mucous membranes lining the digestive tract, caused by chemotherapy or radiotherapy. In 1989, NIH scientists discovered human keratinocyte growth factor (KGF), where "keratinocyte" refers to the major cell type of the intestinal lining and other types of epidermis. NIH then teamed up with Amgen to create a drug, which the FDA approved in 2004 and which carries the commercial name Kepivance, the first drug to treat oral mucositis. Kepivance helps thousands of cancer patients each year, enabling them to better tolerate their treatment. (NCI CCR)

DNA repair, transcription and epigenetic regulation — Recombination of immunoglobulin (Ig) genes is essential to the maturation of antibody molecules during the immune response to invading microbes. The mechanisms driving Ig gene recombination, however, are also known to mutagenize the B cell genome and induce B cell tumors, a family of common blood cancers. NIAMS researchers and their NIH colleagues investigating the molecular basis of efficient recombination and DNA repair discovered a new enzymatic pathway that remodels chromatin surrounding DNA breaks. The discovery made use of state-of-the-art confocal microscopy techniques and kinetic modeling to monitor the chromatin changes occurring at sites of DNA damage. By visualizing the dynamics of RNA polymerases and repair enzymes labeled with fluorescent proteins, the studies revealed the DNA repair enzymes ATM, MRN, and MDC1 shut down gene expression near sites of DNA double-strand breaks to ensure efficient DNA repair. These findings explain in part why ATM-deficient patients are highly susceptible to the development of B and T cell malignancies. Related work has uncovered another repair enzyme, called AID, which directly defines the incidence of B cell tumor development. (NIAMS)

BRAIN AND NEUROLOGICAL DISORDERS

State of the Art in MRI of the Human Brain — The NIH In Vivo NMR Center has a longstanding record for innovative developments in MRI. These include pushing to high-field MRI, the development of a number of important novel contrast mechanisms, and the Imaging Sciences Program in the Clinical Center. In addition to basic research in MRI, the NMR Center has provided facilities for human and animal imaging, as well as MRI signal processing. There are over 60 human protocols and over 90 animal protocols from PIs from across the NIH IRP that make use of these

imaging facilities. Regarding high-field MRI, the 7-Tesla MRI was prototyped at the NIH in collaboration with three industrial partners. The project has led to a great increase in resolution and contrast available for imaging the human brain. Resolution has improved by 20-50 fold over MRI that is routinely available in the clinic. Furthermore, detailed anatomy of white and gray matter in the brain can now be routinely imaged at very high resolution. This work continues the long standing tradition in the NIH In Vivo NMR Center of combining developments in hardware with developments in MRI techniques and with developments in image processing to make significant gains in our ability to image the human body non-invasively. (NHLBI, NIMH, NINDS, NICHD, CC)

Attention Deficit Hyperactivity Disorder — NIMH imaging resources have enabled researchers in the NIMH Child Psychiatry Branch to create an unprecedented database of structural brain MRI scans collected longitudinally, which can be used to measure normal development as well as brain structural signatures of mental disorders, such as Attention Deficit Hyperactivity Disorder (ADHD). This approach has been tremendously rewarding, resulting in major new findings in normal development as well as in pediatric disorders. For example, it had been unclear whether ADHD results from a delay in brain maturation or whether it represents a complete deviation from the template of typical development. NIMH researchers demonstrated that it may be the former, a three-year delay in attaining peak cortical thickness throughout most of the cerebrum. (NIMH)

Schizophrenia — NIMH researchers have a longstanding interest in the etiology and pathophysiology of schizophrenia. With the advent of the human genome project and the rich neuroimaging resources of the intramural program, they have been instrumental in developing a new field of "imaging genetics." Beginning with landmark papers showing roles of polymorphisms in *COMT* and *BDNF* genes in brain function in healthy individuals as well as those with schizophrenia, they have demonstrated the functional roles of the now numerous genetic association signals for schizophrenia. Several NIMH labs have since built a powerful alliance to understand the molecular basis of executive function in humans that provides powerful leads to the understanding of schizophrenia. (NIMH)

Williams-Beuren syndrome — Researchers in the NIMH Clinical Brain Disorders Branch have made important discoveries concerning Williams-Beuren syndrome (WBS), a rare disorder caused by a deletion of many genes on chromosome 7q in which patients develop unusual outgoing social and advanced language skills coupled with mental retardation. Using functional neuroimaging, NIMH researchers found reduced amygdala activation in individuals with WBS for threatening faces but increased activation for threatening scenes. Activation and interactions of prefrontal regions linked to amygdala, especially orbitofrontal cortex, were abnormal, suggesting a genetically controlled neural circuitry for regulating human social behavior. The work demonstrates how research on a rare disease can have broad implications. (NIMH)

Diabetes and cognitive disability — Diabetes is rapidly becoming pandemic in the United States. Among many symptoms is the disease's adverse effect on cognitive health. NIA researchers have discovered how increased levels of a stress hormone in diabetic mice produced by the adrenal gland disrupt the healthy functioning of the hippocampus, the region of the brain responsible for learning and short-term memory. When levels of the adrenal glucocorticoid hormone corticosterone (known as cortisol in humans) are returned to normal, the hippocampus recovers its ability to generate new cells and regains the plasticity needed to compensate for injury and disease and adjust to change. The research suggests the possibility of novel approaches to prevent and treat cognitive impairment by maintaining normal levels of glucocorticoid. (NIA)

COMMUNICABLE DISEASES AND VACCINES

Vaccine development — The NIAID Laboratory of Infectious Diseases (LID) has a long history of successful vaccine development, resulting in the licensed hepatitis A vaccine, research and development of influenza-attenuation techniques that contributed to the development of FluMist, and development of

the first rotavirus vaccine. The Laboratory embodies translational research, from theory to cure, that is core to the NIH mission. The structure and stable funding of the NIH Intramural Research Program has been crucial because of the long timeframe needed for working with difficult pathogens, such as respiratory syncytial virus (RSV) and other pediatric respiratory viruses, rotavirus, hepatitis viruses, and dengue. NIH provides the flexibility, too, to arrange for vaccine manufacture and to conduct nonhuman primate and clinical studies in an environment in which multiple pathogens can be studied by multiple investigators with a sharing of expertise, facilities and lessons learned. Current LID projects include development of a candidate live-attenuated RSV vaccine that has proven to be safe in infants exposed to wild-type RSV. The LID conducts ongoing and world-class research on vaccine development for West Nile, pandemic influenza, Ebola, SARS, and tick-borne encephalitis viruses using reverse genetic systems, some of which, because of the danger of the viruses, can only be performed in a secure, government setting. (NAID)

International vaccine work — Viruses know no borders. The imprimatur and resources of the U.S. government have helped the NIAID Laboratory of Infectious Diseases forge important relationships and collaborations with multiple partners to further global public health. One example is the acquisition of the original virus (an important milestone) used in the hepatitis E vaccine, resulting from close collaborations of the LID with both the U.S. and the Pakistani militaries. Development of the vaccine involved interactions between LID and industry through the CRADA mechanism, and preclinical and clinical testing involved interactions of the LID and U.S. military, respectively, with industry. The LID's ongoing efforts to coordinate and participate in the activities of licensees from Brazil, China and India of the NIH rotavirus vaccine provide another example. This assistance from LID has encouraged the Gates Foundation to provide funding to selected licensees, an acknowledgment of both the fruits of U.S. government research and the value of IRP scientists' continued involvement with the project. (NIAID)

Stopping HIV from growing into a killer — HIV-1 protease is an enzyme needed by the AIDS virus to mature. The enzyme works by cleaving polyproteins at specific places to create the proteins that make HIV infectious. Protease inhibitors are a major class of drugs to fight infections caused by viruses, such as HIV or the hepatitis viruses. But HIV has a high mutation rate, changing its face and making it unrecognizable to inhibitors. HIV drug cocktails try to minimize this problem, but there are limitations. NIDDK researchers have made a breakthrough in HIV research by visualizing the earliest events in the cleaving process. Using paramagnetic relaxation enhancement NMR, a technique perfected at NIH, they revealed the presence of short-lived dimeric encounter complexes in which the N-terminal extension of the polyprotein makes transient intra- and inter-subunit contacts with the substrate binding site, thereby allowing N-terminal cleavage to occur when the correct dimer orientation is sampled within the encounter complex ensemble. This insight may lead to methods to better inhibit HIV-1 protease. This is one of multiple contributions that have led to a better understanding of HIV drug interventions, supported in part by the NIH Intramural AIDS Targeted Antiviral Program. (NIDDK, NCI, NIAID)

HIV/AIDS vaccine development — Through the focused approach of basic and translational science, the Vaccine Research Center has accelerated progress in the science and practical regulation of AIDS vaccine development. One element is the rapid transition of novel vaccine products into clinical trials. The VRC was able to initiate its first clinical trial, a Phase I study of an HIV/AIDS vaccine, less than one year after program initiation. Furthermore, NIH intramural leadership developed and coordinated complex international collaborations (NIAID HIV Vaccine Trials Network, the US Military HIV Research Program, and the International AIDS Vaccine Initiative) necessary for the conduct of the ongoing Phase II vaccine trials and planned Phase IIb efficacy studies. (NIAID)

Tuberculosis — Tuberculosis is on the rise and, more disturbing, some strains are resistant to the current batch of drugs. The NIAID Tuberculosis Research Section helped develop two (SQ-109 and PA-824) of the seven novel compounds against TB currently in clinical development. One particularly strong aspect of this Section is its emphasis on simultaneously carrying out studies in humans and in animal models, which would

be difficult to perform outside of NIH. The Section is known internationally, with collaborators in South Korea at the Masan National Tuberculosis Hospital conducting a large study on patients with "extensively drug resistant" (XDR) tuberculosis. (NIAID)

