Office of Research on Women's Health (ORWH)
Research Summaries, FY 2009

Office of the Director
National Institutes of Health

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ORWH RESEARCH SUMMARIES, FY 2009

ADOLESCENT HEALTH

5P01 HD031921-14
The National Longitudinal Study of Adolescent Health (Add Health)
Harris, Kathleen Mullan
University of North Carolina, Chapel Hill
$200,000
Add Health is currently funded for Wave IV data collection. At the time the project began in 1994-1995, investigators selected a nationally representative sample of adolescents in grades seven through 12. Participants have been followed through adolescence and the transition to adulthood with three in-home interviews. Wave IV will include additional information that encompasses social, behavioral, and biological data. In addition to data contributed in earlier surveys, these subjects, who are now between the ages of 23 and 31 years, will provide biological data to capture the prevailing health concerns as well as biological markers of future chronic health conditions.

AGING

5R37 AG030481-02
National Social Life, Health, and Aging Project
Waite, Linda J.
National Opinion Research Center, Chicago, IL
$400,000
The National Social Life, Health and Aging Project (NSHAP) was established as an innovative, high-quality dataset for use by researchers studying the relationships between social processes and health among older adults. Wave I obtained questionnaire and biomeasure data on a nationally-representative sample of 3,005 community-dwelling adults ages 57-85 in 2005/6. The second wave in NSHAP is designed to obtain data on social networks and social support, marital and co-habitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. They propose to revisit respondents four years after their initial interview. Using these data, they can describe and model the distribution of changes in health, well-being, social networks, social participation and social context. In each case, they shall examine the distributions both for the entire sample and within subgroups defined by key sociodemographic characteristics such as gender, race/ethnicity, and socioeconomic status. They also propose to augment the sample by interviewing the spouse/cohabitating romantic partner. These data will allow us to characterize the impact of marital and romantic relationships on health by examining the effects of one person's characteristics and behaviors on the health of the other. They will also

analyze the partnerships themselves, and assess the relationship between characteristics of the partnership, such as support, closeness and mistreatment, and the health of each of the partners. In sum, they will explore their overarching hypothesis that older adults with strong functioning intimate relationships will show more positive (or less negative) health trajectories that those who have weaker relationships or lack such relationships altogether. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age.

1 R21 NR010368-01A2
Teaching Resourcefulness to Women Caregivers of Elders with Dementia
Zauszniewski, Jaclene
Case Western Reserve, Cleveland, OH
$200,000
Dementia is one of the greatest challenges facing elders in the U.S. and the public health significance of dementia caregiving has permeated the scientific and lay literature for decades. Despite the number of clinical trials testing interventions for reducing caregiver stress, none have tested methods of teaching them resourcefulness skills and none have allowed caregivers to choose a preferred intervention. Resourcefulness Training, the intervention to be tested in this study, is a cost-effective, easy-to-use method for reducing caregiver stress and promoting their optimal mental health. The resourcefulness training (RT) intervention has strong theoretical grounding and there is beginning empirical evidence for its effectiveness in reducing stress, minimizing depressive symptoms, and promoting optimal quality of life for populations other than women dementia CGs. The proposed 2-year pilot study will provide qualitative and quantitative data for determining the necessity, acceptability, feasibility, fidelity, safety, and effectiveness of two innovatively designed methods of RT within the context of a small partially randomized preference trial with 120 women dementia CGs. In RT, the two methods to be tested (expressive writing, EW) and verbal disclosure, VD) are used for practicing / reinforcing resourcefulness skills. However, because research has shown that both EW and VD may be effective stress-reducing techniques, they will also examine those effects without RT. They propose that RT reinforced by EW or VD will provide CGs with essential skills for managing stress and preserving mental and physical health while providing care for their elderly care recipients (CRs). Quantitative data on measures of stress, cognitions, emotions, resourcefulness, and mental and physical health will be collected at baseline (T1) and at 1 week (T2) and 6 weeks (T3) post-intervention. Qualitative data will be obtained from CG journal (EW) / recordings (VD), data collector's field notes, follow-up logs, etc. Baseline Resourcefulness Scale (RS) scores and qualitative data from journals / recordings will be used to examine the necessity of the RT. CGs will be randomized into "random" or "choice" conditions and their data (i.e., journals, recordings, field notes, follow-up logs, participation / retention logs) will be examined to determine acceptability, feasibility, and fidelity of RT. Safety of RT will be monitored for adverse events and reports of psychological distress or elder abuse. Effectiveness of RT-EW and RT-VD (compared to EW and VD without RT) will be examined in relation to specific outcomes at time intervals suggested by Resourcefulness Theory and in relation to factors within the CG, CR, and CG situation. Most importantly, they will learn whether giving CGs a choice of EW or VD with

or without RT improves their outcomes. Conclusions drawn from the critical examination of the six intervention parameters will inform further refinement and testing of RT for dementia CGs in a full scale randomized, controlled trial. Once established, such interventions will be useful in promoting optimal, healthy functioning among dementia CGs so that they can continue to provide adequate care for their CRs without sacrificing their own health and avoid placement of the elder in a long term care facility.

ALCOHOL AND OTHER SUBSTANCE ABUSE

5R21 DA020117-02
Sex Differences in Vulnerability to Cocaine Addiction
Kosten, Therese A.
Baylor College of Medicine
$ 20,000
Understanding sex differences in the initiation to addiction are important goals that need to be addressed. The study proposes a novel yet hypothesis-based approach to examine sex differences in stress responsivity and addiction using established animal procedures. Stress responsivity relates to acquisition of cocaine self-administration, an animal model of vulnerability to addiction. Stress responsivity shows sex differences but reports on self-administration are conflicting. Links between maternal care and stress responsivity of offspring are proposed; greater care relates to lower stress responsivity of adults. Maternal care differs by pup sex; male pups receive more care than female pups. Adult males show lower stress responsivity than females consistent with the link of maternal care with stress responsivity. The proposal hypothesizes that sex-dependent maternal care influences sex differences in stress responsivity and cocaine self-administration in the adult. The investigators will test this by manipulating maternal care via altering litter gender composition (LGC; single- vs mixed-sex litters) because pups of single-sex litters receive more care than pups of mixed-sex litters. LGC influences stress responsivity in infant mice and juvenile and maternal behaviors in rats and mice. They predict both male and female adult rats of single-sex litters will show lower stress responsivity than offspring of mixed-sex litters.

1R21AA018398-01
Interactive Effects of Ethanol and Estrogen on Brain Vasopressin during Puberty
Pak, Toni R.
Loyola University Chicago
$224,250
Women who abuse alcohol are twice as likely to develop anxiety disorders compared with men, a phenomenon in which the underlying biological mechanisms are unknown. The investigators overall objective is to identify the interactive effects of alcohol and estrogen on arginine vasopressin (AVP), a well-established key molecular mediator of anxiety, in order to elucidate the molecular mechanisms predisposing women to increased risk of anxiety disorders. Adolescent binge drinking is a potential risk factor for the development of adult anxiety disorders due to the heightened stress reactivity that occurs as a direct result of increased circulating estrogens during pubertal development. Little is known about the long-term neurobiological consequences of alcohol consumption during puberty, which is a

dynamic and important period of brain development that involves changes in cortical gray matter, synaptic connectivity, and increased neurogenesis. Exposure of alcohol during this critical period of extensive brain remodeling may result in permanent neuronal damage or disruptions in the formation of new neuronal connections, which might manifest as adult behavioral psychoses, including anxiety disorder. The researchers' preliminary data show that alcohol exposure during puberty increased AVP gene expression in specific regions of the brain. Moreover, estrogen exacerbates the effects of alcohol on AVP gene expression. Also, their preliminary data demonstrate that alcohol treatment and estrogen receptor ligands increased AVP gene expression in neuronal cells derived from the hypothalamus, and gene expression is closely correlated with the activity of the gene promoter. Alcohol also activates estrogen-signaling pathways in the brain, which suggests that the underlying mechanisms for alcohol-induced changes in AVP may be mediated by estrogen signaling pathways. To date, specific molecular and neuroendocrine markers that are activated by alcohol during puberty have not been identified. This proposal is focused on a specific candidate gene (AVP) and its downstream signaling pathways that are developmentally shaped during puberty. Significance of the application: Women who abuse alcohol are twice as likely to develop anxiety disorders compared with men, a phenomenon in which the underlying biological mechanisms are unknown. This proposal is focused on a specific candidate gene (AVP) and its downstream signaling pathways that are developmentally shaped during puberty. They expect these studies to show that AVP is permanently altered, either as a direct target for alcohol or indirectly through steroid hormone receptor signaling pathways. Thus, the value of this research lies in the potential for therapeutic approaches that would target specific genes and perhaps reverse brain damage caused by alcohol consumption during pubertal development as well as strengthen reasons for abstaining from alcohol during that time.

1R21HD058989-01A1
Novel Approaches to Understanding Mental Disorder, Substance Abuse and HIV-Risk A
Whitbeck, Leslie B.
University of Nebraska Lincoln
$145,180
The overall research objective of this application seeks to develop state-of-the-science methodologies to address four important gaps in existing research with homeless women: 1) capture the diversity of circumstances among a fluid and hard-to-access population; 2) increase their understanding of mental and substance use disorders (particularly personality disorders) across the diversity of homeless women; 3) improve their understanding trajectories to homelessness through development of an innovative event history calendar approach; and 4) advance knowledge of homeless women's health and HIV-risk by circumstance and trajectories to homelessness. This research will provide measurement development and preliminary studies for a multi-state longitudinal R01 designed to advance their understanding of mental and substance use disorders among homeless women, their movement into and out of homelessness, the consequences of homelessness for women and minor children in their custody, and women's health, HIV-risk, and HIV testing behaviors. The planned longitudinal research will focus on a growing but poorly understood population of the nation's most vulnerable women. Significance of The Application: This application will set the stage for the first multi-state longitudinal diagnostic study of homeless women. It builds on more than a decade of work with hard to access homeless populations and a prior

three-year longitudinal diagnostic study of homeless adolescents. This application will fund the development of innovative measures and sampling techniques specifically for this understudied population and for the piloting of measures with a sample of 200 homeless women in two Midwestern cities.

1R21DA027145-01
An Ethnographic and Economic Investigation of the Fresh Start Program (Detroit)
Roddy, Juliette Kathryn
University of Michigan at Dearborn
$270,375
Aside from journalistic accounts detailing the pitfalls of drug treatment, little research has been done on the recovery process as it actually proceeds within particular programs. Research is not always well incorporated into treatment settings, which may resist innovations due to internal organizational factors. Conducting research in criminal justice settings, including drug courts or programs administered through drug courts, is also problematic. Nonetheless, more such research is needed as treatment and recovery services become central features of the national response to substance abuse, especially in an era of prison downsizing. This will also require research that actively engages with communities and institutions (Sterk 1999). The proposed research will work collaboratively with multiple agencies to investigate the process of treatment and recovery as it occurs in women who participate in Fresh Start. Fresh Start is a substance abuse intervention program for female street sex workers who have come into repeated contact with law enforcement. Fresh Start is a coercive recovery-based program that serves as a direct contrast to voluntary, traditional, treatment-based programs. The program serves as an alternative to jail time for these women, who are arrested in periodic sweeps of neighborhoods where street prostitution is common. Using interdisciplinary methods, they will seek evidence of desired change in social networks, sociospatial contexts, and economic behaviors, resources and outcomes. Treatment professionals and substance abuse researchers agree that both successful drug abuse recovery and exiting street prostitution require changes in social networks and accompanying economic independence. The significance of the application is that these changes can be both quantitatively and qualitatively described by studying street prostitutes who are engaged in the treatment and recovery process through the application of ethnographic and economic instruments and an accompanying mapping of changing social networks. The proposed work has implications for women's health and welfare and the prevention and treatment of sexually transmitted disease.

1R21AA018398-01
Interactive Effects Of Ethanol And Estrogen On Brain Vasopressin During Puberty
Pak, Toni R.
Loyola University Chicago
$224,250
Women who abuse alcohol are twice as likely to develop anxiety disorders compared with men, a phenomenon in which the underlying biological mechanisms are unknown. Their overall objective is to identify the interactive effects of alcohol and estrogen on arginine vasopressin (AVP), a well-established key molecular mediator of anxiety, in order to elucidate the molecular mechanisms predisposing women to increased risk of anxiety

disorders. Adolescent binge drinking is a potential risk factor for the development of adult anxiety disorders due to the heightened stress reactivity that occurs as a direct result of increased circulating estrogens during pubertal development. Little is known about the long-term neurobiological consequences of alcohol consumption during puberty, which is a dynamic and important period of brain development that involves changes in cortical gray matter, synaptic connectivity, and increased neurogenesis. Exposure of alcohol during this critical period of extensive brain remodeling may result in permanent neuronal damage or disruptions in the formation of new neuronal connections, which might manifest as adult behavioral psychoses, including anxiety disorder. Their preliminary data show that 1) alcohol exposure during puberty increased AVP gene expression in specific regions of the brain. Therefore, the experiments proposed in Specific Aim 1 will directly test the hypotheses that there is a critical window of time during pubertal development when the AVP system is most vulnerable to the effects of alcohol and (2) that estrogen exacerbates the effects of alcohol on AVP gene expression. Also, their preliminary data demonstrate that alcohol treatment and estrogen receptor ligands increased AVP gene expression in neuronal cells derived from the hypothalamus, and gene expression is closely correlated with the activity of the gene promoter. Alcohol also activates estrogen-signaling pathways in the brain, which suggests that the underlying mechanisms for alcohol-induced changes in AVP may be mediated by estrogen signaling pathways. Therefore, the experiments proposed in Specific Aim 2 will directly test the hypotheses that (1) acute alcohol exposure increases AVP promoter activity in neuronal cells, (2) that there are specific regulatory regions of the AVP promoter that interact with alcohol, and (3) that estrogen and alcohol interact synergistically to increase AVP promoter activity. To date, specific molecular and neuroendocrine markers that are activated by alcohol during puberty have not been identified. This proposal is focused on a specific candidate gene (AVP) and its downstream signaling pathways that are developmentally shaped during puberty. They expect these studies to show that AVP is permanently altered, either as a direct target for alcohol or indirectly through steroid hormone receptor signaling pathways. Thus, the value of this research lies in the potential for therapeutic approaches that would target specific genes and perhaps reverse brain damage caused by alcohol consumption during pubertal development as well as strengthen reasons for abstaining from alcohol during that time.

CANCER

5U01 GM061373-10
Pharmacogenetics Research Network and Knowledge Base
Flockhart, David Alastair
Indiana Univ-Purdue; Univ at Indianapolis
$230,171
Drugs that interfere with the actions of estrogen represent a cornerstone in the treatment of breast cancer, and are important tools with which to study the actions of estrogen in women. These drugs are increasingly effective in breast cancer, but which drug is best for each woman remains unclear. Their work in the first cycle of the Pharmacogenetics Research Network identified, through a series of laboratory and clinical studies, new genetic patterns that predict effects of the estrogen receptor modulator tamoxifen. They will build on these data to examine the influence of an extended series of candidate genes on the effects of the aromatase

inhibitor class of drugs and to refine the genetic signatures that predict tamoxifen effects. This will involve the following broad specific aims: 1) To identify common genetic variants of the human estrogen receptors and important nuclear coactivators and repressers of these receptors using a combined bioinformatic and direct sequencing approach; 2) To test the hypothesis that these variants alter gene expression or function using in vitro assays; 3) To test the contribution of variants identified during specific aim 1 and 2 to tamoxifen response in the clinical trial of tamoxifen pharmacogenetics already conducted. 4) To characterize the involvement of genetically polymorphic drug metabolizing enzymes in the human metabolism of the available aromatase inhibitors: letrozole, exemestane and anastrozole in vitro. 5) To test the hypothesis that variants in candidate genes identified in aims 1-4 are associated with well curated phenotypic outcomes, including estrogen metabolite concentrations, pharmacokinetics, hot flashes, breast density, bone metabolism and serum lipid subfractions in breast cancer patients receiving anastrozole, exemestane and letrozole. The results of this proposal will generate new information that, linked with their novel tamoxifen pharmacogenetics findings, will generate a series of genetic tools key to optimizing drug selection for women with breast cancer and to their understanding of the mechanisms of estrogen action.

5R21 CA134960-02
Novel Ovarian Cancer Detection Agents from Phage Display
Deutscher, Susan L.
University of Missouri-Columbia, Columbia, MO
$ 20,000
Ovarian adenocarcinomas are the largest class of gynecologic malignancies in the United States with respect to incidence and mortality. While treatable in their earliest stage, advanced or metastatic forms of ovarian cancer are usually deadly. Because ovarian cancer is often asymptomatic in its early stages, ~70% of patients have advanced or metastatic disease at time of diagnosis. Current screening methods include ultrasonography, pelvic exam, and serum screening for CA125. Unfortunately, these tests are not specific for ovarian cancer and invasive surgical biopsy is required for proper diagnosis. Improved early diagnosis and therapy will result from a more directed approach in which antigens specific to or overexpressed on ovarian tumor cells are targeted. New peptide-based molecular probes to facilitate cancer detection and imaging are rapidly evolving due to implementation of bacteriophage (phage) display approaches. Here, it is hypothesized that phage selected in vivo, in human ovarian tumor-bearing mice, once fluorescently labeled, can be easily re-screened in vivo for tumor-homing propensity, thus streamlining the process of development of peptide-based ovarian cancer imaging and therapeutic agents. Radiolabeled versions of the identified peptides will be examined for their ability to image ovarian tumors in mice using Single Photon Emission Computed Tomography (SPECT). A long-term goal of this work is to translate the radiolabled peptides into the clinic for the non-invasive screening and detection of ovarian cancer. Specifically, the study proposes to obtain new classes of ovarian cancer targeting peptides by performing in vivo phage display selections in human ovarian carcinoma-bearing mice. Second, phage selected from the screens will be fluorescently labeled and employed in vivo optical imaging screens to expedite discovery of new ovarian tumor imaging agents. Last, peptides corresponding to phage with optimal in vivo imaging properties will be synthesized and radiolabled with 111In and 99mTc and examined for their

SPECT imaging efficacy in vivo. Novel phage display and peptide radiochemistry approaches are described to advance the detection of ovarian cancer a cancer that deserves much more research and attention.

1 R21 AT005139-01
Exploratory Studies on the Anti-Breast Cancer Function of Bamboo Extract
Panee, Jun
University of Hawaii
$200,000
Breast Cancer is the most common cancer among American women, and existing treatments are expensive, debilitating, and extremely arduous for its victims, and often have long-lasting adverse effects. This project aims to explore the anti-breast cancer function of an ethanol/water extract from bamboo Phyllostachys edulis, one of the most widely distributed and fastest growing plants in the world. The long-term goal of this study is to develop this bamboo extract into a safe, efficient, low cost, and easily accessible dietary supplement for chemoprevention of breast cancer in high-risk populations, such as people carrying mutations of breast cancer susceptibility gene 1 (BRCA1). Breast cancer is the most prevalent cancer among women in the United States. DNA damage induced by chemical exposure and oxidative stress, as well as estrogenic regulation of mammary gland differentiation and tumor growth are among the critical factors affecting the incidence and development of breast cancer. Research carried out in the laboratory of the Principle Investigator (Principal Investigator) focused on the anti-breast cancer function of an ethanol/water extract from bamboo Phyllostachys edulis, one of the most widely distributed and fastest growing plants in the world. The preliminary studies revealed that bamboo extract (BEX) contained a high level of flavonoids, and significantly enhanced the resistance of mammalian cells to varied oxidative stresses. BEX as a dietary supplement (0.5%, w/w) delayed the onset of palpable mammary tumors induced by 7,12-dimethylbenz[a]anthracene (DMBA) in female Sprague-Dawley (SD) rats, decreased the tumor incidence by 44%, and dramatically reduced tumor multiplicity. BEX supplementation also enhanced the activity of sulfotransferases (SULT) in the liver, an enzyme family that conjugates estrogens. The preliminary results indicate that BEX may affect the functions of multiple tissues that synergistically lead to the anti-breast cancer effect. This project will examine the hypothesis under two Specific Aims: Aim 1. To investigate BEX- induced changes in mammary tumors. Magnetic Resonance Imaging (MRI) techniques will be employed in this study to closely monitor the starting time and accurately measure the growth rate of the micro-tumors in the mammary glands before they would be perceptible by the regular palpation method; thereby efficiently evaluating the inhibitory effects of BEX on the initiation and early-stage promotion of the mammary tumor. The gene expression of key factors in cellular senescence, proliferation and apoptosis pathways, and oxidative stress damage on DNA and proteins in the tumor tissues will be assessed at different developmental stages to reveal BEX-induced changes on the molecular levels. Aim 2. To investigate BEX-induced changes in both mammary glands and the liver that favor breast cancer prevention. These include: (i) Inhibition on the carcinogenic effects of DMBA through: (a) regulation of the metabolism of DMBA in the liver and mammary tissues, and (b) amelioration of DMBA-induced oxidative stress in the mammary glands. (ii) Enhancement of estrogen metabolism through up-regulation of SULT activity in the liver. (iii) Acceleration of mammary gland differentiation through its potential phytoestrogenic activity. Successful

performance of this project will direct more focused research into the cellular and molecular pathways, the major target tissues, and the critical time periods through which BEX exerts the anti-breast cancer function. This will lay a firm basis for the Principal Investigator to achieve the long-term goal of characterizing the potentially novel anti-breast cancer compound(s) in BEX, improving the efficiency of the product, and eventually applying this abundant, easily available and sustainable natural resource in the chemoprevention of breast cancer in human subjects.

1R21CA140916-01
Mitochondrial Catalase as a Treatment for Metastatic Breast Cancer
Ladiges, Warren C.
University of Washington
$171,600
The chance of developing invasive breast cancer during a woman's lifetime is approximately 1 in 8 and more than 40,000 women die of metastatic disease each year. Inherent or acquired tumor drug resistance and dose-limiting toxicity limit many agents used in the treatment of invasive breast cancer. Therefore, an important goal is the development of novel non-toxic therapeutic agents that are active against this deadly disease. Based on preliminary data that showed showing mitochondrial catalase (mCAT) reduces metastatic progression of primary breast cancer in mice, suggesting that targeting mitochondria with catalase could be a potential strategy to treat or prevent metastatic breast cancer in women. The data generated in this proposal would confirm their preliminary observations and provide the rationale for developing and/or testing clinically relevant mitochondrial-specific drug delivery systems for treating metastatic breast cancer. The significance of this project is that it is designed to determine the ability of mitochondrially targeted catalase to suppress metastatic breast cancer in mice.

1R21CA141112-01
Gender Selectivity to Colon Cancer Chemoprevention by NSAIDS
Roy, Hemant K., Wali, Ramesh K.
Evanston Northwestern Healthcare
$201,300
Colorectal cancer (CRC) is the second leading cause of cancer deaths among Americans. With proper screening and removal of adenomatous polyps, CRC risk reduction has been very promising. However, only ~50% of the at-risk population (age >50) receives any sort of screening and many undergo tests with suboptimal sensitivity. This underscores the need for developing alternate cancer prevention strategies such as chemoprevention. Of the myriad of purported agents, nonsteroidal anti-inflammatory drugs (NSAIDS) have reliably shown a positive outcome. Indeed, epidemiological, experimental and clinical trials unequivocally point to the CRC preventive benefits of NSAIDS. However, the efficacy is relatively modest (30-50% risk reduction) and requires more than a decade to show significant benefits. In addition, the use of NSAIDS has been shown linked to severe side-effects including ulcers, GI bleeding, hemorrhagic strokes etc, thereby cautioning that the risks may outweigh the benefits of aspirin and NSAIDS in preventing CRC for average risk use. To improve the risk-benefit analysis, it is therefore critical to selectively target subjects that can efficiently respond to chemopreventive efficacy of NSAIDS and at the same time leave out the population least

likely to benefit. It is conceivable that responsive patients could be targeted with lower efficacious doses to avoid associated toxicity. Gender is an important risk factor for CRC with women frequently having biological differences (higher prevalence of proximal lesions, DNA mismatch repair deficient tumors etc). Estrogen is a well-accepted chemopreventive agent against CRC. Moreover, the investigators reported that women have altered susceptibility to both genetic and environmental CRC risk factors. The epidemiological data has some studies suggesting an improved chemopreventive response to NSAIDS although there are discordant reports in the literature. Thus, the issue of whether women are more sensitive to NSAID chemoprevention is unresolved with possibility that NSAID type, dose etc may play a role. The investigators recently conducted a chemoprevention trial using the NSAID celecoxib in a well-validated model of intestinal tumorigenesis, the MIN mouse and noted that in this model, females were more responsive to the chemopreventive effects of celecoxib. The chemopreventive response was found to have regional propensity with stronger efficacy in the proximal intestine. Furthermore, celecoxib treated female mice had higher levels of mucosal estrogen receptor-2 (ER2) levels. The signifiance of the application is that the proposed studies will address the role of estrogen in gender selective chemopreventive efficacy of NSAIDS. These findings will have an important bearing on the healthcare recommendations for colon cancer chemoprevention which have to be cognizant of this gender selective efficacy for maximum cost-benefit potential of NSAIDS.

1R21CA135532-01A1
Regulation of Breast Cancer Progression by FAK Expression in Tumor Macrophages
Bouton, Amy H.; Parsons, J Thomas
University of Virginia Charlottesville
$198,087
The growth and metastatic spread of solid tumors is controlled by signals emanating from tumor cells as well as by immune cells and fibroblasts in the surrounding stroma, components of the extracellular matrix, and soluble growth factors and cytokines. While this complexity creates challenges for therapeutic intervention, it also provides unique opportunities by making available a number of distinct cellular and molecular targets that can be exploited to control tumor growth and progression. The focus of this proposal is on Focal Adhesion Kinase (FAK), a protein tyrosine kinase whose expression is significantly increased in many late-stage cancers, including breast cancer. The applicants hypothesize that FAK expression in two components of the tumor microenvironment, the tumor cells and tumor-associated macrophages (TAMs), plays a critical role in promoting breast tumor progression and metastasis. The applicants will use mouse models of breast cancer to gain an understanding of how FAK expression in breast carcinoma cells and/or the ancillary tumor-associated macrophages controls primary breast tumor growth and metastatic spread.
Globally,knowledge will be about mechanisms through which tumor cells and other cells within the tumor microenvironment communicate to promote breast tumor growth and metastasis. The signifiance of the application is that the study proposes to focus on the role of FAK in both macrophages and tumor cells, this work will uncover novel features of macrophage - tumor cell synergy that contribute to breast tumor behaviors. In addition to providing critical information about how FAK inhibitors should be used to treat breast cancer patients, this work will potentially identify new strategies for targeting distinct cellular compartments within the tumor that can be exploited therapeutically to control tumor growth

and progression. It is anticipated that, through the knowledge gained from these studies, there will be a significant reduction in mortality from breast cancer.

1R21CA134882-01A1
Antagonism of the Ah Receptor in Controlling Breast Cancer Growth and Invasion
Schlezinger, Jennifer J.
Boston University Medical Campus
$214,500
Historically, the aryl hydrocarbon receptor (AhR) has been studied for its transcriptional regulation of genes encoding cytochrome P450 enzymes, which metabolize environmental and endogenous substrates into toxic and mutagenic intermediates. Accumulating studies support the hypothesis that the AhR also plays an important role in malignant epithelial cell growth and invasion apart from its role in formation of mutagens and in the absence of environmental chemicals. This new paradigm is based on several key observations: 1) AhR expression is increased dramatically in carcinogen-induced rat and mouse mammary tumors and in 'spontaneous' human mammary tumor lines. 2) Constitutive AhR activation is indicated by nuclear AhR localization in rat, mouse, and human mammary tumors and by AhR binding to gene promoters in the absence of environmental chemicals. 3) Constitutively active AhR regulates the expression of multiple genes, including CYP1B1, CK21, and Slug, a master regulator of tumor invasion. 4) Recent studies suggest that increased AhR activity in mammary tumors also contributes to cell migration and invasiveness. 5) Molecular downregulation of the AhR suppresses breast cancer cell proliferation and reverts cells to a non-aggressive phenotype. Molecular and biologic strategies have provided significant evidence that the AhR participates, beyond mutagenesis, in multiple mechanisms that contribute to tumor formation, growth and invasion. Therefore, the proposal has the ability to examine effects of constitutively active AhR to determine how chemical antagonism of the AhR may translate into breast cancer prevention or a therapeutic approach to suppress tumor progression. The translational impact of these studies lies in the ability of known and newly identified antagonists to suppress tumor growth and invasion. Here, potentially therapeutic AhR antagonists will be evaluated for their ability to block the biological outcomes of constitutive AhR activity in human mammary tumor cell lines. Collectively, these studies will provide the foundation for preclinical studies on the potential for potent AhR antagonists to prevent and/or treat breast cancer in vivo. The signifiance of the application is that the study hypothesizes that the hyper-expression of a protein, called the aryl hydrocarbon receptor, and its binding to DNA contributes to the growth and progression of breast tumors. The applicants propose that chemicals that impede the function of this receptor (i.e. antagonists) will be effective at downregulating this protein's activity and therefore will suppress breast tumor growth and metastasis. Screening of plant and marine natural product libraries will provide a source of novel antagonists that can be tested for their interaction with this receptor and their mechanism of interference with tumor growth, ultimately resulting in the development of therapeutic agents for the treatment of breast cancer.

N01CP11005
Costa Rica HPV-16/18 Vaccine Trial (CVT)
Hildesheim, Allan,
NCI, Bethesda

$400,000
The ORWH has supported infrastructure costs associated with the Costa Rica HPV Vaccine Trial (CVT) since its inception. In FY09, support in the amount of $400,000 was provided. These funds were utilized to support continued follow-up and clinical management of the 7,466 women enrolled in this community-based, randomized, phase III clinical trial and for the enrollment of participants into the extended follow-up phase of the trial (planned for an additional 6 years beyond the initial, 4-year blinded phase). More specifically, funds provided by ORWH in FY09 supported the following activities: 1) Continued blinded follow-up screening of trial participants, 2) Referral of participants with evidence of high-grade disease to colposcopy and treatment, 3) Initiation of 4-year study visits (final visit under the blinded design - Approximately 2,000 such visits of expected total of 7,000 were performed in FY09), 4) Consenting of women into their Long-Term Follow-up Study (Approximately 2,000 women of expected total of 7,000) were consented in FY09, 5) Initiation of recruitment of new control group for the Long-Term Follow-up- Study (Approximately 700 women of expected total of 3,000) were recruited in FY09, and 6) Additional collection of specimens from the vulva, anus, and oral cavity to allow for the evaluation of vaccine efficacy at sites other than the cervix. The activities funded by ORWH in FY09 and preceding years have resulted in several important publications in the peer-reviewed literature. These are included in the attached reference list.

N02CP31003
Evaluation of Vaccine Efficacy at Extra-Cervical Sites in the Costa Rica HPV-16/18 Vaccine Trial (CVT)
Kreimer, Aimee; Hildesheim, Allan
NCI, Bethesda
$700,000
The ORWH has supported infrastructure costs associated with the Costa Rica HPV Vaccine Trial (CVT) since its inception. In FY09, additional one-shot funds in the amount of $700,000 were provided to this project to allow for the evaluation of the efficacy of the bivalent HPV-16/18 vaccine to protect against HPV-16/18 infection at cutaneous and mucosal sites other than the cervix. Since the HPV-16/18 vaccine has shown near complete protection against HPV-16/18 infection at the cervix, it has been suggested that HPV-16/18 vaccination might also protect against infections at other body sites. In specific, the present effort in Costa Rica will evaluate efficacy of the HPV-16/18 to protect against infections at the anus, vulva and oral cavity. It should be noted that this evaluation is of clinical relevance because infection with oncogenic HPV types, particularly HPV-16, have been linked to the development of cancers at all three of these extra-cervical sites. The funds provided by ORWH in FY09 are being used to support costs associated with high-sensitivity, PCR-based testing of anal, vulvar and oral specimens collected from participants in CVT at their 4-year study visit, the last blinded visit as part of the trial.

1R21CA135237-01A2
Chemoprevention of Tamoxifen-Induced Endometrial Cancer by Black Cohosh and Red C
Dietz, Birgit Maria
University of Illinois at Chicago
$198,211

Chemoprevention of Tamoxifen-induced Endometrial cancer by black cohosh and red clover
Breast cancer is the most common cancer in women. The selective estrogen receptor modulator tamoxifen, which antagonizes estrogen in breast tissue, is efficacious in the treatment and prevention of breast cancer. In tamoxifen treated patients, botanical dietary supplements such as red clover and black cohosh extracts are frequently used for the alleviation of tamoxifen related menopausal symptoms. Very few studies about the modifying effects of these botanicals on tamoxifen's safety and efficacy have been reported. Tamoxifen's major side effect is an enhanced endometrial cancer risk. Tamoxifen's ER1 mediated uterotrophic activity and its reactive metabolites are believed to be responsible for this effect. Black cohosh and red clover contain anti-oxidative, anti-proliferative, anti-inflammatory, and detoxification enzyme inducing compounds, which could inhibit the initiation or retard the promotion and progression of cancerous cells. The central hypothesis of this project is that black cohosh and red clover reduce the carcinogenic effects of tamoxifen on the endometrium by inhibition of cell proliferation and through enhancing detoxification pathways. Recent data suggest that black cohosh and red clover can attenuate tamoxifen-stimulated endometrial cancer growth by inhibiting cell proliferation. They will measure the influence of these botanicals on tamoxifen stimulated endometrial tumor growth in ovariectomized athymic nude mice, an established endometrial cancer model for studying estrogenic influences. The mechanism of interaction will be examined by analyzing the expression of pro-proliferative genes and proteins important for tamoxifen mediated tumor promotion in vivo and in vitro. To further identify active compounds, they will examine the anti-proliferative effect of isolated compounds in endometrial cancer cells and in an immature rat model. Data indicate that both botanical (black cohosh and red clover) upregulate the cellular antioxidative response machinery, thus reducing the carcinogenic effect of tamoxifen's reactive metabolites. This proposal will provide an overall picture of the effect of these botanicals and purified compounds on the efficacy of tamoxifen and on tamoxifen induced endometrial cancer, which is of importance considering the increasing number of breast cancer survivors and women at high risk undergoing tamoxifen treatment. The signifiance of the application is that this proposal hypothesizes that red clover and black cohosh, both frequently used for the alleviation of menopausal symptoms, will reduce tamoxifen-induced endometrial cancer due to their cancer chemopreventive properties.

1R21CA135303-01A1
NIR Hypoxia Imaging of Breast Tumor Response to Neoadjuvant Chemotherapy in Vivo
Jiang, Shudong
Dartmouth College
$199,595
Near-infrared (NIR) multi-spectral imaging is a unique tool for characterizing tissue composition in the female breast. The major advantage of this modality is its ability to provide images of tissue oxygen saturation (StO2) as well as total hemoglobin concentration (HbT), water fraction (H2O%) and elastic scattering parameters. Because microcirculation and oxygenation play such major roles in tumor progression and regression, assessing their variation in response to neoadjuvant chemotherapy may reveal early prognostic biomarkers of treatment response that could be used to alter and/or optimize the course of treatment on a more individualized patient basis. Assessing dynamic contrast enhancement in tumor oxygenation after hyperoxic gas inhalation with NIR spectral tomography appears to be

feasible and may provide easily- acquired, low cost image signatures for predicting therapeutic response to chemotherapy in the breast. The overall goal of this proposal is to develop and evaluate dynamic NIR tomographic oximetry for characterizing the response of locally advanced breast cancers to neoadjuvant chemotherapy by assessing the temporal variation in tumor oxygenation during hyperoxic gas inhalation. Dartmouth College, through the Norris Cotton Cancer Center at the Dartmouth-Hitchcock Medical Center, has significant resources to leverage in order to conduct the proposed study. A group of investigators which includes clinical specialists in diagnostic radiology, surgical oncology, medical oncology, surgical pathology and medical engineering has been configured to develop and evaluate technology for breast imaging for cancer detection, diagnosis and therapy monitoring since 1999. The proposed project is an important component of the research of this group. The signifiance of the application is that this project will develop and evaluate dynamic Near-Infrared (NIR) tomographic oximetry for characterizing the response of locally advanced breast cancers to neoadjuvant chemotherapy by assessing the temporal variation in tumor oxygenation during hyperoxic gas inhalation. NIR oximetry acquired longitudinally during the course of therapy will be correlated with pathological endpoints in order to determine whether early prognostic biomarkers of treatment response can be identified in the dynamic NIR oxygenation signatures that could be used to customize breast cancer treatment decisions to individual patients in the future.

1R21CA142537-01A1
Reactivation of Breast Cancer Micrometastases by Senescent Bone Marrow Stroma
Wieder, Robert
Univ of Med/Dent of NJ-NJ Medical School
$205,920
More than a third of stage I-III breast cancer patients have bone marrow micrometastases at the time of diagnosis providing a source of recurrence. Most recurrences occur in post-menopausal women. Mechanisms of dormancy and recurrence are not well understood, but data suggest a dependence on a close association with bone marrow stroma. The applicants hypothesize that stromal cells undergo senescence due to aging and/or post-menopausal estrogen deprivation and begin to secrete inflammatory cytokines that can stimulate dormant cancer cells to re-awaken. The broad, long-term goals of the proposed investigations are to define mechanisms that govern the establishment of the dormant state in breast cancer cells in the bone marrow and to determine factors and mechanisms responsible for their re-awakening and recurrence of disease. The study will determine if bone marrow stroma can undergo senescence when deprived of estrogen or treated with cytotoxins in vitro and in vivo in a murine model. These outcome of these studies will establish a way of thinking about dormancy as a function of the senescent microenvironment and seek to reverse estrogen-deprivation-induced inflammation to maintain it. The signifiance of the application is that the study proposes to investigate the induction of senescence in mouse bone marrow stroma by estrogen deprivation in vitro and in vivo as manifested by the secretion of inflammatory cytokines and loss of the capacity to support dormancy of breast cancer cells in an in vitro model and the loss of the capacity to support the dormancy of xenografted human breast cancer cells in the bone marrow microenvironment. Experiments will determine if treatment with estrogen or anti-inflammatory agents can restore the capacity of senescent stroma to support dormancy.

R03 CA141564-01
Role of MicroRNAs in initiation and progression of breast cancer
Sempere, Lorenzo
$79,000
Breast carcinoma (BrCa), which is the second most prevalent cancer in women, is a complex, inadequately understood, and often fatal disease when not detected at early stages. A more detailed understanding of the molecular mechanisms and regulatory pathways at work will enormously assist in improving the design and target selection of therapeutic strategies. MicroRNAs (miRNAs) are evolutionary conserved, short non-coding regulatory RNAs that post- transcriptionally modulate gene expression by binding to their cognate target mRNAs via pervasive and versatile mechanisms. Altered expression of specific subsets of miRNAs has been linked to different types of hematologic and solid tumors. Independent studies using BrCa clinical specimens have identified a small subset of miRNAs, which are differentially detected between normal and tumor tissue specimens. Thus, the clinical value of these miRNAs as novel biomarkers for different aspect of BrCa management is being actively investigated. Importantly, functional analyses in cell line systems and xenograft transplantation in mouse models have revealed tumor suppressive and oncogenic functions of some of these miRNAs. This proposal focuses on miRNAs as potential tumor suppressive mechanisms to prevent breast carcinogenesis. The applicants expect that results of this proposal will uncover an etiological contribution of miRNAs and validate the use of these mouse models for future studies concentrating on the role of individual miRNA in BrCa and development of miRNA-based therapeutic strategies. The significance of this proposal is that the in situ hybridization technology offers spatial resolution of miRNA expression unsurpassed by other techniques, which could be readily adapted to routine clinical practice to benefit patients and assist physicians in making crucial decisions.

5R01 CA115315-05
Caregivers' Strengths-Skills: Managing Older Cancer Patients
Raveis, Victoria H.
Columbia University Health Sciences, New York, NY
$46,488
This project will implement and evaluate the efficacy of a short-term problem-solving skills training program for familial caregivers to lower income older (60+) post-treatment cancer patients. The goal of the intervention is to equip family caregivers with problem-solving skills and knowledge that will provide them with a more adaptive means of attending to any symptoms their elderly relative may be experience during the cancer survivorship period. By focusing attention on families' potential role in palliative care efforts during the post-treatment period, they propose that they will be able to impact patients' health related quality of life, by fostering enhanced symptom recognition, improved symptom control, advocacy with health professionals, and adherence to symptom management options. Familial caregivers to older cancer patients who have completed active treatment will be accrued from Community/Migrant Health Centers (C/MHCs). Caregivers and patients will be followed for ten months. The specific aims are to: (1) Deliver a brief problem-solving training program with regard to symptom management (Problem-solving) to enhance caregiver skills (i.e., perceived self-efficacy, social problem-solving and communication) of familial caregivers to

older post-treatment cancer patients. (2) Evaluate the efficacy of problem-solving in enhancing caregiver skills, relative to participating in a caregiver support group (Support): (a) Assess short- and long-term change in caregiver skills reported by caregivers assigned to either the Problem-solving condition or the Support condition; and, (b) Compare change reported by caregivers in the Problem-solving condition, relative to reports by those in the Support condition; (3) Assess the impact of change in caregiver skills on: (a) Change in patients' symptomology and physical functioning, depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with care (patient outcomes); (b) Change in caregivers' depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with patient care (caregiver outcomes). (4) Disseminate information that informs family training in palliation and symptom control to participating C/MHCs and other C/MHCs serving these populations, contingent on demonstrating beneficial program outcomes.

1 R21 CA141241-01
Development and Pilot Test of an Elective BSO Decision Support Guide
Kuppermann, Miriam
University of California San Francisco
$200,000
Results of this study will contribute to the small literature on women's preferences and attitudes toward BSO. This study will generate a clinically useful BSO Decision Support Guide that women of varying literacy levels and diverse cultural backgrounds can use to help them participate in shared decisions about use of BSO. It will also generate questionnaires and data to be used in planning future evaluations of the impact of the guide on informed decision making regarding and use of and satisfaction with BSO concomitant to hysterectomy among average risk women. Ovarian cancer is a common and often fatal condition. Over 600,000 women undergo hysterectomy each year, 90% of which are done for non-cancerous conditions. Historically, many of these women have undergone bilateral salpingo-oophorectomy (BSO) to decrease the risk of ovarian cancer and/or to avoid possible morbidities and future surgery related to benign ovarian neoplasms, endometriosis, and pelvic pain. However, BSO results in a permanent loss of ovarian estrogen and androgens that are known to be associated with maintenance of cardiovascular health, bone health, sexual functioning, and overall health-related quality-of-life. As a result, consideration of ovarian retention for premenopausal women who are not at increased genetic risk of ovarian cancer has been advocated, although no clear guidelines have been established regarding how decisions should be made regarding whether or not to perform elective BSO and the time of hysterectomy for benign condition. Decision aids have been developed and their use has been encouraged, in a number of areas to help patients and providers share in making informed decisions, particularly in situations that include more than one approach to care, uncertain outcomes, and benefits and harms that people value differently. Clearly, decision making around BSO is an area the meets these criteria. They therefore propose to conductive formative research and use it to develop and pilot test a BSO Decision Support Guide, to help patients share with their providers in making informed, preference-based decisions regarding whether or not to undergo BSO concomitant to hysterectomy to prevent ovarian cancer. To accomplish these goals, they will conduct a series of focus groups and one-on-one qualitative interviews to assess how women who will be undergoing, or who have recently undergone, hysterectomy for non-cancerous conditions view elective BSO and to assess their information

needs and desires regarding shared decision making in this context. They will then create a draft BSO Decision Support Guide using information obtained from the literature, from their formative research, and the experience of providers who have counseled women about this choice. After pilot testing the BSO Decision Support Guide among 62 women scheduled to undergo hysterectomy for benign conditions to assess its usefulness and usability for patients and their providers, they will generate a final version that will be ready for use in future studies of the impact of the intervention on decision quality and use of BSO.

P50 CA134254-01A1
Spore in Endometrial Cancer
Goodfellow, Paul
Washington University
$200,000
This Specialized Program of Research Excellence (SPORE) in Endometrial Cancer is submitted by Washington University in St. Louis, the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. It includes four research projects, three supportive cores, and research and career development programs. This proposal brings together basic and applied investigators to conduct innovative and diverse translational investigations aimed at preventing, diagnosing and treating endometrial cancer. The four projects in their application have been carefully designed to have significant potential to change clinical practice within five years. Project 1: FGFR2 as therapeutic target in endometrial cancer Project 2: Methylation markers for prognosis in endometrioid endometrial cancers Project 3: Identifying inherited endometrial cancer & the environmental and genetic factors contributing to somatic loss of mismatch repair Project 4: Novel effectors of ERK signaling and their potential roles in the treatment of endometrial cancer The four projects represent carefully chosen marriages between selected endometrial cancer research priorities and the strengths of Washington University and their collaborators. The critical objectives that they have chosen to focus on are to: 1) improve the treatment of patients with persistent or recurrent endometrial cancer using a molecularly targeted therapy and determine if upfront adjuvant biologic therapies hold promise for improving outcomes in the general endometrial cancer population; 2) develop prognostic markers to help guide the treatment of women with the most common form of uterine tumors, endometrioid endometrial cancer; 3) optimize detection of those women with inherited forms of endometrial cancer so they and their at-risk family members can receive risk-appropriate (intensified) cancer surveillance; and 4) elucidate the role novel effectors of ERK signaling play in uterine cancer and assess opportunities for targeting these in the treatment of endometrial cancers. Three Cores will support these projects: Administration, Tissue & Pathology, and Biostatistics. The Developmental Research Program will support a pathway for continued identification and support of diverse research that could replace or improve current projects, and a Career Development Program will recruit and support candidates committed to training in translational research in endometrial cancer.

Y2 OD9147
Immunogenicity of quadrivalent human papilloma virus vaccine (HPV Types 6, 11, 16, 18) in recipients of reduced intensity hematologic stem cell transplantation (HSCT) (Bench to Bedside Program)

Chenoy, A., et al.
NHLBI/NICHD Intramural Program
$100,000
This project investigates the use of the recently licensed quadrivalent human papilloma virus (HPV) vaccine against HPV types 6, 11, 16, 18 in females age 12 years or older undergoing allogeneic, hematopoietic stem cell transplantation (HSCT) as an approach to reduce post-transplant HPV-related co-morbidity, anogenital dysplasia and malignancy. This population is at excess risk for HPV-related anogenital dysplasia and malignancy following transplantation and stands to benefit greatly from prophylactic HPV vaccination. In addition to determining whether the quadrivalent vaccine is immunogenic in the post-transplant population, this investigation will also determine, in a subset of patients, whether there are differences in HPV vaccine immunogenicity in individuals with identical T cell immunity that have non-identical host cell backgrounds i.e. HSCT donors (male or female) and their respective/paired female transplant recipients.

1R21CA135226-01A1
Brca1, Sporadic Breast Cancer And Aging Women
Avraham, Hava Karsenty
Beth Israel Deaconess Medical Center
$149,600
By defining the targets that are altered in mutated BRCA1-linked breast and ovarian cancers and providing insights into the BRCA1 pathways, this study may lead to potential new therapeutic strategies for the prevention, early diagnosis and treatment of familial breast and ovarian cancers. In addition, results from this work will enhance their understanding of the molecular events that drive breast and ovarian cancers in aging women, and may link BRCA1 and beta-catenin to oxidative stress and breast oncogenesis. The risk of developing breast cancer increases as women get older. The maintenance of DNA represents a fundamental and continuous challenge to every cell in the body. Genomic instability is a hallmark of most cancers as well as a hallmark in aging. Recent evidence strengthened the link between the maintenance of genome integrity, cancer susceptibility and aging. These conditions can be caused by germline mutations in BRCA1, which is an essential caretaker protein in the surveillance of DNA damage. Impaired oxidative stress response plays an important role in breast oncogenesis. Beta-catenin was shown to be a co-factor for the FOXO family, which promotes survival by inducing cell cycle arrest and quiescence in response to oxidative stress. They observed that wild-type (WT) BRCA1, but not mutated BRCA1, interacts with beta-catenin and increases beta-catenin protein expression by promoting lysine-6-linked ubiquitination. Oxidative stress reagent H2O2 increased colocalization and the interaction of BRCA1 with beta-catenin in the nucleus. WT-BRCA1, but not mutated BRCA1, protected the nuclear active form of beta-catenin during oxidative stress responses. The expression of this form of beta-catenin was lower or absent in most of BRCA1 familial breast cancer tissues. Therefore, they hypothesize that: 1) BRCA1 acts as a sensor in regulating beta-catenin mediated oxidative stress and FOXO function; and 2) low expression of WT-BRCA1 or mutations in BRCA1 leads to impaired response to oxidative stress and causes genomic instability, resulting in increased risk of breast cancer in women. Therefore, they aim to examine the effects of BRCA1 on beta-catenin protein expression and stability and to analyze the role of BRCA1 in beta-catenin mediated oxidative stress response. Thus, they specifically

propose the following aims: Aim 1: To investigate the role of Brca1 in the expression and distribution of beta-catenin and its targets (cyclin D1 and c-Myc) during mammary gland development in Brca1 mutant mice, in which Brca1 exon 11 is specifically deleted from the mammary glands by using the Cre-loxP system. Aim 2: To characterize the role of BRCA1 as a sensor in regulating the beta-catenin and FOXO interaction during oxidative stress signaling. Results from this work will enhance their knowledge of the molecular events that drive sporadic breast and ovarian cancer development and progression in aging women.

1R21CA135532-01A1
Regulation Of Breast Cancer Progression By FAK Expression In Tumor Macrophages
Bouton, Amy H
University Of Virginia Charlottesville
$198,087
The growth and metastatic spread of solid tumors is controlled by signals emanating from tumor cells as well as by immune cells and fibroblasts in the surrounding stroma, components of the extracellular matrix, and soluble growth factors and cytokines. While this complexity creates challenges for therapeutic intervention, it also provides unique opportunities by making available a number of distinct cellular and molecular targets that can be exploited to control tumor growth and progression. The focus of this proposal is on Focal Adhesion Kinase (FAK), a protein tyrosine kinase whose expression is significantly increased in many late-stage cancers, including breast cancer. They hypothesize that FAK expression in two components of the tumor microenvironment, the tumor cells and tumor-associated macrophages (TAMs), plays a critical role in promoting breast tumor progression and metastasis. They will use mouse models of breast cancer to gain an understanding of how FAK expression in breast carcinoma cells and/or the ancillary tumor-associated macrophages controls primary breast tumor growth and metastatic spread. By combining genetic manipulation of these mice with FAK inhibitors currently in Phase I clinical trials, they propose to 1) determine how the loss of FAK expression in macrophages alters or ablates macrophage functions that drive breast tumor growth/progression and metastasis (Aim 1); 2) assess how the dual modulation of FAK expression in breast tumor cells and in tumor-associated macrophages alters breast tumor growth and metastasis (Aim 2A); and 3) assess how systemic inhibition of FAK expression alters breast tumor growth and metastasis (Aim 2B). Successful completion of this study will provide new insights into features of the tumor that can predict a clinical response to the FAK-targeted drugs currently in clinical trials and the optimal timing for these treatments. More globally, they will learn about mechanisms through which tumor cells and other cells within the tumor microenvironment communicate to promote breast tumor growth and metastasis. They anticipate that this work will help to move the paradigm for breast cancer treatment away from the tumor cells per se and toward the full complement of factors that contribute to tumor growth and metastasis.

1R21CA135237-01A2
Chemoprevention Of Tamoxifen-Induced Endometrial Cancer By Black Cohosh And Red C
Dietz, Birgit Maria
University Of Illinois At Chicago
$198,211

Chemoprevention of Tamoxifen-induced Endometrial cancer by black cohosh and red clover
Breast cancer is the most common cancer in women. The selective estrogen receptor modulator tamoxifen, which antagonizes estrogen in breast tissue, is efficacious in the treatment and prevention of breast cancer. In tamoxifen treated patients, botanical dietary supplements such as red clover and black cohosh extracts are frequently used for the alleviation of tamoxifen related menopausal symptoms. Very few studies about the modifying effects of these botanicals on tamoxifen's safety and efficacy have been reported. Tamoxifen's major side effect is an enhanced endometrial cancer risk. Tamoxifen's ER1 mediated uterotrophic activity and its reactive metabolites are believed to be responsible for this effect. Black cohosh and red clover contain anti-oxidative, anti-proliferative, anti-inflammatory, and detoxification enzyme inducing compounds, which could inhibit the initiation or retard the promotion and progression of cancerous cells. The central hypothesis of this project is that black cohosh and red clover reduce the carcinogenic effects of tamoxifen on the endometrium by inhibition of cell proliferation (Aim I) and through enhancing detoxification pathways (Aim 2). To support this hypothesis they propose the following specific aims: 1. What is the effect of red clover or black cohosh on tamoxifen-stimulated endometrial cancer? Recent data suggest that black cohosh and red clover can attenuate tamoxifen-stimulated endometrial cancer growth by inhibiting cell proliferation. They will measure the influence of these botanicals on tamoxifen stimulated endometrial tumor growth in ovariectomized athymic nude mice, an established endometrial cancer model for studying estrogenic influences. The mechanism of interaction will be examined by analyzing the expression of pro-proliferative genes and proteins important for tamoxifen mediated tumor promotion in vivo and in vitro. To further identify active compounds, they will examine the anti-proliferative effect of isolated compounds in endometrial cancer cells and in an immature rat model. 2. What is the effect of black cohosh or red clover on detoxification pathways of reactive tamoxifen metabolites? Their data indicate that both botanical upregulate the cellular antioxidative response machinery, thus reducing the carcinogenic effect of tamoxifen's reactive metabolites. They will study the ability of these botanicals to induce the detoxification enzymes, quinone reductase and glutathione-S-transferase, in the uterus and liver of adult rats. They will also analyze whether black cohosh and red clover prevent tamoxifen induced oxidative stress in these animals. Additionally, they will examine the effect of the botanicals on tamoxifen's metabolism to active or reactive metabolites in the blood. To elucidate the compounds responsible for the various effects, isolated constituents will be assayed in vitro. The completion of these specific aims will provide an overall picture of the effect of these botanicals and purified compounds on the efficacy of tamoxifen and on tamoxifen induced endometrial cancer, which is of importance considering the increasing number of breast cancer survivors and women at high risk undergoing tamoxifen treatment.

1R21CA135303-01A1
NIR Hypoxia Imaging Of Breast Tumor Response To Neoadjuvant Chemotherapy In Vivo
Jiang, Shudong
Dartmouth College
$199,595
Near-infrared (NIR) multi-spectral imaging is a unique tool for characterizing tissue composition in the female breast. The major advantage of this modality is its ability to provide images of tissue oxygen saturation (StO2) as well as total hemoglobin concentration

(HbT), water fraction (H2O%) and elastic scattering parameters. Because microcirculation and oxygenation play such major roles in tumor progression and regression, assessing their variation in response to neoadjuvant chemotherapy may reveal early prognostic biomarkers of treatment response that could be used to alter and/or optimize the course of treatment on a more individualized patient basis. Assessing dynamic contrast enhancement in tumor oxygenation after hyperoxic gas inhalation with NIR spectral tomography appears to be feasible and may provide easily- acquired, low cost image signatures for predicting therapeutic response to chemotherapy in the breast. The overall goal of this proposal is to develop and evaluate dynamic NIR tomographic oximetry for characterizing the response of locally advanced breast cancers to neoadjuvant chemotherapy by assessing the temporal variation in tumor oxygenation during hyperoxic gas inhalation. They hypothesize that tumors with initially larger and faster changes before and after breathing 100% oxygen will have better clinical responses to neoadjuvant chemotherapy. This hypothesis will be quantitatively assessed by 1) advancing the current NIR multi-spectral tomography system to image dynamic oxygenation changes within the tumor, induced by breathing 100% oxygen, with a 0.1 Hz image frame rate, 2) quantifying the tumor oxygenation response with respect to hyperoxic inhalation at different times during the course of therapy, and 3) quantifying the pathological and clinical outcomes of response in order to test for correlation with oximetry changes recorded early in the treatment course. Dartmouth College, through the Norris Cotton Cancer Center at the Dartmouth-Hitchcock Medical Center, has significant resources to leverage in order to conduct the proposed study. A group of investigators which includes clinical specialists in diagnostic radiology, surgical oncology, medical oncology, surgical pathology and medical engineering has been configured to develop and evaluate technology for breast imaging for cancer detection, diagnosis and therapy monitoring since 1999. The proposed project is an important component of the research of this group. In addition to the principal investigators, Professor Shudong Jiang and Dr. Peter A. Kaufman, MD, (Medical Oncology), Professors Keith D. Paulsen, Brian W. Pogue and Dr. Wendy A. Wells, MD, (Department of Pathology) will be significant collaborators engaged to accomplish the proposed specific aims, as an adjunct to currently funded grants involving breast imaging research.

1R21CA140916-01
Mitochondrial Catalase As A Treatment For Metastatic Breast Cancer
Ladiges, Warren C.
University Of Washington
$171,600
The chance of developing invasive breast cancer during a woman's lifetime is approximately 1 in 8 and more than 40,000 women die of metastatic disease each year. Inherent or acquired tumor drug resistance and dose-limiting toxicity limit many agents used in the treatment of invasive breast cancer. Therefore, an important goal is the development of novel non-toxic therapeutic agents that are active against this deadly disease. They have preliminary data showing that mitochondrial catalase (mCAT) reduces metastatic progression of primary breast cancer in mice, suggesting that targeting mitochondria with catalase could be a potential strategy to treat or prevent metastatic breast cancer in women. The aims of this proposal are 1) to further characterize the ability of mCAT to suppress breast cancer metastasis in mice; and 2) develop an inducible system in mice for controlling the expression of mCAT in a time and

cell dependent manner. The data generated in this proposal would confirm their preliminary observations and provide the rationale for developing and/or testing clinically relevant mitochondrial-specific drug delivery systems for treating metastatic breast cancer.

1R21CA140936-01
Improving Flexible Sigmoidoscopy In Women By Optical Analysis of Microvasculature
Backman, Vadim
Northshore Univ Healthsystem Res Inst
$214,425
Despite a myriad of screening tests available, colorectal cancer (CRC) remains the second leading cause of cancer deaths among Americans. Approximately half the population does not undergo any CRC screening because of cost, access and concerns about discomfort with both the procedure and colonic purge. Flexible sigmoidoscopy (endoscopic evaluation of the distal colon) is performed in the community and has many advantages over other recommended tests (e.g. colonoscopy, CT colography) such as being relatively inexpensive, more widely available (performed by primary care physicians) and proven efficacy at decreasing both CRC mortality and incidence. However, flexible sigmoidoscopy is insensitive in women given their predilection for proximal neoplasia. Indeed, while flex sig identifies two-thirds of advanced adenomas in men, it only detects one-third in women highlighting the need for adjunctive approaches. Their multi-disciplinary CRC prevention group has focused on bridging novel optical technologies to clinical practice. Using 4-dimensional elastic light scattering fingerprinting (4D-ELF), they published that in CRC models, the peri-cryptal capillary blood content was increased prior to any histological abnormalities (a phenomena they termed EIBS (early increase in blood supply). They developed an endoscopically- compatible fiber-optic probe and demonstrated that EIBS was detectable at a distance from neoplastic lesions. In the rectum, EIBS was detectable in patients harboring advanced neoplasia elsewhere in their colon. Importantly, rectal EIBS was more robust in women (~60% increase versus neoplasia-free controls) than men (~25%) for proximal advanced neoplasia (that was not visualizable by flexible sigmoidoscope). We, therefore, hypothesize that rectal EIBS measurement will detect advanced proximal neoplasia in women. They will obtain rectal EIBS analysis on women undergoing colonoscopy. They will identify diagnostic EIBS parameters and determine the impact of demographic factors (e.g. age, race, smoking, medication use) on these markers. This data will be used to formulate a prediction rule for advanced proximal adenomas. They will then prospectively validate this prediction rule on a separate cohort of women simulating real world flexible sigmoidoscopy screening conditions prior to full colonoscopy. This will provide the rationale to performing future multi-center trials of rectal EIBS as an adjunct to flex sig in women. If successful, this practical and relatively inexpensive approach may be pivotal for the resurgence of flexible sigmoidoscopy as an accurate, cost-effective and patient-friendly CRC screening option in women.

1R21CA134882-01A1
Antagonism Of The Ah Receptor In Controlling Breast Cancer Growth And Invasion
Schlezinger, Jennifer J
Boston University Medical Campus
$214,500

Historically, the aryl hydrocarbon receptor (AhR) has been studied for its transcriptional regulation of genes encoding cytochrome P450 enzymes, which metabolize environmental and endogenous substrates into toxic and mutagenic intermediates. Accumulating studies support the hypothesis that the AhR also plays an important role in malignant epithelial cell growth and invasion apart from its role in formation of mutagens and in the absence of environmental chemicals. This new paradigm is based on several key observations: 1) AhR expression is increased dramatically in carcinogen-induced rat and mouse mammary tumors and in 'spontaneous' human mammary tumor lines. 2) Constitutive AhR activation is indicated by nuclear AhR localization in rat, mouse, and human mammary tumors and by AhR binding to gene promoters in the absence of environmental chemicals. 3) Constitutively active AhR regulates the expression of multiple genes, including CYP1B1, CK21, and Slug, a master regulator of tumor invasion. 4) Recent studies suggest that increased AhR activity in mammary tumors also contributes to cell migration and invasiveness. 5) Molecular downregulation of the AhR suppresses breast cancer cell proliferation and reverts cells to a non-aggressive phenotype. Molecular and biologic strategies have provided significant evidence that the AhR participates, beyond mutagenesis, in multiple mechanisms that contribute to tumor formation, growth and invasion. Therefore, they can exploit their ability to examine effects of constitutively active AhR to determine how chemical antagonism of the AhR may translate into breast cancer prevention or a therapeutic approach to suppress tumor progression. Thus, they propose a new hypothesis: Targeting the constitutively active AhR with naturally occurring, non-toxic antagonists represents a feasible therapeutic approach to inhibit breast tumor growth and invasion. Three specific aims are proposed: 1. Investigate strategies to maximize antagonism of the AhR by examining the potential for synergistic interaction in mixtures of antagonists, performing a high-throughput screen for novel, potent antagonists from natural product extract libraries (NCI Natural Products Repository) and examining the 'chemical knockout' approach for improving AhR inactivation. 2. Define the molecular mechanisms of chemical antagonism of the constitutively active AhR in a breast cancer model by establishing antagonist effects on AhR transactivation of endogenous gene expression and examining antagonist-mediated changes in AhR-DNA interactions. 3. Establish the functional consequences of chemically antagonizing the constitutively active AhR using optimal AhR antagonists. The translational impact of these studies lies in the ability of known and newly identified antagonists to suppress tumor growth and invasion. Here, potentially therapeutic AhR antagonists will be evaluated for their ability to block the biological outcomes of constitutive AhR activity in human mammary tumor cell lines. Collectively, these studies will provide the foundation for preclinical studies on the potential for potent AhR antagonists to prevent and/or treat breast cancer in vivo.

1R21CA141112-01
Gender Selectivity To Colon Cancer Chemoprevention By NSAIDS
Roy, Hemant K
Northshore Univ Healthsystem Res Inst
$201,300
Colorectal cancer (CRC) is the second leading cause of cancer deaths among Americans. With proper screening and removal of adenomatous polyps, CRC risk reduction has been very promising. However, only ~50% of the at-risk population (age >50) receives any sort of screening and many undergo tests with suboptimal sensitivity. This underscores the need for

developing alternate cancer prevention strategies such as chemoprevention. Of the myriad of purported agents, nonsteroidal anti-inflammatory drugs (NSAIDS) have reliably shown a positive outcome. Indeed, epidemiological, experimental and clinical trials unequivocally point to the CRC preventive benefits of NSAIDS. However, the efficacy is relatively modest (30-50% risk reduction) and requires more than a decade to show significant benefits. In addition, the use of NSAIDS has been shown linked to severe side-effects including ulcers, GI bleeding, hemorrhagic strokes etc, thereby cautioning that the risks may outweigh the benefits of aspirin and NSAIDS in preventing CRC for average risk use. To improve the risk-benefit analysis, it is therefore critical to selectively target subjects that can efficiently respond to chemopreventive efficacy of NSAIDS and at the same time leave out the population least likely to benefit. It is conceivable that responsive patients could be targeted with lower efficacious doses to avoid associated toxicity. Gender is an important risk factor for CRC with women frequently having biological differences (higher prevalence of proximal lesions, DNA mismatch repair deficient tumors etc). Estrogen is a well-accepted chemopreventive agent against CRC. Moreover, their group has reported that women have altered susceptibility to both genetic and environmental CRC risk factors. The epidemiological data has some studies suggesting an improved chemopreventive response to NSAIDS although there are discordant reports in the literature. Thus, the issue of whether women are more sensitive to NSAID chemoprevention is unresolved with possibility that NSAID type, dose etc may play a role. They recently conducted a chemoprevention trial using the NSAID celecoxib in a well-validated model of intestinal tumorigenesis, the MIN mouse. They noted that in this model, females were more responsive to the chemopreventive effects of celecoxib. The chemopreventive response was found to have regional propensity with stronger efficacy in the proximal intestine. Furthermore, celecoxib treated female mice had higher levels of mucosal estrogen receptor-2 (ER2) levels. They hypothesize that in colorectal cancer, NSAIDS present an increased chemopreventive efficacy in females which may be secondary to modulation of estrogen receptor ER2 expression. PUBLIC HEALTH RELEVANCE: Colorectal cancer is one of the major public health issues in US with life time risk of being diagnosed with this cancer is about 6%. This cancer usually develops slowly (10- 15 years) through multiple genetic and phenotypic transitions from normal colonic mucosa to adenoma and then to carcinoma. This protracted progression provides ample time for interventions such as endoscopic screening and removing adenomatous polyps. This has been promising but only about half of the at-risk population (age >50) receive any sort of effective screening. This underscores the need for developing alternate cancer prevention strategies such as chemoprevention. Number of studies shows that nonsteroidal anti-inflammatory drugs (NSAIDS) exert chemopreventive benefits against CRC. However, the overall efficacy is relatively modest (30-50% risk reduction) and requires more than a decade to show significant benefits. In addition, the use of NSAIDS has been shown to be linked to severe side-effects including ulcers, GI bleeding, hemorrhagic strokes etc, thereby causing some uncertainty in its use for preventing CRC for average risk use. To improve the risk-benefit analysis, it is therefore critical to selectively target subjects that can efficiently respond to chemopreventive efficacy of nonsteroidal anti-inflammatory drugs (NSAIDS). It has recently been shown that women with CRC may respond to dietary nutrients or pharmacological agents differently than men as they may have differing pathologies, risk factors and hormone status. The epidemiological studies suggest an improved chemopreventive response in women to NSAIDS although there are discordant reports in the literature. Thus, the issue of whether

women are more sensitive to NSAID chemoprevention is unresolved with possibility that NSAIDS type, dose etc may play a role. The proposed studies will address the role of estrogen in gender selective chemopreventive efficacy of NSAIDS. These findings will have an important bearing on the healthcare recommendations for colon cancer chemoprevention which have to be cognizant of this gender selective efficacy for maximum cost-benefit potential of NSAIDS.

1R21CA142537-01A1
Reactivation of Breast Cancer Micrometastases By Senescent Bone Marrow Stroma
Wieder, Robert
Univ Of Med/Dent Of Nj-Nj Medical School
$205920
More than a third of stage I-III breast cancer patients have bone marrow micrometastases at the time of diagnosis providing a source of recurrence. Most recurrences occur in post-menopausal women. Mechanisms of dormancy and recurrence are not well understood, but data suggest a dependence on a close association with bone marrow stroma. They hypothesize that stromal cells undergo senescence due to aging and/or post-menopausal estrogen deprivation and begin to secrete inflammatory cytokines that can stimulate dormant cancer cells to re-awaken. The broad, long-term goals of their investigations are to define mechanisms that govern the establishment of the dormant state in breast cancer cells in the bone marrow and to determine factors and mechanisms responsible for their re-awakening and recurrence of disease. They propose to determine if bone marrow stroma can undergo senescence when deprived of estrogen or treated with cytotoxins in vitro and in vivo in a murine model. Their specific aims are: 1. to determine if in vitro estrogen deprivation can induce a senescent phenotype in bone marrow stromal cultures incapable of supporting breast cancer dormancy in an in vitro model and 2. to determine if in vivo estrogen deprivation induces a senescent phenotype in bone marrow stroma rendering it incapable of supporting breast cancer dormancy in vitro and in vivo. They will establish and characterize the phenotype of secretory senescence by subjecting stromal monolayers to oxidative and hypoxic stress and estrogen deprivation and measure the expression and activation of TGF¿, Cox-2, IL-6, IL-8 and SA-¿Gal, known markers associated with senescence. They will determine if estrogen deprivation in vitro and in vivo and cytotoxicity in vitro can induce senescence measured by these molecular markers and by the loss of support of breast cancer dormancy in an in vitro clonogenic co-culture model and in a left ventricle injection bone marrow metastasis model. Experiments will also determine whether estrogen-deprivation renders stroma more susceptible to chemical injury and whether administration of Cox-2 inhibitors or estrogen can reverse these effects. These studies will establish a way of thinking about dormancy as a function of the senescent microenvironment and seek to reverse estrogen-deprivation-induced inflammation to maintain it.