Malaria — NIAID researchers studying the human malaria parasites (*Plasmodium falciparum*) have discovered the chloroquine resistance gene, a 15-year project involving genetic cross-analysis that will lead to better malaria drugs. From this research, the NIAID Laboratory of Malaria and Vector Research (LMVR) also identified the *var* gene family underlying *P. falciparum* antigenic variation and, as of 2008, a new pathway for parasite invasion of human red blood cells. Maintaining the full *P. falciparum* parasite life cycle in a laboratory is difficult and is done at only a few labs in the world. Yet university labs do not possess the expertise under one roof to accomplish such a comprehensive project. LMVR includes a full insectary in which mosquitoes infected with malaria parasites are safely managed and also has the resource of NIAID-supported chimpanzee and monkey facilities for research. (NIAID)

Pioneering research from Montana on prions — The small but highly productive group of NIAID prion researchers at the Rocky Mountain Laboratories (RML) in Montana are among the most cited in the world for this field. Their pioneering research has led to discoveries that ran contrary to the dogma of the field, such as the nature of prions, their molecular mechanism of propagation, the explanation of strains, the estimation of interspecies transmission barriers, and the development of treatments for TSE, transmissible spongiform encephalopathies. This has required consistent funding that would have otherwise been denied outside of the intramural program because of its high-risk and against-the-tide nature. Specifically, the group has published the first assessments of the relative transmissibilities of BSE (mad cow disease), chronic wasting disease and scrapie to humans and other species; identified the first known inhibitor of PrPSc formation (the disease-associated form of the prion protein); and in the past several years has identified promising classes of anti-prion compounds, including some that have demonstrable efficacy late in the disease-incubation period. (NIAID)

Knowing friends and enemies: structural studies on energy-dependent proteases, prions and viruses — NIH researchers have performed a series of structural studies on prions, viruses and proteases, molecules that break down proteins. Highlights include a thorough mapping of the structure and modes of interactions for the Clp family of chaperone-assisted proteases; a model of how prions turn deadly in their misfolding, involving the formation of amyloid backbone; determining the structures and antigenic properties of capsids of hepatitis B virus; investigation of the structural variability of the archetypal alpha-retrovirus, the Rous Sarcoma Virus; and the first analysis of the three-dimensional structure of a pleiomorphic virus by cryo-electron tomography, revealing novel features of the envelope of herpes simplex virus and its tegument, including the presence of actin filaments, presumably appropriated from the host cell. In addition, advanced imaging techniques has allowed researchers to visualize how a key part of HIV changes shape after binding to immune system cells or to infection-fighting antibodies. NIH researchers also found five different structural types of influenza virus, with some of them completely lacking a matrix protein layer which had previously been thought to be essential for virus formation. (NIAMS, NCI, NIAID)

Progress on Crohn's and other inflammatory digestive diseases — The NIH intramural program enables the transition from thought to expression, from theory to therapy. In the mid-1990s NIAID researchers demonstrated how antibodies to interleukin-12, a cell signaling molecule, abrogate colitis in mice, suggesting the potential utility of anti-IL-12 antibodies for treatment of Crohn's disease. In fewer than 10 years, they led a collaborative, 15-site clinical study that demonstrated for the first time that antibody directed against IL-12 can provide significant and lasting clinical improvement of Crohn's disease. The NIH intramural program provided the infrastructure of funding, the CRADA to work with industry, and a clinical center to test the product. (NIAID)

Parasitic Diseases: Leishmaniasis and Schistosomiasis — Cutaneous leishmaniasis, a disease characterized by painful skin ulcers and affecting millions of people worldwide, occurs when the parasite *Leishmania major*, or a related species, is transmitted

by the bite of an infected sand fly. NIAID scientists have discovered the parasite does its damage by not only evading but also by exploiting the body's wound-healing response to sand fly bites, which changes the textbook picture of the lifecycle of the leishmaniasis parasite and identifies the inflammatory cell known as the neutrophil as the predominant cell involved during the initiation of infection. The work employed advanced microscopy techniques, which allowed real-time imaging of the skin of living mice infected with *Leishmania major*. Schistosomiasis, from a parasitic flatworm causing severe diarrhea, affects 20 million worldwide and kills nearly 300,000 people annual. NIH's Chemical Genomics Center (NCGC) has helped to identify chemical compounds known as oxadiazoles, which can inhibit an enzyme vital to survival of this *Schistosoma* flatworm and which could lead to a treatment for schistosomiasis. NCGC has brought pharmaceutical-scale chemical screening, informatics and medicinal chemistry to bear on neglected diseases that affect millions globally, but are not worked on by the pharmaceutical industry because they cannot generate the needed financial returns.

ADVANCES IN GENETICS

Clinical genomics — NHGRI has launched two large projects to address important basic, clinical and behavioral research questions in the area of clinical genomics, the study of how genes play a role both in the development of disease and in the response to therapy. The findings of these studies will provide important insights regarding how best to advance genomic approaches and technologies into clinical practice, in effect "personalizing" drug therapy.

The ClinSeq project: At the forefront of the genetic revolution is the ClinSeq project, investigating the technical, medical and genetic counseling issues of large-scale medical DNA sequencing in a clinical research setting. By sequencing thousands of targeted regions of a person's DNA and returning relevant individual results to that person, NIH is bringing the era of "personalized" medicine to fruition. Specifically, this project seeks to develop the technologic and procedural infrastructure to facilitate this type of research and demonstrate that it is feasible to sequence and interpret large amounts of genomic sequence data and return individual results to subjects. This project leverages the unique capabilities of the NIH Intramural Program, namely those available through the NIH Clinical Center and the NIH Intramural Sequencing Center. (NHGRI, CC)

The Multiplex Initiative: The Multiplex Initiative aims to understand the reasons why people elect or do not elect to receive genetic information, how patients interpret such information, and how they ultimately use this information in making healthcare decisions. This large, multi-center study has developed a prototype genetic test for 15 polymorphisms (similar to genetic mutations) associated with increased risk for eight common conditions. The study design enables the evaluation of approaches that facilitate decision-making about genetic tests, assess methods for communicating test results, and explore whether health system factors influence health outcomes. Early results are already providing insight regarding how healthy individuals might respond to genetic susceptibility testing. (NHGRI)

Treatment and Natural History of Rare Genetic Disorders — One of NIH's greatest strengths is the study of rare diseases, which provide keen insight into the cause and treatment of common diseases. The NHGRI had made significant advances in understanding the genetics underlying a number of rare clinical disorders. These studies make use of the unparalleled resources of the NIH Clinical Center, allowing NHGRI investigators to study these rare clinical disorders in an environment that actively supports the kind of translational research that would be very difficult to conduct elsewhere.

Adenosine Deaminase-Deficient Severe Combined Immune Deficiency (ADA-SCID): All four of the pediatric patients who received gene therapy for ADA-SCID in the NIH Clinical Center have demonstrated improved or improving immune function. The two patients treated in the second version of this trial are now living normal lives and attending school, with no supplemental treatment. This study represents the first successful treatment of an inherited disease using gene therapy approaches in the United States. (NHGRI, CC)

Alkaptonuria: About 1 in 500,000 babies are born with alkaptonuria, an enzyme deficiency that results in the increased production of homogentisic acid. The resulting accumulation causes joint destruction by the time patients reach their 20s and severe heart problems by their 40s. The herbicide nitisinone, surprisingly, can

block the step in the biochemical pathway that leads to homogentisic acid production. NHGRI has recruited 40 alkaptonuria patients to test whether nitisinone, in the form of a drug called Orfadin, can reduce their symptoms. A clinical trial on a drug aimed at a rare disease such as alkaptonuria could not be done anywhere else in the world. (NHGRI, CC)

Gaucher Disease: Gaucher disease, the inherited deficiency of the lysosomal enzyme glucocerebrosidase, is a rare storage disorder, most frequently encountered among Ashkenazi Jews. The NHGRI has demonstrated that having a mutation in the Gaucher gene is a risk factor for developing parkinsonism. Scientists at the NIH Chemical Genomics Center have identified three classes of inhibitors that could serve as a therapeutic for Gaucher disease by directing the mutant enzyme to the lyososome. These compounds might have therapeutic potential for some patients with Parkinson disease, another rewarding example of how studies of a rare disease can have implications not only for the patients that suffer from that particular disorder, but also can provide insights into other, more common complex disorders.