1R03CA139545-01
Targeting The Phosphoinositide KINASE Chain To Prevent Breast Cancer Metastasis
Kunz, Jeannette
Baylor College Of Medicine
$76750

Breast cancer is the most commonly diagnosed form of cancer in women 40-55 years of age and it is the second major cause of cancer deaths behind lung cancer for all women. Metastatic breast cancer, where cancer cells spread by motile mechanisms and establish tumors at distant vital sites, is much harder to eradicate and is the primary cause of patient death from breast cancer. Understanding the molecular principles that determine the efficiency of tumor metastasis is therefore critical to the prevention and treatment of breast tumors. Traditional cancer therapeutics are aimed at preventing tumorigenesis of normal breast tissue and inhibiting growth of established cancers. However, few therapeutic strategies target cell migration and invasion, although the pathological deregulation of these processes is a major cause of morbidity associated with the disease. Cell migration and invasion are coordinately regulated by the small GTPase Rac1 and the localized production of the lipid phosphatidylinositol-4,5-bisphosphate (PI4,5P2). The hyperactivation of Rac1 signaling has been observed in many cancers, particularly in cancers of the breast, and this is directly linked to increased metastatic potential and poor patient survival. A role for PI4,5P2 signaling in cancer progression has so far not been reported. However, recent evidence described in the preliminary studies section of this proposal has established that PIPK1a, a member of the Type I phosphatidylinositol-4-phosphate kinase family, which generates PI4,5P2, is a critical regulator of cell migration and cell-matrix adhesion. They have defined a biochemical pathway in which PIPK1a mediates Rac1 activation in response to integrin and growth factor signals. Rac1, in turn, controls signaling to downstream effectors, including a second member of the PIPKI family, PIPK1b, to promote the assembly of F-actin and of focal adhesion sites necessary for migration and invasion. These results therefore establish a pathway in which PIPK1a is the pinnacle of a signaling cascade that links transmembrane receptors to the regulation of actin and focal adhesion assembly during cell motility. Because cell migration and adhesion are critical for cancer metastasis, PIPK1a may be a target for the prevention of cancer progression. The long-term goal of these studies is to validate PIPK1a as a target for therapeutic intervention in metastatic disease using tissue culture cell models and the athymic nude mouse model of breast cancer. The proposed research also involves pilot studies designed to assess the efficacy of a newly identified natural small-molecule inhibitor of PIPK1a in the control of breast cancer progression. They will use a combination of basic research, chemical genetic and in vivo approaches to systematically address the role of the PIPK1a pathway in cell migration and invasion in a 3-dimensional matrix, in anchorage-independent growth, and in cancer progression in vivo using the athymic nude mouse. The proposed research not only has the potential to impact therapeutic design to prevent breast cancer metastasis, but will also advance their understanding of signaling mechanisms that may be critical for breast cancer metastasis.

1R03CA141564-01
Role Of Micrornas In Initiation And Progression Of Breast Cancer
Sempere, Lorenzo
Dartmouth College
$79000
Breast carcinoma (BrCa), which is the second most prevalent cancer in women, is a complex, inadequately understood, and often fatal disease when not detected at early stages. A more detailed understanding of the molecular mechanisms and regulatory pathways at work will enormously assist in improving the design and target selection of therapeutic strategies.

MicroRNAs (miRNAs) are evolutionary conserved, short non-coding regulatory RNAs that post- transcriptionally modulate gene expression by binding to their cognate target mRNAs via pervasive and versatile mechanisms. Altered expression of specific subsets of miRNAs has been linked to different types of hematologic and solid tumors. Independent studies using BrCa clinical specimens have identified a small subset of miRNAs, which are differentially detected between normal and tumor tissue specimens. Thus, the clinical value of these miRNAs as novel biomarkers for different aspect of BrCa management is being actively investigated. Importantly, functional analyses in cell line systems and xenograft transplantation in mouse models have revealed tumor suppressive and oncogenic functions of some of these miRNAs. This proposal focuses on miRNAs as potential tumor suppressive mechanisms to prevent breast carcinogenesis. They will utilize a genetic approach in mouse models of BrCa to test the hypothesis that global impairment of miRNA functions enhances tumor growth and aggressiveness. Of note, their experimental strategy will be similar to the one successfully used by Tyler Jacks and colleagues to uncover tumor suppressive roles of miRNAs in a K-Ras-driven mouse model of lung cancer. They will target chromosomal deletion of miRNA- processing enzyme Dicer in mammary gland epithelia using the Cre/LoxP system. The effects of global loss of miRNA functions will be studied in well-established mouse models of BrCa. Mammary gland restricted expression of Polyoma virus middle T antigen (PyMT), Neu/HER-2 or Wnt-1 causes BrCa with different latencies and histological features reminiscent of specific human BrCa subtypes. They expect that results of this proposal will uncover an etiological contribution of miRNAs and validate the use of these mouse models for future studies concentrating on the role of individual miRNA in BrCa and development of miRNA-based therapeutic strategies.

CARDIOVASCULAR DISEASE

5R03 AG032631-02
Cardiovascular Events in Women’s Ischemia Syndrome Evaluation
Kelsey, Sheryl F.
University of Pittsburgh, Pittsburgh, PA
$20,000
Much attention has been focused on the differences between men and women presenting with heart attacks and angina pain. The Women’s Ischemia Syndrome Evaluation (WISE) study has been a successful and productive four-center prospective study of women clinically referred for coronary angiography for evaluation of symptoms suggestive of ischemia. The goals of WISE were to improve diagnostic testing for ischemic heart disease and to explore female-specific ischemic heart disease pathophysiology. A National Death Index (NDI) search will be used to extend mortality follow-up for WISE women to an average of eight years (maximum 10). Experienced site coordinators will prepare materials to submit to NDI and send results to the coordinating center where updated mortality data will be added to the WISE database. Using the existing database, coronary risk factors, hormonal status, psychosocial, genetic factors, and results of diagnostic tests will be evaluated as predictors of long-term mortality. Initiated in September 1996, recruitment of 936 women was completed in a timely manner by March 2000. Support was awarded for an additional five years of follow-up, and the database was closed in March 2006. A rich longitudinal database on these

women is thus available. Patient names reside at the clinical sites, but to maintain confidentiality, are not included in the WISE database at the coordinating center. Extension of cardiovascular mortality data will more clearly define prognostic factors for long-term mortality in women with ischemia with and without obstructive disease. With an additional targeted analysis, development of a simple, reproducible, angiographic technique to identify micro-vascular dysfunction, by correlating TIMI Frame Count with Doppler Wire determined coronary flow reserve measured in response to adenosine in WISE women with suspected ischemia but no significant coronary artery disease is possible. Availability of a simple diagnostic technique allows clinicians to target these women for aggressive medical therapy aimed at early coronary artery disease and improved prognosis.

1R21HL093181-01A1
Role of 15-Lipoxygenase in Enhanced Pulmonary Vasoconstriction in Females
Pfister, Sandra L.
Medical College of Wisconsin
$220,200
Pulmonary arterial hypertension encompasses a group of diseases characterized by high pulmonary artery pressure and pulmonary vascular resistance. Vasoconstriction, vascular remodeling and thrombosis all contribute to the increased vascular resistance. Central to the proposed studies is that while relatively rare, idiopathic pulmonary arterial hypertension is a medically significant disease that occurs more frequently in young women. The disease is usually catastrophic for those afflicted. Mechanisms to explain the sex- difference in pulmonary arterial hypertension have not been well studied. The main focus of the grant application is to use a rabbit model to explore the role of sex in a novel signaling pathway that regulates pulmonary vascular tone. Results will lay the fundamental conceptual groundwork for future studies to understand more completely the pathogenesis of pulmonary hypertension in women. Furthermore, this work is intended to advance new concepts in women's health research and the study of sex/gender differences. Specifically, prior research by the investigators provided the first evidence that in pulmonary arteries obtained from female rabbits, endothelium-dependent contractions to both arachidonic acid and methacholine were enhanced when compared to responses in males. Pharmacological studies with inhibitors of arachidonic acid metabolism indicated that the factor was a lipoxygenase metabolite. The investigators showed in their prior studies that lipoxygenase metabolites are increased in females compared to males and the protein expression of 15-lipoxygenase is greater in female pulmonary arteries. While sex differences in vascular responses to various vasoactive agents have been documented, no studies have investigated the role of sex differences on lipoxygenase metabolism of AA in pulmonary arteries. This proposal is designed to explore the specific hypothesis that differences in AA metabolism by 15-LO contribute to the increased endothelium-dependent pulmonary vasoconstriction in females compared to males. To further develop this novel hypothesis, studies will be performed in pulmonary artery vascular preparations using chemical, biochemical, physiological and pharmacological approaches. These proposed studies will not only provide new insights into the role of endogenous arachidonic acid-derived factors in the pathogenesis of pulmonary arterial hypertension but will also advance their knowledge in women's health research by identifying possible mechanisms that contribute to sex-related differences in the incidence of pulmonary arterial hypertension. Significance of The Application: While relatively rare, idiopathic

pulmonary arterial hypertension is a medically significant disease that occurs more frequently in young women. The disease is usually catastrophic for those afflicted. Identifying endogenous pulmonary factors that may predispose females to the development of pulmonary hypertension is timely and important considering the abundance of clinical data indicating sex differences in vascular disease. Furthermore, this work is intended to advance new concepts in women's health research and the study of sex/gender differences.

1R21HL093626-01A1
Mechanisms Underlie Inverse Gender Discrepancy in Ischemic Protection
Shi, Nian-Qing
University of Wisconsin Madison, Madison, WI
$222,750
The proposed research will employ KATP channel mutant mice that are defective in the sulfonylurea receptor 2 (SUR2) to evaluate gender difference in ischemic protection, regulation of estrogen in sarcolemmal and mitochondrial SUR2 forms and obtain new insights in ion channel regulation in cardiovascular diseases. Myocardial infarction (MI) is a major health problem worldwide due to its acute nature and lack of effective prevention schemes. Gender difference in ischemic protection exists, with relatively lower MI incidences in pre-menopausal females than age-matched males. Emerging evidence indicates that the female-specific advantage in ischemic protection is mediated by estrogen. In the ischemic protection network, KATP channels (KATP) are postulated to play protective roles, but their relative importance remains to be controversial. Composed by a Kir6.2 pore and an SUR2 regulatory subunit, KATP activity is recorded in cardiac sarcolemmal or mitochondrial inner membrane. Their recent data show that disrupting the SUR2 gene at an earlier exon 3 causes an early lethality and the mutants only lived 8 days. However, disrupting SUR2 at middle exons 12-16 interrupts the SUR2 long forms, but the novel SUR2 short forms remain expressed. They have identified 2 splice variants that are generated by a rare intra-exonic splicing (IES) event in SUR2 mRNA to produce transcripts encoding the 55-kDa SUR2 short forms in heart mitochondria. Characterization of SUR2 KO has revealed an inverse pattern of gender difference in cardioprotection. Completed tests in KO males show that they are constitutively protected, with reduced infarcts after ischemia, while KO females have larger infarcts and cannot be preconditioned. mRNA levels of both IES variants markedly increase in the preconditioned KO males but they reduce dramatically in the preconditioned KO females. This interesting discrepancy offers a new platform of using SUR2 mutant mice to investigate gender difference in ischemic protection. The proposed research intends to explore the molecular mechanisms underlying gender difference in cardioprotection in relation to KATP channels, especially mitochondrial KATP. They hypothesized that estrogen modulates expression of sarcolemmal and mitochondrial SUR2 forms in mice. They further hypothesized that levels of the IES variants encoding the mitochondrial SUR2 short forms are critical to protection. In Aim 1, they will characterize ischemic protection in both genders of WT and KO mice, and study whether estrogen modulates expression of the SUR2 forms. In Aim 2, estrogen regulation in mitochondrial SUR2 will be investigated, and a 55A "rescued" female mouse model will be tested whether they can improve protection. Interactions of estrogen receptor 2 and the IES variants will be explored. Results from this research not only provide new insights in gender-specific response to cardioprotection but also identify new drug targets for future clinical treatments against MI.

1R01TW008288-01
Weight, Diet, Genes and CVD Risk Factors (Hypertension and Diabetes)
Lee, Nanette Requintina
University of San Carlos, Cebu, Philippines
$50,000
This study will examine the independent and combined effects of genetic predisposition and modifiable factors such as weight and dietary patterns on the risks of having hypertension and diabetes, two major cardiovascular disease (CVD) risk factors. The demographic and health trends in the Philippines exemplify those of other developing Asian countries where CVD-related morbidities and deaths are prevalent and increasing. Thus, studying the mechanisms that can lead to the development of hypertension and diabetes among Filipinos can provide critical information that may guide more tailored prevention efforts for these populations, potentially narrowing global health disparities. Cardiovascular diseases (CVD) are the leading causes of morbidity and mortality in the world (1- 3). Hypertension and diabetes, two of the major CVD risk factors, are complex diseases caused by the combined actions of genetic and environmental factors (4-8). Few studies have examined the interaction of these factors and fewer, if any, have looked at their effects in populations of developing Asian countries that are plagued with increasing levels of obesity and rapidly changing food environments (9, 10). The information gap may be due to the lack of population-based studies with adequate depth and detail. There is a paucity of information on dietary and adiposity trends derived from longitudinal studies and there are inadequate genetic data, especially among Asians who tend to develop CVD risk factors at lower body mass index thresholds (11, 12). Aims and Methods: The proposed study aims to understand how weight history, dietary patterns, and genetic variants independently and jointly affect blood pressure and fasting glucose among adult Filipino women (ages 38 to 71 yr in 2007) using the Cebu Longitudinal Health and Nutrition Survey (CLHNS), an ongoing community-based study of over 2000 women (and their infants) which began in 1983. This is a unique dataset that contains not only rich genetic information on these women but also dietary and anthropometric measurements obtained since baseline, recent blood pressure (1998-2007) and fasting glucose (2005) measurements, and other individual-, household-, and community-level data collected over a span of 24 years of rapid country-wide socio-economic changes. Specifically, using multivariate regression methods they will determine the: (a) effect of weight history (i.e. duration of overweight) on the risk of having hypertension and/or diabetes; (b) association between dietary patterns (identified through cluster analysis) and hypertension and/or diabetes; (c) independence and co-occurrence of hypertension and diabetes and how these relate to weight and dietary patterns; and (d) effects of genetic variants on hypertension and diabetes, focusing on gene variants that have been associated with hypertension or diabetes by previous association studies. Further, the study will explore significant interaction of effects among genetic variants, overweight history and dietary patterns in affecting hypertension or diabetes.

1R21HL093665-01A1
Sex Differences In Myocardial Ischemia Triggered By Emotional Factors After Mi
Vaccarino, Viola
Emory University
$232500

Coronary heart disease (CHD) is the major cause of death in American women, and every year a similar number of women and men die due to CHD. Growing evidence supports important differences in the pathophysiology, clinical presentation and prognosis of CHD between women and men; yet much remains to be learned about the unique characteristics of CHD in women. Young and middle-aged women have higher mortality and complication rates after an acute myocardial infarction (MI) compared with men of similar age. Reasons for these differences are unknown; they are not explained by traditional CHD risk factors, other comorbidity or treatments, and occur despite the fact that women have less coronary atherosclerosis and more preserved ventricular function than men. One third to two thirds of patients with CHD have myocardial ischemia that is induced by psychological stressors. Such ischemia is often painless and unrelated to severity of coronary artery disease; nonetheless it is associated with adverse outcomes. Emotional factors such as depression and psychological trauma are more common in women with CHD than in men and may predispose women to stress-induced ischemia. Depression, for example, is present in up to 40% of women with MI younger than 60 years. However, emotionally-triggered ischemia has hardly been studied in women before. The overall objective of this proposal is to evaluate differences in stress-induced ischemia between 50 women and 50 men younger than 60 years who were hospitalized for acute MI in the previous 6 months in Emory- affiliated hospitals. They hypothesize that myocardial ischemia due to emotional factors is more common in women than in men, while exercise-induced ischemia is as common, or even less common, in women. The aims of this study are: (1) Using single photon emission tomography (SPECT) [Tc-99m] sestamibi myocardial perfusion imaging, to compare myocardial perfusion during rest, during exercise, and during an emotionally stressful challenge in women and men. (2) To investigate biological mechanisms for the sex differences in ischemia induced by emotional stress, including differences in hemodynamic (blood pressure, heart rate), neurobiological (cortisol and autonomic nervous system) and inflammatory responses to the stressful challenge. (3) To investigate behavioral/psychosocial explanatory factors for the sex differences in ischemia induced by emotional stress (depression, history of trauma, and socio-economic environment). Younger women with MI represent an understudied patient group despite their higher rate of adverse events compared with men. Investigation of this group will provide critical information for the prevention of CHD in women. Their study may uncover a unique pathway which may explain sex differences in the outcome of MI.

3R21HL093665-01A1S1
Sex Differences In Myocardial Ischemia Triggered By Emotional Factors After Mi
Vaccarino, Viola
Emory University
$291952
Coronary heart disease (CHD) is the major cause of death in American women, and every year a similar number of women and men die due to CHD. Growing evidence supports important differences in the pathophysiology, clinical presentation and prognosis of CHD between women and men; yet much remains to be learned about the unique characteristics of CHD in women. Young and middle-aged women have higher mortality and complication rates after an acute myocardial infarction (MI) compared with men of similar age. Reasons for these differences are unknown; they are not explained by traditional CHD risk factors, other comorbidity or treatments, and occur despite the fact that women have less coronary

atherosclerosis and more preserved ventricular function than men. One third to two thirds of patients with CHD have myocardial ischemia that is induced by psychological stressors. Such ischemia is often painless and unrelated to severity of coronary artery disease; nonetheless it is associated with adverse outcomes. Emotional factors such as depression and psychological trauma are more common in women with CHD than in men and may predispose women to stress-induced ischemia. Depression, for example, is present in up to 40% of women with MI younger than 60 years. However, emotionally-triggered ischemia has hardly been studied in women before. The overall objective of this proposal is to evaluate differences in stress-induced ischemia between 50 women and 50 men younger than 60 years who were hospitalized for acute MI in the previous 6 months in Emory- affiliated hospitals. They hypothesize that myocardial ischemia due to emotional factors is more common in women than in men, while exercise-induced ischemia is as common, or even less common, in women. The aims of this study are: (1) Using single photon emission tomography (SPECT) [Tc-99m] sestamibi myocardial perfusion imaging, to compare myocardial perfusion during rest, during exercise, and during an emotionally stressful challenge in women and men. (2) To investigate biological mechanisms for the sex differences in ischemia induced by emotional stress, including differences in hemodynamic (blood pressure, heart rate), neurobiological (cortisol and autonomic nervous system) and inflammatory responses to the stressful challenge. (3) To investigate behavioral/psychosocial explanatory factors for the sex differences in ischemia induced by emotional stress (depression, history of trauma, and socio-economic environment). Younger women with MI represent an understudied patient group despite their higher rate of adverse events compared with men. Investigation of this group will provide critical information for the prevention of CHD in women. Their study may uncover a unique pathway which may explain sex differences in the outcome of MI.

CHRONIC FATIGUE SYNDROME

1R01NS055670-01
Autonomic Nervous System in Chronic Fatigue Syndrome
Biaggioni, Italo
Vanderbilt University, Nashville TN
$383,438
The overall goal of this application is to determine the role of the autonomic nervous system in the abnormalities associated with Chronic Fatigue Syndrome. They propose to test the hypothesis that the sympathetic nervous system contributes to the cardiovascular and inflammatory abnormalities present in the Chronic Fatigue Syndrome (CFS) and, in particular in the subset of patients characterized by postural tachycardia (POTS). CFS and POTS are seen mostly in otherwise normal young women, and are the cause of significant disability. Their preliminary indicates a decrease in plasma volume in patients with POTS, which can contribute to, and be the consequence of, sympathetic activation. Their preliminary studies also indicate an interaction between the sympathetic nervous system and nitric oxide mechanisms; this may also create a negative feedback mechanism whereby a decrease nitric oxide results in sympathetic activation, and increased sympathetic activity results in impaired nitric oxide mechanisms. They have developed a paradigm that will allow us to define selectively the contribution of endothelial nitric oxide to blood pressure regulation and will

apply this approach to patients with CFS and POTS. In addition, their preliminary studies indicate that sympathetic activity is associated with inflammatory processes. In particular, C-reactive protein are increased in patients with POTS and, conversely, decreased in patients with low sympathetic tone due to pure autonomic unsuccessful undertaking. They propose to measure validated indices of sympathetic activity, inflammation and oxidative stress in patients with CFS and POTS, and compare them to appropriate control groups, including patients with CFS without POTS, POTS without CFS, and normal controls. If their hypothesis is correct, and sympathetic activity contributes to the pathophysiology of CFS, then chronic inhibition of sympathetic tone will result in improvement of symptoms, cardiovascular alterations, volume defects, and inflammatory abnormalities present in CFS.

1R01AR053821-01A2
HERV-K18 as a Risk Factor for CFIDS
Huber, Bridgitte T.
Tufts University, Boston
$146,500
The etiology of Chronic Fatigue Syndrome (CFS) is far from understood and is likely due to multiple genetic components. Infection with EBV and treatment with IFN-a have been implicated in the pathogenesis. Their laboratory has shown that EBV-infection, and exogenous IFN-a?, activate transcription of the env gene of a Human Endogenous Retrovirus, HERV-K18. This provirus is normally silent, but when induced it encodes a superantigen (SAg), which is a class of proteins that is capable of deregulating the immune system. Three alleles of HERV-K18 env have been documented, K18.1, K18.2, K18.3, whose gene products have SAg activity, but are predicted to differ biochemically and functionally. Their working hypothesis is that HERV-K18 is a risk factor for CFS. In a pilot study, the allele and genotype distributions of the HERV-K18 env gene were compared between various groups of CFS patients and healthy controls. Although only a limited number of samples were available in the various cohorts, the odds ratios that were obtained were statistically significant. The most intriguing interpretation of these data is that they provide genetic evidence for the unique etiology of at least one group of CFS patients. Thus, it may be possible to delineate different subtypes of CFS, depending on the clinical history of the patients. It is now proposed to substantiate these pilot results, using a much larger cohort of 400 CFS patients associated with EBV that has been assembled by the co-investigator, Dr. Renee Taylor. Dr. Ben Katz, board certified in both Pediatrics and Pediatric Infectious Diseases, will clinically evaluate the patient cohort, and Dr. Inga Peter, a genetic epidemiologist and biostatistician, will oversee the statistical analyses. In addition, the expression pattern of the HERV-K18 SAg during active disease versus intermission will be measured. Furthermore, T cell stimulatory activity of this SAg, expressed on peripheral blood lymphocytes of patients during the course of the disease, will be tested ex vivo, using a T cell hybridoma reporter assay that has been developed in their lab. Since SAg-activated T cells produce massive quantities of chemokines, lymphokines and neurokines, the expression of the HERV-K18 SAg could influence not only the immune system, but other organs as well. A positive association between CFS and either HERV-K18 alleles or expression patterns would open new avenues for the development of clinical treatments of this chronic disease. CFS is a disease that affects a significant number of people worldwide, yet the underlying mechanism(s) of pathogenesis remains unclear. The herpesvirus EBV and IFN-a have been suggested to be associated with CFS, although these

concepts are far from accepted. They propose a novel genetic aspect in the EBV/ CFS association, namely the presence of certain HERV-K18 alleles that differ in their superantigen activity.

1R13NS066634-01
From Infection to Neurometabolism: A Nexus for CFS
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$10,000
The Centers for Disease Control and Prevention (CDC) defined chronic fatigue syndrome (CFS) as unremitting fatigue often accompanied by chronic widespread pain, cognitive impairment, and sleep disturbance and post-exertion malaise. Last year, the CDC estimated that at least 4 million American adults suffer with CFS. Population based studies of CFS have found at least 2 CFS are either receiving disability or are unemployed. Further, economic impact studies have determined that costs to the U.S. economy are in excess of $20 billion each year. The past 20 years of NIH funded research on CFS resulted in more than 5000 peer reviewed biomedical publications describing the biology of CFS including infection, genetic polymorphisms and brain metabolism. Research of current CFS investigators is rooted in the two decades of accumulated knowledge. Ongoing research and results can be coordinated in order to expedite control and prevention strategies for CFS. To do this, they are organizing a small, 3-day workshop for 30 scientists at the Banbury Center at Cold Spring Harbor Laboratory. The Banbury Center meetings are recognized internationally as being among the world's best discussion workshops for a variety of topics ranging from neuroscience to science policy. Investigators funded by the NIH as well as the CFIDS Association of America and conducting research on biomarkers for early detection, objective diagnosis and treatment of CFS will be invited to participate. Domain experts in infectious disease, physiology and neuroscience will be invited to chair sessions and evaluate the work presented by the CFS researchers. There are three objectives to this workshop: 1) to have funded CFS investigators present their latest research, 2) to identify common interests and study synergies and 3) to coordinate CFS-funded investigators into an expanded research network. The anticipated outcome of this meeting is the identification of CFS investigators interested in collaborating in an ongoing CFS research network. This project is directly applicable to the NIH mission "to advance significantly the Nation's capacity to protect and improve health".

1R01NS055672-01
Cognitive Behavioral Stress Management for Chronic Fatigue Syndrome
Antoni, Michael H.
University of Miami, Coral Gables, FL
$343,219
This is a 4-year study that uses a 10-week telephone based cognitive behavioral stress management intervention (T-CBSM) to illuminate neuroimmune mechanisms underlying the effects of stress and stress management on physical health status and immune regulation in individuals with chronic fatigue syndrome (CFS) relative to participants receiving a health promotion telephone (T-HP) intervention. CFS is characterized by physical symptoms which bring about severe limitations in lifestyle behaviors and vocational activities. Associated symptoms include debilitating fatigue, low grade fever, lymph node pain and tenderness,

cognitive difficulties, and mood changes. There is growing evidence that CFS patients may also show abnormalities in HPA axis functioning and on several indices of immune functioning. Chronic stress is also associated with a flattened diurnal secretion pattern for cortisol. An inability to maintain regulation in the HPA axis may contribute to the pathophysiology of CFS via diminished control of pro-inflammatory cytokines and associated physical symptoms related to chronic immune activation and inflammation. Given the debilitating nature of CFS, they propose to deliver the T-CBSM intervention through a telecommunications system (i.e. Telecare) designed to enhance access to formal and informal care for a population that may have difficulty accessing traditional psychotherapeutic settings. In their prior work with individuals with CFS, they have shown that individuals in a structured group CBSM intervention report significantly improved quality of life, perceived stress, fatigue, memory, muscle pain, and post-exertional malaise compared to individuals in the control condition. The Telecare system has been successful in delivering a supportive intervention for older caregivers of dementia patients. This study is novel in expanding their prior work to individuals with CFS who have reported difficulty participating in structured groups due to physical burden. The study design is a 2 X 3 randomized experimental design with group (T-CBSM, n=60 vs. T-HP, n=60) as the between-group factor, and time (Pre-intervention, Post-intervention and 6 month follow-up) as the within-group factor. Their primary objective is to evaluate the extent to which a T-CBSM intervention Aimed at building skills in anxiety reduction, distress tolerance, stressor appraisals, and adaptive coping strategies may improve physical health status and immune regulation in CFS by modulating neuroimmune interactions.

CRANIOFACIAL

2 R01 DE012758-11A1
Estrogen and Psychological Stress in TMJD Pain
Bereiter, David
University of Minnesota Twin Cities
$200,000
Pain in the jaw joint and muscles of mastication is the most common form of persistent facial pain. Female gender and co-occurrence with depressive illness and psychological stress are recognized risk factors in developing persistent jaw pain. Their understanding of the neurobiology of persistent jaw pain will be improved by the use of new animal models that consider these known risk factors. Temporomandibular joint/muscle disorders (TMJD) represent a family of conditions that present with pain in the temporomandibular joint (TMJ) and muscles of mastication. Chronic TMJD occurs mainly in young women and is strongly associated with elevated levels of psychological stress. Chronic TMJD patients display minimal signs of tissue injury and benefit little from conventional anti-inflammatory drug therapies. The symptoms of chronic TMJD suggest a central neural dysfunction or problem of pain amplification. By contrast, most animal models of TMJ nociception rely on overt inflammation and do not account for known risk factors (i.e., estrogen status and stress). In this application they will use an established model of psychological stress, the repeated forced swim test (FST), known to induce persistent hyperalgesia and will determine its effects on TMJ nociceptive processing in female rats under high and low estrogen conditions. They will

test the hypothesis that changes in estrogen status and psychological stress act through the periaqueductal gray-rostral ventromedial medulla (PAG-RVM), the main supraspinal pain modulatory system, to influence TMJ nociception. Since serotonergic (5HT) mechanisms mediate a significant portion of PAG- induced effects on spinal systems, they will test if specific 5HT receptors are involved in modulation of TMJ nociceptive processing at the dorsal horn level. They will stimulate TMJ afferent fibers by injection of the non-inflammatory agent, ATP, and record single neuron activity at the trigeminal subnucleus caudalis/upper cervical dorsal horn region (Vc/C1-2), the principal site of termination for TMJ nociceptors. Masseter muscle electromyographic (EMG) activity will allow us to assess treatment effects on a peripheral behavioral correlate of TMJ nociception. Three Specific Aims are proposed. Aim 1 will determine if estrogen status alters PAG-induced modulation of TMJ-evoked unit activity, masseter muscle EMG and c-fos immunoreactive neurons at the Vc/C1-2 region in sham and FST-conditioned rats. Aim 2 will determine if local actions of 5HT receptors at the caudal brainstem level contribute to PAG-induced modulation of TMJ nociception. Aim 3 will determine if local actions of 5HT receptors alone at the caudal brainstem level modify the responses to TMJ stimulation independent of overt PAG stimulation. These studies will provide new information on the influence of estrogen status and psychological stress on the neurobiology of brainstem systems thought to be critical for TMJD pain.

DIABETES

1R21HL093699-01A1
Gender Specific Complications Of Diabetic Autonomic Neuropathy: A New Mouse Model
Galper, Jonas Bernard
Tufts Medical Center
$238500
Diabetic Autonomic Neuropathy (DAN) is characterized by impairment of autonomic responsiveness of the heart. DAN has been associated with an increased incidence of arrhythmia and sudden death in diabetics. Although the overall incidence of sudden death is lower in women than in men, the risk of sudden death associated with diabetes in women is greater than in men. Studies in postmenopausal women demonstrated that combined estrogen/progestin therapy reduced the incidence of diabetes. Comparison of heart rate variability showed that the parasympathetic response of the heart was increased in young women compared with men; this difference was attenuated after menopause, but maintained in women on hormone replacement therapy (HRT). These data suggested the hypothesis that menopausal women might be more likely to develop DAN and that HRT might protect the heart from development of DAN and decrease the incidence of arrhythmia and sudden death. The Akita mouse manifests a gender difference in the development of diabetes: males develop severe hyperglycemia and secondary effects of diabetes, while females exhibit only a mild hyperglycemia. Using male Akita mice, they have previously developed an animal model for DAN that is characterized by the appearance of spontaneous ventricular arrhythmias following myocardial infarction (MI). Here they propose to test the hypothesis that the female Akita mouse might serve as an animal model for the study of Gender Specific Complications of DAN. Specifically, they will test the hypotheses 1) that ovariectomy of female Akita mice

results in the development of the diabetic phenotype and secondary effects of diabetes as demonstrated by the development of hyperglycemia, proteinuria and a decreased parasympathetic inhibition of Isoproterenol-stimulated L-type Ca2+ currents, and that estrogen reverses this effect 2) that estrogen replacement protects ovariectomized female Akita mice against the development of spontaneous ventricular arrhythmias following MI and 3) that gene array studies will establish a subset of genes that are differentially expressed in ovariectomized mice who develop arrhythmias following MI, which might serve as candidate genes for the treatment and prevention of this effect of diabetes in women. Studies in this application propose to establish a unique animal model, which might offer a new gender specific therapeutic approach to diabetes and the complications of DAN.

5U01 DK048489-16
Post DPP Follow-Up Study
Fowler, Sarah E.
George Washington University, Washington, DC
$870,000
The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive life-style intervention or metformin to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the sub-cohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1. Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2. Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding micro-vascular and neurologic complications; 3. Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4. Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP.

N02DK72927-8-0-1**Gestational Diabetes Awareness Campaign**

Joint project between ORWH and NIDDK, through the National Diabetes Education Program
$1,000,000

It's Never Too Early to Prevent Diabetes is a translational research initiative to develop new ways to promote findings of the Diabetes Prevention Program (DPP) Study on the prevention of type 2 diabetes in women with a history of gestational diabetes (GDM), and to prevent development of diabetes in their offspring. The National Diabetes Education Program (NDEP) is jointly sponsored by the NIH and the CDC with the support of more than 200 partner organizations to translate research findings into improved public health. NDEP's Gestational Diabetes Mellitus (GDM) initiative (background attached) has developed, tested and provided limited dissemination of messages and materials that address the lifelong risk of developing type 2 diabetes of women with a history of GDM and the lifelong risk of developing diabetes of their offspring. The materials are based on the landmark Diabetes Prevention Program, spearheaded by NIDDK with support of multiple ICs and the ORWH. Three pilot programs will be undertaken to extend the reach of NDEP materials and develop innovative strategies to reach women with a history of GDM and the health care professionals who care for them and their children.

Health Care Provider Education
Engage the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the American Hospital Association, Lamaze International, the National Medical Association, the National Hispanic Medical Association, among others to develop, initiate and evaluation a program to deliver education and information about the lifelong risk for developing diabetes is delivered to mothers and families in several settings, including Pre-natal care classes – Lamaze, etc., OB-Gynes, and Pediatricians.

GDM Risk Alerts
Engage state/local government partner to develop pilot project to follow-up by mail and other contacts with mothers and families who delivered a baby weighing 9 pounds or more, a defined risk factor for GDM. Birth certificates carry the key information, state and local health department vital statistics offices record and report it. A program will be developed and evaluated that sends follow-up alerts at one year anniversary of the birth certificate mailing.

Targeted Social Media/Media Relations/Promotion Outreach
Outreach and process evaluation of social media/media relations program. Initiatives to include Engagement of "mommy blogs" and other social media tools; Focused outreach to television newscasters who are pregnant – local and national. Posters/displays for pediatricians' offices, clinics, etc; Outreach to pregnancy and parenting publications, and Outreach to TLC A Baby Story to encourage inclusion of GDM storyline.

1R21HL093699-01A1
Gender Specific Complications of Diabetic Autonomic Neuropathy: A New Mouse Model

Galper, Jonas Bernard
Tufts Medical Center
$238,500
Diabetic Autonomic Neuropathy (DAN) is characterized by impairment of autonomic responsiveness of the heart. DAN has been associated with an increased incidence of arrhythmia and sudden death in diabetics. Although the overall incidence of sudden death is lower in women than in men, the risk of sudden death associated with diabetes in women is greater than in men. Studies in postmenopausal women demonstrated that combined estrogen/progestin therapy reduced the incidence of diabetes. Comparison of heart rate variability showed that the parasympathetic response of the heart was increased in young women compared with men; this difference was attenuated after menopause, but maintained in women on hormone replacement therapy (HRT). These data suggested the hypothesis that menopausal women might be more likely to develop DAN and that HRT might protect the heart from development of DAN and decrease the incidence of arrhythmia and sudden death. The Akita mouse manifests a gender difference in the development of diabetes: males develop severe hyperglycemia and secondary effects of diabetes, while females exhibit only a mild hyperglycemia. Using male Akita mice, the investigators have previously developed an animal model for DAN that is characterized by the appearance of spontaneous ventricular arrhythmias following myocardial infarction (MI). The researchers propose to test the hypothesis that the female Akita mouse might serve as an animal model for the study of Gender Specific Complications of DAN. Significance of The Application: Diabetic Autonomic Neuropathy (DAN) is characterized by impairment of autonomic responsiveness of the heart and an increased incidence of arrhythmia and sudden death. Data suggest the hypothesis that menopausal women might be more likely to develop DAN and that hormone replacement therapy might protect the heart from development of DAN and decrease the incidence of arrhythmia and sudden death. The investigators propose to test the hypothesis that the female Akita mouse might serve as an animal model for the study of Gender Specific Complications of DAN and the protective effects of estrogens against the development of diabetes and its secondary complications in the heart.