Hermansky-Pudlak Syndrome: Hermansky-Pudlak syndrome (HPS) type 1 is a type of albinism that results in fatal pulmonary fibrosis for patients in their 30s to 50s. This disease largely affects Puerto Ricans. The NHGRI is conducting a clinical trial of pirfenidone, an antifibrotic with promising results so far. This is another example of a clinical study that can only be done by and at the NIH, for the patients mostly are poor, blind, Spanish-speaking, and not accustomed to spending time away from home. The NIH Clinical Center provides the necessary resources and comforts. (NHGRI, CC)

Hereditary Inclusion Body Myopathies: While humans with hereditary inclusion body myopathies (HIBM) develop muscle-wasting diseases, mice initially develop kidney disease and may develop muscle problems later. Investigators at the NHGRI created a mouse model for UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE) deficiency, a condition that leads to impaired sialic acid synthesis. Treatment with a sialic acid precursor (N-acetylmannosamine, or ManNAc) rescued the mice from perinatal lethality caused by the kidney disease. These findings indicate that ManNAc treatment is an appropriate way to provide sialic acid to HIBM patients, and a clinical protocol to further study this approach is under review by the NHGRI IRB. Key to research success so far has been the availability of experts in diverse fields and the ability to switch from muscle to kidney studies within a single research (and funding) environment. (NHGRI, CC)

Proteus Syndrome: The NHGRI is performing a natural history study of the rare overgrowth disorder Proteus syndrome, also known as Elephant Man disease. NHGRI scientists have delineated diagnostic criteria for this disorder and have discovered two previously unrecognized phenotypes. This work is coupled to an ambitious bench research project to delineate the etiology of Proteus syndrome. (NHGRI)

Autosomal Recessive Polycystic Kidney Disease: NIH is home to the world's experts on autosomal recessive polycystic kidney disease, which affects 1 in every 20,000 individuals. Nearly 90 patients with this disease (as well as closely related diseases) have been seen in the NIH Clinical Center over the past five years. The NHGRI is conducting a clinical trial to better understand the medical complications of this and an associated liver disease to identify characteristics that can help in the design of new treatments. Scientists would have difficult securing funding and conducting this type of research outside of the NIH Clinical Center. (NHGRI, CC)

Genetic factor behind stress response and appetite — The NIAAA Laboratory of Neurogenetics identified gene variants that affect the expression of a signaling molecule called neuropeptide Y, which regulates diverse functions, including appetite, weight, and emotional responses. This discovery, announced in 2008, may have major ramifications for drug development and behavior modification research, spanning from drug addiction to obesity. (NIAAA)

Wine, cheese, genes and long life: SardiNIA — In some parts of the Italian island of Sardinia, about 1 out of 200 people live over 100 years, a rate about 50 times greater than that in the United States. NIA scientists hope to learn the secrets of this longevity, and they are active in a groundbreaking study of the Sardinian population. Through a combination of genotyping and phenotyping, researchers have found both genetic components and lifestyle factors adding to the Sardinians' robust health.

The study involves NIA experts on cardiovascular science, cognition and genetics and partners with European colleagues. (NIA)

Extending human lifespan: primate aging studies — The NIH Animal Center in Poolesville, Md., is home to the NIA Primate Aging Study. Here, NIH scientists conduct the largest and most comprehensive long-term study on calorie restriction, aging and lifespan with rhesus monkeys. Effective anti-aging interventions should result in decreasing the incidence and delaying the age of onset of characteristic age-related diseases and pathology. In addition, there must be maintenance of cellular, organ, physiologic, and behavioral function into old age. By using criteria in the three main categories of mortality, morbidity, and function, the NIA hopes to clearly establish whether calorie restriction retards the rate of aging in rhesus monkeys, biologically similar to humans. (NIA)

Genome-wide Association Studies (GWAS) — The completion of the NIH-led Human Genome Project in 2003 has given birth to GWAS, studies that can look across the entire human genome to find multiple genes associated with various diseases and traits, such as cancer, diabetes or obesity. The NCI Cancer Genetic Markers of Susceptibility (CGEMS) initiative has already pinpointed multiple genetic loci that modify the risk of breast and prostate cancers. Further studies are targeting non-Hodgkin lymphoma and cancers of the pancreas, lung, bladder, kidney, and brain. These molecular epidemiologic investigations represent the starting point for a variety of experimental approaches designed to identify the functional genetic variants that increase or decrease the risk of cancer, and thus provide new insights into risk prediction as well as preventative and therapeutic interventions. (NCI DCEG)

Genes and African American kidney disease susceptibility — African Americans have a threefold increased risk for end-stage kidney disease (ESKD) and are at increased risk for the leading causes of ESKD: diabetic kidney disease, hypertensive kidney disease and glomerulonephritis. Researchers from NIDDK and their colleagues in NCI have used admixture mapping to identify a gene that underlies a common form of glomerulonephritis, called focal segmental glomerulosclerosis (FSGS). This gene is *MYH9*, encoding the heavy chain of non-muscle myosin heavy chain IIA. The team found a *MYH9* variant to be associated with FSGS and a related disease, HIV-associated nephropathy. Furthermore, the same variant was found to be associated with hypertensive kidney disease. The susceptibility variant is common among African Americans (60 percent of alleles) and uncommon among European Americans (4 percent of alleles), explaining a substantial fraction of the racial disparity for kidney disease. (NIDDK)

Lung disease: genetics, environment or both? — The NIEHS Environmental Genetics Group uses state-of-the-art methods in inhalation toxicology, pulmonary physiology and molecular genetics to study the role of genetics as a susceptibility factor in environmental lung disease. This is one of the few groups in the world able to dedicate complete focus on a single, significant problem to define the interaction between genetics and environment. Epidemiological studies have associated exposures to outdoor and indoor pollutants with increased morbidity and mortality in urban cities throughout the United States and other industrialized countries. Yet not everyone develops lung disease despite similar exposure. NIEHS researchers have identified quantitative trait loci (QTL) for susceptibility to the inflammatory responses to ozone, sulfate-associated particles and hyperoxia. Candidate genes for the QTLs have been identified, and functional analyses have confirmed important roles for each. Applying *in vivo* and *in vitro* findings in translational investigations to human populations has provided extraordinary insight into disease mechanisms. Current research is providing insight on ozone-induced inflammation, the *Nrf2* gene and acute lung injury, particle-induced cardiopulmonary injury, and innate immunity and viral infection. (NIEHS)

IMMUNOLOGY AND AUTOIMMUNE DISEASES

Immunosuppressive drugs for transplants and more: Janus kinase 3 — NIAMS researchers discovered Janus kinase 3 (Jak3), a molecule key to regulation of the immune system, and took that discovery all the way through the development of a new class of immunosuppressive drugs now in clinical trials

for rheumatoid arthritis, kidney transplantation and psoriasis. The work was based on a theory explored freely in the NIH intramural program: that mutations of Jak3 would underlie a form of severe combined immunodeficiency (SCID). When this prediction proved true, NIAMS researchers established a CRADA with Pfizer to further investigate the structure and function of Jak3. Jak3 antagonists are now in worldwide Phase IIb trials, and at least five other companies are testing Jak inhibitors in various settings. (NICHD, NHLBI, NIAID, NHGRI, NIAMS, CC)

Common autoimmune diseases and *STAT4* polymorphisms — Autoimmune diseases such as rheumatoid arthritis, Coeliac disease and Diabetes mellitus type 1 affect millions of people worldwide. Multiple NIH institutes and the FDA contributed to what is now known as the Jak/Stat pathway in the etiology of these diseases. NIAMS researchers in particular were the first to show that Interleukin 12 activates the gene *STAT4*, laying the foundation for subsequent work defining the role of STAT4 in helper T-cell differentiation. This has led to the discovery that polymorphisms (similar to mutations) of *STAT4* confer increased risk for rheumatoid arthritis, lupus and Sjogren's syndrome. (NIAMS, NIDDK, NIAID, NHLBI, FDA-CBER)

Progress on Job's syndrome: Th17 cells — The NIH is the leading organization studying Job's syndrome, also called Hyper IgE syndrome (HIES), a disorder characterized by immune and skeletal abnormalities, such as rashes, chronic infections, recurrent fractures and scoliosis. Researchers teaming up from several NIH institutes used positional cloning to initially identify the location of the gene responsible for HIES; identified dominant-negative *STAT3* mutations as the cause for HIES; and demonstrated that *STAT3* is involved in the differentiation of CD4+ T cells to become inflammatory interleukin-17-producing cells, so-called Th17 cells. In 2008 NIH researchers published results showing how Th17 cells are an important aspect of this Job's syndrome. As with the study of most rare diseases, such breakthrough work on Job's syndrome may lead to a deeper understanding of immune and skeletal disorders. (NIAMS, NIAID, NHRGI, NIDDK, CC)

Multichain immune recognition receptors — NIH researchers in the 1980s defined a new class of receptors, which are structures or sites on a cell's surface or interior that bind with hormones, antigens, drugs or other molecules. These are now known as multichain immune recognition receptors, and of these the IgE receptor, cloned by NIAMS researchers, has become a paradigm. IgE receptors play an important role in allergies and hypersensitivities. NIH researchers also were first to clone the T cell antigen receptor, a crucial component of immunity. In more recent years, researchers from across the NIH greatly advanced the understanding of multichain immune recognition receptors. This includes the identification of a class of protein tyrosine kinases, the Tec family, which has a critical role in T-cell signaling. Most recently, NIAMS researchers have identified the need for two types of kinases (a type of enzyme) to activate T cells, as well as co-stimulatory signals needed to interact with Fc receptors on natural killer cells and other immune systems cells. These discoveries provide new avenues of investigation for therapeutic intervention in autoimmune and allergic diseases. (NIAMS, NIDCR, NICHD, NIAID, NCI)

CAUSES AND TREATMENTS FOR ADDICTION

The biology of addiction — NIH researchers have helped demonstrate that addiction creates biological changes in the brain that are difficult to remedy with behavioral modifications alone. Drug and alcohol abuse also alter the way the brain processes information. NIAAA has undertaken a multi-laboratory investigation on precisely how drugs and alcohol affect learning. The labs have created an unparalleled research setting in which live, transgenic mice can be studied in depth. The use of many types of transgenic mice enables researchers to study animals with or without various key traits involved in addiction and learning, providing vigorous evidence for theories on addiction. The totality of tools available—from the transgenic mice to fiber-optic-mediated deep-brain scans, as well as the breadth of physiological and behavior elements under study—makes this a potentially high-reward endeavor. University-based laboratories likely would not have the span of expertise needed to undertake such research. Results to date indicate that separate brain pathways are

involved in early, goal-directed responses to rewarding substances such as drug of abuse, and later habitual drug seeking. This research indicates that drugs of abuse may bias the brain toward habitual behavioral patterns when drugs or drug-related contexts are encountered. This line of research will help us to understand the changes in brain molecules, cells and circuits that underlie drug seeking and addiction, and can facilitate testing of treatments aimed at reducing drug and alcohol abuse and addiction. (NIAAA)

Alcoholism treatment: the neurokinin 1 receptor — The NIAAA Laboratory of Clinical and Translational Studies has successfully completed a project on targeting the neurokinin 1 receptor (NK1R) as a mechanism for treatment of alcoholism. In less than three years, this work has gone from a situation where no data were available for this target in alcoholism, to where target validation in animal models is in place, translation into human surrogate marker data for efficacy is available, and two major pharmaceutical companies have been convinced by the data to initiate full scale clinical trials in alcoholism. This high-risk but clearly high-reward research would have been difficult, if not impossible, to perform outside of NIH because there were no preliminary data to support a grant application. Nor were pharmacological tools available for this receptor in laboratory rodents. (NIAAA)

Cocaine — NIDA researchers have found the mechanism by which cocaine interferes with neural progenitor cell proliferation, which is likely the major cause of cocaine's adverse effect on brain development. This research could lead to methods for preventing cocaine from adversely affecting brain development in the children of cocaine-abusing mothers, and NIDA researches already have identified a drug that might be used for this purpose. This study took five years, a time span too long for most extramural projects, and depended upon NIDA's previous work in the development of cell lines. In particular, the mechanisms involved were worked out using the AF5 neural progenitor cell line, which was developed using a modified oncogene, which in turn depended on highly speculative work, such as creating vectors for delivery of this oncogene and modifying the oncogene itself. This has been basic groundwork conducted over 10 years. (NIDA)

Drug craving — Researchers in NIDA's Behavioral Neuroscience Research Branch are studying the effect of the cocaine withdrawal period on cue-induced drug seeking. In their initial study, the researchers found a progressive increase of the responsiveness to cocaine cues over the first months of withdrawal, a phenomenon they termed "incubation of cocaine craving." The researchers have since characterized the role of mesolimbic brain-derived neurotrophic factor, or BDNF, in the persistent responsiveness to cocaine cues after withdrawal. They are now investigating the role of the amygdala extracellular signal-regulated kinase (ERK) signaling pathway in this incubation. This work could not have been undertaken extramurally because it took more than six years to develop a novel experimental procedure to selectively lesion neurons involved in a given behavioral task. It is unlikely that such a line of research would have been funded by extramural grants because of lack of pilot data during the first several years of this project. (NIDA)

SENSORY: EYES, EARS

The eye-brain connection — The NEI Laboratory of Sensorimotor Research is one of very few laboratories in the world investigating the association of brain activity and behavior in awake, nonhuman primates. This extraordinary resource enables NEI scientists to study the link between the activity of groups of neurons and conscious visual perception. This research may soon translate into cures for several eye-movement disorders. (NEI)

Vision gene repository — The National Ophthalmic Disease Genotyping Network (eyeGENE™) facilitates research into the genetic causes of eye diseases. Since the early 1990s, scientists at the NIH and elsewhere have identified nearly 500 genes that cause or contribute to inherited eye diseases. Genetic mutations are associated with many ocular diseases, including glaucoma, cataracts, strabismus, corneal dystrophies and many forms of retinal degenerative disease. Gene-based therapies are actively being pursued to ameliorate genetic eye diseases that once were considered untreatable. However, molecular diagnostic testing for these diseases is not widely available to patients wishing to know whether they could benefit from

the treatments under development. NIH's eyeGENE addresses this need through its nationwide network of genetic testing laboratories and by facilitating research into these diseases. (NEI)

Age-related macular degeneration — In 2007, the NEI launched a large, prospective randomized, placebo-controlled clinical trial called AREDS to evaluate the effects of oral supplementation with lutein/zeaxanthin and omega-3 long chain polyunsaturated fatty acids (LCPUFAs) for the treatment of age-related macular degeneration (AMD). AMD is the leading cause of blindness in the developed world, accounting for more than 50 percent of those blind in the United States. More than 4,000 patients are in the study, and another 4,000 are being recruited. The initial study found that daily supplements of antioxidant vitamins and minerals could reduce the risk of developing advanced AMD by 25 percent. Data also suggested that higher dietary intake of lutein/zeaxanthin and omega-3 LCPUFAs was associated with a decreased risk of advanced AMD. (NEI)

Here's meds in your eye: a novel drug-delivery method — NEI scientists study rare retinal diseases such as Retinitis Pigmentosa (RP) with the goal of developing therapies for both rare and common retinal diseases. Such rare diseases provide fascinating and crucial insight into how and why retinal diseases emerge. One major challenge is to deliver therapeutic agents to the retina. Encapsulated cell technology (ECT) is a promising approach. NEI is perfecting a technique in which ECT devices are constructed with a semi-permeable polymer membrane filled with human retinal pigment epithelium cells that have been genetically transfected with the ciliary neurotrophic factor (CNTF) gene to produce the CNTF protein. These are surgically implanted into the eye. This therapeutic protein is produced inside the ECT device and exits through the semi-permeable membrane, thereby providing a continuous supply of the rescue factor for many months and possibly for years. Clinical trials are underway. (NEI, CC)

Deafness genes — The NIDCD Laboratory of Molecular Genetics has made extensive contribution to identify and characterize genes that cause deafness. This includes the identification of mutations causing one of the most common forms of inherited deafness, nonsyndromic recessive deafness, and also a mutation associated with Usher syndrome type 1, which causes deafness and blindness. Other key genes include unconventional myosin XVA, cadherin 23, protocadherin 15 and claudin 14. Improved understanding of the mutated genes is providing important information on hearing and brain processing. The identification of the relevant genes also permits early and more accurate diagnosis for certain forms of hereditary hearing and communication impairments, as well as loss of sight. (NIDCD)

Childhood hearing loss: EVA — The NIDCD Otolaryngology Branch has made significant progress in understanding enlarged vestibular aqueducts (EVA), which are inner ear malformations commonly associated with hearing loss in children. A main contributor is Pendred syndrome, but other causes have not been carefully analyzed. NIDCD researchers have launched a clinical trial to identify and understand the genetic factors that lead to EVA and hearing loss. NIDCD has helped to establish that many cases of EVA are associated with mutations in the Pendred syndrome gene PDS/SLC26A4, which encodes an integral membrane protein that is thought to transport or exchange chloride, iodide, bicarbonate or other bases in the inner ear. Some cases of EVA are caused by other genetic or environmental factors, alone or in combination with a single SLC26A4 mutation. The NIDCD EVA study hopes to identify those other factors, as well as the molecular basis for observed SLC26A4 genotype-phenotype correlations. (NIDCD)

BREAKTHROUGHS IN CELLULAR AND MOLECULAR BIOLOGY

The NIH-Human Stem Cell Facility — The NIH intramural program has played a leading role in developing stem cell resources for the scientific community at large. The NIH-Stem Cell Facility (NIH-SCF) administered in NINDS was established to implement the use of human embryonic stem cells in medical research. Initially, the NIH-SCF acquired all the lines on the NIH stem cell registry; grew these cells through multiple passages with no major alteration in karyotype; and showed that the cells could be sub-cloned with reasonable efficiency. This work established confidence in the basic qualities of

the human embryonic stem (hES) cells available for use with U.S. federal funds. A lack of simple tools to characterize the undifferentiated state of hES cells has made it difficult for widespread proliferation of hES cells. This problem has significantly delayed the widespread use of hES cells. These difficulties are being addressed by an interaction between the NIH-SCF and NINDS Laboratory of Molecular Biology, which has placed the NIH intramural program at the forefront of research on human pluripotent cells. This impact is proceeding on three fronts making efficient use of intramural resources and collaborations:

Intramural connections: The NIH-SCF is assisting other NIH teams to use hES cells. These cells are difficult to grow and coax into specialized cells. Researchers refer to the technique as an art form. NIH-SCF offers training to make NIH researchers self-sufficient in using hES cells, a "teach a person to fish" approach, as opposed to merely supplying researchers with a steady supply of stem cells. The program has helped establish several new and exciting projects involving replenishing diseased bone, heart, retinal and other cells. (NINDS)

Growing stem cells: The NIH-SCF continues to make progress in solving the problem of growing high-quality undifferentiated hES cells. The NIH-SCF has established methods to image the activation of stress response pathways in hES cells and characterized gene expression in 16 hES cells in undifferentiated and differentiated conditions. This work will provide simple tools to enable the assessment of the state of hES cells, which is a prerequisite for their standardized use. (NINDS)

Human iPS cell lines: NINDS has generated and characterized human iPS cell lines, or induced pluripotent stem cell lines, artificially derived from a non-pluripotent cell such as an adult somatic cell, as opposed to an embryo. The NINDS Laboratory of Molecular Biology has an outstanding track record in basic and translational research related to stem cells. News that adult human cells could be reprogrammed by lenti-viral delivery of four genes has stimulated a project to generate reprogrammed iPS cells and compare them with hES cells. NIH researchers have now generated 12 iPS lines (NIHi1-12) that carry all four reprogramming genes (*Oct4*, *Sox2*, *c-myc* and *Klf4*). Whole genome transcript analysis shows that the 12 iPS and 16 hES cells are remarkably similar in the undifferentiated state and conform to the model for stem cell self-renewal signaling developed in NINDS. The pattern of gene expression in differentiated states is now being assessed. These cells will be made available to the NIH community through the NIH-SCF, providing easy access to this exciting new stem cell technology. (NINDS)