5U01 DK057136-11
Look AHEAD: Action for Health in Diabetes
Espeland, Mark Andrew
Wake Forest University Health Sciences, Winston-Salem, NC
$100,000
Look AHEAD is randomized clinical trial examining the long-term health effects of an intensive weight loss intervention in approximately 5,145 overweight volunteers with type 2 diabetes. Participants are randomized to an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity, or to a control program of diabetes support and education. The primary outcome of Look AHEAD is the aggregate occurrence of severe cardiovascular events (fatal and non-fatal Ml and stroke and cardiovascular deaths) over a planed follow-up of 11.5 years. The original grant application provided funding for the first 7 years of the study (1 year for study design and 6 for execution of the trial). The present grant application is for an additional 7 years of funding to complete the Look AHEAD trial. All aspects of the study have proceeded extremely well - the sample of 5,145 was recruited on time; retention has been excellent and the intervention

has been effective in producing initial weight loss and maintaining it over time. All 16 clinical sites have been successful in recruitment, retention, and delivery of the intervention and the DSMB has been very positive about the execution of the trial. The present application reviews the overall design of Look AHEAD, progress to date, and plans for the future. Specific Aims are to retain the cohort over time, continue to complete annual in-person visits and semi-annual telephone interviews for outcome assessments and continue to administer the lifestyle intervention. These procedures will enable us to analyze the effects of the intervention on serious cardiovascular- related factors and complications, and cost-effectiveness of the intervention.

5R01HL090514-03
Obesity, Inflammation And Thrombosis: Look Ahead
Ballantyne, Christie
Baylor college of Medicine, Houston, TX
$20,000
The increased number of obese diabetic individuals, coupled with their high cardiovascular morbidity, mortality, and healthcare expenditures, poses an enormous public health problem for the United States. Obese diabetic patients have increased inflammation and impaired coagulant balance, which are both thought to contribute to increased risk for atherothrombotic events. Although lifestyle modification with diet therapy, exercise, and weight management is recommended as foundation therapy by multiple national organizations, there are no prospective clinical trials that have shown significant cardiovascular event reduction by weight loss achieved by any modality. The Look AHEAD (Action for Health in Diabetes) study is a large multicenter trial designed to examine whether weight loss through intensive lifestyle intervention (ILI) with both diet and exercise will reduce cardiovascular events in obese diabetic individuals compared with a control group that receives diabetes support and education (DSE). The Look AHEAD trial has quantitatively assessed which aspects of lifestyle were modified by individuals (diet, physical activity) and effects on adiposity, fitness, and traditional risk factors (blood pressure, lipids, glycemic control). The proposed aims have been designed in conjunction with the Look AHEAD investigators to examine the effects of diet and exercise on inflammation and impaired coagulant balance. In this grant, they propose the following aims: 1) examine the association between measurements of obesity (weight, body mass index, waist, etc.) at baseline and levels of proinflammatory (IL-6, CRP) and anti-inflammatory (adiponectin isoforms) adipocytokines and parameters of impaired coagulant balance (PAI-1, fibrinogen, D-dimer, TAFI) in 50% of patients enrolled in the Look AHEAD trial and how this relationship is influenced by dietary intake, physical activity, fitness, gender, ethnicity, and presence of cardiovascular risk factors and disease; 2) compare the effects of ILI versus DSE on changes in inflammatory markers and impaired coagulant balance between baseline and year 1 and examine how changes are related to changes in adiposity, dietary intake, fitness, and physical activity; 3) examine how greater reductions in weight loss lead to greater changes in parameters that measure pathways of inflammation, oxidative stress, neurohormonal regulation, and impaired coagulant balance in a case-control study.

3-U01-DK056992-11S1
Gene X Behavior Interaction in the Look AHEAD Study

Wing, Rena R. (Contact); Mccaffery, Jeanne M.
The Miriam Hospital, Providence, RI
$301,213
The interplay of genetic and behavioral factors is critical to understanding obesity and behavioral weight loss intervention has emerged as a key strategy in combating obesity. In this application, they propose to identify specific genes that predict individual differences in weight loss in response to behavioral intervention to help identify individuals that struggle with weight loss despite behavioral efforts. Obesity is a major public health problem, with millions of Americans suffering from weight-related health complications, including Type 2 diabetes, coronary heart disease, hypertension, and osteoarthritis. Behavioral weight loss intervention has emerged as a key strategy in combating obesity and the associated health consequences. However, individuals differ in their degree of success in these programs and genetic factors are known to play a role. In this application, they propose to identify specific genes that predict individual differences in weight loss in response to behavioral intervention to help identify individuals who struggle with weight loss despite behavioral efforts. Specifically, they will determine whether obesity genes interact with lifestyle intervention in predicting weight loss at year 1 of the Look AHEAD trial (U01DK056992), an NIH-funded, multi-center randomized controlled trial with the primary goal of determining whether weight loss achieved through an intensive lifestyle intervention can reduce cardiovascular morbidity and mortality among persons with type 2 diabetes. At year 1, participants assigned to Intensive Lifestyle Intervention (ILI), focusing on changes in diet and physical activity, lost an average of 8.6% of their weight (N= 2,496; 97.1% follow-up) relative to losses of 0.7% among individuals assigned to the Diabetes Support and Education (DSE) group (N= 2,463, 95.7% follow-up), who received diabetes support and education groups alone. Consent for genetic analyses was provided by 3,759 participants. Genotype data from the IBC chip, including over 4,000 markers within genes previously associated with obesity, will allow us to test their central hypothesis that genes that predispose to obesity interact with lifestyle treatment to influence weight loss following intensive lifestyle intervention. They conduct these aims with the explicit goal of bringing together a team with expertise in behavioral research, genetic epidemiology and molecular biology to create transdisciplinary researchers who are able to bridge across the disciplines and identify key gene x behavior interactions in the context of the Look AHEAD trial.

DIETARY SUPPLEMENTS/CAM

5P50 AT000155-10
Botanical Dietary Supplements for Women’s Health
Farnsworth, Norman R.
University of Illinois, Chicago, IL
$95,158
The UIC/NIH Center for Botanical Dietary Supplements Research was established in the fall of 1999 to address the issues of standardization, quality, safety, and efficacy of botanical dietary supplements. The Center then adopted and will continue to implement a multidisciplinary strategy to achieve its basic and clinical research objectives. Participating faculty Co-investigators and collaborators are drawn from the Departments of Medicinal

Chemistry and Pharmacognosy and Biopharmaceutical Sciences in the College of Pharmacy; the Department of Medicine (Section of Endocrinology and Metabolism) in the College of Medicine; and the Department of Math, Statistics, and Computer Science in the College of Liberal Arts. The Center studies botanicals with potential benefits for women's health, focusing on plants that are reported to alleviate the symptoms of menopause and premenstrual syndrome. Botanical extracts are subjected to rigorous chemical evaluation followed by both in vitro and in vivo biological testing. Standardized botanical extracts that appear efficacious and demonstrate adequate safety profiles in in vitro and animal models will be candidates for clinical, Phase I trials. Hops (Humulus lupulus L.) will undergo Phase I evaluation in this grant cycle. In order to achieve this comprehensive agenda for the development of chemically- and biologically-standardized botanical dietary supplements, the renewed BRC research program will be organized as follows: Standardization of Botanicals; Mechanism of Action of Botanicals (Menopause); Studies of Metabolism, Bioavailability, and Toxicity. Two additional programs will be undertaken: a Pilot Project Program and a Training and Career Development Program. The experiments proposed in this application will greatly enhance their understanding of the mechanism of action of botanicals and whether they are safe and efficacious for women's health.

GENITOURINARY

3U01DK058229-09S2
Urinary Incontinence Treatment Network: DCC
Tennstedt, Sharon L.
New England Research Institutes, Inc.
$250,000
This proposal is submitted in response to RFA-DK-06-501 for continuation of the Urinary Incontinence Treatment Network (UITN) Data Coordinating Center (DCC) at New England Research Institutes, Inc. The DCC is responsible for the scientific management of the studies, including directing, training, and monitoring the performance of Clinical Centers in enrollment, data collection, and data management as well as for all data analysis, and reports to the DSMB. In Phase I and continuing to Phase II, NERI has provided several unique and innovative tools and capabilities, including a proprietary Web-based data management system, an automated patient randomization system, and an electronic repository for UDS tracings. The DCC is also responsible for network communications and meeting support and provides a secure study website and a public website. DCC scientists play a leadership role in all network activities, including protocol development, standing committees and work groups, manuscript development and presentations. Phase II will focus on conduct of the TOMUS trial as well as continuation of the observational follow-up studies for the SISTEr and BE-DRI studies (i.e., E-SISTEr and E-BE-DRI) of Phase I. Primary Aims of TOMUS are to compare objective and subjective cure rates for stress incontinence at 12 and 24 months between the retropubic and transobturator midurethral sling procedures. Performance of these procedures is increasing rapidly with limited data available on safety and efficacy. Therefore, this study will compare the efficacy and safety of the retropubic and transobturator (inside-out and outside-in) procedures in a 2-arm RCT; 588 women with stress Ul will be enrolled. Primary Aim of E-SISTEr is to compare long-term (60 mos.) effectiveness and durability of

the Burch colposuspension and autologous fascial sling for treatment of stress Ul in a randomized cohort of 655 women. Primary Aim of E-BE-DRI is to examine long-term (26 mos.) durability of the addition of behavioral treatment to drug therapy for treatment of urge Ul in a randomized cohort of 307 women. The UITN is a multi-disciplinary, multi-center group of Investigators dedicated to high impact clinical research regarding the prevention, evaluation and management of Ul to improve the quality of life for adults. The UITN is conducting 3 studies of treatments for both stress and urge urinary incontinence.

H1N1 Research

3U10 HD047905-05S2
Pregnancy and Drug Metabolizing Enzymes and Transporters
Caritis, Steve
Magee-Women's Research Institute, Pittsburgh, PA
$285,225
The purpose of this proposal is to establish an Obstetric-Fetal-Pharmacology Research Unit (OPRU) at the University of Pittsburgh and to summarize the components of the applicant's OPRU. They will demonstrate their willingness to cooperate with other OPRUs to establish a Network of OPRUs to identify and study common problems related to the use of pharmacologic agents during pregnancy. They provide three protocols for assessment by the Network for future exploration. The Pittsburgh OPRU is composed of a large clinical facility (Magee-Womens Hospital) with more than 8000 deliveries and a wide array of women with medical or obstetric complications. A CRC satellite at Magee provides an optimal site for recruitment and study of pregnant women. These clinical facilities are linked to the Center for Clinical Pharmacology (CCP), which provides a core laboratory for classical pharmacology analyses and a pharmacogenetic laboratory for genotyping, mRNA expression and sequencing endpoint measurements. A proteomics laboratory is also linked to the CCP. In addition to these clinical and analytical resources is a breeding rhesus monkey colony housed at Magee-Womens Hospital. A basic science component completes the Pittsburgh OPRU. A diverse group of basic scientists and clinical researchers has been interacting through the CCP and will add considerable breadth and depth to their OPRU. The leadership of the Pittsburgh OPRU provides a diverse and experienced group of researchers with a long history of collaboration and investigation in the area of maternal-fetal pharmacology. The leadership has experience in collaborative endeavors and is prepared to cooperate with other OPRUs to conduct collaborative research.

3U10HD047892-05S2
UW Obstetric-Fetal Pharmacology Research Unit
Hebert, Mary
University of Washington
$235,000
The overall objective of this grant proposal is to establish an Obstetric-Fetal Pharmacology Unit at the University of Washington. The major goal of the pharmacology unit will be to characterize the pharmacokinetics and pharmacodynamics of drugs that are of therapeutic value during pregnancy and whose clinical pharmacology is altered by the pregnant state. The

general research focus will be cytochrome P450 enzymes and membrane transporters. This proposal describes the available environment and resources at the University of Washington for establishing a successful and productive Obstetric-Fetal Pharmacology Research Unit. As a demonstration of their research interests and capabilities the following translational research studies that integrate their strengths in clinical and basic sciences are proposed to evaluate the following study aims. 1. They aim to determine whether the in vivo activities of CYP2C9 and organic cation transporter (OCT) are altered through stages of pregnancy using the following phenotype markers: glyburide for CYP2C9 and metformin for OCT. Phase I (population pharmacokinetic analysis) and Phase II (pharmacokinetic/pharmacodynamic analysis) studies are proposed to investigate the effects of pregnancy on the aforementioned drug-metabolizing enzymes and transporters (second and third trimesters vs. 3 months postpartum period). 2. They aim to determine the efficacy and safety of insulin vs. glyburide vs. glyburide plus metformin for treatment of gestational diabetes mellitus. A Phase III efficacy and safety trial is proposed to evaluate the effects of gestational diabetes as well as the treatments on maternal, fetal and infant / child developmental outcomes.

HIV/AIDS

5R03 TW008203-02
Gender Differences Among Women and Men Enrolled in China's National Free Antiretroviral Treatment
Zhang, Fujie
National Center/Aids/Std Control/Prevent, Beijing
$56,206
The aims of this application are to: (1) evaluate gender differences in antiretroviral treatment outcome; and (2) if gender differences are detected, examine factors associated with these differences. Specific Aim 1 will be accomplished by testing a set of hypotheses that women differ from men on the following measures of response to first-line antiretroviral therapy (ART) including: (a) all-cause and HIV-related mortality in the first 24 months after initiating therapy; (b) immunologic response, as measured by change in CD4+ cell count in the first 24 months; (c) virologic response as measured by the proportion of patients who reached the undetectable level of viral load in the first 24 months; (d) ART-related side effects associated with different regimens, including symptoms and laboratory-based diagnoses within the first 24 months; and (e) time to stopping first- line ART after initiating therapy. Specific Aim 2 will be accomplished by performing multivariable analysis for any outcome found to differ significantly between women and men. Covariates that might explain the treatment outcome differences will be examined to determine if they differ in proportion between women and men. Those that do will be inserted into the multivariate model to determine if any are statistically significant. All analyses will be conducted using a national ART Database established by the China Center for Disease Control and Promotion (China CDC). This large database collects demographic and clinical care information on all patients participating in the free-ART program, which provides a unique resource for examining gender- related differences in community-based HIV treatment outcomes. Determining whether these differences exist and understanding their causes will benefit HIV-infected individuals not only in China but perhaps throughout the developing world. China has successfully implemented an antiretroviral treatment (ART) program, but many challenges remain in managing the

program. The proposed study is a secondary data analysis of the China National Antiretroviral Treatment Database. The findings from the proposed analysis will provide invaluable information on the understanding of treatment differences between HIV-infected women and men in community-based ART programs and will assure the future success of the ART program in China. The analysis may also provide much-needed information to guide the assessment of other community-based HIV treatment programs in developing countries.

1-R21-DA-025543-01
Race and HIV-Risk: Contextual and Neurocognitive Influences On Sex Partnerships
Floyd, Leah
Johns Hopkins University
$204,426
The primary aim of this application i is to address gaps in literature focused on HIV risk and disparities among females. In the United States as rates have increased among females, the rate of HIV/AIDS diagnoses for African American females approaches 25 times the rate for white females. Despite the broad base of findings documenting health disparities in HIV, extant studies cannot explain why African Americans continue to be disproportionately affected. Currently, there is a hidden HIV epidemic among young adult African American females with no history of substance abuse. These women are at increased risk for contracting HIV by virtue of their social networks. The proposed is to study cross sectional epidemiologic examination of racial/ethnic differences in sexual partnerships among 220 females (110 Black and 110 White) residing in low socioeconomic status (SES) neighborhoods. Guided by ecosocial theory, the applicants seek to explain why these differences exist across race/ethnicity. Identifying social factors that influence partner selection and individual level factors that may serve to reduce the adverse effects of living in disadvantage neighborhoods will inform HIV prevention interventions for African American and underserved women. The significance of the application is that the proposed research project: (1) should provide insight into why African American females have higher rates of HIV than their white counterparts; (2) highlight the importance of considering the contextual influences of drugs, that is how drug markets change social structures and altered sexual norms and behaviors of entire communities; and (3) increase understanding of the processes through which neighborhood factors influence HIV risk.

AIDS International Training and Research Program (AITRP)
This program supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries to conduct multi-disciplinary biomedical and behavioral research to address the AIDS epidemic in their country. Grants are awarded to U.S. institutions with strong HIV-related research training experience and with HIV-related research collaborations with institutions in low- and middle-income countries. These institutions--in partnership with their foreign collaborating institutions--identify health scientists, clinicians, and allied health workers from the foreign countries to participate in their joint research training programs. For FY 2009, several awards were made to programs in: Haiti, China, Malawi, Cameron, Brazil, and India.

2D43TW001039-11

AIDS International Training And Research Program
Adimora, Adaora A.
University of North Carolina Chapel Hill
$20,000
Fogarty trainees are serving in key leadership positions and are in the center of exciting and critical research activities. Working with their collaborating institutions they have assessed the priority health needs of their partner countries and propose a research training program that addresses the countries' research needs as well as the developmental plans of their collaborating institutions. This is the second competitive renewal application for the UNC AIDS International Training and Research Program. They propose to continue to provide training in three countries: The Peoples Republic of China, Malawi and Cameroon. Investigators at UNC have worked in China since 1979, Malawi since 1989, and Cameroon since 1998. The UNC AITRP has embraced several guiding principles. First, they use training to build strong ties to key in-country organizations. Trainees with guaranteed "return jobs" in these organizations are preferentially selected. Second, their training opportunities build on funded research projects and bridge many of the strengths of UNC. Wherever possible they combine basic, clinical and epidemiological training and research in order to build critical mass. Third, they have used the Fogarty training to promote international research, working with many collaborators and funding agencies. Fourth, they have developed south-to-south and international collaborations to facilitate training and ongoing research opportunities. For example, University of the Witwatersrand is a training site for Malawi personnel, and they have developed a strong collaboration with the London School of Hygiene and Tropical Medicine for training of physicians from Malawi (a former British protectorate). Fifth, they have looked for opportunities for evolution and innovation. Such efforts have been particularly important in the development of a new Department of Public Health at the Malawi College of Medicine (which has received dedicated Fogarty support), extensive research ethics and IRB training in China, and rapid technology transfer in all three UNC AITRP countries. Sixth, they are committed to in- country leadership and ongoing mentorship after the trainee has completed their program.

2D43TW001042-11
Emory AIDS International Training And Research Program
DEL RIO, CARLOS
Emory University, Atlanta
$20,000
Located in Atlanta, the Emory AIDS International Training and Research Program (AITRP) has established itself as an interdisciplinary training environment, that is producing highly qualified HIV/AIDS researchers. The collaborating countries of the Emory AITRP proposed for this application are Mexico, Georgia, Vietnam, Rwanda and Zambia. The specific aims of the research training program include: 1. To build academic capacity in partner countries through the support of in-country education and training. 2. To build HIV/AIDS research human resource capacity through the support of degree-seeking, long-term training. 3. To fill identified gaps in partner country research training capacity through the provision of specialized medium and short-term training. 4. To build in-country capacity to conduct implementation science research that will allow their trainees to become involved in the

evaluation of the impact of a variety of interventions that are currently occurring in their collaborating countries such as PEPFAR.

2 D43 TW001038-11
AIDS International Training and Research Program
Harrison, Lee
AIDS Internat'l Training/Research, Pittsburgh, PA
$20,000
The proposed Pitt AITRP training will substantially enhance the ability of Brazil, Mozambique, and India to conduct crucial HIV prevention research. They propose to continue the AIDS International Training and Research Program (AITRP) at the University of Pittsburgh (Pitt). Their mission is to provide Brazilian, Indian, and Mozambican health professionals with multidisciplinary tools needed to conduct cutting-edge HIV prevention research in their countries. The Director and Co-Director are, respectively, Dr. Lee Harrison, Professor of Epidemiology and Medicine, and Dr. Phalguni Gupta, Professor of Infectious Diseases and Microbiology. An exciting change in their program is the addition of a site in Beira, Mozambique, which has striking training needs and where Pitt has established close collaborations with the Universidade Catolica de Mozambique. The addition of Mozambique and the training of a large cadre of well-trained Brazilian investigators over the past ten years allow us to dramatically reduce their training efforts in Brazil and shift resources to Mozambique. As a component of their training program, they will leverage the extensive training already provided to Brazil by conducting south-to-south training between these two Portuguese-speaking countries. Ongoing research in Brazil includes HIV vaccine trials, studies of effectiveness of antiretroviral therapy in public clinics, and changes in causes of death among HIV-infected patients. In India, ongoing projects include studies of genetic heterogeneity of Indian HIV strains, CDS suppression of HIV, HIV incidence studies to identify high- risk populations, and development of a novel Clostridium perfringens-based oral HIV vaccine. Research at their new site in Mozambique is currently limited and they will use the training provided by the Pitt AITRP to jump start a much-needed research agenda there. Trainees from all three countries will have access to the substantial HIV research activities at Pitt, including research in epidemiology, behavioral sciences, and laboratory sciences. During the next five years, they propose to establish an extensive training program in Mozambique; provide limited, selected training for Brazil; and provide laboratory and behavioral sciences training for India. Their successful track record during the first 10 years, the excellent training opportunities they propose, and collaboration with key institutions in their three countries assure that their program will continue to be highly productive.

2D43TW001035-11
Vanderbilt University-Cidrz Aids International Training and Research Program
Vermund, Sten H.
Vanderbilt University
$20,000
The Vanderbilt University Center for Infectious Disease Research in Zambia (VU-CIDRZ) training partnership with their international collaborators is designed to strengthen both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care in developing countries. The Vanderbilt

University (VU) Center for Infectious Disease Research in Zambia (CIDRZ) AITRP, formerly the VU-University of Alabama at Birmingham AITRP, seeks renewal of its grant, now in its tenth year due to an NIH-initiated one-year extension. They contribute research training to both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care. The VU-CIDRZ training partnership with their international collaborators is designed to train foreign scientists and key research support staff to conduct independent research and training in their home countries, as well as perform at an internationally credible level in collaborations with local and foreign scientists. They now seek to renew their AITRP with a continued focus on Zambia (since 1998), Pakistan (since 1994), India (since 2000), China (since 2000), and their newest partnership in Mozambique (VU training partnership since 2006 and developmental AITRP engagement since 2007). They have completed their older training commitments in Mongolia, Jamaica, and Russia and will complete their training commitments for Bangladesh upon the graduation of a current doctoral training (anticipated in 2011). They have restricted their AITRP training partnerships to five focus cities in order not to dilute their impact to where they have funded overseas research and strong research training partners. At the same time, they have leveraged support in each of the five venues such that their AITRP resources will go much further than permitted by the grant's funding alone. They will continue to provide a diverse portfolio of long, medium, and short-term training options. To date 58 trainees have received graduate degrees, 97% of whom have returned to work in their home countries, 8 are currently in degree programs and over 2,000 have been trained through their in-country advanced short- courses. They believe VU remains an ideal university partner for this initiative for several significant reasons.The migration of the training program to VU offers the opportunity for trainees to receive the absolute highest quality of graduate training and exposure to innovative HIV/AIDS/STD/TB related research, resources, and faculty mentors. The program is uniquely positioned within the infrastructure of the VU Institute for Global Health (VU IGH),directed by Dr. Vermund with its "center-without-walls" philosophy that nurtures noncompetitive partnerships among and within VU and with partner institutions around the globe. They feel that the innovative features of their renewal and their proven track record address the unmet needs in international AIDS training.

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1 UH2 AI083264-01
Ravel, Jacques
The Microbial Ecology of Bacterial Vaginosis: A Fine Scale Resolution Metagenomic (The Human Microbiome Project)
University of Maryland, Baltimore
$125,000

Bacterial vaginosis (BV) is the most common vaginal disease in women, and yet its cause and effective treatment remain unknown. BV is associated with many adverse health outcomes, such as preterm delivery of low birth weight babies and increased risk for infection by HIV. This research will contribute valuable information on the causes of BV, help develop improved methods for preventing and treating BV, and may help reduce major reproductive health problems associated with BV. The vaginal microbiota play an important protective role in maintaining the health of women. Disruption of the mutualistic relationship that exists between bacterial communities in the vagina and their hosts can lead to bacterial vaginosis

(BV), a condition in which lactic acid producing bacteria are supplanted by a diverse array of strictly anaerobic bacteria. BV has been shown to be an independent risk factor for adverse outcomes including preterm delivery and low infant birth weight, acquisition of sexually transmitted infections and HIV, and development of pelvic inflammatory disease. National surveys indicate the prevalence of BV among U.S. women is 29.2%, and yet, despite considerable effort, the etiology of BV remains unknown. Moreover, there are no broadly effective therapies for the treatment of BV, and reoccurrence is common. In the proposed research they will test the overarching hypothesis that vaginal microbial community dynamics and activities are indicators of risk to BV. To do this, they propose to conduct a high resolution prospective study in which samples collected daily from 200 reproductive-age women over two menstrual cycles are used to capture molecular events that take place before, during, and after the spontaneous remission of BV episodes. They will use modern genomic technologies to obtain the data needed to correlate shifts in vaginal microbial community composition and function, metabolomes, and epidemiological and behavioral metadata with the occurrence of BV to better define the syndrome itself and identify patterns that are predictive of BV. The five specific aims of the research are: (1) Evaluate the association between the dynamics of vaginal microbial communities and risk to BV by characterizing the community composition of vaginal specimens archived from a vaginal douching cessation study in which 39 women self-collected vaginal swabs twice-weekly for 16 weeks; (2) Enroll 200 women in a prospective study in which self-collected vaginal swab samples and secretions are collected daily along with data on the occurrence of BV, vaginal pH, and information on time varying habits and practices; (3) Determine the gene content (metagenome) of vaginal microbial communities to assess the metabolic potential of representative vaginal communities in women before, during, and after the spontaneous remission of BV; (4) Characterize suites of expressed genes (metatranscriptome) in communities representative of vaginal community types in healthy women, as well as before, during, and after the spontaneous remission of BV; and (5) Apply model-based statistical clustering and classification approaches to associate the microbial community composition and function, with metadata and clinical diagnoses of BV. The large body of information generated will facilitate understanding of vaginal microbial community dynamics, the etiology of BV, and drive the development of better diagnostic tools for BV. Furthermore, the information will enable a more personalized and effective treatment of BV and ultimately, prevent adverse sequelae associated with this highly prevalent disruption of the vaginal microbiome.

Microbicides Innovation Program (MIP).

In collaboration with the NIH Office of AIDS Research (OAR), National Institute of Allergy and Infectious Diseases (NIAID), NICHD, and NIMH, ORWH has funded a number of R21/R33 innovation projects to support exploratory and developmental research on new microbicides and microbicides strategies and technologies in the goal of advancing promising strategies and technologies into the preclinical and clinical development of new agents. RFAs, all using the title Microbicides Innovation Program (MIP), have been issued in recent years to expand the research base in this area. The development of safe, effective acceptable topical microbicides to prevent the sexual transmission of HIV could play a major role in worldwide reduction of new HIV infections. An effective and acceptable microbicide

potentially could save millions of lives. Topical microbicides are agents that can result in inhibition of the transmission of HIV and/or other sexually transmitted infections (STIs), which may be cofactors in HIV transmission. The purpose of the MIP is to support novel and underexplored strategies in the field of topical microbicides.

Summaries for the individual MIP awards follow:
5R21 AI079740-02
Mucus-penetrating nanoparticles for sustained microbicide delivery
Cone, Richard A.; Hanes, Justin S. (contact)
Johns Hopkins University, Baltimore, MD
$13,637
They have developed mucus-penetrating nanoparticles (MPP) suitable for sustained delivery of small-molecule microbicides (Lai et al, Proceedings of the National Academy of Sciences 2007; 104(5):1482-7). Conventional particles (CP) are mucoadhesive and stick to the outer layers of mucus that are shed most rapidly out of the vagina. By densely coating MPP with low molecular weight polyethylene glycol (PEG) they found that unexpectedly large MPP 100-500 nm in diameter can be engineered to rapidly penetrate human cervicovaginal (CV) mucus and thereby reach the unstirred layer of mucus adhering to the epithelial surface. These MPP will likely significantly increase vaginal residence time and improve epithelial microbicide distribution. The aim of this R21/R33 project is to develop MPP for the sustained delivery of small-molecule microbicides to increase their protective efficacy, acceptability, and user reliability. 'User failure' is the primary failure mode of barrier methods, and microbicides are likely to be used more reliably if applied daily on a coitally-dissociated basis. Another failure mode well-documented in animal models is inadequate microbicide distribution - the infectious inoculum reaches surfaces unprotected by the microbicide. MPP can provide a once-a-day, coitally-dissociated method that is likely to achieve complete and essentially uniform epithelial distribution. MPP will not likely provide the month-long delivery of a vaginal ring, but MPP have advantages that are not immediately apparent: 1) The vaginal epithelium is highly permeable to small water-soluble molecules - thus uniform epithelial distribution can best be achieved by uniform sustained delivery of small water soluble microbicides directly to the entire epithelial surface, not just to the vicinity of a vaginal ring. 2) Uterine peristalsis exposes the upper reproductive tract to vaginally deposited pathogens, and reliable protection of the upper tract is more likely to be achieved by MPP that can transport, and then locally deliver, small water-soluble molecules to the epithelia surfaces of the upper tract. In the R21 phase they propose to develop acyclovir-loaded MPP to evaluate in their mouse HSV models for efficacy, duration, vaginal distribution, and toxicity. The MPP will be composed biodegradable copolymers that they have shown are capable of sustained delivery of a wide range of bioactive molecules. The key milestone for R21 will be to develop acyclovir-MPP that provide at least one day of protection in the mouse. In the R33 phase, they will use the knowledge gained from the R21 phase to speed the development of an anti- HIV-MPP for sustained release of the best anti-HIV microbicide candidate then available (Fall, 2010), with tenofovir being a likely choice. The R33 anti-HIV-MPP will be optimized for drug delivery based on R21 results, and be tested for toxicity in mouse models and for efficacy in the Hu-BLT-SCID mouse/HIV model by Dr. Victor Garcia at UT Southwestern. World-wide, there is a great need for methods women can use to protect against AIDS and other sexually transmitted diseases. Several small-molecule vaginal microbicides are being

developed that block HIV from infecting and/or replicating in target cells. The aim of this project is to enhance the protective efficacy of these small-molecule microbicides by developing mucus-penetrating nanoparticles that will improve coverage of susceptible tissues to increase reliability of protection, and to increase duration of protection so that the microbicides can be applied regularly, on a daily basis, and not require coitally-related applications.

5R21 AI079763-02
Novel Mucosal Models Predictive of Microbicide Safety
Herold, Betsy C. (contact); Keller, Marla J.
Yeshiva University, Bronx, NY
$13,637
The proposed Microbicide Innovation Program fosters the development of new model systems (dual chamber and murine) that have the potential to substantially advance microbicide science. This approach is designed to improve methods for assessment of microbicide safety. The optimal microbicide should protect against infection without disrupting the mucosal environment or its mediators of host defense. The clinical trial failures with nonoxynol-9 and cellulose sulfate highlight the challenges in microbicide research and the need to establish better markers predictive of microbicide safety. The proposed studies address this gap. The primary objective of the R21 component is to establish two synergistic models of microbicide safety: an in vitro dual chamber model using primary human cervical epithelial cells and a murine model. Preliminary findings with these models demonstrate that the models would have predicted the increase in HIV acquisition observed in recently completed clinical trials. The microbicides disrupt the epithelium in vitro, as evidenced by a loss in transepithelial electrical resistance and in structural proteins and these changes are associated with an increased migration of cell-free HIV across the epithelium. In parallel studies, the drugs also trigger substantial changes in genital tract tissue architecture in mice following repeated vaginal application and the observed changes are associated with an increased susceptibility to genital herpes infection. Establishment of these two complementary models will contribute to efficient assessment of microbicide safety. During the R33 phase, both models will be translated into the preclinical pipeline by evaluating leading microbicide candidates, singly and in combination. Candidate microbicides will be introduced in the presence of cervicovaginal secretions and challenged in vitro with virus introduced in semen. The migration of both cell-free and cell-associated HIV will be tested in the dual chamber model system. In addition, during the R33 phase, the in vitro model will be expanded to assess the impact of microbicides on cells derived from women with human papillomavirus (HPV) associated dysplasia. While it is critical to assess the effect of microbicides on healthy genital tract cells and mucosa, it is highly likely that many women who choose to use a microbicide will be infected with a sexually transmitted infection. HPV is the most common sexually transmitted infection worldwide and changes in genital tract epithelium in response to microbicides may differ in women with HPV. These results will provide critical new data on microbicide safety in women with a sexually transmitted infection. Biomarkers predictive of microbicide safety are urgently needed. Tissue and murine models may provide more efficient strategies to assess microbicide safety by expanding existing models to include testing of primary cells. Development of an effective dual chamber and murine model may prove to be important in determining which candidate microbicides to move forward in the

development pipeline. In addition, these models may provide a means to test the safety of microbicides in healthy women as well as those with underlying STIs.

5R21 AI079767-02
Novel Vaginal Microbicides Based On Stable AAV-Neutralizing Antibody Gene Transfer
Marasco, Wayne A.
Dana-Farber Cancer Institute, Boston, MA
$13,637
In the global AIDS pandemic, more than half of new HIV-1 infections are acquired by women through intravaginal HIV exposure. Although cervico-vaginal epithelial cells lining the mucosal surfaces of the female lower genital track provide the initial defense system against HIV-1 infection, the protection is often incomplete. Transport of HIV-1 across this mucosal barrier is absolutely critical for HIV-1 colonization and subsequent virus dissemination and thus enhancing anti-HIV-1 humoral immunity at the mucosal cell surface by the local expression of anti-HIV-1 neutralizing antibodies (nAbs) that block epithelial cell attachment and virus entry may provide an important new intervention that could slow the spread of HIV/AIDS. This R21/R33 Project represents the combined efforts of the Marasco (Antibody Engineering, Gene Therapy), Anderson (Mucosal Immunity) and Mansfield (HIV/AIDS Macaque Model) laboratories to investigate whether stable adeno-associated virus (AAV)-nAb gene transfer to the cervico-vaginal epithelial stem cells can provide a strategy that will lead to durable protection against HIV-1. In the R21 phase, they will first determine which of 9 AAV serotypes provides optimal gene transfer of GFP without toxicity to primary human (Hu) and rhesus macaque (Rh) primary genital epithelial cells (PGECs) comprising endocervical, ectocervical and vaginal epithelial cells with special focus on stable gene transfer into p63+CK17+epithelial stem cells which are capable of renewing stratified epithelium. Persistence of AAV-GFP transduction, potential toxicities and effects of proinflammatory cytokines, hormonal conditions, semen and vaginal secretions on transduction efficiency and transgene persistence will be examined. They will construct a miniaturized version (minibody) of broadly neutralized human anti-gp120 Mab b12 in both the IgG1 and dimeric IgA2 format and assess b12 neutralizing activity against HIV-1/SHIV by both Ab treatment studies and AAV gene delivery to organotypic human vaginal and endocervical models and Hu & Rh PGECs. Upon successful demonstration of in vitro protection, the R33 phase will begin where they will first conduct an AAV-transduction dose escalation study in Rh (n=12) to evaluate depth, uniformity and extent of p63+,CK17+ stem cell transduction, the PK of b12scFv-FcG1 and b12scFv-FcA2 secretion, and toxicity. This will be followed by a second intravaginal transduction study with the optimal dose of the two AAV-b12scFv vectors each alone and together followed by vaginal challenge with SHIV (Rh=15-16). Finally, they will evaluate enhanced SHIV protection through mixtures of gel-forming polymers and AAV to increase in vivo AAV transduction and b12scFv-Fc secretion (Rh=9). Overall, 13 hypotheses will be tested. These important studies fulfill a major objective of the R21/R33 program to support research that may be high risk/impact and have the potential to advance AIDS microbicide strategies. Given the safety profile, low immunogenicity and rapid advancement of AAV based gene therapy in numerous clinical trials, it is likely that success of this novel approach could be quickly translated to human studies. HIV-1 infections are acquired most often through sexual contact and more than half of new infections are acquired by women through intravaginal HIV exposure. They propose

to develop a genetic microbicide that when delivered to the mucosal surface of the cervix and vagina will allow the lining cells to stably produce a neutralizing human anti-HIV antibody that blocks HIV-1 attachment and infection. A protective genetic microbicide delivered to the female lower genital track could dramatically slow the spread of HIV/AIDS.