Skeletal stem cells: disease and therapy — Researchers in the NIDCR Skeletal Biology Section and the Skeletal Clinical Studies Unit have performed "bench to bedside to bench" studies to develop and investigate the theory that any intrinsic or extrinsic factor that alters the activity of the subset of skeletal stem cells within the bone marrow stromal cell population will cause a skeletal disorder. This discovery arose from their basic, translational and clinical studies of fibrous dysplasia of bone and the McCune-Albright Syndrome, caused by somatic activating missense mutations of a gene, Gs-alpha, leading to overproduction of cAMP and consequent replacement of normal bone and marrow with structurally abnormal and weak bone and a fibrotic marrow. This work, which may lead to therapy, took advantage of the NIH's ability to efficiently recruit and study patients with a rare genetic defect. (NIDCR)

Form and function: how the cell got its tubules — Most human cells are filled with a variety of organelles with fascinating and characteristic shapes that dictate their function. Yet how these shapes are formed and maintained is largely unknown. NIDDK researchers studying the tubular structure of the endoplasmic reticulum (ER) have discovered how to make such tubules *in vivo* with proteins in and around the ER. Tubules dominate a section of the ER called smooth ER, which is involved in steroid metabolism and drug detoxification. Their presence increases the surface area in the smooth ER for enzyme production and storage. This very basic research advance from NIDDK may have broad implications for drug design, as scientists attain a better understanding of subcellular form and function. (NIDDK)

Protein trafficking—The Section on Protein Biogenesis in the NICHD Cell Biology and Metabolism Program investigates the trafficking of newly synthesized secretory and membrane proteins. A notable advance

in 2008 was the discovery of the first component (named TRC40) of a novel membrane protein insertion pathway for tail-anchored proteins. These proteins play critical roles in virtually all aspects of cell biology, and their discovery likely will be recognized for its fundamental importance in normal cellular function. The Section is now using TRC40 to identify additional components of the pathway. In parallel work, the Section identified a new protective pathway, termed pre-emptive quality control (pQC), which attenuates the adverse consequences of protein misfolding in the endoplasmic reticulum. The researchers are now examining the importance of pQC in mouse models of neurodegeneration and identifying the molecular basis of the pathway in vitro. (NICHD)

Cartilage tissue substitutes — NIAMS researchers have developed electrospun nanofibrous biomaterial scaffold for tissue engineering. This novel approach is highly biocompatible for cell-based tissue engineering, including adult stem cells as well as differentiated cells. In addition, the nano-scale of the scaffold fibers demonstrates bioactivity that mimics that of native extracellular matrix macromolecules. This could be used for cartilage, adipose and muscle tissue engineering.

How blood and lymphatic vessels form — The NICHD Section on Vertebrate Organogenesis in the Program in Genomics of Differentiation is investigating how networks of blood and lymphatic vessels arise during vertebrate embryogenesis. Understanding mechanisms of vessel formation is a subject of intense clinical interest because of the roles played by blood and lymphatic vessels in cancer and ischemia. The Section uses zebrafish, uniquely suited for studying vessel formation because of its optically clear embryo that facilitates high-resolution imaging of vessels in living animals. The Section has developed confocal microangiography, compiled an atlas of vascular anatomy of the developing zebrafish, developed numerous vascular-specific transgenic fish lines, and established high-resolution *in vivo* imaging of zebrafish blood vessels, all of which make it possible to elucidate a pathway of artery specification, establish a role for neuronal guidance factors in vascular patterning, illuminate vascular tube formation *in vivo*, and identify a lymphatic vascular system in the zebrafish. (NICHD)

Root of disease, from depression to cancer: sigma-1 receptors — Facing many informational, technical and conceptual challenges spanning over a decade, NIDA has unraveled the function of intracellular proteins called sigma-1 receptors, which were in fact first identified by NIDA in 1982. Sigma-1 receptors are now identified as an important chaperone protein in the brain and are implicated in many human diseases, such as addiction, depression, cancer and stroke. The receptor resides throughout the body but is particularly concentrated in the central nervous system. The work has broad implications, for sigma-1 receptors may be intracellular amplifiers creating a supersensitized state for signal transduction in the biological system, involved in learning and memory, pain perception and numerous basic biological functions. (NIDA)

CARDIOVASCULAR DISEASES

Framingham moves to Bethesda — The Framingham Heart Study became part of the NIH Intramural Research Program in 2008. This is among the longest continuous longitudinal health studies ever conducted, starting in 1948 in Framingham, Mass., and now comprising three generations of adults. Now "at" NIH, researchers can leverage 60 years of data collection with intramural resources, such as gene expression profiling and bioinformatics. NHLBI researchers have begun numerous projects, such as an ambitious gene expression study with phenotypes and 500,000 genotyped SNPs from Framingham participants using a new type of microarray on a 96-sample peg plate instead of the standard chip, a technique not yet available to most university researchers. This is all housed in an open-door environment with multiple institutes and smart colleagues investigating related fields, such as metabolic disorders and cancer. Framingham, in essence, is stronger than ever. (NHLBI, CC)

The beating heart under the microscope — The NIA Laboratory of Cardiovascular Sciences has a broad set of goals to understand how the cardiovascular system ages and fails. No academic laboratory can match its scope. Fundamental basic science insights are made on the most basic processes of pacemaker activity, excitation-contraction coupling and muscle energetics. The vascular biology program has identified important aspects of how

arteries respond to damage, which led to the development of paclitaxel-coated stents. This intervention has reduced restenosis rates (artery narrowing) after angioplasty by over 70 percent. Human observational studies are used primarily to raise mechanistic hypotheses that are then tested in cells, tissue and animal models. Translational work takes the findings from these paradigms and moves them into the development and testing of interventions, typically through clinical trials. Two examples are the ongoing clinical research evaluating erythropoietin to limit infarct (tissue death) size and the testing of fenoterol as an inotropic agent for application in heart failure. (NIA)

Real-Time MRI: Emergency room and image-guided therapies — By putting together a research team of clinicians, engineers, physiologists, and computer scientists, the NHLBI worked with industry to create one of the first real-time MRI devices for freezing heart motion as well as providing a real time imaging feedback for therapeutic approaches. Cutting through the usual barriers in conventional hospital settings, an MRI program was created in the emergency room of a community hospital to evaluate heart attack patients in the emergency room. This was also coupled with a stroke program with NINDS. This program has continued to have a major impact on cardiac imaging from the emergency room, to longitudinal studies coupled to genomic studies in large populations. Using this real-time capability, it also became clear that these rapid images of the soft tissue could provide valuable guidance for interventional procedures. Towards this goal, NIH scientists are generating an interactive imaging platform that the clinician could guide to track devices or surgical procedures. Using this technology, some of the first image-guided procedures were conducted guiding intravascular catheters as well as surgical replacement of cardiac valves. This program is continuing with the belief that this unique imaging modality will be the eyes for robotic surgery in the future. The aspects of the intramural program that contributed to the rapid development of this technology was the ability to create interdisciplinary research teams to conduct rather high risk projects that would have been difficult to do elsewhere. The ability to rapidly move this technology into community medicine was also facilitated by working as an outside entity within the hospital system not impeded by existing structures or financial bias. (NHLBI, NINDS)

DATASETS

Health disparities — The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study examines persistent black-white health disparities in overall longevity, overall health status, and the incidence and severity of age associated diseases such as cardiovascular disease and cerebrovascular disease. HANDLS is a multidisciplinary, prospective longitudinal epidemiologic study examining the influences and interaction of race and socioeconomic status (SES) on the development of age-associated health disparities, including cardiovascular and cerebrovascular disease among minority and lower SES subgroups. Researchers have thus far uncovered social, lifestyle and genetic difference contributing to the disparity. (NIA)

Information banks rich with data — NLM's National Center for Biotechnology Information (NCBI) is a national resource for biomedical information, containing the largest biomedical and life sciences databases in the world. NCBI's PubMed, for example, provides a Web search interface to over 18 million journal citations in MEDLINE, a database also created and maintained by NLM. GenBank is another invaluable NCBI database, containing an annotated collection of all publicly available DNA sequences. More important, NCBI continues to develop tools to enable researchers and the general public to efficiently mine these treasure troves of data, all free of commercial interests. NLM's Lister Hill National Center for Biomedical Communications produces databases and tools that support clinical and informatics research. ClinicalTrials.gov, the world's largest trials registry, has recently been expanded to serve as a repository of summary results data for drug and device studies. Lister Hill's lexical and imaging tools underpin extensive research and development efforts across the country. Such resources, providing a foundation for most biomedical research nationwide, if not worldwide, can only thrive in the environment of secure funding provided by the NIH intramural program. (NLM)

Appendix D: Major Shared and Multi-Institute Research Resources in the NIH Intramural Research Program

The NIH Intramural Research Program has a long history of interactions and shared resources among its investigators. These include core facilities that support crucial research activities, such as a sequencing center, a magnetic resonance imaging facility, a mass spectroscopy service, and a protein expression service. The most prominent example is the Warren Grant Magnuson Clinical Center, the nation's largest hospital devoted entirely to clinical research, providing comprehensive services and facilities in support of clinical research sponsored by the Institutes and Centers. In addition, the NIH Office of Intramural Training and Education organizes and sponsors a variety of training and career development activities for the entire intramural community. Various mechanisms are used to support these resources, including contributions from participating NIH Institutes and Centers such as the management funds, user fees, and program support from the Office of Intramural Research.

RESOURCES AVAILABLE TO ALL INSTITUTES AND CENTERS

Research Resource	*Location*	*Participants*	*Governance*	*Contact*	*Research Services*	*Review*
Bioengineering (Lab of Bioengineering and Physical Sciences)	Building 13	Lead IC: NIBIB	NIBIB	Richard Leapman, scientific director	Drug delivery, molecular interactions, image analysis, instrumentation development, supramolecular structure, nanoscale immunodiagnostics; http://www.nibib.nih.gov/Research/intramural/LBPS	Shared Resources Subcommittee (SRS), ICs, Coordination Committee
Center for Information Technology (CIT)	Building 12 complex	All ICs	CIT	Benes Trus, acting director	Image processing, bioinformatics, computational methods and algorithms, computer engineering, bioscience, molecular modeling, mathematical and statistical computing, supercomputing, software development; http://www.cit.nih.gov/science.html	SRS, ICs
Division of Medical Arts	Building 10, B2 level	All ICs	Office of Research Services (ORS)	Lem Canady, chief	Medical illustration, photomicroscopy, photomacroscopy, scientific posters; http://medarts.nih.gov/	
Division of Library Services	Building 10	All ICs	ORS	Suzanne Grefsheim, director	Full-service library, including electronic journals, electronic document desktop delivery and translations; http://nihlibrary.nih.gov	Users committee, ICs
Division of Scientific Equipment and Instrumentation Services	Building 13	All ICs	ORS	Johnny Robbins, chief	Maintain scientific equipment and computers; design and fabricate custom instruments; lease and sell scientific and medical equipment; http://dseis.od.nih.gov (NIH Intranet only)	SRS, ICs
Division of Veterinary Resources	Building 14–28 complex; Bethesda; Poolesville	All ICs	ORS	Charmaine Foltz, acting director	Veterinary services (surgery, radiology, pharmacy, nutrition, animal behavior and enrichment); animal husbandry, procurement, quarantine, and health surveillance; diagnostics (pathology, bacteriology, parasitology, serology, mouse phenotyping)	SRS, ICs

MULTI-INSTITUTE SHARED SERVICES

Research Resource	*Location*	*Participants*	*Governance*	*Contact*	*Research Services*	*Review*
Biotechnology Core Laboratory	Building 6, Room B1–33	Lead IC: NIDDK; major client: NICHD		Joseph Shiloach, director	Production and purification of biological material, especially scale-up protein production and purification; http://www2.niddk.nih.gov/NIDDKLabs/AllLabs/CoreFacilities/BiotechnologyCoreLaboratory.htm	BSC, ICs
Bone Marrow Stromal Cell Transplantation Center	Building 10	Steering Committee: CC, NIDCR, NIAID, NIAMS, NIBIB, NCI, NINDS	Oversight Committee: NINDS, NIAID, NCI, NIDCR	Harvey Klein (CC), Pamela Robey (NIDCR)	Production facility for bone marrow stromal (mesenchymal) stem cells for clinical research	
Center for Human Immunology (CHI)	CRC	Available to all ICs	Steering Commitee	Neal Young, director	Translational research in immunology, autoimmunity and inflammation; http://www1.od.nih.gov/oir/sourcebook/ir-communictns/chi.htm	SRS, SDs
Center for Inherited Disease Research	Bayview Research Campus, Baltimore	Lead contracting IC: NHGR; all ICs may participate	Review: CIDR Board of Governors	David Valle, Johns Hopkins University	Genotyping, DNA banking, statistical genetics consultation, mouse genotyping; http://www.cidr.jhmi.edu	CIDR Access Committee (Camilia Day, NHGRI)
NIH Clinical Center	Building 10	Available to all ICs	ABCR, NIH Director	John Gallin, director	Research hospital that accommodates 234 inpatients and outpatients and provides comprehensive services and facilities in support of clinical research sponsored by the ICs; http://www.cc.nih.gov	Joint Comm. on Accreditation of Healthcare Organizations, BSC; Advisory: CC Research Steering Committee, CC Board of Governors

MULTI-INSTITUTE SHARED SERVICES (continued)

Research Resource	*Location*	*Participants*	*Governance*	*Contact*	*Research Services*	*Review*
Facility for Biotechnology Resources (FBR): CBER Biotechnology Core Facility	Building 29, Rooms 200-208	Participants: NHGRI, NIDCD, NHLBI, NIDDK, NICHD, NEI, NIAMS, NIDCR, CC, NCI - fee-for-service	CBER	Nga Y. Nguyen, CBER FDA	Services include: amino acid sequence analysis; DNA sequencing; oligonucleotide synthesis; peptide synthesis; mass spectrometry services; analytical and preparative HPLC services; capillary electrophoresis; http://128.231.52.66/default.htm (NIH Intranet only)	CBER
Genomics Core	Building 8	Lead IC: NIDDK; available on fee-for-service basis for other ICs		Michael Krause, director; George Poy, technologist	Expression arrays, Illumina sequencer; http://www2.niddk.nih.gov/NIDDKLabs/GENOMICS/GCLHome.htm	NIDDK SD
Integrative Neural Immune Program	Multiple locations	NIMH, NINDS, NCI, NIAID, NIAMS, NIA		Esther Sternberg, director	Lecture series, conferences, workshops, retreat; training that bridges neuroscience and immunology; cyberlab to oversee virtual cores; http://intramural.nimh.nih.gov/inip/	
Imaging Probe Development Center (IPDC)	9800 Medical Center Dr., Building B, Room 3042, Rockville, Md.,	Lead IC: NHLBI	Roadmap Initiative	Garry Griffiths, director	Production of new imaging probes for the intramural NIH research community; http://nihroadmap.nih.gov/molecularlibraries/ipdc/contact.asp	
Mass Spectroscopy	Building 8A, Room B2A19–21; Building 10	Lead ICs: NIDDK, NHLBI, NIMH, NIAID, NINDS	Advisory Group		QTOF–LCMS; high-resolution magnetic sector; MALDI, LC-ion trap	BSC, ICs
Microarray Services (1)	Multiple sites	NHGRI, NCI, NIA			Chips prepared by special arrangement	ICs
Microarray Services (2)	Building 12A	CIT with contributions from NINDS, CC, NHLBI, NIAID, NCI		Peter Munson (CIT), John Powell (CIT)	Analysis, database storage and retrieval, bioinformatics services for microarray data	ICs
Mouse Imaging Facility	Building 10, In Vivo NMR Center	Lead ICs: NINDS, NHLBI; Participants, all ICs but NIEHS are paid charter members	Steering Committee	Alan Koretsky, director	Mouse radiologic imaging (from fall 2001); 7T rodent MRI, microCT, high-frequency ultrasound, laser Doppler; http://intranet.nmrf.nih.gov/ (NIH Intranet only)	SRS, ICs, steering committee
NIH Chemical Genomics Center (NCGC)	9500 Medical Center Drive, Rockville, Md.	Lead IC: NHGRI		Chris Austin, director	Ultrahigh-throughput screening center of the Molecular Libraries Screening Center Network that generates chemical probes to understand molecular and cellular functions and serve as starting points for drug development, particularly for rare and orphan diseases; http://www.ncgc.nih.gov/	
NIH Intramural Sequencing Center (NISC)	5625 Fishers Lane, 5th Floor, Rockville, Md.	Participants: NHGRI, NCBI, NIDCD, NIAAA, NIDA, NHLBI, NIDDK, NICHD, NEI, NIAMS, NINDS, NIDCR, NIEHS, NIMH	Users Committee	Eric Green, director	Production-scale DNA sequencing, assimilation and analysis of sequence data, instrumentation, sequence analysis software; http://www.nisc.nih.gov	
NIH Magnetic Resonance Imaging Facility	Building 10, In Vivo NMR Center	Lead IC: NINDS; all ICs except NIEHS	Steering Committee	Alan Koretsky, director	Human and animal MRI; other IC MRI instruments available; http://intranet.nmrf.nih.gov/ (NIH Intranet only)	SRS, ICs, steering committee
PET Imaging	Building 10, Room 1C401	Lead IC: CC	Steering Committee	Peter Herscovitch, director	State-of-the-art facility with three medical cyclotrons and ten hot cells to produce positron-labeled radiopharmaceuticals, as well as four PET scanners; http://www.cc.nih.gov/pet/index.html	
Protein Expression Lab	Building 6B, Room 1B130	Lead IC: NIAMS; Participants: NHGRI, NCBI, NIDCD, NIAAA, NIDA, NHLBI, NIDDK, NICHD, NEI, NIAMS, NINDS, NIDCR, NIEHS, NIMH; any IC may request service		Paul Wingfield, chief	Expression, purification, and structural characterization of HIV and HIV-related proteins via a variety of techniques; protein EXE software; supply HIV-1 protease; http://www.niams.nih.gov/Research/Ongoing_Research/Branch_Lab/Protein_Expression/default.asp	IATAP, ICs
Stem Cell Unit	Building 35, Room 3A201	Lead IC: NINDS	Steering Committee	Ron McKay, director	Facility uses a standardized paradigm to conduct side-by-side comparisons of the available cell lines on the NIH Human Embryonic Stem Cell Registry and shares the results with the scientific community; http://stemcells.nih.gov/research/nihresearch/scunit	
Structural Biology NMR	Buildings 5, 6A, and 50	All ICs	Steering Committee	Lead ICs: Ad Bax (NIDDK), Nico Tjandra (NHLBI)	Study of macromolecular structure and interaction; 500, 600 and 800 MHz cryoprobe NMR spectrometers; 900 MHz spectrometer	ICs
Synchrotrons:						
1. Advanced photon source	Argonne National Lab	DOE		http://www.aps.anl.gov	High-brilliance X-ray beams	
2. National synchrotron light source	Brookhaven National Lab	Lead IC: NCI; major users: NIDDK, NIEHS, NIAID, NHLBI		http://www.nsls.bnl.gov	Intense focused beamlines throughout the spectrum	

Appendix E: Summary of Intramural Global Health Activities

One of the five major themes defining Dr. Francis Collins' goals as NIH Director is to use the talent and resources of the NIH to improve global health. Towards this end, the intramural program has inventoried the many programs and projects that we have developed to address global health problems.