5R21 AI079776-02
HIV Integrase as a Target for Topical Microbicide Development
Klotman, Mary E.
Mount Sinai School of Medicine of NYU
$13,637
Over 4 million individuals were newly infected with HIV in 2006 with sexual transmission the predominant mode of infection worldwide, highlighting the need for effective prevention strategies. Unfortunately clinical trials to date, with the first generation of candidate topical microbicides to block sexual transmission, have been disappointing as both nonoxynol-9 (N-9) and more recently cellulose sulfate (CS) either did not block transmission or actually enhanced transmission. These results highlight the continued need for highly efficacious and safe microbicide candidates. This project will address the safety and efficacy of a new class of specific anti-retrovirals as topical microbicide candidates, integrase inhibitors. The integrase inhibitor, GS-9160, is a potent inhibitor of HIV which has been extensively studied in animals and most recently in a Phase I human trial and has had no significant toxicity. The potential of this drug as a candidate microbicide will be evaluated in two phases. In the R21 phase, a candidate gel formulation of GS-9160 will be generated in collaboration with Gilead Sciences and evaluated for in vitro drug loading and stability. The drug and candidate formulation with favorable loading will be evaluated in cervical and vaginal epithelial cell monolayers and cervicovaginal explants for release and uptake, cytotoxicity and efficacy against primary and laboratory isolates. The parallel evaluation of gene expression induced by formulated GS-9160 in human and rhesus macaque (RM) cervicovaginal explants along with a similar analysis of tissue and cervical vaginal lavage (CVL) fluid derived from in vivo RM studies in the R33 phase will validate the cervicovaginal explant model as a screen for host responses in vivo. If the candidate formulation has an acceptable safety profile as determined by the absence of a proinflammatory response (comparable to N-9) and inhibits HIV infection in the explant model, the R33 phase will be initiated with testing of local and systemic pharmacokinetics and toxicity associated with vaginal delivery of formulated GS-9160 in (RM) followed by an efficacy study in RM vaginally challenged with R5 SHIV. The proposed studies will directly address whether integrase inhibitors as a class should be added to the pipeline for microbicide development. In addition, studies proposed will validate the genital explant model as a screen for host responses in vivo Over 4 million individuals were newly infected with HIV in 2006 with sexual transmission the predominant mode of infection worldwide, highlighting the need for effective prevention strategies. Topical microbicides that could be applied by the user to protect against sexual transmission of HIV have to date been disappointing in clinical trials. This proposal exams the topical microbicide potential of a very potent antiretroviral drug that inhibits integration of the virus into host cells. If successful in these studies it would be added to a new generation of topical microbicides in the pipeline that specifically target HIV.

5R21 AI079777-02

Combinations of entry inhibitors as anti HIV-1 microbicides
Liwang, Patricia J.
University of California, Merced, CA
$13, 637
Given the high rate of sexual transmission of HIV-1, particularly in the developing world, the need for a topical microbicide is critical. The long term goal of this research is to develop an anti-HIV microbicide using HIV-1 fusion inhibitors. In particular, they have found that the combination of certain chemokine variants with gp41-binding proteins results in highly potent inhibition of HIV-1, both in fusion assays (IC50= 1 pM) and in viral assays in PBMC (IC50=0.7 nM, R5 tropic strain Ba-L). The Aims of the proposal are as follows: First, combinations of CCR5 binding proteins and gp41-binding peptides will be tested in both fusion assays and in viral assays with multiple clades of HIV as well as primary strains in order to determine which combinations provide the most potent protection. Then it will be determined if a higher level of inhibition efficiency can be obtained by combining both a variant chemokine and a gp41-binding protein on a single polypeptide chain. During the R33 phase of the project, it is proposed to carry out pre-clinical evaluation of the most potent inhibitors and combinations, including, stability to pH and ionic strength, cell toxicity and irritation in animal models. The most promising inhibitors will then be tested in two different ways. In Aim 4 they will be expressed by Lactobacillus jensenii, an organism that is naturally found in vaginal mucosa, and as such represents a method of delivery of protein microbicides having great potential. Finally, in Aim 5, the best entry inhibitors will be evaluated in a humanized mouse model that has been shown to be able to be infected with HIV. Anti-HIV microbicides are molecules that can be used topically to prevent the spread of the HIV-1 virus through sexual transmission. The proposed experiments will study the combination of CCR5-binding proteins and gp41-binding proteins to synergistically inhibit HIV and as components of a microbicide.

5R21 AI079785-02
Scalable production of recombinant protein microbicides
Ma, Julian
St. George’s Hospital Medical School, London
$13,637
HIV microbicides are designed to be applied topically before sexual intercourse to inactivate the virus and prevent infection. Some of the most promising microbicide candidates have been proteins, but their clinical development and evaluation has been hampered by the lack of available material and/or the prospect of having to manufacture vast quantities of recombinant protein very cheaply. Plant biotechnology offers some potential solutions. Whilst the production of microbicides at agricultural scale is a long term aim, it is likely that the first generation products will emerge from plants grown in containment, under conditions more recognizable as conventional medicine production systems. It has long been established that recombinant proteins can be expressed in all tissues of the plant, including roots. Indeed, some recombinant proteins produced by transgenic plants are actively secreted from the root system in a process known as rhizosecretion. This gives rise to the possibility that transgenic plants could be grown in greenhouses under hydroponic conditions, using a defined culture medium. Moreover, the microbicide product could be harvested from hydroponic culture medium, rather than plant tissue, which would greatly simplify purification, and allow harvest

over the lifetime of the plant. Hydroponic cultivation of plants is already a well established technique in the horticultural industry and is also currently used for the production of natural medicinal compounds. The objective of this proposal is to establish a contained hydroponic tobacco plant culture approach for production of two microbicide protein candidates, cyanovirin-N and MAb 4E10, and to develop optimization strategies for growth and production that will deliver previously unavailable protein microbicides at a level to allow clinical evaluation. They will establish production at small commercial scale. In the first (R21) phase of the proposal, they intend to demonstrate feasibility of the approach and have established production driven milestones for entry into the second (R33) phase, in which they will develop manufacturing and purification according to Good Practice regulatory requirements ultimately to deliver protein microbicides for clinical trials. Cyanovirin-N and MAb 4E10 are two of the most promising protein microbicide candidates currently available. However, the clinical development of both has been held back by production difficulties, and their efficacy and safety profiles are still to be determined. This project is aimed at developing a production platform for CV-N, MAb 4E10 and ultimately other recombinant protein microbicides, which will advance these products to human clinical trials.

5R21 AI079791-02
Intravaginal ring microbicide formulations comprising multiple anti-HIV agents
Smith, Thomas J.
Oak Crest Institute of Science, Pasadena, CA
$13,637
The broad long term goal of this project is to empower women to protect themselves from HIV infection through the development of improved microbicides based on their clinically proven sustained release technology platform. Using this platform drug delivery devices for a broad range of drugs have been approved by the FDA and are in current clinical use. The ganciclovir intraocular implant: the Vitrasert(r), approved for the treatment of AIDS related CMV retinitis releases the relatively soluble antiviral ganciclovir into the eye for a period of eight months. The Retisert(r) releases the relatively insoluble steroid fluocinolone acetonide for up to three years. They propose to utilize this platform to develop sustained release vaginal ring microbicide formulations for the antiretroviral agents tenofovir and TMC 120. In the first two years of this project (R21) they will evaluate the hypothesis that, when incorporated into a ring formulation, the prodrug tenofovir disoproxil fumarate is superior to the parent drug tenofovir as candidate microbicide. In the second phase of the project (R33) they will manufacture and test ring formulations containing multiple antiviral agents. They hypothesize that, using their unique drug delivery platform, there will be no loss of elution characteristics with the incorporation of multiple drugs into their system. The successful completion of this project will result in the submission of an investigational new drug exemption (IND) leading to clinical trials for these formulations. Each day 15,000 people are infected by HIV, the majority in sub-Saharan Africa and a growing percentage women infected though heterosexual sex. The broad long term goal of this project is to empower women to protect themselves from HIV infection through the development of improved vaginal ring formulations for microbicides based on the sustained release drug delivery of antiviral agents. Their clinically proven sustained release drug delivery platform uniquely allows us to deliver drug of both high and low aqueous solubility. They propose to utilize this platform technology to develop long-term vaginal ring formulations for the potential

microbicides tenofovir and TMC-120.

5R21 AI079792-02
HIV sexual transmission in mice: study of microbicide efficacy
Potash, Mary Jane
St. Luke's-Roosevelt Inst for Hlth Scis
New York, NY
$13,637
This application is submitted in response to RFA-AI-07-034. They have constructed a model of systemic infection of immunocompetent mice by chimeric HIV-1, EcoHIV. Their previous studies indicate that EcoHIV replicates in lymphocytes and macrophages in infected mice, infection in mice is sensitive to antiretroviral drugs, productive infection persists for months inducing immune responses, and HIV-1 DNA vaccination can block infection in mice. Preliminary results reported here show that sexual transmission of EcoHIV in mice is rapid and efficient. Their overall goal in this application is to develop the mouse infection system to investigate the mechanisms of sexual transmission of HIV-1 as a platform to test efficacy of candidate microbicides. The Specific Aims of are: 1) to optimize conditions for sexual transmission of EcoHIV in mice and evaluation of interventions. 2) to identify the cell types involved in sexual transmission of EcoHIV. 3) to test the inhibition of sexual transmission of EcoHIV by antiretroviral-based microbicides. 4) to determine the HIV-1 subtype dependence of sexual transmission and efficacy of antiretroviral based microbicides against different HIV-1 subtypes. 5) to determine whether combination administration of an HIV-1 DNA vaccine followed by a microbicide can prevent sexual transmission of subtype B EcoHIV. Chimeric HIV-1 will be transmitted to conventional, immunocompetent female mice by mating with males infected through inoculation. Virus burden in multiple organs will be measured by real-time PCR and productively infected cells will be identified by flow cytometry and confocal microscopy. Accomplishment of Aims 1-3 will provide a firm foundation for and justification to extend the model to Aims 4-5 in studies directly relevant to the current HIV-1 epidemic and realistic means to control it. HIV-1 infection continues to spread worldwide, primarily by sexual transmission. The public health community responded to this pandemic by research into microbicides, compounds that women can apply to prevent transmission of HIV-1 during intercourse. Unfortunately, there is no simple way to determine which of many microbicides being developed actually blocks HIV-1 transmission before women begin their use. Some of the first to be tested by women in clinical trial actually increased HIV-1 transmission. This application is designed to develop a system for preclinical testing of microbicides in mice to determine their ability to reduce or prevent sexual transmission of HIV-1. They have shown that a form of HIV-1 that they genetically engineered to infect mice is very easily transmitted during mating. They propose to optimize this system to determine how well microbicides block sexual transmission of HIV-1. They shall also test in mice how the forms of HIV-1 that are widely distributed today can be controlled by microbicides. They have already shown that vaccination can reduce susceptibility to HIV-1 in mice. They also plan to both vaccinate mice and then treat with microbicides to determine if it is possible to completely prevent sexual transmission of the virus. Their hope is that the model of sexual transmission of HIV-1 in mice can accelerate the development of safe and effective microbicides that can be used to control the AIDS pandemic.

5R21 AI079798-02
HIV Microbicides and the Vaginal Microbiome
Zeichner, Steven L. (contact); Ravel, Jacques
Children's Research Institute, Washington, DC
$13,637

Vaginal HIV microbicides offer great promise to reduce HIV transmission, but phase 3 microbicide trials have failed. In some studies, patients using the microbicides had higher HIV transmission rates than did subjects using placebos. There is no clear explanation for these failures, but one hypothesis holds that microbicides alter the vaginal microbial flora in ways that increase inflammation or activate potential HIV host cells, enhancing transmission. Studies examining the effects of microbicides on the vaginal flora found few significant effects on the microbiome, but they used conventional culture techniques. Recent studies using molecular, culture-independent techniques showed that the flora in many human microbial environments, including the vagina, is much more complex than previously appreciated and that conventional culture techniques only detect a small fraction of the microbes in the environment. They propose to use these new culture-independent techniques to explore the hypothesis that microbicides alter the vaginal microbiome in ways that can potentially enhance HIV transmission via these specific aims: 1) Examine the vaginal microbial flora before and after microbicide application in a CONRAD repeat phase 1 study of nonoxynol-9 (N-9), cellulose sulfate (CS), and placebo using Affymetrix PhyloChip microarrays 2) Examine the portfolio of expressed genes in the vaginal microbiome before and after microbicide application using microbial cDNA sequencing in the phase 1 study, and 3) Examine the microbial species composition before and after microbicide application in the CONRAD CS phase 3 study that failed using the PhyloChip and direct 16S rRNA gene sequencing. The main milestone they propose to transition from the initial R21 phase of the project to the R33 phase is the demonstration that microbicide use leads to a significant alteration in the vaginal flora as assessed by the PhyloChip. Determining whether microbicide application is associated with vaginal microbiome changes that could enhance HIV transmission would aid understanding of the failure of the previous phase 3 trials and would help future microbicide development efforts because, if harmful changes in vaginal flora are associated with microbicide use, future microbicide development efforts would require careful measures to avoid inducing potentially harmful changes in the vaginal microbiome. Vaginal microbicides for the prevention of HIV sexual transmission offer great theoretical promise to reduce HIV sexual transmission and blunt the HIV pandemic, particularly in regions with the highest HIV prevalence rates. Unfortunately, several large late phase trials of HIV microbicides have failed for unknown reasons, with the research subjects using the microbicides having rates of HIV transmission higher than subjects using placebos. They hypothesize that one factor contributing to the failure of the microbicides is that their use produces a harmful change in the microbial flora living in the vagina, which leads to inflammation or activation of the cells that HIV replicates in, increasing the risks of HIV transmission. In their study, they propose to use new molecular biological techniques to comprehensively catalog essentially all of the microbes living in the vagina and determine how the use of HIV microbicides alters the population of the microbes. Determining that the use of HIV microbicides lead to a significant, potentially harmful alteration in the population of vaginal flora would help explain the failure of the existing microbicides to prevent HIV transmission and may help enable the development of new, more effect HIV microbicides.

5R21 AI079801-02
Microbicide properties of RT inhibitor combinations
Parniak, Michael A.
University of Pittsburgh, Pittsburgh, PA
$13,637
Topical microbicides are an important strategy to minimize heterosexual transmission of HIV. Several single agent microbicides are in clinical trials, including one based on the nonnucleoside reverse transcriptase inhibitor (NNRTI) UC781 that they discovered as a potential microbicidal agent. However, combination microbicides may be preferable, yet only a single combination microbicide is currently under evaluation. There is also an urgent need to identify new pipeline microbicidal agents. They have found that the nucleoside RT inhibitor (NRTI) 4'-ethynyl-2-fluoro-deoxyadenosine (4'E-2FdA) provides a potent and prolonged barrier to HIV- 1 infection of cells in the subsequent absence of exogenous drug, a property previously only noted for NNRTI such as UC781. The memory effect barrier is imparted by 4'E-2FdA at drug levels orders of magnitude less than those needed for protection by the nucleotide tenofovir, currently in clinical assessment for microbicide use. They hypothesize that microbicides comprising combinations of different classes of highly potent RT inhibitors, namely the NNRTI UC781 and an NRTI such as 4'E-2FdA, will provide an optimal barrier to HIV-1 transmission. They therefore propose these Specific Aims for this R21/R33 phased innovation application: R21 Aim 1. To evaluate the in vitro (cell-based) microbicidal properties of NRTI and UC781 alone and in combination. These studies include assessment of antiviral activity and memory effect protection imparted by NRTIs and UC781 alone and in combination using primary cells (PBMCs, CD4+ T-cells, macrophages) and different HIV drug-sensitive and drug-resistant strains, isolates and clades. R21 Aim 2. To elucidate the mechanism of 4'E-2FdA (and analogs) induced protective barrier or memory effect in HIV susceptible cells. These studies include characterization of uptake, conversion to triphosphate and intracellular stability of the NRTI-TPs, as well as detailed kinetic evaluations of the NRTI substrate activity with enzymes involved in metabolism of the NRTIs. R21 Deliverables: Identification of a lead NRTI and two back-ups for use with UC781 for development as a combination microbicide. R33 Aim 1. To formulate the NRTI/NNRTI combinations selected in the R21 phase into an appropriate delivery system for vaginal topical use. NRTIs and NNRTIs have different chemical properties, thus appropriate delivery systems must be identified to enable incorporation and release of the active agents. They will prepare and evaluate both gel and rapidly dissolving film formulations for the combination microbicide. R33 Aim 2. To evaluate the anti-HIV microbicidal activity of formulated NRTI/NNRTI combinations in an ex vivo cervical explant tissue model. These studies will use a newly developed physiologically relevant polarized cervical tissue model to assess the impact of formulated microbicides alone and in combination on HIV transmission and infectivity. R33 Deliverables: Identification of an appropriate delivery formulation for the selected NRTI/NNRTI combination for entry into subsequent preclinical safety and efficacy studies. This project seeks to develop anti-HIV microbicides based on the non-nucleoside RT inhibitor UC781 in combination with novel 4'-substituted nucleosides, a combination found to provide profound and protracted protection of susceptible cells against HIV infection in vitro. Their studies will provide potent new formulations to the microbicide development pipeline for entry into clinical evaluation.

5R21 AI079852-02
New Shiv R5 Env's (Based On All Subtypes) For Effective Microbicide Testing
Arts, Eric J.
Case Western Reserve University, Cleveland, OH
$13,637
SIV strains containing HIV-1 env genes (SHIVenv) have been successfully employed to infect macaques through intravenous and mucosal routes. These macaque models have been crucial for studies on HIV pathogenesis, vaccine, and microbicide testing. However, few SHIVenv strains can maintain stable and prolonged infections. Several challenges are apparent in the testing of anti-HIV-1 microbicides and many of these stem from poor animal models to test efficacy. In the R21 proposal, they have outlined a system to construct and test the infectivity of SHIV based on the env and pol genes of subtype A, B, C, and D from acute/early infections. In aim 1, they will utilize a rapid yeast recombination cloning approach to shuttle approximately 400 HIV-1 env genes into an HIV-1NL4-3 or SIV backbones of mac239 and KB-9. The HIV-1 subtype A, C, and D env genes will be PCR amplified from the endocervix or blood of Ugandan and Zimbabwean women within three months or after three years of infection. Over 20 HIV-1 env chimeric viruses have already been constructed and tested using env genes from these patient samples. HIV and SIV env chimeric viruses will be included in subtype-specific pools if the clone is capable of replication on cell lines expressing human or rhesus CD4/CCR5 (respectively) and in human or rhesus PBMCs (respectively). In aim 2, the pathogenicity of these pools will then be accessed (1) using vaginal explants and (2) through vaginal exposure in macaques. The clones that establish infection in both the explant tissue and macaques can then be reconstituted into the pathogenic subtype A, B, C, and D pools for the microbicide studies described in the R33 section of this proposal (aim 3). First, they will determine if higher concentrations of cmpd167 or PSC- RANTES are required to inhibit the pathogenic subtype A, B, C, and D pools of HIV or SHIVs (as compared to the standard SHIVSF162-P3) in human or rhesus vaginal explant tissues. They determine the identity of any HIV or SHIV clone(s) that are capable of infection even in the presence of the drug. These specific HIV-1 clones (produced from original DNA clones) can then be tested for sensitivity to CMPD167 and PSC-RANTES and to determine if infection was related to drug resistance. Finally and most importantly, microbicides CMPD167 and PSC-RANTES will be vaginally applied to rhesus macaques prior to exposure with the infectious subtype A, B, C, and D pools as well as the standard SHIVSF162-P3. They suspect that the majority of the treated macaques will be protected from SHIVSF162-P3 infection. In contrast, the protective effects of the microbicides may be reduced and that in some animals, a slight delay in viremia (as compared to untreated animals) may be the result of infection by specific clone in the SHIV pool with reduced sensitivity to CMPD167 and PSC-RANTES. Vaginal microbicides provide an excellent method to protect women from HIV-1 infection but testing these products prior to human use remains a challenge. A monkey species (e.g. Rhesus macaques) and virus cousin of HIV-1 (SHIV) are used to test the level of protection by these compounds. In this proposal, they have designed new SHIVs that are more closely related to HIV-1 and provide more stringent testing of microbicides for future human use.

1R21AI079772-01A1

Development of a Novel Semen-Activated Prodrug as an Anti-HIV Microbicide
Buckheit, Robert W., Jr.
Imquest Biosciences, Frederick, MD
$37500
The S-acyl-2-mercaptobenzamide thioester (SAMT) inhibitors are low molecular weight compounds which target multiple steps in the HIV replication pathway, but primarily function to specifically inactivate cell-free HIV immediately upon exposure to the reactive compounds and to suppress the production of infectious HIV from virus-infected cells. These NCp7-targeted, virus inactivating compounds act by stripping coordinated zinc ions from the nucleocapsid (NC) protein in the infectious virion or maturing virus particle. In the process, the compounds irreversibly cross-link the nucleocapsid proteins rendering the virion noninfectious and defective. Thus, the NCp7 inhibitors interfere with two potential virus transmission mechanisms required for the infection of target cells in the vaginal environment. In the R21 phase of this proposal they propose to develop new microbicides composed of polymeric prodrugs for delivery of the SAMTs. This delivery mechanism limits the tissue absorption of the SAMT until it comes in contact with the viral inoculum in semen by attaching it to a high molecular weight biocompatible polymer. They will conjugate the SAMT inhibitors to the polymer carrier through enzyme-cleavable linkages that will release the active drug product in the presence of specific enzymes in semen. This delivery approach offers several advantages in the context of microbicide action since (1) the NCp7 inhibitors can inactivate cell-free and cell-associated virus in semen, they will target the virus before it can diffuse in an infectious form to or into tissue, (2) they will add moieties to the polymer backbone that will increase the stability of the SAMT inhibitors by decreasing the pH local to the conjugated drug by the Donnan effect, and (3) since microbicides will be used by women repeatedly over many years, a polymeric prodrug approach will allow precise control over the tissue concentrations and exposure to anti-HIV compounds, limiting the chance to develop viral resistance and limiting toxicity. Critical to the development of this prodrug approach, biological evaluations will be performed to confirm the efficacy of the SAMTs in the presence of seminal plasma and vaginal fluids. Additionally, the enzymatic activation of the compound from its prodrug form will be evaluated in specially designed in vitro assays to mimic the events which must occur in the vagina and to quantify the kinetics of drug activation and virus inactivation in the presence of semen and other appropriate biological matrices. Finally, the biological properties of both semen and vaginal fluids on the efficiency of transmission of HIV to target cells will be evaluated to define the potential synergies between the antiviral activity of constituents of semen and the biological activity of the thioester inhibitors.

1R21AI082738-01
Microbicide delivery system to target lymphoid organs
Labib, Mohamed.
Advanced BioDevices, Princeton, NJ
$37500
Sexual transmission of HIV-1 involves complex processes involving exposure of the female genital tract to virus or infected cells and their transport to other sites, including local lymph nodes, where the virus replicates and establishes infection. It has been shown that Langerhans cells (LC) and dendritic cells (DC) capture the virus either from the vaginal surface or from

top epithelium layers and transport it to draining and local lymph nodes, where it infects CD4+ T-cells. Intense development of topical microbicides is underway with the ultimate goal of decreasing the sexual transmission of HIV-1. Current efforts have been directed to inactivating the virus either at the surface of the vagina before entry, or in the squamous or stroma layers of the vaginal epithelium. Their physical transport modeling predicts that molecular drugs delivered as topical gels cannot reach draining or local lymph nodes. One possible way to deliver drugs to lymphoid sites surrounding the vagina is to use drug-loaded nanoparticles. Their preliminary results provide evidence indicating that nanoparticles can be delivered to local lymph nodes via vaginal application in a mouse model. To further develop this platform for use as a microbicide or prophylactic strategy, they propose the following plans for the R21/R33 application. In the R21 phase, they will study the delivery of quantum dots having different surface chemistry, including conjugation with targeting molecules, to determine the mode of their transport to different lymphoid sites. In the R33 phase, they will use drug-loaded nanoparticles and verify the applicability of this platform to target important sites in the female genital tract. Physical models will be developed to understand the transport processes and to guide the development of the nanoparticle delivery system.

1R21AI079771-01A1
Small-Molecule Inhibitors Of Gp41-Mediated Fusion As Hiv-1 Topical Microbicides
Lu, Min
Cornell University, New York, NY
$37,500
In the continuing absence of an effective vaccine, topical microbicides offer a credible alternative preventive strategy to reduce sexual transmission of HIV-1. Several viral fusion and entry inhibitors have been shown to prevent SHIV infection of rhesus macaques by the vaginal and/or rectal routes and are in preclinical and early clinical development as microbicide candidates. HIV-1 membrane fusion is mediated by a series of large-scale structural transitions in the gp41 envelope glycoprotein. Evidence indicates that a transient gp41 species known as the prehairpin intermediate is a potential target for drugs that inhibit HIV-1 entry. The long-term goal of this research plan is to use modern molecular and structural methods to identify and develop a novel small-molecule gp41 fusion inhibitor for inclusion in a topical HIV-1 microbicide. To achieve this, they will capitalize on specific surface features revealed by their recent structure determination of an autonomously folded, trimeric coiled-coil subdomain of gp41 that provides an atomic model for the putative prehairpin conformation, as well as small-molecule lead compounds developed by means of an innovative structure-based drug design technology. They propose the following specific aim for the R21 component of this project: 1) To identify and optimize two series of novel small-molecule compounds that inhibit HIV-1 membrane fusion by targeting the gp41 prehairpin intermediate. They will design and synthesize two sets of analogs of active triazinone and biphenyl compounds, characterize the equilibrium properties of interactions with the N-trimer coiled coil, and evaluate their anti-HIV-1 activity and mechanism of action. Bound inhibitors will be visualized by x-ray crystallography in order to allow refinement of binding affinity. The specific aims of the R33 phase of the project are: 2) To characterize the specificity, potency and toxicity of improved small-molecule compounds with enhanced gp41 inhibitory activity. They will conduct in vitro studies in primary cells and human cervicovaginal tissue explants to determine the virucidal activity of select small-molecule

gp41 inhibitory compounds against diverse primary HIV-1 isolates, and their potentially toxic or inflammatory effects. They will also use the rabbit vaginal irritation model to evaluate the irritation potential of the fusion inhibitors. 3) To assess the in vivo potency and breadth of activity of optimized small-molecule fusion inhibitors alone and in combination with entry inhibitors targeting HIV-1 gp120 (BMS-378806) and CCR5 (CMPD167) using the NOD/SCID-hu BLT mouse vaginal transmission model. They will evaluate the protection of humanized BLT mice from vaginal challenge with multiple HIV-1 variants by small-molecule fusion inhibitors alone and in synergistic combination with BMS-378806 and CMPD167. Their emphasis is to identify a new class of potent HIV-1 fusion inhibitors suitable for development as a component of a microbicide formulation.

1R21AI082701-01
Gp340 And Syndecan Inhibition Based Microbicide For Hiv
Weissman, Drew
University of Pennsylvania, Philadelphia, PA
$37500
Education and microbicides active against HIV represent the best approaches to controlling the epidemic worldwide in the absence of a protective vaccine. Their research program studies the earliest events in genital tract transmission. They have identified a protein expressed by genital tract epithelial cells that could serve as a potential target for inhibition of transmission of HIV called gp-340. They have demonstrated that gp-340 is expressed on the cell surface of vaginal and cervical epithelial cells, in vivo, in vitro, and ex vivo and binds HIV envelope. Of significance to genital tract transmission, gp-340 binding of virus leads to an increase in both the infectivity and half-life of the virus. Gp-340 expressed by genital tract tissue and cell lines also mediates transcytosis of HIV, the vesicular transport of macromolecules from one side of a cell to the other. A second molecule called syndecan has been studied and shown to have similar trans-infection and transcytosis properties and is also expressed by genital tract cells. They have identified a peptide inhibitor of envelope binding to gp-340 that blocks both gp-340 mediated trans-infection and transcytosis in in vitro and ex vivo models of genital tract transmission. This peptide contains a portion of a motif that inhibits syndecan mediated transinfection, as well, and they will modify this peptide to inhibit envelope binding to both macaque gp340 and syndecan and develop it into a microbicide. This potential role of gp-340 and syndecan to act at a stage of infection after delivery to the lumen of the genital tract but prior to interaction with and infection of target cells is very attractive and novel in microbicide design. They hypothesize that interfering with this process will inhibit or block genital tract transmission. In the initial R21 portion of this proposal, they will establish in vitro macaque systems of genital tract transmission. If they demonstrate that macaque gp340 and syndecan mediate trans- infection and transcytosis and V3 loop derived peptides or improved versions block macaque gp340 and syndecan mediated transinfection and transcytosis, they will proceed with the R33 portion of the grant. The specific aims of this are: microbicide development with in vitro testing and to test the effect of blocking gp340 and syndecan-HIV Env interaction on genital tract SIV transmission in the rhesus macaque vaginal transmission model. Through these specific aims, they will develop a new type of microbicide and determine the role of genital tract gp-340 and syndecan in HIV transmission. If successful, these studies will deliver a new microbicide based on host cell interactions with HIV that promote genital tract transmission to preclinical trial studies.

N01AI60017-4-0-1
Research Support Services For The DAIDS
Arlondria, Garrison; Hockensmith, Robert
BL SEAMON CORPORATION
$5000
This contract provides research support services that are critical to the research mission of the Division of Acquired Immunodeficiency Syndrome (DAIDS), NIAID. This contract provides the following services: travel support and meeting and conference support, administrative and technical support.

2 U2R TW006896-06
Haiti AIDS Research Training: Models To Implementation
PAPE, JEAN WILLIAM
THE GHESKIO CENTERS, PORT-AU-PRINCE, HATI
$20,000
The specific areas of integrated clinical, operational, and health services research that will form the basis of the proposed ICOHRTA training program include: 1) adult antiretroviral treatment; 2) prevention of mother to child HIV transmission and antiretroviral treatment of HIV- infected mothers and infants; 3) tuberculosis with emphasis on multidrug resistant TB and HIV co- infection; 4) AIDS malignancies; 5) adolescents and HIV/AIDS; and 6) behavioral research. Research training will focus on translating models of HIV and TB care and prevention to large-scale national implementation. The goal of GHESKIO-Cornell ICOHRTA training program is to increase capacity in integrated clinical, operational, and health services research in support of Haiti's national scale-up of HIV and tuberculosis services. Haiti is the poorest country in the Western Hemisphere and has the highest rates of both HIV infection and tuberculosis. It is estimated that 3% of the adult population isHIV-infected and that the prevalence of tuberculosis is 402/100,000 population (100xUS rates). In response to this epidemic, the Haitian Ministry of Health asked GHESKIO to form a national HIV and TB Network, a collaboration of 32 public and private health care organizations across the country that is charged with "scaling-up" to provide a standardized package of HIV and tuberculosis services to 500,000 persons by 2014. The services include voluntary counseling and HIV testing, management of tuberculosis and sexually transmitted infections, prevention of mother to child HIV transmission, and comprehensive HIV care of children, adolescents, and adults. The Haitian Ministry of Health has asked GHESKIO (Haitian Study Group for the Study of Kaposi's Sarcoma and Opportunistic Infections) to lead this network through training, supervision, monitoring and evaluation, and through the conduct of operational and health services research. GHESKIO is an international research and training institution that has benefited from 25 years of uninterrupted NIH funding and research capacity building with Cornell University, and support from the Fogarty International Center. GHESKIO is recognized as a center of research excellence, and is a member of the NIH HIV Vaccine Trials Network (VTN), the AIDS Clinical Trials Group (ACTG) and a recipient of support from the United Nations Global Fund for AIDS, TB and Malaria and the President's Emergency Plan for AIDS relief (PEPFAR). In the current proposal, GHESKIO will continue as the primary training institution and extend research capacity to other organizations in Haiti that are participating in the GHESKIO HIV and Tuberculosis Network. The program will

continue to emphasize medium- and long-term training in Haiti. Since its inception four years ago the ICOHRTA has provided training to 120 Haitian biomedical personnel, all of whom are working in Haiti, providing HIV/TB services and conducting operational and health services research. GHESKIO, in collaboration with Haitian and International partners, will develop training curricula in clinical, operational, and health services research methodology and in ethics, program management, and scientific writing. A Masters in Public Health Degree program, established with ICOHRTA support, will continue to be offered in Haiti by Quisqueya University, in partnership with GHESKIO and Cornell University.

IMMUNITY/AUTOIMMUNITY

1R21HL093181-01A1
Role Of 15-Lipoxygenase In Enhanced Pulmonary Vasoconstriction In Females
Pfister, Sandra L
Medical College Of Wisconsin
$220,200
Pulmonary arterial hypertension encompasses a group of diseases characterized by high pulmonary artery pressure and pulmonary vascular resistance. Vasoconstriction, vascular remodeling and thrombosis all contribute to the increased vascular resistance. Central to the proposed studies is that while relatively rare, idiopathic pulmonary arterial hypertension is a medically significant disease that occurs more frequently in young women. The disease is usually catastrophic for those afflicted. Mechanisms to explain the sex- difference in pulmonary arterial hypertension have not been well studied. The main focus of the current proposal is to use a rabbit model to explore the role of sex in a novel signaling pathway that regulates pulmonary vascular tone. Results will lay the fundamental conceptual groundwork for future studies to understand more completely the pathogenesis of pulmonary hypertension in women. Furthermore, this work is intended to advance new concepts in women's health research and the study of sex/gender differences. Specifically, their research provided the first evidence that in pulmonary arteries obtained from female rabbits, endothelium-dependent contractions to both arachidonic acid and methacholine were enhanced when compared to responses in males. Pharmacological studies with inhibitors of arachidonic acid metabolism indicated that the factor was a lipoxygenase metabolite. They also present the first data that lipoxygenase metabolites are increased in females compared to males and the protein expression of 15-lipoxygenase is greater in female pulmonary arteries. While sex differences in vascular responses to various vasoactive agents have been documented, no studies have investigated the role of sex differences on lipoxygenase metabolism of AA in pulmonary arteries. This proposal is designed to explore the specific hypothesis that differences in AA metabolism by 15-LO contribute to the increased endothelium-dependent pulmonary vasoconstriction in females compared to males. To further develop this novel hypothesis, studies will be performed in pulmonary artery vascular preparations using chemical, biochemical, physiological and pharmacological approaches. Two specific aims will be explored: 1) To chemically identify and biologically characterize the vasoconstrictor 15-lipoxygenase metabolite(s) produced by the rabbit pulmonary artery endothelium and 2) To examine the cellular mechanisms contributing to enhanced 15-lipoxygenase expression in females compared to males. These proposed studies will not only provide new insights into

the role of endogenous arachidonic acid-derived factors in the pathogenesis of pulmonary arterial hypertension but will also advance their knowledge in women's health research by identifying possible mechanisms that contribute to sex-related differences in the incidence of pulmonary arterial hypertension.

5R01 AR049772-07
Predictors of Pregnancy Outcome in SLE and APS
Salmon, Jane E.
Hospital for Special Surgery, New York, NY
$200,000
Pregnancy complications in women with the antiphospholipid syndrome (APS) and/or SLE include recurrent miscarriage, preeclampsia, placental insufficiency, and intrauterine growth restriction (IUGR). The mechanisms leading to placental and fetal injury in vivo are incompletely understood and treatment remains sub-optimal. They have identified complement as an early effector in pregnancy loss and/or IUGR associated with placental inflammation in a mouse model of APS and shown that complement activation causes the release of anti- angiogenic factors and abnormal placental development. The PROMISSE Study (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) is a first-time effort to translate their novel findings in mice to humans and determine if elevations of complement split products predict pregnancy complications in patients with antiphospholipid (aPL) antibodies and/or SLE. In the first 4 years of this prospective, observational study of pregnant patients grouped and analyzed according to the presence or absence of aPL antibodies and preexisting SLE, they have enrolled 342 pregnant patients in 7 centers, obtained detailed medical and obstetrical information monthly, and serially collected plasma, serum, DNA, RNA, and urine. Preliminary data suggest that elevated levels of complement activation products antecede and predict poor fetal outcome, consistent with their hypothesis that complement is a proximal mediator of fetal loss and IUGR. They propose to increase their target sample size from 400 to 700 pregnant patients to maintain study power given lower than expected outcome rates, and to leverage the infrastructure and rich collection of patient data and samples by expanding the array of biomarkers and scope of adverse pregnancy outcomes. Specifically, in Aim 1 they will determine whether elevations of split products generated by activation of complement pathways predict poor fetal and/or maternal outcome in patients with aPL antibodies and/or SLE and, in Aim 2, whether the balance of circulating angiogenic and antiangiogenic factors predicts preeclampsia or delivery of IUGR infants. In Aim 3, a new direction, they will use the PROMISSE cohort to affirm in humans their recent findings in mice, that certain anti-DNA antibodies cross-react with N-methyl D- aspartate receptors (NMDAR) and cause neuronal death with ensuing cognitive and behavioral impairment. They propose to quantitate anti-NMDAR antibody levels throughout pregnancy in PROMISSE SLE patients and test the hypothesis that in utero exposure to maternal anti-NMDAR antibodies alters behavior and cognitive development in offspring by evaluating cortical function tasks in 12 month and 3.5 year old children. This competitive renewal and extension of the PROMISSE Study provides an outstanding opportunity to translate knowledge from mouse models to patients, define pathogenic mechanisms, identify predictors of poor pregnancy outcome in APL and/or SLE, and define novel therapeutic targets to prevent such outcomes.Patients with systemic lupus erythematosus (SLE) and/or antiphospholipid (aPL) antibodies are at increased risk for

miscarriage, preeclampsia and fetal growth restriction - major causes of maternal, fetal, and neonatal morbidity and mortality in the US and worldwide - whose etiology and mechanism remain unknown and for which therapy is limited. In addition to causing placental dysfunction, maternal autoantibodies may also directly impair fetal brain development. Identification of biomarkers that predict poor pregnancy outcome in these patients will elucidate mechanisms of disease, define targets for treating patients, and generate clinically applicable indicators to permit initiation of interventional trials in patients at greatest risk for pregnancy complications.

1R21AI083894-01
Role of Sex Differences in the Expression & Function of Regulatory T Cells in SLE
Singh, Ram Pyare
University of California Los Angeles
$192,500
Regulatory CD4+T cells and CD8+T cells have important roles in suppressing autoimmune disease in the peripheral immune system. Impaired function of regulatory/suppressor T cells contributes to development of autoimmunity. The goal of this project will be studying the quantities and functions of T regulatory cells in healthy controls and patients with SLE, comparing males to females in both groups (given the fact that lupus disease is much more frequent in females than in males). The first aim is to quantify, immunophenotype, and perform functional analysis of the Treg cell subsets in healthy controls, and in male lupus vs female lupus. The second aim is to compare gene expression profiles of CD4+CD25+hiTreg and CD8+Ts cells in male vs female lupus patients and to compare them with healthy controls. Finally, the investigators will test the effect of testosterone and estradiol in these cells in vitro to see their effects on cell phenotypes, gene expression, signaling and regulatory functions. The overall purpose is to understand the molecular network of these CD4+T regulatory cells and CD8+ suppressor cells in systemic autoimmunity. Signifiance of the application is that the study proposes to the applicants propose to study regulatory T cells (CD4 and CD8) (comparing male to female SLE patients and male to female healthy individuals) for quantities, suppressive capacities and differences in gene expression. The ability of sex hormones to change Treg numbers, functions, and gene expression will be studied.

5R01 AR044422-11
NARAC - The Genetics of Rheumatoid Arthritis
Gregersen, Peter K.
Feinstein Institute for Medical Research, Manhasset, NY
$182,442
This renewal application has the overall goal of identifying all of the major common genetic variants that underlie susceptibility to rheumatoid arthritis, and to begin to identify rare susceptibility alleles, if they exist. In preliminary data they have identified a number of candidate genes and regions on the basis of linkage analysis in multiplex RA families, as well as by whole genome association studies using approximately 550,000 SNPs on a panel of over 900 RA patients and matched controls. They now wish to identify the specific causal variants and understand their mode of action. In specific aim 1 they will identify the causal genetic variants within the common genes that confer risk for rheumatoid arthritis. They have already

identified several genes and regions of interest, including STAT4 on chromosome 2q. In specific aim 1a they will replicate these initial associations in case-control datasets totaling up to 5,000 patients. Various methods of genomic control for population stratification will be utilized for these replication studies. In specific aim 1b they will carry out fine mapping of candidate regions. This will generally involve haplotypic analysis using custom sets of SNP markers. In specific aim 1c they will utilize various approaches to identify the likely causative genetic variants in the gene under study. Examples of the approaches to be used in specific aim 1c are given for STAT4. In specific aim 2, they will apply a staged approach to identify gene-gene and gene-environment interactions that contribute to RA susceptibility. The top performing markers in the univariate analyses of specific aim 1a and 1b will be examined for interactions using Classification and Regression Tree (CRT) as well as traditional logistic regression methods. Top performing models will be tested in replication datasets of cases and controls. In specific aim 3, they will identify rare genetic variants that contributes to RA susceptibility. This specific aim is based on preliminary analysis indicating that slightly deleterious SNPs (sdSNPs) are a significant component of the genetic burden underlying complex disease. These sdSNPs are enriched in the low frequency (MAF < 5%) component of the SNP population. They will initially investigate a limited number of candidate genes with high-throughput sequencing on the Solexa platform, along with follow up analysis in large case control datasets. Larger scale and more comprehensive approaches to this issue may be employed in the later years, depending on technical advances in the field.

N01-DE-32636
International Research Registry Network for Sjogren's syndrome
Daniels, Troy, Greenspan, John
University of California, San Francisco
$300,000
This contract focuses on the continuation of the International Research Registry Network for Sjögren's syndrome. As part of this registry, key elements being collected include, using a set of standardized diagnostic criteria for the recruitment of Sjögren's syndrome patients, the collection, processing, storage, shipment and analysis of clinical information and biological specimens (tissue, blood, saliva, and tears) from patients and families with Sjögren's syndrome, and to disseminate to researchers clinical information and biological specimens from patients with Sjögren's syndrome. During this year, all research sites are focused on enrolling eligible study participants and have begun the process of two-year recall evaluations of the pSSw and level 2 controls (called partial SS phenotype) groups. Enrollment of blood relatives and unrelated DNA control donors also is continuing. Currently, data analyses has begun to assess the progress towards developing a framework for the classification criteria.

5R21 AR 056370-02
OGT Over expression in Women with Lupus
Richardson, Bruce C.
University of Michigan at Ann Arbor
$20,000
Lupus afflicts women 9 times more often than men. Estrogen contributes to lupus severity, but does not completely explain the increased risk. Impaired DNA methylation, a repressive epigenetic modification, causes overexpression of T cell genes that contribute to lupus. DNA

methylation also silences one X chromosome in women. CD40LG is an X-linked gene known to be overexpressed in lupus and contribute to autoantibody production, on the inactive X demethylates and is overexpressed in women but not men with lupus, predisposing women to lupus. Other X-linked genes may also demethylate, predisposing to autoimmunity. The investigators surveyed methylation sensitive T cell genes, and identified O-linked N-acetylglucosamine transferase (OGT) as another X-linked gene overexpressed in demethylated female T cells. OGT couples N-acetylglucosamine (GlcNAc) to serines and threonines in a variety of proteins including signaling molecules, modifying function in a manner analogous to phosphorylation and referred to as the hexosamine signaling pathway (HSP). HSP abnormalities are implicated in diabetes and neurodegeneration, but little is known regarding its role in T cells. The researchers hypothesize that demethylation of OGT on the inactive X results in overexpression in women, altering HSP signaling and contributing to pathogenic T cell function by modifying signaling. The investigators plan to test this hypothesis by: 1) Comparing OGT mRNA and protein levels in control and demethylated CD4+ and CD8+ T cells from healthy men and women with levels in CD4+ and CD8+ T cells from men and women with inactive lupus, active lupus, and disease/age controls, and confirming OGT demethylation by bisulfite sequencing, 2) Determining if OGT overexpression impairs T cell ERK, JNK and/or p38 pathway signaling and modifies T cell gene expression patterns, and 3) Determining the functional significance of T cell OGT overexpression on the development of autoimmunity using transgenic mice with a T cell specific inducible OGT transgene. These studies will characterize a new pathway regulating T cell gene expression, and characterize how abnormalities in the pathway may predispose women to autoimmunity.

5R21 AI079616-02
Do Estrogen Receptors In B Cells And Dc Mediate Sex Bias In Murine Lupus?
Farris, A. Darise; Kovats, Susan
Oklahoma Medical Research Foundation, Oklahoma City, Ok
$193,750
Systemic lupus erythematosus (SLE) is an autoimmune disease that preferentially affects women (9:1) in their reproductive years, indicating that sex specific factors including the sex hormone estradiol play an important role in lupus pathogenesis. Murine models of lupus show natural earlier expression of disease and ensuing mortality in female mice. The Sle1 and Sle3 lupus susceptibility loci present in NZM2410 mice direct increased penetrance of disease in females, which is consistent with studies showing that elevation of systemic estradiol or exposure to estrogenic environmental compounds accelerate lupus development. An understanding of the mechanisms underlying the female preponderance of SLE requires that they precisely determine how endogenous estrogens and estrogen receptors (ER) regulate the function of immune cells such as B lymphocytes and dendritic cells (DC), which express ER and have been implicated in lupus pathogenesis. However, current models for the study of estrogen effects on immune cells often have involved systemic exposure to supra-physiological levels of estradiol or global loss of ER, which creates hormonal imbalances. Elevated systemic levels of estradiol result in a profound depletion of hematopoietic progenitors, leading to alterations in numbers and phenotype of B cells and DC. To circumvent these effects of ER ligands on immune cell development, the study proposes to develop and use a novel model of murine lupus in which ER alpha expression may be

specifically ablated in differentiated B cells or DC. The investigators will use lentiviral transgenesis to deliver Cre recombinase driven by the CD19 or CD11c promoters to lupus prone B6.Sle13 bicongenic mice bearing a conditional ERalpha allele. This approach will determine whether aberrant DC or post-bone marrow B cell phenotypes associated with the sex sensitive Sle1 and Sle3 loci are mediated by direct effects of endogenous estrogens on B cells or DC. Aim 1, will determine if the elevated DC numbers or hyper-activated DC phenotypes leading to pro-inflammatory cytokine production in female B6.Sle13 bicongenic mice are a result of the direct action of endogenous estrogen on DC. Aim 2, will determine whether perturbations in transitional B cell subsets and subsequent enhanced loss of serologic tolerance in female B6.Sle13 bicongenic mice are a result of the direct action of endogenous estrogen on committed B cells and/or DC. The successful implementation of this lentiviral transgenesis strategy to delete ERalpha in specific cell types will establish a versatile model that could be used to study the role of ERalpha signaling in any cell type during the development of lupus nephritis. This knowledge will help to understand why autoimmune diseases preferentially afflict women.

1 R01 AR057327-01
Sociodemographic Disparities in Lupus Nephritis: Healthcare Access and Outcomes
Costenbader, Karen
Brigham and Women’s Hospital
$200,000
Lupus is an autoimmune disease that mainly afflicts disadvantaged groups in the U.S., often causing kidney failure. The reasons why some groups suffer worse outcomes are not known. They will investigate how differences in healthcare access are related to "gaps" in outcomes for lupus kidney disease. Access to quality healthcare is a challenge for minority and disadvantaged groups in the U.S. Systemic lupus erythematosus (lupus), a complex autoimmune disease, can cause nephritis and, in severe cases, end-stage renal disease. Lupus nephritis is a potentially preventable outcome that disproportionately afflicts vulnerable groups: women, racial and ethnic minorities, the poor, those lacking medical insurance and education, and children and the elderly. They have found that the incidence of lupus end-stage renal disease rose dramatically from 1995-2004 in the U.S., in particular among those 20-39 years old, women, and racial and ethnic minorities. More new cases now occur among Blacks than whites. The causes of these growing disparities are unknown. They hypothesize that multiple barriers to quality healthcare for lupus nephritis exist for disadvantaged patients and are responsible for premature, excess, and avoidable morbidity and mortality. Their goals are to identify and prioritize potentially remediable barriers to healthcare access for lupus nephritis and end-stage renal disease, leading to both future research and policy interventions. Their uniquely qualified interdisciplinary research team will address nationwide socio-demographic variation in lupus nephritis healthcare and the potentially modifiable factors responsible for outcome disparities. They will constitute two nationwide cohorts: one with > 5000 patients with incident lupus nephritis from 2000-2004, and a second with >14,000 patients with incident lupus end-stage renal disease from 1995-2009 and investigate the factors that contribute to access to care and disparities. They have developed a conceptual model for understanding the determinants of health disparities in lupus nephritis and posit that potentially modifiable factors, such as subspecialist care, provider and medical center volume, medical insurance, and adherence to therapy, contribute to long-term outcomes in lupus

nephritis, including the development of end-stage renal disease and death. Lupus patients from the affected communities will likely have great insight into their findings and should be involved in the development of strategies for overcoming observed barriers. They will perform focus groups of community lupus patients and investigate the barriers to quality healthcare for lupus nephritis and end-stage renal disease from patients' perspectives. The multidisciplinary research team will be composed of investigators with expertise in healthcare disparities research, biostatistics, pharmaco-epidemiology, administrative claims data, lupus epidemiology and quantitative research methodologies. The findings will be widely disseminated to the lupus community, physicians and healthcare workers. The results will provide guidance to clinicians and policy makers on strategies to reduce barriers and improve access to care and outcomes for all Americans with lupus nephritis.

1 R01 AR054842-01A2
Longitudinal Determination of Outcomes of Adolescents with Fibromyalgia
Kashikar-Zuck, Susmita
Children’s Hospital Medical Center, Cincinnati
$200,000
This project will be the first controlled prospective longitudinal study of adolescents with juvenile primary fibromyalgia syndrome (JPFS). The results will greatly increase their knowledge about the prognosis for patients with JPFS, and the complex relationship between physical and emotional symptoms in fibromyalgia syndrome. Findings will be of direct clinical relevance with respect to knowledge about physical, emotional and social outcomes for JPFS patients, and early identification of those who may be at risk for long term suffering and disability. The study will lay the groundwork for future clinical trials aimed at early and targeted interventions for JPFS. Fibromyalgia syndrome (FMS) is a chronic and often debilitating condition that results in marked difficulties in daily functioning, psychiatric comorbidity and decreased quality of life. Many adult FMS patients report that their symptoms began earlier in life, when the symptoms may have been more amenable to early intervention. However, the developmental course of FMS and its associated symptoms from adolescence through adulthood has never been documented. Prospective longitudinal studies of patients diagnosed with fibromyalgia in adolescence are urgently needed. In this study, they propose to prospectively follow 96 patients diagnosed with JPFS and 48 healthy controls into their young adult years. These participants are currently enrolled in their completed and ongoing JPFS research, and have completed baseline assessment (Time 1, Mean age 15 years). A Time 2 protocol has been recently implemented to assess current functioning (Mean age 19 years). So far they have demonstrated excellent cohort retention (90%), and preliminary results suggest that as a group, JPFS patients continue to have significant physical and emotional difficulties, but there is considerable variability in outcomes. Participants are now approaching the crucial young adult years, a time of rapid change and new challenges that places greater stress on coping resources for those who are already dealing with chronic pain. They are proposing two additional assessments for the entire cohort in the young adult years (Time 3, Mean Age = 22 years; and Time 4, Mean Age = 24 years). In this controlled, prospective longitudinal study, the primary objective is to first establish whether JPFS patients continue to have greater physical symptoms and impairment, psychiatric symptoms and social difficulties in young adulthood than healthy controls. The secondary objective is to examine developmental trajectories of two key outcomes: physical impairment and depressive

symptoms, from adolescence through young adulthood. For each outcome, they hypothesize three distinct trajectories: those who show low initial impairment and continue to show little impairment into young adulthood, those who are initially impaired and get worse over time, and those who are initially impaired but improve over time. They will test whether trajectories of physical impairment and depressive symptoms are independent of one another, and in doing so, they will be able to disentangle aspects of mood from impairment associated with FMS. Moreover, they will test whether change in FMS symptom severity is differentially associated with physical impairment or depressive symptoms. Finally, they will test whether treatment via cognitive-behavioral therapy in adolescence has any persisting effects on long-term outcomes. Information will be gathered from participants and family member/ significant others via on-line surveys. Psychiatric interviews and tender point exams will be conducted in person. The long-term goal is to develop more refined methods to identify patients who are at risk for negative trajectories of physical and emotional outcomes and to design early, targeted interventions.

Autoimmune Centers of Excellence

The Autoimmune Centers of Excellence (ACE) focus on supporting clinical trials and mechanistic studies, pilot research projects, and other group activities such as working groups or subcommittees formed by the Steering Committee with narrow focus and short duration (e.g., establishing immuno-competence criteria or comparing measurements of regulatory T cells).

1U19AI082719-01
Autoimmunity Center of Excellence (ACE) at Stanford
Fathman, Charles
Stanford University, Stanford, CA
$30,000

DESCRIPTION (provided by applicant): The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune disease. The major theme of the Stanford Autoimmunity Center of Excellence (the Center) is the study of the regulation of CD4 T cells in pathogenesis and treatment of autoimmune diseases. The Center will support and be supported by other ACE groups across the United States; and will take advantage of Stanford's documented leadership in basic and clinical research, technology development, and education in clinical immunology. Success of the Center will be supported by the interrelationships previously established at Stanford among clinician scientists from multiple departments studying autoimmune diseases in multiple organs and tissues. The Stanford ACE will be composed of outstanding basic and clinical investigators from multiple disciplines at Stanford Medical School and proposes both a basic Research Project, centered on CD4 T cell unresponsiveness, and a translational Research Project to study a new T cell lineage (termed Th17 cells) that is characterized by the ability of these lymphocytes to secrete high levels of the proinflammatory cytokine interleukin-17 (IL-17). Proposed clinical research projects encompass three different autoimmune diseases [diffuse systemic sclerosis (SSc), psoriatic arthritis and systemic juvenile idiopathic arthritis (SJIA)] that afflict adults and children, as well as organ systems including joints, skin, blood elements, and blood vessels, and will both

test efficacy of therapy and develop tests to characterize the mechanisms of action of these therapeutics. The proposed Pilot and Feasibility Project proposes a two year research plan in Systemic Juvenile Idiopathic Arthritis (SJIA) patients to identify and validate urine peptide biomarkers that predict (a) response to TNF inhibition; (b) response to IL-1 inhibition; and (c) impending disease flare. In addition, this proposal will provide other ACE groups access to cutting edge reagents and technology platforms for studying human autoimmune diseases, and dissemination of Educational Materials that can be used by other ACEs to teach clinical immunology concepts to high school, undergraduate, graduate, postgraduate, and clinical fellows and faculty. The Stanford ACE proposes to support integrated basic, pre-clinical and clinical research by proposing and then conducting basic and translational research into the mechanism of CD4 T cell unresponsiveness; two clinical trials that include novel therapies and mechanistic studies of these therapies for autoimmune diseases; and a pilot proposal that intends to develop new bi omarkers of disease. PROJECT 1A: Clinical Component (Genovese, M) CLINICAL COMPONENT DESCRIPTION (provided by applicant): Stanford University Medical Center (SUMC) has an extraordinary tradition of medical, translational, and basic science research. An outstanding array of resources, faculty, and facilities will be available to support the proposed ACE site at Stanford University. This proposal brings together a skilled group of translational researchers with a track record of productivity in both laboratory and clinical research focusing on human autoimmune mediated diseases. Stanford has brought together various disciplines to demonstrate both accomplishment and ability to work together with the following fields represented: Adult Rheumatology, Dermatology, Pulmonary Medicine, and Pediatric Rheumatology. The projects chosen for this submission highlight the significant collaborations that exist between Rheumatology (Adult and Pediatric), Dermatology and Pulmonary Medicine. Both clinical trials projects explore dermatologic and rheumatologic manifestations of diseases such as Psoriatic arthritis and Systemic Sclerosis. Clinical Trial Concept 1: The use of an anti- IL-17 mab in the treatment of active Psoriatic Arthritis Primary Hypothesis: The proportion of patients achieving the ACR 20 response from Baseline to Week 14 among active Psoriatic Arthritis (PSA) subjects treated with IL-17 mab is larger than the proportion achieving ACR 20 response from Baseline to Week 14 among active PSA subjects treated with placebo Objectives: The goal of this study is to determine the safety and efficacy of a monoclonal antibody to lnterleukin-17 (IL-17 mab) in the treatment of PsA with active skin and joint disease. Clinical Trial Concept 2: The use of CTLA-4lg (abatacept) in subjects with diffuse systemic sclerosis Primary hypothesis: Given several lines of evidence supporting the role of activated T cells in affected skin, they hypothesize that inhibiting T cell activation may lead to significant clinical improvement in skin manifestations in patients with diffuse systemic sclerosis (dSSc), and that changes in tissue and blood autoantibody and cytokine profiles will be associated with clinical response. Objectives: The primary goal of this study is to determine the safety and efficacy of CTLA-4lg (Abatacept) for the treatment of cutaneous manifestations of dSSc RELEVANCE (See instructions): The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune (Al) disease. The Stanford ACE proposes clinical research projects that encompass three different autoimmune diseases (SSc, psoriatic arthritis and SJIA), and proposes to study the MoA of therapeutics for preventing or treating different Al diseases.

1 U19 AI082714-01

Oklahoma Autoimmunity Center of Excellence
James, Judith
Oklahoma Medical Res Foundation, Oklahoma City, OK
$30000
DESCRIPTION (provided by applicant): The Oklahoma Medical Research Foundation is home to outstanding clinical and basic science investigators who have research interests in the etiology and pathogenesis of autoimmune diseases and seek to identify novel therapeutics for more effective patient treatments. The scientific expertise, extensive clinical trial experience, access to geographically distinct patient populations, as well as unique patient registries, repositories and core technologies provide a solid foundation for the Oklahoma Autoimmunity Center of Excellence (ACE) application to which they have added a multidisciplinary team of clinical and basic science investigators. The focus of the Oklahoma ACE application is on expediting the translation of scientific discoveries in autoimmunity to clinical application in the diagnosis and treatment of systemic autoimmune diseases. To accomplish this, the Oklahoma ACE comprises two research projects, a proposed pilot research project, a Clinical Center (Joan Merrill, PI) and an administrative core (Judith James, PI). The research projects focus on thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and Sj"gren's syndrome, which are also focuses of the Clinical Center. Multiple sclerosis, rheumatoid arthritis, pediatric arthritis, insulin-dependent diabetes, idiopathic thrombocytopenia and pediatric lupus are other key disease emphases of the Clinical Center. Two complimentary, but unique, research projects focus on understanding early events in the development of lupus autoimmunity and in defining targetable genetic associations in Sj"gren's syndrome. The pilot project uses complimentary methods to address roles of elevated interferon activity in patients with TTP and a novel animal model of thrombocytopenia. In addition, two clinical trials are proposed; both of which enhance or build upon the basic science projects. The first studies efficacy and mechanistic affects of anti-IFN in select SLE patient subsets by applying a patient centric, dose optimization strategy. The second tests the efficacy and early MRI changes of a novel MEK1/MEK2 inhibitor in RA with additional mechanistic studies. The Administrative Core will provide leadership and management through acting on behalf of the Oklahoma ACE members within the ACE Network and NIH Program, ensuring fiscal responsibility for the ACE, and providing an educational foundation for a multi-disciplinary approach to autoimmune disease research. Thus, the Oklahoma ACE will unite Oklahoma-based clinical and basic science experts to facilitate access to unique patient populations for participation in clinical trials and to understand basic mechanisms of etiology and pathogenesis. The Oklahoma ACE brings together adult and pediatric rheumatologists, neurologists, endocrinologists, dermatologists, hematologists, dentists, ophthalmologists, geneticists, immunologists, molecular biologists, epidemiologists and biostatisticians to provide a multidisciplinary approach to discovering and applying novel therapeutics in systemic autoimmune diseases. Through strong basic science projects paired with clinical expertise the Oklahoma ACE will provide unique research and clinical opportunities to the ACE Network. CLINICAL COMPONENT: CLINICAL CENTER (Merrill, J) CLINICAL COMPONENT DESCRIPTION (provided by applicant): The Oklahoma ACE Clinical Center brings together disease-specific and interdisciplinary clinics in systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sj"gren's syndrome, thrombotic thrombocytopenic purpura, insulin dependent diabetes mellitus, pediatric SLE and juvenile inflammatory arthritis to forward translational

research in autoimmunity. Patients from each of these disease populations are available and committed to participate in potential national ACE investigations. With adult and pediatric rheumatologists, adult and pediatric endocrinologists, neurologists, hematologists, dermatologists, ophthalmologists and dentists, as well as basic scientists from various areas of immunology, molecular biology, genetics, epidemiology and biostatistics, their investigative team is poised to make basic advances regarding disease pathogenesis and to help translate these discoveries to the clinic. The Clinical Pharmacology program at OMRF will serve as the primary home for the SLE, RA, Sjogren's syndrome and TTP clinics. Currently leading or participating in more than 20 active clinical trials, this clinical center is accustomed to participating in clinical trials, managing confidential patient information, and providing multidisciplinary care. In addition, the Clinical Pharmacology space provides investigators access to state-of-the-art research tools directly adjacent to the patient care unit. Pediatric IDDM and rheumatology clinics are housed across the street at OUHSC and a large, community based multiple sclerosis clinic will participate for MS patient investigation. Joan Merrill, MD serves as the leader of their Clinical Center. She is the current medical director of the Lupus Foundation of America and a leader in SLE clinical trial development. She has served as the lead investigator on large, multi-site trials. Combining her extensive knowledge of clinical trial design and the known heterogenic presentation of SLE, she proposes to devise patient-centric clinical trials that use biomarkers of disease to optimize therapeutic doses. Their Clinical Center proposes two potential clinical concepts. Based upon their basic science investigation regarding pivotal roles for increased interferon activity in pre-clinical SLE, Sj"gren's syndrome and potentially TTP, their first trial examines the efficacy and biologic impact of anti-INF alpha in SLE patients with arthritis and select dermatologic manifestations. The second trial proposes use of a first-in-class target of MEK1/MEK2 inhibition in RA to assess impact on MRI progression of disease and on select biomarkers. Both of these trials have mechanistic studies proposed to address key scientific questions regarding pathogenesis and response. The Oklahoma Autoimmunity Center of Excellence Clinical Center will provide interdisciplinary investigators with unique populations of well-characterized patients to participate in ACE network autoimmune disease clinical trials. With their rich Native American heritage and large rural populations, the patients provided by the Oklahoma ACE will be previously understudied and provide unique insights for therapeutic trials.

1 U19 AI082715-01
A Systems Biology Approach For Pediatric And Adult Autoimmune Diseases - ACE
Pascual, Maria Virginia
Baylor Research Institute
$30000
DESCRIPTION (provided by applicant): They propose to create an Autoimmunity Center of Excellence that will incorporate the efforts of clinicians, human immunologists (both basic and translational), physician-scientists with clinical expertise and research experience in autoimmunity, bioinformaticians, and geriomics/systems biologists. Together, the assembled group has an extensive background in clinical trials and a proven track record for merging basic and clinical science. This team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. Within this collaborative setting, a systems biology approach is proposed to focus on both pediatric and adult autoimmune diseases. The goals of the Center are: 1) To assess the efficacy of novel targeted therapies, 2) To develop simple and

robust biomarkers using state-of-the-art genomic approaches, 3) To understand the role of recently identified T cell subsets in disease pathogenesis, and 4) To assess antigen-specific responses in pediatric and adult autoimmune diseases. These projects will provide a better understanding of the pathogenesis of specific autoimmune diseases and allow us to develop a strategy to assess disease activity based on novel transcriptional markers as well as to identify autoantigen-specific immune responses. The Center will deliver: 1) Innovative clinical trials targeting specific cytokines in psoriasis & dermatomyositis. 2) Development of biomarkers for dermatomyositis, psoriasis, lupus and multiple sclerosis. 3) Identification of novel therapeutic targets in dermatomyositis. 4) Development of assays to test autoantigen-specific immune responses. 5) Development of a unique microarray database of human autoimmune diseases. CLINICAL COMPONENT (Cush, J) CLINICAL COMPONENT DESCRIPTION (provided by applicant): Baylor Institute for Immunology Research aims to bring together a distinguished team of clinical investigators to conduct cutting-edge clinical trials on specific autoimmune diseases. This unique group of investigators and clinicians has appointments at Baylor University Medical Center, UT Southwestern Medical Center, Texas Scottish Rite Hospital in Dallas and Northwestern University. These talented individuals have been enlisted from diverse programs with subspecialties in dermatology, rheumatology, neurology, pediatrics, and human immunology. They provide a set of inimitable resources for clinical trials and have a proven track record for merging basic and clinical science. Indeed, this team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. With such outstanding collaborative players, a systems biology approach is proposed here which investigates both pediatric and adult autoimmune disease. To this end, two Phase II randomized, double-blind, placebo-phase controlled clinical trials are proposed. The first trial investigates whether blocking IL-1 with Anakinra will result in objective disease improvement for patients with Juvenile Dermatomysitis. The trial design will demonstrate: 1) if the time to improvement for patients receiving Anakinra early in the study will be earlier than those who receive later treatment; and 2) if the proportion of patients improved at week 8 of the blinded phase will be significantly greater in the early treatment group. Mechanistic studies will utilize gene expression profiling assays to find a novel diagnostic test for JDM as well as disease activity measures and biomarkers to follow and predict patients' response to therapy. The second clinical project proposes to use a-IL-17 in patients with plaque psoriasis as well as psoriatic arthritis. Specifically, this study will assess the safety and efficacy of a-IL-17 in these patients and determine both the time to achieve endpoints of a PASI 75 or ACR20 and sustainability of such responses at 24 weeks. Associated studies will establish blood transcriptional markers to predict clinical responses in patients treated with a-IL-17, determine if transcriptional scores can be used to assess disease activity, and analyze the effect(s) of IL-17 blockade on B and T cell subsets. A dynamic team of clinical investigators assembled at BUR to conduct state-of-the-art clinical trials on autoimmune disease would be of great value and accelerate the process of bringing research from the laboratory bench to the bedside. This team proposes two important trials that will assess a-IL-1 treatment in Juvenile Dermatomyositis and IL-17 blockade in psoriatic diseases.

2U19AI056363-06
Mechanisms of Beta Cell Responses In Autoimmune Disease - ACE
St Clair, Eugene W
Duke University

$30000
DESCRIPTION (provided by applicant): This application is a competitive renewal of the Autoimmunity Center of Excellence (ACE) at Duke. Its research focus will continue to be modulation of B cell responses in autoimmune disease. The ACE will be under the leadership of Dr. E. William St. Clair, Professor of Medicine and Immunology. For the past 5 years, Duke has been a productive member of the ACE network, contributing new insights into the developmental pathways of B cells and the mechanisms of B cell directed therapy. The proposed ACE builds on these discoveries and will support 2 new basic science projects, 5 ongoing and 2 new clinical trials, and an Administrative Core, and continue to emphasize a strong and fluid integration between the bench and the bedside. Tedder and colleagues have recently found that a phenotypically unqiue subset of B cells secreting IL-10 (called B10 cells) serve as critical negative regulators during adaptive CD4+ T cells responses, and dramatically suppress Th1 immune responses and autoimmune disease in mice. For Basic Research Project 1, they will examine the hypothesis that antigen-specific regulatory B10 cells modulate autoimmune responses in mice and man and that they can be manipulated for therapeutic gain. A picture is gradually emerging about the precursors of self-reactive B cells in autoimmune disease. Kelsoe and coworkers in Basic Research Project 2 will investigate developmentally regulated expression of activated cytidine deaminase (AID) in human fetal and neonatal pre-, pro, and immature/transitional B cells and its relationship to the generation of self-reactive B cells in human autoimmune disease, potentially eludidating another pathway of B cell self-reactivity outside the confines of normal tolerance mechanisms. They propose two new clinical trials to investigate lymphotoxin-beta receptor fusion protein as a treatment for primary Sj"gren's syndrome, and rituximab therapy for bullous pemphigoid. A Pilot Research Project is also proposed to engineer tetramers of self-antigen enabling the identification and characterization of self-reactive B cells, which will have implications for the goals of the clinical and other basic research projects. Overall, the Duke ACE will bridge these basic and clinical studies to advance their understanding of autoimmune disease. The B cell is a type of immune cell essential to autoimmunity. The goal of the proposed Autoimmunity Center of Excellence at Duke is to improve their understanding of the roles played by B cells in human autoimmune disease. The projects are designed to be highly integrative between the bench and the bedside, with collaborations between basic and clinical scientists. These studies may lead to better treatments. CLINICAL COMPONENT: Clinical Component (ST CLAIR, W) CLINICAL COMPONENT DESCRIPTION (provided by applicant): The Clinical Research Component of the Autoimmunity Center of Excellence shares with the Basic Research omponent an overall goal of advancing their understanding about the role of B cells in the pathogenesis of autoimmune diseases. This component will be directed by Dr. E. William St. Clair. During the past 5 years, the Duke ACE has brought 3 new clinical trial concepts to the ACE Steering Committee, resulting in 1 completed trial, 1 ongoing trial, and 1 protocol in development. They are also participating in 3 other ongoing ACE-sponsored clinical trials. Therefore, substantial clinical research activity will carry over to the next funding cycle. Their center is organized to support clinical trials in rheumatology, dermatology, gastroenterology, hematology, and neurology. They have access to several large patient populations, including patiens with rheumatoid arthritis, systemic lupus erythematosus, primary Sj"gren's syndrome, scleroderma, autoimmune blistering disease, psoriasis, inflammatory bowel disease, autoimmune hepatitis, anti-phospholipid antibody syndrome, and myasthenia gravis. Each of these disease areas has leadership from one or

more physician-investigators with significant clinical trial experience, including an example of a productive inter-institutional collaboration. The physician leadership is supported by an ample infrastructure that provides clinical research space, infusion facilities, experienced clinical coordinators, and an Immune Monitoring Component. The Clinical Research Component aligns with the ACE at a thematic level, with substantial collaborations between basic and clinical scientists. To this end, the proposed clinical trial concepts will focus on B cell directed therapy. In one case, they propose to examine the clinical efficacy of lymphtoxin-beta receptor fusion protein in the treatment of primary Sj"gren's syndrome, and have already secured commitment from the industry sponsor to provide study drug for this trial. The other application will investigate rituximab as initial therapy for bullous pemphigoid. The mechanistic studies for these proposed trials as well as current trials are highly integrated with the basic research projects. The Clinical Research Component will make a significant contribution to the ACE enterprise during the upcoming funding cycle. The Clinical Research Component will support clinical trials sponsored by the Autoimmunity Centers of Excellence in several disease areas, including rheumatology, dermatology, gastroenterology, hematology, and neurology. It has been productive during the current funding cycle, and has the capability, as shown in this application, to generate new ideas for clinical trials that can be translated into well-designed studies.