In general, global health initiatives can be categorized based on the number of individuals affected and the severity of the disease; the feasibility of the effort; the portability of the intervention; and the sustainability of the program, including the need for training of scientists from throughout the world. NIH intramural activities in global health illustrate the importance of each of these factors.

The Big Three: tuberculosis, malaria, and HIV

The three infectious diseases that produce the most morbidity and mortality in the world, prematurely ending the lives of millions of children and adults, and severely affecting the welfare and productivity of millions more, are tuberculosis, malaria, and HIV. Intramural NIH, especially NIAID, has strong basic pathogenesis, epidemiology, vaccine development, and treatment programs for all of these diseases. In addition, as these diseases come under control, it is clear that chronic diseases that now are prominent in the developed world, such as major mental disorders, cancer, and heart disease, will become more prevalent in developing countries. Thus, most of the translational studies in the intramural program targeted at these diseases will also have global significance in the coming years.

...and other persistent health problems

For a global health intervention to be practical, it must be relatively inexpensive and easy to deliver to distant sites. The NIH intramural program, especially NCI, NICHD, and NIAID, continues to develop vaccines to prevent diseases with global impact such as cervical cancer (HPV), malaria, anthrax, rotavirus, West Nile fever, leishmaniasis, Ebola and Marburg fevers, Influenza, SARS, Chikungunya virus, Shigellosis and Salmonellosis. In addition, extensive epidemiology programs in NCI, NIAID, NHLBI, NHGRI, NIAMS, NEI, NIA and NIEHS help define patterns of disease and suggest effective interventions for environmentally associated cancers, aplastic anemia, and genetically related diseases such as hypertension, obesity, prostate cancer, cleft palate, vision loss, and the aging process.

Much of the world, especially parts of sub-Saharan Africa, suffers from poor distribution of health services. Thus, it is essential that diagnostic tools, vaccines, and disease treatments be robust enough to be useful in the small villages that may be most affected by disease, especially infectious disease. Several institutes, such as NIAID and NIDCR, have collaborations aimed at improving portability of diagnostics including testing in saliva and sputum for infectious agents, and NIBIB in collaboration with the Gates Foundation is working to improve imaging technology for diseases of the developing world.

Training and Sustainability

Any prolonged positive affect on global health will require the development of infrastructure that can continue to monitor disease and train the future physicians and scientists in their home country to do the research needed to support public health efforts. One dramatic example of the way in which intramural NIH has built research capacity in other countries is the development by NIAID of International Centers for Excellence in Research (ICER). There are ICERs in Mali, Uganda, India, Cambodia, Peru, Thailand, South Korea and Tanzania, each of which builds local research capacity and focuses on diseases endemic in these countries. NIH Intramural staff oversee and provide training for these ICERs. In addition, several other institutes have established long term collaborations to study the epidemiology of disease in many countries of the world.

Intramural NIH is perhaps the largest training site in the world for international scientists who will return to their home countries to build research capacity. We have over 1,800 visiting fellows at the NIH and over 400 visiting scientists, the majority of whom return home to occupy scientific and medical leadership positions. The biomedical research establishments of many countries of the world have been built by NIH alumni.

A list of NIH intramural global health efforts follows.

Diseases/Conditions

* Aging process (NIA)
* Alcoholism (NIAAA)
* Arthritis and musculoskeletal diseases (NIAMS)
* Cancer (NCI, NIDCR)
* Cardiovascular and hematologic diseases (NHLBI)
* Childhood diseases (NICHD)
* Dental and craniofacial disorders (NIDCR)
* Disease imaging (NIBIB)
* Environmental effects on disease (NIEHS)
* Eye diseases (NEI)
* Hereditary deafness and stuttering (NIDCD)
* HIV/AIDS (NIAID, NCI)
* Methamphetamine and nicotine addiction (NIDA)
* Multiple infectious diseases including TB, malaria, HIV and tropical diseases (NIAID)
* Neurological, psychiatric disorders (NINDS, NIMH)
* Obesity and diabetes (NIDDK)

Current Initiatives

Genomics

* 1000 Genomes Project with UK, China and Germany (NHGRI)
* Behçet's disease with Turkey, UK and Greece (NIAMS)
* Cleft lip and palate in Syria (NHGRI)
* Genome-wide approaches to malarial drug resistance and leishmaniasis (NIAID)
* Genetics of deafness and stuttering in a Pakistani population (NIDCD)
* GWAS of Burkitt's lymphoma in Uganda (NCI-DCEG)
* GWAS of Africans and Chinese to study obesity, hypertension, renal function, and podoconiosis (NHGRI)
* GWAS of lung cancer in non-smoking women in China (NCI)
* Liver cancer via genetic and translational studies with China and Thailand (NCI-CCR)
* Prostate cancer in Barbados and Finland (NHGRI);
* Neurogenetic studies with Mali (NINDS) and UK, Finland, Nigeria and Italy (NIA)
* Systemic juvenile arthritis with UK, Argentina, Canada, France, Italy and Turkey (NIAMS)

Epidemiology

* Aging studies with Italy, Iceland, Russia, Japan (NIA)
* Air pollution in Mexico (NIEHS)
* Aplastic anemia in Thailand (NHLBI)
* Cancer: Gallbladder cancer in Chile; HPV vaccine and natural history studies in Costa Rica; AIDS cancer registry and Burkitt's lymphoma in Uganda; lung cancer due to environmental pollutants in China; non-Hodgkin lymphoma in China and Taiwan; prostate cancer in Ghana; radiation exposure in Japan and Kazakhstan, benzene exposure in workers in China [with CDC]; esophageal and upper gastrointestinal cancers in China, Iran, Kenya, UK (NCI)
* Chemical exposure and reproduction and development in Norway (NIEHS)
* Eye disease with Pakistan, Brazil, Australia, UK and WHO (NEI)
* Viral: HIV, STDs, HPV, HepB and C, rotavirus vaccine studies, hemoglobin mutations affecting malaria (NIAID)

Prevention

* Addiction to methamphetamines, ecstasy, nicotine, cocaine, heroin with Korea, Japan and China (NIDA)
* HIV- and STD-prevention studies in Uganda (NIAID)
* Human monoclonal antibodies for prophylaxis and treatment of infectious diseases caused by microbes including dengue virus and henipaviruses with Malaysia and Australia (NCI-CCR)

Diagnostics

* Autoimmune and immune disorders, a global initiative to develop Luciferase Immunoprecipitation systems for serology (NIDCR)
* Head and neck cancers (NIDCR)
* Hemorrhagic fevers and tuberculosis, improved diagnosis (NIAID)
* Lymphoid malignancies, standardized diagnosis (NCI-CCR)

Small molecule research

* Griffithsin to prevent uptake of HIV with New Zealand (NCI)
* Protease inhibitor (Darunavir) for international patients with HIV (NCI)
* Drugs for TB, anthrax and chlamydia (NIAID)

Vaccine development

* HPV in Costa Rica (NCI)
* Multiple vaccines including Malaria, Anthrax, Rotavirus, West Nile, Leishmaniasis, Ebola, Marburg, Influenza, SARS, Chikungunya, HIV and Chlamydia (NIAID, NCI)

Clinical trials

* In Mali with International Centers for Excellence in Research, ICER: malaria (NIAID)
* In Tanzania: tuberculosis (NIAID with ICER); radiation of glioblastoma multiforme, Xeroderma pigmentosum (NCI-CCR)
* In Uganda with ICER: HIV and Ebola vaccines (NIAID VCR)
* In Cambodia with ICER: tuberculosis, lymphatic filarisis and leishmaniasis (NIAID)
* In Thailand: neurocysticercosis (NIAID with ICER); liver cancer (NCI-CCR)
* In China: malaria (NIAID with ICER); esophageal cancer (NCI-CCR)
* In South Korea with ICER: non-tuberculosis mycobacteria (NIAID)
* In India: HIV and STDs, HepB and malaria (NIAID with ICER); HPV vaccine (NCI); viral infections of the brain (NINDS)
* In Costa Rica: HPV vaccine (NCI-CCR and -DCEG)
* In Peru with ICER: tuberculosis (NIAID)
* In Croatia: lung cancer (NCI-CCR)
* In Germany, France, Italy, Netherlands, UK: Ewing's sarcoma antibody to IGF-1 receptor (NCI-CCR)
* In Sweden: multiple myeloma and AML (NCI)
* In South Africa and in the Caribbean: malaria, filariasis and HIV vaccines (NIAID)
* Obstetrical pediatric malaria

Other priority areas

* HIV transmission prevention with chemopreventives (microbicides) in Russia (NCI-CCR, NIH Office of AIDS Research)
* Inner ear gene therapy via AAV vectors, in Italy (NIDCR)
* Saliva gland disease, pig model for gene therapy in China (NIDCR)
* Sjögren's syndrome in Hungary and Greece (NIDCR)

Current Partnerships

Scientific partnerships

* Aging-related traits and disease risk factors in a Sardinian population cohort (NIA)
* Cancer Center in Jordan (NCI-CCR)
* Consortium of Cohorts, international genetic evaluation of cancer (NCI-DCEG)
* Gates HIV Research Consortia, clinical research in infectious diseases, (NIAID-VRC)
* Human Brain Consortium with Western European countries, severe viral infections (NINDS)
* International Centers for Excellence in Research, ICER (NIAID)
* International Head and Neck Tissue Array Initiative (NIDCR)
* King Hussein Cancer Center and King Hussein Institute for Cancer and Biotechnology in Jordan (NCI, CCR)
* NLM Partnerships for information dissemination including NCBI databases
* NTP collaboration with WHO on effects of chemicals on health (NIEHS)

Training partnerships

NIH intramural research program currently supports pre- and post-doctoral training for 1,893 visiting fellows and advanced research opportunities for 404 research fellows from 92 countries. There are also formal international exchange training programs with 10 countries and graduate partnership programs with four countries. The NIH intramural research program through the NIH Office of Technology Transfer has been conducting a program to train scientists, managers and other qualified personnel from research organizations, universities, and similar health or science and technology institutions from India, China, South Korea, Chile, Mexico, the Philippines, South Africa, Ghana, Zambia, Brazil, Argentina, Croatia and Hungary.