1R01TW008151-01A1
Molecular Epidemiology of Drug Resistance and Population Genetic Structure of Pla
Lu, Fangli
$50,000

This project will be of significant benefit to public health programs aimed at identifying and combating drug-resistant malaria, and have the potential to benefit the health of a substantial proportion of the world's population. The data will provide valuable information for extending the life span of individual antimalarial drugs and developing more appropriate malaria control policies in China. Malaria remains a serious public health problem in China. In the subtropical Yunnan Province and the tropical Hainan Island of China, malaria has been the most endemic with high transmission of both Plasmodium falciparum and P. vivax. However, most of the attention in terms of research and interventions has been focused in Africa and Southeast Asia, very few studies of malaria in China have been conducted. Because of extensive use, chloroquine (CQ) has now lost its efficacy due to the emergence of resistant strains in most parts of the world. Meanwhile, suspension of the use of CQ has resulted in reappearance of CQ sensitivity. However, there were differences in the evolution of CQ resistance between parasites from Yunnan and Hainan, the exact mechanism needs to be investigated. Sulfadoxine-pyrimethamine (SP) targets the dhfr and dhps genes of P. falciparum, and point mutations that confer resistance have been widely reported worldwide. Documenting the identity and extent of SP resistance is also critical for policy decisions regarding antimalarial drugs. In addition, P. vivax causes a large burden of morbidity in the world including China but traditionally has been understudied. Based on these, their long-term goal of this proposal is 1) to identify single-nucleotide polymorphism (SNP) and characterize the geographic distribution of genetic diversity, population structure, and haplotype variability at drug resistant loci of P. falciparum from Yunnan and Hainan, China, 2) to examine the geographic population structure, levels of genetic diversity of P. vivax using

microsatellite and SNP, and 3) to yield valuable information for making more effective malaria control policies in China. In the past several years they have developed the molecular methods to study the genetics, population diversity, and evolution of malaria parasites, and have done some preliminary studies on malaria field isolates from Yunnan and Hainan using genetic markers, thus enabling us to study the molecular epidemiology of these important malaria parasites in this proposal. The specific aims are to: 1. Determine genetic polymorphisms associated with CQ resistance (CQR) in P. falciparum field isolates from Yunnan and Hainan provinces, China. 2. Determine the point mutation prevalence in the dhfr (pyrimethamine drug resistance) and dhps (sulfadoxine drug resistance) genes associated with SP resistance in P. falciparum field isolates from Yunnan and Hainan provinces, China. 3. Assess the changes of P. vivax genotypes using pvcsp, pvmsp1, pvmsp3-1 genes, and microsatellite markers and determine the geographic structure and specific epidemiological characteristics of P. vivax transmission in Yunnan and Hainan, China. 1

MENOPAUSE

Menopause Strategies: Finding Lasting Answers for Symptoms and Health
(MsFLASH Network)
Women going through the menopause transition may experience a variety of symptoms, ranging from vasomotor symptoms (hot flashes and night sweats) to sleep disturbance, mood disorders, loss of sexual desire, and vaginal dryness. As many as two-thirds of all women report vasomotor symptoms, and over 85% report at least one menopausal symptom as they transition through menopause. For the 25% of women whose symptoms are severe, the resulting discomfort greatly diminishes their quality of life. For many decades, menopausal hormone therapy (MHT) using estrogen (or, in a woman with a uterus, a combination of estrogen and a progestin) has been the therapy of choice for relieving menopause-related symptoms. But recently, several large clinical trials, and in particular, the Women's Health Initiative, have found an increased risk of serious health problems, such as blood clots, stroke, heart disease, breast cancer and cognitive impairment, in women using estrogen-progestin regimens. Not surprisingly, women are reluctant to use MHT for menopausal symptoms and in search of alternative strategies to improve their quality of life.

The primary goal of the MsFLASH Network is to conduct multiple collaborative clinical protocols to evaluate a variety of strategies (e.g., pharmacological, botanical, behavioral, etc.) to alleviate vasomotor symptoms (VMS) and to assess the role of these strategies and changes in the burden of VMS on menopause-related sleep disturbance, mood disorders and vaginal dryness. Secondary objectives of the Network are to:

- Provide necessary multidisciplinary scientific input in reproductive endocrinology, gynecology, oncology, behavioral medicine, psychiatry, sleep, physiology, biostatistics, psychometrics, pharmacology, complementary and alternative medicine (CAM) and clinical trials methodology
- Implement the rapid identification/development of standard definitions and terminology, data collection instruments and needed new methodologies for assessment and analysis of participant outcomes

- Insure the success of recruitment by providing access to a broad base of populations of interest (of different race/ethnicities, types of menopause (spontaneous or induced by surgeries, treatments and conditions which propel women of reproductive age into the menopause transition)
- Establish a knowledge base that will advance therapeutic decision making through a better conceptualization of menopausal symptoms; testing of promising strategies; and advancement of strategies shown to be efficacious and safe
- Establish collaborations between the practice community and the clinical field sites
- Disseminate validated findings to the medical and scientific communities

A number of different treatment strategies are under consideration. Possible treatments to be studied during the five-year project period include:

- Antidepressants such as paroxetine (Paxil) or escitalopram (Lexapro)
- Paced respiration (slow deep breathing also known as relaxation breathing)
- Yoga
- Low-dose estradiol patch and low-dose estradiol gel
- Exercise programs, both moderate and vigorous

5 U01 AG032699-02
Menopausal Symptoms Initiative-Finding Lasting Answers for Sweats and Hot Flashes
LaCroix, Andrea Z.
Fred Hutchinson Cancer Research Center, Seattle
$200,000
The long-term objective of NIA's RFA-AG-08-004 entitled, "New Interventions for Menopausal Symptoms (U01) is to accelerate progress in identifying effective remedies for vasomotor symptoms (VMS) in women going through the menopausal transition. They have created a network of scientists who are highly knowledgeable about the menopausal transition and experienced in the conduct of women's health trials to fulfill this mission. This Data Coordinating Center (DCC) application is being submitted in conjunction with the network entitled, "The Menopausal Symptoms Initiative-Finding Lasting Answers to Sweats and Hot Flashes (MSI-FLASH)". Their DCC will be jointly led by Andrea LaCroix and Garnet Anderson who have served together as Co-Principal Investigators of the Women's Health Initiative Clinical Coordinating Center (Seattle) for more than a decade. The MSI-FLASH network has five clinical sites located in Boston (Lee Cohen and Hadine Joffe, PIs), Indianapolis, IN (Janet Carpenter, PI), Oakland, CA (Barbara Sternfeld and Bette Caan, PIs), Philadelphia (Ellen Freeman, PI) and Seattle (Katherine Newton and Susan Reed, PIs). This multidisciplinary investigator group proposes five randomized controlled trials testing a range of behavioral, mind-body, hormonal and pharmacologic interventions to treat hot flashes. The specific objectives of the DCC are to: 1) Provide and coordinate all necessary leadership activities to facilitate collaboration and productivity among network scientists during all phases in the lifecycle of VMS clinical trials from hypothesis formulation to publication, dissemination, and data sharing; 2) Build upon 15 years of experience and well established human and operational resources to coordinate 5 or more multi- site randomized trials including support of protocol development, recruitment, intervention, data collection and management, and statistical analysis; and 3) Create the infrastructure to involve an expanded network of scientists from the US and worldwide to facilitate the development and use of

common methodologies and measurements for VMS trials inside and outside of this trial network so that emerging new treatments for hot flashes can be rapidly identified and rigorously tested for efficacy and safety with comparable results.

5U01AG032682-02
Msi Flash: An RCT Of Yoga And Ultra Low-Dose Estrogen Gel For Vasomotor Symptoms
Newton, Katherine M.
Group Health Research Institute, Seattle, Wa
$95,148
In this site application they propose a multicenter, factorial design, RCT of yoga, ultra low-dose estradiol (E2) gel and placebo gel to be conducted in Seattle, Indianapolis and Boston. The primary aims are to: 1. Evaluate the effects of yoga vs. no yoga on: a) subjective VMS frequency; and b) VMS bothersomeness; and 2. Evaluate the effects of ultra-low dose estrogen (E2) gel vs. placebo gel on: a) subjective VMS frequency; and b) bothersomeness. Their hypotheses are that 1. The effect of yoga will be greater than no yoga on: a) subjective VMS frequency and b) VMS bothersomeness; and 2. The effect of ultra-low dose E2 gel will be greater than no E2 gel on: a) subjective VMS frequency; and b) bothersomeness. Their secondary aims are: 1. To evaluate the effects of yoga and ultra-low dose E2 gel on other common menopause outcomes including: a) objective VMS frequency (Bahr monitor); b) sleep (PSQI, Actigraph"); and c) mood (CESD, HADS); and 2. To examine whether the combined effect of yoga and ultra low-dose E2 on their primary and secondary outcomes is greater than the effect of either alone. To accomplish their specific aims they will: 1) recruit and randomize 400 women to one of 4 treatment arms for 12 weeks (placebo gel; yoga + placebo gel; ultra low-dose E2 gel; yoga + ultra low-dose E2 gel); 2) measure primary and secondary outcomes at baseline and 12 weeks; and 3) compare changes in outcomes in yoga and ultra low-dose E2 gel groups to placebo; and 4) compare changes in primary and secondary outcomes for yoga + ultra low-dose E2 gel to the effects of either intervention alone (if yoga alone is efficacious).

3U01 AG012553-15A1S2
Study of Women’s Health Across the Nation III
Tyrrell, Kim Sutton
University of Pittsburgh, Pittsburgh, PA
$125,000
The Study of Women’s Health Across the Nation (SWAN) is a multicenter, multiethnic, community based longitudinal study designed to characterize the biological, symptomatic and psychosocial changes that occur during the menopausal transition and the effects of these changes on women’s health during and after the transition. Current and prior funding (SWAN I and II) has supported a baseline and six annual follow-up examinations during which 895 (48%) women will have transitioned to postmenopause. This application requests funding to complete four additional follow-up visits (SWAN III) to allow an adequate evaluation of the late perimenopause and early postmenopause, a period that has not been well studied, particularly among non-white women. They will continue their current tracking of changes in reproductive hormones, bleeding patterns, symptoms, bone loss, cardiovascular (CV) risk factors blood pressure, body size, and other related characteristics and will undertake new scientific endeavors in targeted areas. These include measurement of vascular stiffness to

assess early CV disease, assessment of vertebral morphometry at four sites using DEXA technology, and the addition of one cognitive function test. In addition, they will focus on linking the midlife experience to age-related outcomes (e.g. cognitive function, urinary incontinence) and chronic diseases (e.g. fractures, diabetes and hypertension). Specimens from the additional follow-up visits will continue to contribute to the SWAN biological specimen repository (annual blood and urine samples as well as DNA and immortalized cells). This is a separately funded component that broadens the opportunities to address future hypotheses about health and disease in aging women. As women reach the end of early postmenopause (two years following the final menstrual period), they will shift from an annual to a bi-annual follow-up examination schedule with mail and telephone contact in the alternating years. This will permit cost-effective and less intensive follow-up. SWAN's organization and operations have been modified to enhance productivity and they are poised to publish important biological, symptom and behavioral results pertaining to the menopause transition. With SWAN III, many of the original goals of SWAN will be brought to fruition. They will build upon the rich foundation developed during SWAN I and II and link these data to important menopause-related and health outcomes in SWAN II.

5R01 AG027675-04
Neurobiology of the Menopausal Transition
Smith, Yolanda R.
University of Michigan at Ann Arbor
Ann Arbor, MI
$47,579.00
This project is part of an RFA jointly funded by NIA and ORWH on the biology of the peri-menopause, impact on health and aging in non-reproductive somatic and neuronal tissues. This and other projects funded under this RFA focus on increasing their understanding of the underlying biologic mechanisms associated with the increased risk for, or decreased protection leading to, health problems and conditions associated with the menopausal process in middle-aged women. The focus is on how the hypothalamic-pituitary-ovarian axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within non-reproductive somatic and neuronal target tissues, the role of steroid hormone biosynthesis and/or metabolism within non-reproductive somatic and neuronal tissues on pathophysiologic processes within these tissues across the perimenopause, and the role of aging on these pathophysiologic processes.

5R01 AG027678-04
Biological Mechanisms of Arterial Stiffening with Age and Estrogen Deficiency
Moreau, Kerrie
University of Colorado, Denver, CO
$47,579
The purpose of this project is to determine the key functional mechanisms by which the loss of female sex hormones, particularly estradiol (E2), contribute to the age-related decrease in large artery compliance. The overall hypothesis is that basal large artery compliance will decrease in response to acute sex hormone suppression in pre- and perimenopausal women due in part to a decrease in vascular endothelial-dependent vasodilatory tone mediated, in part, to the development of vascular oxidative stress. However, E2 administration during sex

hormone suppression will decrease vascular oxidative stress, improve endothelial vasodilatory tone and restore arterial compliance to basal levels. Secondary and tertiary hypotheses are that the changes in arterial compliance and vasodilatory function with sex hormone suppression and E2 will be related to unfavorable, and favorable, respectively, changes in vascular endothelial cell protein expression including oxidant (e.g., NADPH) and antioxidant (e.g., glutathione peroxidase) enzymes, vasoconstrictors (endothelin- 1), and estrogen receptor alpha (ERalpha). To test these hypotheses, healthy pre-, peri-, and postmenopausal women will be studied at before and following acute sex hormone suppression (gonadotropin releasing hormone antagonist [GnRHant]) with or without E2 add-back therapy. The GnRHant intervention will enable us to study the direct mechanisms associated with sex hormone deficiency and the E2 add-back intervention will enable us to isolate the independent effects of E2. Insight into the molecular mechanisms mediating the decrease in large artery compliance will be obtained using a novel translational research technique to determine changes in vascular endothelial cell protein expression of genes involved in the regulation of cellular and systemic adaptations to aging and sex hormone deficiency including oxidative stress, nitric oxide bioavailability, and the potent transcription factor ERalpha proteins. The results should provide new insight into the integrative biological mechanisms by which sex hormone deficiency modulates the age-related reduction in large artery compliance in women as they transition through the menopause.

5R01 AG027684-04
Impact of Endocrine Aging on Brain and Immune Responses
Sohrabji, Farida
Texas A&M University Health Science Ctr., College Station, TX
$47,579
This project seeks to determine the mechanisms by which reproductive aging and estrogen replacement alter the inflammatory response and consequently the neuronal environment. In a series of studies, they have established that estrogen replacement to young adult animals increases trophic support in the forebrain and attenuates inflammation following neural injury. However estrogen replacement at reproductive senescence, which is physiologically akin to menopause, fails to increase trophic factors and paradoxically, increases inflammatory mediators following neural injury. Collectively these data suggest that the timing of estrogen replacement in relation to reproductive aging may critically determine whether estrogen has a benign or deleterious outcome. Their central hypothesis is that the age-related decline in endogenous hormones triggers compensatory changes in estrogen receptor systems in specific immune cells, thus increasing the central and peripheral inflammatory response. This hypothesis will be tested in three Specific Aims, using animal and human tissue models that span the reproductive spectrum, namely, normally cycling (pre-menopause). irregularly cycling (perimenopause) and reproductive senescent (postmenopause). In Specific Aim 1. they will test the hypothesis that permissive changes in the blood brain barrier will cause a more rapid and robust neural inflammation in reproductive senescent animals as compared to normally cycling or irregularly cycling animals. Animals will be injected systemically with the bacterial pathogen lipopolysaccharide (LPS) and inflammatory mediators will be measured in peripheral organs and the brain. Additionally, they will examine endothelial cells of the blood-brain barrier for reproductive age-related changes in this barrier. In Specific Aim 2. they will determine if the inflammatory response of peripheral blood mononuclear cells

(PBMC) is affected by clinically-relevant variables namely, the route of hormone administration (oral versus transdermal) and diet (regular versus high cholesterol). The Response Quotient, derived from an ex vivo LPS challenge assay, will be measured in rat and human blood samples to determine if salient lifestyle variables increase the risks associated with reproductive aging. Finally, in Specific Aim 3 they will test the hypothesis that compensatory alterations of the estrogen receptor system, resulting from ovarian decline, is a principal mechanism underlying estrogen's deleterious effects in reproductive senescence. Changes in the pattern and levels of estrogen receptor (ER)-alpha will be evaluated by immunohistochemistry and Western blots, while functional changes will be evaluated using signaling arrays. Human and rodent PBMC's and rodent cerebral endothelial cells from each reproductive stage will be studied. Collectively, these studies will test the hypothesis that in order for estrogen replacement to be beneficial, therapy must be initiated before compensatory responses to ovarian decline.

5R01 AG027697-04
Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO
Mohankumar, Puliyur S.
Michigan State University, East Lansing, MI
$47,579.00
This project is part of an RFA jointly funded by NIA and ORWH on the biology of the peri-menopause, impact on health and aging in non-reproductive somatic and neuronal tissues. This and other projects funded under this RFA focus on increasing their understanding of the underlying biologic mechanisms associated with the increased risk for, or decreased protection leading to, health problems and conditions associated with the menopausal process in middle-aged women. The focus is on how the hypothalamic-pituitary-ovarian axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within non-reproductive somatic and neuronal target tissues, the role of steroid hormone biosynthesis and/or metabolism within non-reproductive somatic and neuronal tissues on pathophysiologic processes within these tissues across the perimenopause, and the role of aging on these pathophysiologic processes.

5R01 AG027702-04
Estrogen: Neuroprotection in the Perimenopause
Etgen, Anne M.
Yeshiva University, Bronx, NY
$47,579
Alterations in the hypothalamic-pituitary-ovarian axis in perimenopausal women are associated with multi- organ risk factors for disease, yet the biological mechanisms underlying this increased disease risk are largely unknown. This proposal addresses unanswered questions regarding the vulnerability of the middle- aged brain to global ischemia. In young female rats, the presence of physiological levels of estradiol before and after global ischemia, as might occur during cardiac arrest, reduces hippocampal CA1 neuron loss and associated cognitive impairments. Whether estradiol retains its neuroprotective actions in middle-aged females, and whether the age-related decline in insulin-like growth factor-l (IGF-I) increases vulnerability to ischemia-induced neurodegeneration and cognitive impairment, are unknown. This proposal aims examines the roles of age, estrogen and IGF-I

in the survival and function of hippocampal neurons in a rat model of global ischemia. The underlying hypotheses are (1) that the middle-aged brain retains its responsiveness to the neuroprotective actions of estradiol if the duration of estrogen withdrawal is brief (critical period hypothesis) or circulating levels of IGF-I are maintained, and (2) that estrogen acts in the middle-aged brain to activate specific cell survival pathways and thereby intervenes in apoptotic cascades to prevent death of neurons otherwise destined to die. Specific Aim 1 uses stereological cell counting and behavioral tests to evaluate the outcome of global ischemia in middle-aged female rats that are intact, ovariectomized at various intervals prior to insult, or ovariectomized and treated with estradiol at various intervals after ovariectomy. If estradiol does not preserve neurons and cognitive function in older hormone-deprived animals, we, will also determine if IGF-I can reinstate estrogen protection. Specific Aim 2 examines the apoptotic death cascades triggered by global ischemia and identifies the site at which estrogen intervenes in these cascades. They will examine 1) mitogen-activated protein kinase and cAMP response element binding protein at early times after ischemia; 2) the anti-apoptotic gene Bcl-2 and activation of caspase 3 at later times after ischemia; 3) inactivation of Akt and subsequent activation of the forkhead transcription factor FKHRL1 at early times after ischemia. These experiments will provide new information on the potential for hormone therapy instituted during the perimenopausal transition to protect the brain from damage due to global ischemia.

5R01 AG027713-04
Menopause: Decreased Response to Increasing Inflammation
Maggi, Adriana Caterina
University of Milan
$46,199
The long-term goal of their research is to find treatments for the prevention of the disorders associated with menopause which are safer and more efficacious than present hormone replacement therapy (HRT). The failure of present HRT to fulfill medical and women's needs has to be ascribed to an insufficient knowledge of the biology of menopause. The aim of their research is focused on the understanding the consequences of cessation of ovarian functions on the physiology of non-reproductive organs such as bone, brain, arteries and fat. In particular their studies and the studies proposed in the present project will focus on the effects of estrogen decreased production at menopause transition and after in non-reproductive organs. Given recent results demonstrating that in non-reproductive organs of fertile female mice estrogen receptors (ERs) are activated by factors other than estrogens, their Specific Aim #1 will focus on assessing the extent to which ERs are transcriptionally active during menopause transition and after. They will then try to identify the factor(s) involved in ER activation. This part of the project relates to questions which so far could be addressed only partially with the current technology. The generation of a novel model of reporter system, the ERE-Luc mouse, will enable us to precisely quantify ER activity in the organs of interest and facilitate the search of factors involved in ER unliganded activation. Specific Aim #2 will give us the opportunity to test an original hypothesis that would explain the widespread protective effects provided by the estrogen-ER system. This hypothesis is based on numerous very recent observations made in ours and several other groups showing that estrogens and cognate receptors may exert a strong anti-inflammatory action by inhibiting the immune response of cells of the monocyte lineage. They here propose that menopause consists in a

decreased response to increased inflammation. They will test this hypothesis by the direct assessment of ER relevance on macrophage activity through the generation of a novel conditional ERalpha K.O. mouse. Furthermore, using brain as a paradigmatic non-reproductive organ, they will measure basal and induced activity of brain inflammatory cells. Finally, the specific involvement of ER anti-inflammatory activity in the development of menopause-associated diseases will be tested with the study of the activity in menopause of another class of intracellular receptors devoted to the control of inflammation, the PPARs.

5R21 AG032598-02
Genetics of Reproductive Life Period and Health Outcomes
Murabito, Joanne M.
Boston University Medical Campus, Boston, MA
$241,900
The overall research objective of this grant is to elucidate the contribution of menopause and reproductive factors versus aging per se to health conditions common in women in later life. More than half the variation in age at menarche and menopause is attributable to genetic factors yet the genes regulating these traits remain largely unknown. Data from longitudinal studies, such as the Framingham Heart Study (FHS), provide a wealth of data across adulthood including reproductive factors, disease occurrence, and health behaviors in both women and men. The FHS is multigenerational and includes an extensive genetics database with extant genotyping from a 550K genome-wide scan obtained through the NHLBI's SNP Health Association Resource (SHARe) project. They postulate that novel genetic variants influencing the age of menarche and natural menopause can be identified using a dense genome-wide association study (GWAS). This proposal aims to identify genetic variants that influence age at menarche and age at natural menopause through a GWAS using extant 550K genotyping data; to perform in silico replication of significant associations in independent samples; to examine the associations between genetic variants and osteoporosis-related traits obtained using dual x-ray absorptiometry (DXA) and hand radiogrammetry, in women as well as in men; to perform a phenome scan using the genotypes associated with reproductive aging to identify other associated phenotypes that may provide additional insights into underlying biological mechanisms mediating the associations in women. The phenome scan will also be performed in men to explore sex-specific associations. The use of the 550K genotyping will be resource effective and their work will be publicly available through the FHS SHARe Project located at the NCBI permitting investigators around the world to embark on this research. Insights from this project may lead to the discovery of genes related to female reproductive aging and associated health outcomes and in turn lead to innovative diagnostic and therapeutic interventions to improve the overall health of women and possibly of men.

3U01AG012531-16A1S1
SWAN: Study of Women's Health Across The Nation
Finkelstein, Joel S.
Massachusetts General Hospital, Boston, MA
$75000
The Study of Women's Health Across the Nation (SWAN) is a multi-center, multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and

risk factors for age-related diseases. The goals of the original RFA were to answer the following questions: How do hormones change with the menopausal transition? What factors affect the timing of the transition? What are the symptoms that accompany menopause and who is at risk? How do cardiovascular risk factors change with the transition and is there ethnic variation? What are the rates of bone loss with the transition? When does bone loss begin and what are the risk factors? What are the health consequences of menopause and who is at risk? SWAN is compiling the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. SWAN is now poised to study the effects of these menopause-related changes on subsequent healthy aging and on age-related diseases in the post-reproductive period. SWAN I was first funded in September 1994 by the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the Office of Research on Women's Health (ORWH) in response to RFA AG-94-002, Menopause and Health in Aging Women. The first competing continuation of SWAN (SWAN II) was funded in 1999 and the second (SWAN III) in 2004. SWAN I, II and III have been supported by a cooperative agreement mechanism, with 9 funded components: 7 clinical centers, a central reproductive hormone laboratory (CLASS), and a coordinating center. A second central laboratory (MRL) was originally funded as a subcontract to the Coordinating Center (CC). In addition, a Core Repository of serum, plasma, and urine specimens and a DNA Repository were established in June 2000 under separate funding (U01 AG 17719, PI: Dr. MaryFran Sowers). For non-study-related reasons, site operations at New Jersey Medical School stopped in April 2004. The basis of this action was allegations made by two study employees who resigned abruptly. The SWAN PI and study coordinator were subsequently exonerated from these allegations. Please see Appendix 12 for a more complete report. The grant was transferred to the Albert Einstein College of Medicine in 2005. Since that time, the New Jersey PI and project director have worked tirelessly to overcome the obstacles to re-implement the study. As of June 1, 2008, a total of 155 women have successfully completed their clinic visit and five more visits are scheduled. They project that by the end of SWAN III, data will be available for 250 women. This has been very encouraging and thus Nanette Santoro, PI of the New Jersey SWAN site has been approved by the NIA to prepare a U01 application to cover further contacts for the Hispanic women. Please note that the SWAN IVproject applications pertain to the remaining six sites only. Information relative to the New Jersey site is covered in the separate application submitted by Dr. Nanette Santoro. From over 16,000 women aged 40-55 years who were screened during 1995-1997, 3302 women aged 42-52 years were enrolled in SWAN's longitudinal cohort (approximately 450 at each of 7 clinical centers). They completed their baseline clinic visit during 1996-1997. Of the 3302 women enrolled, 1550 were Caucasian, 935 African American, 286 Hispanic, 250 Chinese, and 281 Japanese. A subset of 880 menstruating women was enrolled in the Daily Hormone Study (DHS) started in 1997, which is designed to examine cyclical daily hormone and symptom patterns during the menopausal transition.

MENTAL HEALTH

1R21HD058989-01A1
Novel Approaches To Understanding Mental Disorder, Substance Abuse And HIV-Risk A

Whitbeck, Leslie B
University Of Nebraska Lincoln
$145,180
This R21 application seeks two years of support to develop state-of-the-science methodologies to address four important gaps in existing research with homeless women: 1) capture the diversity of circumstances among a fluid and hard-to-access population; 2) increase their understanding of mental and substance use disorders (particularly personality disorders) across the diversity of homeless women; 3) improve their understanding trajectories to homelessness through development of an innovative event history calendar approach; and 4) advance knowledge of homeless women's health and HIV-risk by circumstance and trajectories to homelessness. This research will provide measurement development and preliminary studies for a multi-state longitudinal R01 designed to advance their understanding of mental and substance use disorders among homeless women, their movement into and out of homelessness, the consequences of homelessness for women and minor children in their custody, and women's health, HIV-risk, and HIV testing behaviors. The planned longitudinal research will focus on a growing but poorly understood population of the nation's most vulnerable women. The specific aims of this R21 developmental application are to 1) develop and pilot a sampling plan that will better reflect the diversity of homeless women; 2) develop and pilot an innovative events history calendar for use with homeless women; 3) program and pilot Axis 1 (UM-CIDI) and Axis II (DIPD-IV) diagnostic interview schedules for computer-assisted personal interviews with homeless women; 4) develop and program women's health and HIV-risk measures; and 5) pilot the measures with 200 homeless women in two Midwestern cities.

1R21DA025543-01
Race And HIV-Risk: Contextual And Neurocognitive Influences On Sex Partnerships
Floyd, Leah
Johns Hopkins University
$204,426
The primary aim of this R21 application in response to NIDA's ANSWHR Initiative (PAS-07-381) is to address gaps in literature focused on HIV risk and disparities among females. In the United States as rates have increased among females, the rate of HIV/AIDS diagnoses for African American females approaches 25 times the rate for white females. Despite the broad base of findings documenting health disparities in HIV, extant studies cannot explain why African Americans continue to be disproportionately affected. Currently, there is a hidden HIV epidemic among young adult African American females with no history of substance abuse. These women are at increased risk for contracting HIV by virtue of their social networks. The proposed study requests two years of support for a cross sectional epidemiologic examination of racial/ethnic differences in sexual partnerships among 220 females (110 Black and 110 White) residing in low socioeconomic status (SES) neighborhoods. Guided by ecosocial theory, they seek to explain why these differences exist across race/ethnicity. They will consider the extent to which neighborhood social and economic factors (e.g., drug markets) interact with race/ethnicity to produce different levels of HIV risk. They will expand drug abuse and HIV prevention research by, in addition to considering individual differences, examining the influences of neighborhood drug markets on the sexual behaviors, sexual partnerships and rates of a sexually transmitted disease among

young adult females residing in disadvantaged neighborhoods. Finally, the proposed study will move beyond descriptive social epidemiology and into identifying neurocognitive processes that mediate/moderate relationships between neighborhood factors and individual behavior. As, a small yet growing base of research suggests, to the extent that individuals are able to make decisions, solve problems and control impulses, neurocognitive functions may serve as protective factors or pathways through which external social factors influence individual behavior. Identifying social factors that influence partner selection and individual level factors that may serve to reduce the adverse effects of living in disadvantage neighborhoods will inform HIV prevention interventions for African American and underserved women. If successful, the proposed research project: (1) should provide insight into why African American females have higher rates of HIV than their white counterparts; (2) highlight the importance of considering the contextual influences of drugs, that is the influence of drug markets on social structures and sexual norms and behaviors; and (3) identify modifiable individual level factors linking neighborhood social and economic factors to individual HIV risk behaviors.

5R01 MH075921-04
Antimanic Use During Pregnancy
Wisner, Katherine L.
University of Pittsburgh, Pittsburgh, PA
$200,000
Bipolar disorder (BP) is a serious psychiatric condition that affects 0.5 -1.5% of individuals in America. The age of onset of BP is during the initial childbearing years. Seventy percent of women with established BP will suffer recurrent episodes post-birth. Continuous medication administration is the mainstay of treatment for BP. Although the information available to physicians who treat pregnant women with unipolar depression has increased over the past decade, data to inform decisions about treatment of BP has not advanced similarly. Information about anticonvulsant use during pregnancy has been garnered solely from the study of women with epilepsy, who have increased risk for malformations independent of drug treatment. Data about atypical antipsychotic use in pregnancy is almost non-existent in either women with BP or schizophrenia. The majority of studies have not included the range of outcome measures that comprise the contemporary portfolio of the reproductive toxicity outcomes. Pharmacologists have produced data for altered physiologic states (renal or hepatic disease) and for other patient subpopulations (children and elderly). The need for similar studies in pregnancy is certainly no less than for these populations. New information must be obtained to guide risk-benefit decision-making to a new level of sophistication. This is a prospective observational study of women with BP during pregnancy and the mother-infant pairs n the first postpartum year. They plan to enroll 200 women with BP and 58 women without BP (for 140 and 40 completers, respectively). Decisions about treatment during pregnancy will be made by the woman with her physician (not associated with the study) prior to study enrollment. The major aims of the study are to define a cohort of pregnant women with DSM-IV defined BP and to: 1) Characterize the BP illness course in the population through pregnancy and the first postpartum year, with careful documentation of treatment(s) and gestational timing. 2) Evaluate function in the maternal role as well as occupational, educational and social domains. 3) Define pregnancy and infant outcomes in both medicated and unmedicated women with BP and compare them to those of unmedicated women without

BP. Separation of the effects of medication from the disorder is critical to advance risk assessment. 4) Assess the infants' development through the first year of life. 5) Perform serum levels at 20, 30, and 36 weeks gestation to allow level/dose ratio monitoring for women who take medications during childbearing. The mother-infant serum levels of women with BP who breastfeed their infants also will be assayed. 6) Conduct pharmacokinetic (PK) studies on the subset of women who take lithium, the most common drug used to manage BP during pregnancy in their Center, at 20- 24 weeks, 32-36 weeks, and 12-16 weeks after birth. No such PK data are currently available.

5R21 MH083964-02
Sex Stress Emotional Disorders: Uniting Preclinical And Epidemiologic Research
Costello, Elizabeth J.
Duke University
$20,000
The overall research objective of this grant is to (1) bring together researchers who have made important advances in preclinical, experimental, and epidemiological research on stress responsitivity and psychopathology; (2) to integrate their findings across disciplines and identify key questions related to gender disparities; and (3) to plan a new program of research that takes a developmental approach to sex differences in stress responsivity as they affect depression and anxiety disorders in young people. The program of work has three aspects: (1) Two annual meetings of the workgroup members to identify key questions and plan a program of analysis of existing data sets. Meetings will be designed so that participants will learn as well as teach. At the second meeting, each work group member to commit to be first author on one or more specific papers. (2) A program of data analysis to be carried out at the Center for Developmental Epidemiology, Duke University. Analyses will be reported to the group by email; group members can request additional follow-up analyses. Monthly conference calls between meetings will discuss output of analyses and plan further work. (3) An application for an Interdisciplinary Developmental Science Center for Mental Health (IDSC) or similar mechanism, to be submitted in October 2010. Questions to be addressed include the following: 1. What has been learned from animal research about sex differences in the effects of early adversity on neurobiological parameters, such as the HPA axis, the autonomic nervous system, and neural systems implicated in psychopathology? 2. What has been learned from laboratory and epidemiological research with humans about sex differences in the effects of early adversity on neurobiological parameters, such as the HPA axis, the autonomic nervous system, and neural systems implicated in anxiety and depression in the first decades of life? 3. Where do these bodies of work agree, where do they conflict, and where are they most important gaps? They expect that the answers to questions 1 to 3 will lead to the planning of a Center application to focus on such questions as: 4. How does gender moderate the effects of childhood stress on mental health and neurobiological function; i.e., what are the interactions between stress response systems and sex steroids? 5. What are the sex-specific effects of stress and life events in different developmental stages or during transitions between stages (e.g., puberty) on risk for anxiety and depression? 6. How does the timing of differences in onset of anxiety and depression in males and females relate to sex differences in psychological and neurobiological functioning?