Clinical Research Training: For the 2009-2010 academic year, the Introduction to the Principles and Practice of Clinical Research (IPPCR) course is being videocast simultaneously to nine international sites, and an additional three sites receive archived

lectures the next day (due to logistical challenges of time zones prohibiting real time access). The 2009-2010 Principles of Clinical Pharmacology course is videocast simultaneously to four international sites. In addition, modified live versions of both courses have been taught in China over the past 12 months, and there are plans to offer a course in Nigeria and Russia soon (NIH CC). NINDS runs a training program for medical students in medicine and neurology (Ethiopia). Since 1993, NHLBI has run a reciprocal training program in hematology/oncology in Vietnam with the NIH Clinical Center; courses are held almost annually in Ho Chi Minh City, Hanoi and Hue.

Technology transfer partnerships

The NIH intramural research program has become a key player in transferring new, innovative technologies for neglected diseases in both emerging and developing countries. From a variety of NIH institute providers, license agreements have been put in place by the NIH Office of Technology Transfer with emerging-economy companies (especially in Brazil, China, India, and South Africa) who can now approach neglected diseases as local, business opportunities. Agreements to date have focused on vaccines (Hib, rotavirus, typhoid fever, HPV, hepatitis A, dengue, meningitis) and anti-virals (ddl).

Planned Initiatives for the Next Three Years

Highlighting scientific opportunities

* African Genome Project (NHGRI)
* Neuroscience Center in Shanghai (NIMH)
* Collaboration on early onset schizophrenia in Banglore, India (NIMH)

Effort to fill existing gaps

* 1000 Genomes Project (NHGRI)

Potential partnerships

* International Collaboration on the Genetics of Neural Tube Defects, further international enrollments
* Pesticide exposure in South Africa (NIEHS)

Appendix F: NIH Institutes and Centers

NIH INSTITUTES

National Cancer Institute (NCI) - Est. 1937
NCI leads a national effort to eliminate the suffering and death due to cancer. Through basic and clinical biomedical research and training, NCI conducts and supports research that will lead to a future in which we can prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

National Eye Institute (NEI) - Est. 1968
NEI conducts and supports research that helps prevent and treat eye diseases and other disorders of vision. This research leads to sight-saving treatments, reduces visual impairment and blindness, and improves the quality of life for people of all ages. NEI-supported research has advanced our knowledge of how the eye functions in health and disease.

National Heart, Lung, and Blood Institute (NHLBI) - Est. 1948
NHLBI provides leadership for a national program in diseases of the heart, blood vessels, lung, and blood; blood resources; and sleep disorders. Since October 1997, the NHLBI has also had administrative responsibility for the NIH Woman's Health Initiative. The Institute plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects.

National Human Genome Research Institute (NHGRI) - Est. 1989
NHGRI supports the NIH component of the Human Genome Project, a worldwide research effort designed to analyze the structure of human DNA and determine the location of the estimated 30,000 to 40,000 human genes. The NHGRI Intramural Research Program develops and implements technology for understanding, diagnosing, and treating genetic diseases.

National Institute on Aging (NIA) - Est. 1974
NIA leads a national program of research on the biomedical, social, and behavioral aspects of the aging process; the prevention of age-related diseases and disabilities; and the promotion of a better quality of life for all older Americans.

National Institute on Alcohol Abuse and Alcoholism (NIAAA) - Est. 1970
NIAAA conducts research focused on improving the treatment and prevention of alcoholism and alcohol-related problems to reduce the enormous health, social, and economic consequences of this disease.

National Institute of Allergy and Infectious Diseases (NIAID) - Est. 1948
NIAID research strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten millions of human lives.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) - Est. 1986
NIAMS supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases.

National Institute of Biomedical Imaging and Bioengineering (NIBIB) - Est. 2000
NIBIB improves health by promoting fundamental discoveries, design and development, and translation and assessment of technological capabilities in biomedical imaging and bioengineering, enabled by relevant areas of information science, physics, chemistry, mathematics, materials science, and computer sciences.

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) - Est. 1962
NICHD research on fertility, pregnancy, growth, development, and medical rehabilitation strives to ensure that every child is born healthy and wanted and grows up free from disease and disability.

National Institute on Deafness and Other Communication Disorders (NIDCD) - Est. 1988
NIDCD conducts and supports biomedical research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language that affect 46 million Americans.

National Institute of Dental and Craniofacial Research (NIDCR) - Est. 1948
NIDCR provides leadership for a national research program designed to understand, treat, and ultimately prevent the infectious and inherited craniofacial-oral-dental diseases and disorders that compromise millions of human lives.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) - Est. 1948
NIDDK conducts and supports basic and applied research and provides leadership for a national program in diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Several of these diseases are among the leading causes of disability and death; all seriously affect the quality of life of those who have them.

National Institute on Drug Abuse (NIDA) - Est. 1973
NIDA leads the nation in bringing the power of science to bear on drug abuse and addiction through support and conduct of research across a broad range of disciplines and rapid and effective dissemination of results of that research to improve drug abuse and addiction prevention, treatment, and policy.

National Institute of Environmental Health Sciences (NIEHS) - Est. 1969
NIEHS reduces the burden of human illness and dysfunction from environmental causes by, defining how environmental exposures, genetic susceptibility, and age interact to affect an individual's health.

National Institute of General Medical Sciences (NIGMS) - Est. 1962
NIGMS supports basic biomedical research that is not targeted to specific diseases. NIGMS funds studies on genes, proteins, and cells, as well as on fundamental processes like communication within and between cells, how our bodies use energy, and how we respond to medicines. The results of this research increase our understanding of life and lay the foundation for advances in disease diagnosis, treatment, and prevention. NIGMS also supports research training programs that produce the next generation of biomedical scientists, and it has special programs to encourage underrepresented minorities to pursue biomedical research careers.

National Institute of Mental Health (NIMH) - Est. 1949
NIMH provides national leadership dedicated to understanding, treating, and preventing mental illnesses through basic research on the brain and behavior, and through clinical, epidemiological, and services research.

National Institute of Neurological Disorders and Stroke (NINDS) - Est. 1950
The mission of the NINDS is to reduce the burden of neurological diseases -- a burden borne by every age group, every segment of society, and people all over the world. To accomplish this goal the NINDS supports and conducts research, both basic and clinical, on the normal and diseased nervous system, fosters the training of investigators in the basic and clinical neurosciences, and seeks better understanding, diagnosis, treatment, and prevention of neurological disorders.

National Institute of Nursing Research (NINR) - Est. 1986
NINR supports clinical and basic research to establish a scientific basis for the care of individuals across the life span--from the management of patients during illness and recovery to the reduction of risks for disease and disability; the promotion of healthy lifestyles; the promotion of quality of life in those with chronic illness; and the care for individuals at the end of life. This research may also include families within a community context, and it also focuses on the special needs of at-risk and under-served populations, with an emphasis on health disparities.

National Library of Medicine (NLM) - Est. 1956
NLM collects, organizes, and makes available biomedical science information to scientists, health professionals, and the public. The Library's Web-based databases, including PubMed/Medline and MedlinePlus, are used extensively around the world. NLM conducts and supports research in biomedical communications; creates information resources for molecular biology, biotechnology, toxicology, and environmental health; and provides grant and contract support for training, medical library resources, and biomedical informatics and communications research.

NIH CENTERS

Center for Information Technology (CIT) - Est. in 1964
CIT incorporates the power of modern computers into the biomedical programs and administrative procedures of the NIH by focusing on three primary activities: conducting-computational biosciences research, developing computer systems, and providing computer facilities.

Center for Scientific Review (CSR) - Est. in 1946
CSR is the focal point at NIH for the conduct of initial peer review, the foundation of the NIH grant and award process. The Center carries out peer review of the majority of research and research training applications submitted to the NIH. In addition, the Center serves as the central receipt point for all such Public Health Service (PHS) applications and makes referrals to scientific review groups for scientific and technical merit review of applications and to funding components for potential award. To this end, the Center develops and implements innovative, flexible ways to conduct referral and review for all aspects of science.

John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) - Est. in 1968
FIC promotes and supports scientific research and training internationally to reduce disparities in global health.

National Center for Complementary and Alternative Medicine (NCCAM) - Est. in 1999
NCCAM is dedicated to exploring complementary and alternative medical (CAM) practices in the context of rigorous science; training CAM researchers and disseminating authoritative information.

National Center on Minority Health and Health Disparities (NCMHD) - Est. in 1993
The mission of NCMHD is to promote minority health and to lead, coordinate, support, and assess the NIH effort to reduce and ultimately eliminate health disparities. In this effort NCMHD will conduct and support basic, clinical, social, and behavioral research, promote research infrastructure and training, foster emerging programs, disseminate information, and reach out to minority and other health disparity communities.

National Center for Research Resources (NCRR) - Est. in 1962
NCRR provides laboratory scientists and clinical researchers with the environments and tools they need to understand, detect, treat, and prevent a wide range of diseases. With this support, scientists make biomedical discoveries, translate these findings to animal-based studies, and then apply them to patient-orientated research.

NIH Clinical Center (CC) - Est. in 1953
CC is the clinical research facility of the National Institutes of Health. As a national resource, it provides the patient care, services, and environment needed to initiate and support the highest quality conduct of and training in clinical research.

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