1R21MH086731-01

Cellular and Molecular Basis of Hippocampal Atrophy in Depressed Female Monkeys
Shively, Carol A.
Wake Forest University Health Sciences
$222,000
Clinical and experimental studies suggest that hippocampal volumes may be smaller in individuals with depression, although the cellular mechanisms underlying this relationship are unclear. Stressful life events are associated with an increased risk of depression, and animal models, exposed to chronic stress have been used previously to investigate hippocampal shrinkage in depression. Although the data from preclinical stress models are compelling, the degree to which stress responses in animal models are relevant to human depression remains controversial, particularly since women are at two-fold greater risk of depression and the animal models are mostly male rodents. Evaluation of the causes of reduced hippocampal volume in an experimental model that more closely resembles human depression would be valuable. The investigators developed a primate model of depression in adult female cynomolgus monkeys which closely resembles human depression, and recently observed that depressed monkeys have relatively small anterior hippocampi. The overall goal of this proposal is to evaluate hippocampal morphologic, cellular, and molecular characteristics in depressed and nondepressed female monkeys to determine whether the smaller hippocampi of depressed female monkeys are accompanied by reductions in neuropil and synaptic, spinous, and dendritic integrity. The investigators have a unique and valuable collection of fixed, frozen hippocampi derived from the population of adult female monkeys in which the behavioral and physiological characteristics of depression were studied premortem for 4 years. Using the tissue from 8 depressed and 8 nondepressed monkeys the researchers will determine astrocyte, pyramidal, and granule neuron size and number, and protein and mRNA levels of markers of synaptic, spinous, and dendritic integrity in the cornu ammonis (CA) CA1, CA2, CA3, and DG of the anterior and posterior HC of behaviorally depressed and nondepressed monkeys. The results of this study will establish the use of the model in future investigations of the mechanisms of depression and the efficacy of interventions for depression. Significance Of The Application: Depression is a significant health problem in the US, particularly in women, as 20% of reproductive-aged women experience clinically significant depression. Unfortunately very little research has been conducted in female animal models of depression. The use of the first primate model of adult depression in females proposed here, which has greater similarity to human neurobiology and depression than rodent models, will advance their understanding of the neurobiology of depression especially in women.

5R21 MH084215-02
Sex Differences In The Entorhinal Cortex
Scharfman, Helen E.; Nathan S. Kline
Nathan S. Kline Institute For Psych Res, Orangeburg, NY
$20,000
This project will evaluate whether sex differences exist in a part of the brain where they have not previously been recognized, the entorhinal cortex, and address their implications. They hypothesize that there is increased neuronal activity in the female medial entorhinal cortex and this disrupts processing of new information, particularly spatial information. Based on Preliminary findings, estrogen appears to play a key role by facilitating NMDA receptor

mediated activation of entorhinal neurons. The implications are important because they could help address sex differences in cognitive function, and lead to new considerations for treatment of learning disorders. There are many differences between females and males in the brain, behavior, and disease. One of these is established in rodents as well as man: spatial memory. What could be the underlying basis? In this project they test the hypothesis that there are robust sex differences in the rodent medial entorhinal cortex that could explain sex differences in spatial memory. The medial entorhinal cortex seems a logical candidate given it is critical to spatial representation in the rat, and lies in an ideal anatomical position because it is situated between hippocampus and cortex. Their preliminary data, using slices of entorhinal cortex, shows a sex difference in evoked responses to afferent input in entorhinal cortex: in slices from females, responses are repetitive or prolonged relative to males, a sex difference that is blocked by the NMDA receptor antagonist D-APV. When estrogen levels are high, these events are most robust, and when estrogen is low, or a prepubertal animal is evaluated, they are relatively rare. They hypothesize that the responses of entorhinal neurons to afferent input are increased in the female rat relative to males, and this disrupts information processing and synaptic plasticity, i.e., long-term potentiation (LTP). Because the difference appears to be localized to superficial layers, the perforant path projection to hippocampus may be selectively influenced, and this is important because the perforant path is the major afferent system to hippocampus from entorhinal cortex. In this proposal, they will establish the cellular physiology in slices of entorhinal cortex of female and male rats, test sex differences in LTP in the entorhinal cortex and hippocampus, and address whether puberty and estrogen are key factors, as Preliminary data suggest. Together the results will shed light on an area of the brain where sex differences are relatively unexplored, and could have important implications for understanding cognitive function, as well as treating learning disorders.

5DP OD003312-03
Emotions are Emergent Events Constrained by Affective and Conceptual Processes
Barrett, Lisa
Boston College
$391,250
Emotional states are central to mental and physical health. NIH invests tremendous resources in research on emotion, much of it devoted to animal models. Ironically, this research is guided by a scientific paradigm that is grounded in human experience. People experience fear and see it in others, so scientists assume there must be a literal (modular) neural circuit for fear in the mammalian brain. Rats freeze when they hear a tone paired with a foot shock, so they are presumed to be in a state of fear (versus surprise, anger, or even a general state of alarm) and undergoing “fear learning.” Scientists also presume that a map of the neural circuitry of freezing behavior will yield a neural mechanism for fear that is largely preserved in humans, and a decade of neuroimaging studies have focused on locating a homologous neural circuit in the human brain. In the last five years, I have traced the roots of this “natural kind” model, conducted a comprehensive review of the literature to examine its veracity, and found it wanting (Barrett, 2006a).1 In response, I have fashioned a new systems-level model, called the Conceptual Act Model, grounded in the neuroanatomy of the human brain. My model parsimoniously incorporates neuroscience findings from rats, primates, and humans, and explains the mechanisms that produce the range and variety of behavioral and introspective instances that they call “emotion” (Barrett, b, c; Barrett, Mesquita, Ochsner, &

Gross, 2007; Barrett, Ochsner, & Gross, 2007; Duncan & Barrett, 2007). The Conceptual Act Model asks different – and perhaps better – questions about what emotions are and how they function in mental and physical health. The NIH Director's Pioneer Award will allow me the intellectual freedom and resources to continue building evidence for the Conceptual Act Model of emotion, thereby shaping a new paradigm to guide the scientific study of emotion.

MUSCULOSKELETAL SYSTEMS

1R21AI083894-01
Role Of Sex Differences In The Expression & Function Of Regulatory T Cells In SLE
Singh, Ram Pyare
University Of California Los Angeles
$192500
Regulatory CD4+T cells and CD8+T cells have important roles in suppressing autoimmune disease in the peripheral immune system. Impaired function of regulatory/suppressor T cells contributes to development of autoimmunity. The goal of this project will be studying the quantities and functions of T regulatory cells in healthy controls and patients with SLE, comparing males to females in both groups (given the fact that lupus disease is much more frequent in females than in males). The first aim is to quantify, immunophenotype, and perform functional analysis of the Treg cell subsets in healthy controls, and in male lupus vs female lupus. The second aim is to compare gene expression profiles of CD4+CD25+hiTreg and CD8+Ts cells in male vs female lupus patients and to compare them with healthy controls. Finally, they will test the effect of testosterone and estradiol in these cells in vitro to see their effects on cell phenotypes, gene expression, signaling and regulatory functions. The overall purpose is to understand the molecular network of these CD4+T regulatory cells and CD8+ suppressor cells in systemic autoimmunity.

1 K99 AR057426-01
Function and Behavior Phenotype of Inflammatory Arthritis in the Rat Knee and TMJ
Allen, Kyle
Duke University
$80,000
Degenerative joint disorders, such as arthritis, affect a substantial percentage of the US population and have a significant economic burden. The focused use of disease modifying drugs and cellular Strategies for tissue regeneration offer great potential to treat these disorders; however, the safety and efficacy of these treatment strategies must first be evaluated in pre-clinical models. The purposes of this proposal, and the career aims of the principal investigator, are to create and refine techniques to evaluate joint function and symptoms in pre-clinical, animal models of arthritis and to investigate the potential for disease-modifying therapeutics to modify functional and symptomatic sequelae associated with arthritis. This proposal begins with the mentored phase where interleukin 1p (IL-lp) overexpression in the knee joint will be used as a rat model of unilateral inflammatory arthritis. The functional and symptomatic sequelae of this arthritis will be evaluated using custom-designed gait and pain sensitivity tests. Moreover, two ILIp antagonists, interleukin 1

receptor antagonist (111 Ra) and soluble interleukin 1 receptor type II (slHRII), will be evaluated for their ability to modify functional and symptomatic sequelae associated with knee arthritis. The PI will then transition skills and knowledge gained during the mentored phase to the study of temporomandibular joint (TMJ) disorders and their functional and symptomatic sequelae. In the independent stage, techniques and methods to assess the sequelae of TMJ disorders will be developed for rodent models, including systems to evaluate orofacial sensitivity, bite force, dietary habits, and sleep patterns. The intra-articular ILip over-expression model will then be adapted to initiate TMJ arthritis, and the developed technologies will be applied and assessed for their ability to modify the associated functional and symptomal sequelae. This proposal addresses the developments of novel treatment and assessment strategies for knee arthritis and TMJ disorders, drawing significantly on the PI's experience in TMJ research and the mentor institution's expertise in osteoarthritis and drug delivery. Moreover, this research plan will assist the PI in transitioning to a faculty position and establish an independent research program evaluating therapeutic interventions for TMJ disorders and degeneration.

The Osteoarthritis Initiative

The OAI is a nationwide research study, sponsored by the NIH, that is intended to accelerate knowledge about how to prevent and treat knee osteoarthritis, one of the most common causes of disability of adults.

N01AR22262-12-0-1
Clinical Centers For The Osteoarthritis Initiative: Rhode Island
Eaton, Charles B.
Memorial Hospital of Rhode Island, Pawtucket, RI
$162500

Knee osteoarthritis (OA) is the most common cause of disability in adults. The "Osteoarthritis Initiative (OAI): A Knee Health Study" is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and follow participants who have knee OA or are at high risk for developing knee OA for at least a four-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and X-rays will be completed at each of four annual follow-up visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee OA. Levels of knee pain and physical disability will be assessed at study start and at each of the follow-up visits by questionnaire and examination.

N01AR22259-12-0-1
Clinical Centers For The Osteoarthritis Initiative
Hochberg, Marc
University of Maryland, Baltimore
$162,500
Knee osteoarthritis (OA) is the most common cause of disability in adults. The "Osteoarthritis Initiative (OAI): A Knee Health Study" is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and follow participants who have knee OA or are at high risk for developing knee OA for at least a four-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and X-rays will be completed at each of four annual follow-up visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee OA. Levels of knee pain and physical disability will be assessed at study start and at each of the follow-up visits by questionnaire and examination.

N01AR22261-13-0-1
Clinical Centers For The Osteoarthritis Initiative
Jackson, Rebecca
Ohio State University
$162,500
Knee osteoarthritis (OA) is the most common cause of disability in adults. The "Osteoarthritis Initiative (OAI): A Knee Health Study" is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and follow participants who have knee OA or are at high risk for developing knee OA for at least a four-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and X-rays will be completed at each of four annual follow-up visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee OA. Levels of knee

pain and physical disability will be assessed at study start and at each of the follow-up visits by questionnaire and examination.

N01AR22260-13-0-1
Clinical Centers For The Osteoarthritis Initiative
Kwoh, Kent
University of Pittsburgh
$162500
Knee osteoarthritis (OA) is the most common cause of disability in adults. The "Osteoarthritis Initiative (OAI): A Knee Health Study" is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and follow participants who have knee OA or are at high risk for developing knee OA for at least a four-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and X-rays will be completed at each of four annual follow-up visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee OA. Levels of knee pain and physical disability will be assessed at study start and at each of the follow-up visits by questionnaire and examination.

NEUROLOGY/NEUROSCIENCES

1R21MH084041-01A1
Identification And Validation Of Human Hypothalamic Nuclei In-Vivo And Ex-Vivo Us
Makris, Nikolaos
Massachusetts General Hospital
$265125
There is increasing evidence regarding the importance of the hypothalamus for understanding women's health and sex differences in relation to neurological, psychiatric, endocrine and sleep disorders. In fact, hypothalamic nuclei, key regulators of autonomic and endocrine functions, are some of the most highly sexually dimorphic nuclei in the brain and implicated in psychiatric and medical disorders with known sex differences. They would argue that an understanding of hormonal effects on the brain and the regulation of other organs and/or systems, such as the cardiovascular and reproductive systems, are critical as downstream effects of hypothalamic activity. Thus an understanding of the neuroanatomy of hypothalamic nuclei and how they are differentially disrupted in men and women in specific disorders will

contribute to elucidating sex differences in clinical medicine. However, the identification of hypothalamic nuclei in-vivo in humans has not been realized. This is important since studies have shown the association of the hypothalamus, endocrine dysfunction and sex differences in psychiatric disorders. In fact, the paraventricular hypothalamic nucleus (PVN) is enlarged in patients with major depressive disorder (MDD), in PVN neurons that are dense in corticotropin releasing hormone (CRH) and estrogen receptor (ER)1. In their recent work in schizophrenia (SCZ) they identified structural abnormalities using MRI in the hypothalamus particularly in the PVN in women. Furthermore, in healthy women they showed, using functional MRI, regulation of brain activity in hypothalamic nuclei such as the PVN, dependent on gonadal hormone changes over the menstrual cycle. The principal focus of this study is to use a new in-vivo methodology for the assessment of the hypothalamus comparing neuroimaging data using 7 Tesla magnetic resonance imaging (MRI) and human postmortem validation. The proposed study aims to identify the PVN in-vivo and ex-vivo in the human hypothalamus using high field MRI, to investigate the relationship of the MRI methodology and the histological technique, and to establish the correlates of the histological structures with the MRI representations. In addition to the PVN, which is critical for its role within the hypothalamic-pituitary-adrenal (HPA) axis and its dysfunction in MDD and SCZ, they will identify the supraoptic nucleus (SON), which will be used as a control region. High-resolution 7 Tesla MRI will be carried out in thirty healthy subjects, and four ex-vivo human hypothalamic samples. Their overarching goal is an innovative methodological one: to identify the PVN of the human hypothalamus in healthy adult women and men in-vivo. They expect this method, once defined, to be applied clinically in subjects with MDD and SCZ.

1R21MH086731-01
Cellular And Molecular Basis Of Hippocampal Atrophy In Depressed Female Monkeys
Shively, Carol A.
Wake Forest University Health Sciences
$222000
Clinical and experimental studies suggest that hippocampal volumes may be smaller in individuals with depression, although the cellular mechanisms underlying this relationship are unclear. Stressful life events are associated with an increased risk of depression, and animal models, exposed to chronic stress have been used previously to investigate hippocampal shrinkage in depression. Although the data from preclinical stress models are compelling, the degree to which stress responses in animal models are relevant to human depression remains controversial, particularly since women are at two-fold greater risk of depression and the animal models are mostly male rodents. Evaluation of the causes of reduced hippocampal volume in an experimental model that more closely resembles human depression would be valuable. They have developed a primate model of depression in adult female cynomolgus monkeys which closely resembles human depression, and recently observed that depressed monkeys have relatively small anterior hippocampi. The overall goal of this proposal is to evaluate hippocampal morphologic, cellular, and molecular characteristics in depressed and nondepressed female monkeys to determine whether the smaller hippocampi of depressed female monkeys are accompanied by reductions in neuropil and synaptic, spinous, and dendritic integrity. They have a unique and valuable collection of fixed, frozen hippocampi derived from the population of adult female monkeys in which the behavioral and physiological characteristics of depression were studied premortem for 4 years. Using the

tissue from 8 depressed and 8 nondepressed monkeys they will determine astrocyte, pyramidal, and granule neuron size and number, and protein and mRNA levels of markers of synaptic, spinous, and dendritic integrity in the cornu ammonis (CA) CA1, CA2, CA3, and DG of the anterior and posterior HC of behaviorally depressed and nondepressed monkeys. The results of this study will establish the use of the model in future investigations of the mechanisms of depression and the efficacy of interventions for depression. The research is particularly responsive to the FOA entitled 'Advancing Novel Science in Women's Health Research' (PAS-07-381). The results of the proposed study will be used in support of a competitive NIH application.

1R21NS066307-01
Sex-Specific Gene Regulation Of Neuronal Chloride Co-Transporter, Kcc2
Liedtke, Wolfgang B
Duke University
$234000
Chronic pathological pain and certain epileptic syndromes are neuropsychiatric disorders that share an increased female prevalence and refractoriness to treatment. The latter feature is considered to be linked to pathologically increased neuronal excitability caused by increased neuronal chloride (Cl-), which in turn is rooted in down-regulation of the dominant neuronal Cl--transporter, KCC2, which extrudes Cl-. Here they propose experiments to elucidate sex-specific regulation of the kcc2 gene by estrogens, based on a hypothesis that neuronal Cl- is dysregulated in response to neuronal injury in a sexually dimorphic manner, with the consequence of rendering women more susceptible to the above diseases. They have obtained exciting preliminary results (1) showing that kcc2 transcription is regulated by the repressor REST/NRSF which binds to a novel RE1/NRSE DNA binding site in kcc2 regulatory regions, (2) demonstrating this regulation to underlie the early developmental transformation of GABAergic transmission from excitatory to inhibitory, (3) developing a novel method to culture cortical primary neurons from individual rat E17 embryos which are being sex-typed by X-and Y-chromosome specific DNA markers. The latter method, straightforward yet possibly a groundbreaking novelty, permits strictly separate female vs. male primary cortical neuronal culture. They intend to elaborate molecular mechanisms how neuronal Cl- and KCC2 are regulated sex-specifically by exposing male vs. female neurons to 17-¿-estradiol and xenobiotic estrogen-mimetics. For this, they will electroporate kcc2 reporter gene constructs, wildtype and mutated for binding sites, driving a secreted luciferase reporter, which will facilitate establishment of a time-course of kcc2 transcription. For direct determination of Cl-, the fluorescent Cl--indicator clomeleon will be co-transfected. Cultures will be exposed to physiologically relevant concentrations of estradiol and practically relevant concentrations of xeno-estrogens (coumestrol, bisphenol-A, dieldrin). Use of the latter compounds will allow us to address modulation of estrogen responses by these ubiquitous compounds. Any sex-specific regulation will be confirmed in primary cultures derived from gene-targeted mice (estrogen-receptor (ER)-a, -¿ and non-classical-ER-knockin). These experiments will be conducted in a highly collaborative environment at Duke University, involving molecular and physiology neuroscience labs, in addition molecular endocrinology and environmental toxicology input. Results can be expected to shed new light on a fundamental matter, neuronal Cl--regulation, which very likely has sex-specific regulation as a basis for increased female prevalence in therapy-refractory neuropsychiatric diseases.

1R21MH084041-01A1
Identification and Validation of Human Hypothalamic Nuclei In-Vivo and Ex-Vivo Us
Makris, Nikolaos
Massachusetts General Hospital
$265,125
There is increasing evidence regarding the importance of the hypothalamus for understanding women's health and sex differences in relation to neurological, psychiatric, endocrine and sleep disorders. In fact, hypothalamic nuclei, key regulators of autonomic and endocrine functions, are some of the most highly sexually dimorphic nuclei in the brain and implicated in psychiatric and medical disorders with known sex differences. The investigators argue that an understanding of hormonal effects on the brain and the regulation of other organs and/or systems, such as the cardiovascular and reproductive systems, are critical as downstream effects of hypothalamic activity. Thus an understanding of the neuroanatomy of hypothalamic nuclei and how they are differentially disrupted in men and women in specific disorders will contribute to elucidating sex differences in clinical medicine. However, the identification of hypothalamic nuclei in-vivo in humans has not been realized. This is important since studies have shown the association of the hypothalamus, endocrine dysfunction and sex differences in psychiatric disorders. In fact, the paraventricular hypothalamic nucleus (PVN) is enlarged in patients with major depressive disorder (MDD), in PVN neurons that are dense in corticotropin releasing hormone (CRH) and estrogen receptor (ER)1. In their recent work in schizophrenia (SCZ) they identified structural abnormalities using MRI in the hypothalamus particularly in the PVN in women. Furthermore, in healthy women they showed, using functional MRI, regulation of brain activity in hypothalamic nuclei such as the PVN, dependent on gonadal hormone changes over the menstrual cycle. The principal focus of this study is to use a new in-vivo methodology for the assessment of the hypothalamus comparing neuroimaging data using 7 Tesla magnetic resonance imaging (MRI) and human postmortem validation. The investigators' overarching goal is an innovative methodological one: to identify the PVN of the human hypothalamus in healthy adult women and men in-vivo. They expect this method, once defined, to be applied clinically in subjects with MDD and SCZ. Significance of The Application: Hypothalamic nuclei will be identified in living humans using high field magnetic resonance imaging (MRI) (i.e., a 7 Tesla scanner) and in ex-vivo human hypothalamic tissue. The MRI results will be compared with postmortem human tissue to assure methodological validation. These hypothalamic nuclei are key regulators of autonomic and endocrine functions implicated in numerous psychiatric and medical disorders with known sex differences such as depression and schizophrenia. Understanding sex differences and the hypothalamic involvement in relation to neurological, psychiatric, cardiovascular, endocrine and sleep disorders is very relevant for public health in general and women's health in particular.

1R21NS066307-01
Sex-Specific Gene Regulation of Neuronal Chloride Co-Transporter, KCC2
Liedtke, Wolfgang B.
Duke University
$234,000
Chronic pathological pain and certain epileptic syndromes are neuropsychiatric disorders that share an increased female prevalence and refractoriness to treatment. The latter feature is

considered to be linked to pathologically increased neuronal excitability caused by increased neuronal chloride (Cl-), which in turn is rooted in down-regulation of the dominant neuronal Cl--transporter, KCC2, which extrudes Cl-. The investigators propose experiments to elucidate sex-specific regulation of the kcc2 gene by estrogens, based on a hypothesis that neuronal Cl- is dysregulated in response to neuronal injury in a sexually dimorphic manner, with the consequence of rendering women more susceptible to the above diseases. They have obtained exciting preliminary results (1) showing that kcc2 transcription is regulated by the repressor REST/NRSF which binds to a novel RE1/NRSE DNA binding site in kcc2 regulatory regions, (2) demonstrating this regulation to underlie the early developmental transformation of GABAergic transmission from excitatory to inhibitory, (3) developing a novel method to culture cortical primary neurons from individual rat E17 embryos which are being sex-typed by X-and Y-chromosome specific DNA markers. The latter method, straightforward yet possibly a groundbreaking novelty, permits strictly separate female vs. male primary cortical neuronal culture. They intend to elaborate molecular mechanisms how neuronal Cl- and KCC2 are regulated sex-specifically by exposing male vs. female neurons to 17-¿-estradiol and xenobiotic estrogen-mimetics. Any sex-specific regulation will be confirmed in primary cultures derived from gene-targeted mice (estrogen-receptor (ER)-a, -and non-classical-ER-knockin). These experiments will be conducted in a highly collaborative environment at Duke University, involving molecular and physiology neuroscience labs, in addition molecular endocrinology and environmental toxicology input. Results can be expected to shed new light on a fundamental matter, neuronal Cl--regulation, which very likely has sex-specific regulation as a basis for increased female prevalence in therapy-refractory neuropsychiatric diseases. Significance of The Application: Neuronal chloride dictates nerve cells' excitability, and is reduced in chronic pathological pain as well as in certain forms of epilepsy, diseases characterized by therapeutic refractoriness and strong female preponderance. Experiments are described that will elucidate the regulation of the dominant electroneutral chloride transporter of mature neurons, KCC2. Estrogen and xenobiotic estrogen-mimetics will be used for stimulation of primary cortical neurons in culture, which will be maintained strictly separate for male vs. female, based on a novel methodology platform described here. Neurons derived from late-pregnancy embryos of rats and mice, the latter genetically encoded to lack functional estrogen-receptors, will be subjected to assays probing function and regulation of the kcc2 gene, namely reporter gene assays and measurement of neuronal chloride.

5R37HL069064-08
Respiratory Plasticity Following Spinal Cord Innjury
Mitchell, Gordon
University of Wisconsin
Madison, WI
$20000
The fundamental hypothesis guiding this proposal is that chronic treatments, known to enhance serotonergic modulation of respiratory motor output, strengthen respiratory synaptic pathways to spinal (phrenic) motoneurons, thereby improving respiratory function during recovery from spinal cord injury. In specific, they will investigate the effects of Chronic Intermittent Hypoxia (CIH) and spinal deafferentation via Cervical Dorsal Rhizotomy (CDR) on synaptic pathways to phrenic motoneuronsprior to acute spinal hemisection orfollowing

chronic spinal hemisection. Their laboratory has previously shown that both CIH and CDR enhance serotonergic modulation of phrenic motor output, but appear to do so by different mechanisms. They have also shown that spinal serotonin receptor activation enhances both functional and ineffective (crossed-spinal) synaptic pathways in rats. Thus, they will apply these unique models of serotonin-dependent respiratory plasticity to test the hypothesis that they will restore respiratory drive to phrenic motoneurons on the injured (hemisected) side, and enhance respiratory drive to phrenic motoneurons on the uninjured (non-hemisected) side. In Aims 1 and 2, they will test the hypotheses that pretreatment with either CIH or CDR enhances evoked and spontaneous phrenic activity in intact and crossed-spinal pathways in anesthetized rats. In the:next three aims, they will apply CIH following chronic spinal hemisection to test the hypotheses that CIH enhances evoked and spontaneous phrenic activity in anesthetized rats (Aim 3), restores ventilatory responses to chemoreceptor stimulation in unanesthetized rats (Aim 4), and increases ventral spinal concentrations of brain derived neurotrophic factor below the hemisection (Aim 5). This study provides an unprecedented opportunity to determine whether two unique experimental treatments restore respiratory motor function below a well-defined cervical spinal injury, and provides the basis for highly novel therapeutic approaches in the treatment of respiratory insufficiency following spinal cord injury.

NUTRITION

Y1CN5010-52-0-1
National Food and Nutrient Analysis Program (NFNAP)
NCI - USDA
$25,000
The NFNAP is a research program that seeks to achieve sound estimates of dietary components and thus, improvements in nutrient values with particular focus on components with possible roles in human health. The project, directed by the Nutrient Data Laboratory (NDL), Agricultural Research Service, USDA, was initiated in 1997 and recently renewed in collaboration with the NIH National Cancer Institute and the Office of Dietary Supplements, ORWH, and other supporting NIH Offices, Institutes, and the FDA. The primary outcome of the program will be a body of nutrient data representative of the U.S. population intake and consumption patterns with unprecedented analytical quality.

This is a collaborative, interdisciplinary project with the NFNAP. Specifically, the two leading causes of death in women in the U.S. are: (1) cardiovascular disease; and, (2) cancer. The NFNAP may prove particularly relevant to these women's health issues because the food consumption and composition databases target those foods that are major contributors of public health significance in the U.S.

Specifically, the five objectives of the NFNAP are to: (1) Sample and analyze selected Key Foods; (2) Institute a monitoring program for Key Foods; (3) Develop databases for foods consumed by U.S. ethnic subpopulations; (4) Develop and update databases for bioactive food components; and (5) Develop and validate databases for dietary supplement composition.

Moreover, the NFNAP may be significant to research on women's health on several different levels. Better estimates of the mean nutrient content of foods and variance indicators will permit more accurate assessment of nutrient intakes by individuals. This will improve the ability to detect etiologic relationships, delineate biologic mechanisms, assess time trends in nutrient intake, and define populations at nutritional risk. Further, the NFNAP may provide background data supporting nutritional guidance and communications focused specifically on women.

OBESITY/OVERWEIGHT

1R21HL097252-01
Intervening On Spontaneous Physical Activity To Prevent Weight Regain In Women
Nicklas, Barbara J
Wake Forest University Health Sciences
$205,728
Recommendations for more effective long-term weight loss strategies may need to consider the role of gender differences. If, as shown in female vs. male animal models, negative energy balance resulting in weight loss results in greater compensatory reductions in energy expenditure in women compared to men, obesity treatments may need to be tailored in women to override these reductions in total energy expenditure. Their approach focuses on a behavioral strategy (self-monitoring) to eliminate the compensatory reduction in non-exercise 'spontaneous' physical activity (SPA) seen in women who lose weight by means of a hypocaloric diet and structured exercise training. Their long-term research goal is to establish empirical evidence for innovative treatment options that are more effective in producing weight loss and preventing weight regain in women. The main goal of this pilot is to provide preliminary data and effect estimates to begin to test their overall hypothesis that prevention of weight loss-induced reductions in SPA will be more beneficial for long-term maintenance of weight loss in women than in men. They propose to conduct a pilot study using a 2-arm, 10-month design in 72 obese, older (55-70 yrs) men and women (n=36 per group). Participants will be randomized to a 5-month standardized weight loss intervention involving a hypocaloric diet and aerobic exercise (DIET+EX) or to the same weight loss intervention with addition of a behavioral component that targets self-monitoring (SM) of SPA (SM+DIET+EX), and then followed for another 5 months after weight loss. The specific aims of this R21 exploratory/developmental application are: Primary-To examine whether SPA self- monitoring results in less body weight regain in the follow-up phase in both men and women; Secondary-To examine whether: 1) women regain more weight than men in the follow-up phase; 2) SPA self-monitoring and gender have an effect on change in weight in the intensive weight loss phase; 3) SPA self-monitoring and gender have an effect on change in SPA in the intensive weight loss phase; 4) there is an association between SPA changes in the weight loss phase and weight regain in the follow-up phase. They anticipate that the results will lead to a larger and longer trial to definitively test their hypothesis, which could potentially provide evidence against the current standard of care (i.e., exclusive prescription of structured moderate-intensity exercise) for obesity therapy in women and may lead to sex-specific treatment guidelines.

5R21 HL093532-02
DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women
Powell, Theresa L; Krummel, Debra Ann
University of Cincinnati, Cincinnati, OH
$234,000
Obesity prevalence is increasing worldwide and with the difficulty to treat this condition, the need for early intervention is urgent. Obesity in pregnancy is rapidly becoming a major obstetric complication since it increases the risk of gestational diabetes and pre-eclampsia, and predisposes the mother for later metabolic and cardiovascular disease. A common problem for the baby is fetal overgrowth, which is associated with traumatic birth injuries and the development of the metabolic syndrome in childhood or later in life. The obese, pregnant woman has increased serum levels of pro-inflammatory cytokines and low circulating levels of adiponectin leading to decreased insulin sensitivity, which has been suggested to link obesity in pregnancy to metabolic and cardiovascular disease later in life. Fetal growth is determined by placental nutrient supply and their preliminary data show that placental nutrient transport is increased in obesity. Up-regulation of placental nutrient transporters in obesity may be caused by the abnormal maternal metabolic profile, since high insulin and pro-inflammatory cytokines and low adiponectin have been shown to stimulate placental nutrient transport. Approximately one third of all women enter pregnancy being obese and despite the serious adverse consequences for the health of the woman and her child, no specific treatment is currently available. The aim of the study is to supplement the diet of obese pregnant women with docosahexaenoic acid (DHA), a safe, low cost, readily available dietary component that they have shown is extremely low in the diet of their mid-western urban population (10% of recommended levels for pregnancy). This omega-3 fatty acid has been shown to have a significant impact on improving insulin sensitivity and circulating levels of pro-inflammatory cytokines and adiponectin in non-pregnant obese women. DHA has been studied extensively as a dietary supplement in pregnancy as a potential mechanism to improve cognitive function in children. However the effect of DHA maternal metabolic status and placental function has not been previously reported. The study hypothesizes that DHA supplementation will improve maternal insulin sensitivity, reduce pro-inflammatory cytokines, increase circulating adiponectin, down-regulate placental nutrient transport and reduce fetal growth. The approach for this pilot study will be to recruit 90 obese (BMI 30-45), pregnant women in mid gestation and randomize these subjects into placebo or DHA treatment (800 mg/day) groups. Subjects will be studied again in late gestation after 12 weeks of supplementation. Aim 1 will determine the effect of DHA supplementation on maternal inflammatory status and insulin sensitivity. Aim 2 will establish the impact of DHA supplementation in obese pregnant women on placental nutrient transport and fetal growth.

3R21 HL093532-02S1
DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women
Krummel, Debra Ann
University of Texas, San Antonio
$169,872
This project augments the parent grant in order to recruit more Hispanic and African-American participants. Obesity prevalence is increasing worldwide and with the difficulty to treat this condition, the need for early intervention is urgent. Obesity in pregnancy is rapidly

becoming a major obstetric complication since it increases the risk of gestational diabetes and pre-eclampsia, and predisposes the mother for later metabolic and cardiovascular disease. A common problem for the baby is fetal overgrowth, which is associated with traumatic birth injuries and the development of the metabolic syndrome in childhood or later in life. The obese, pregnant woman has increased serum levels of pro-inflammatory cytokines and low circulating levels of adiponectin leading to decreased insulin sensitivity, which has been suggested to link obesity in pregnancy to metabolic and cardiovascular disease later in life. Fetal growth is determined by placental nutrient supply and their preliminary data show that placental nutrient transport is increased in obesity. Up-regulation of placental nutrient transporters in obesity may be caused by the abnormal maternal metabolic profile, since high insulin and pro-inflammatory cytokines and low adiponectin have been shown to stimulate placental nutrient transport. Approximately one third of all women enter pregnancy being obese and despite the serious adverse consequences for the health of the woman and her child, no specific treatment is currently available. The aim of the study is to supplement the diet of obese pregnant women with docosahexaenoic acid (DHA), a safe, low cost, readily available dietary component that they have shown is extremely low in the diet of their mid-western urban population (10% of recommended levels for pregnancy). This omega-3 fatty acid has been shown to have a significant impact on improving insulin sensitivity and circulating levels of pro-inflammatory cytokines and adiponectin in non-pregnant obese women. DHA has been studied extensively as a dietary supplement in pregnancy as a potential mechanism to improve cognitive function in children. However the effect of DHA maternal metabolic status and placental function has not been previously reported. The study hypothesizes that DHA supplementation will improve maternal insulin sensitivity, reduce pro-inflammatory cytokines, increase circulating adiponectin, down-regulate placental nutrient transport and reduce fetal growth. The approach for this pilot study will be to recruit 90 obese (BMI 30-45), pregnant women in mid gestation and randomize these subjects into placebo or DHA treatment (800 mg/day) groups. Subjects will be studied again in late gestation after 12 weeks of supplementation. Aim 1 will determine the effect of DHA supplementation on maternal inflammatory status and insulin sensitivity. Aim 2 will establish the impact of DHA supplementation in obese pregnant women on placental nutrient transport and fetal growth.

PAIN

1R21DE019267-01A1
Sex Differences In Acute Pain And Analgesic Responses: Psychosocial And Genetic I
Hastie, Barbara A
University Of Florida
$218,495
Sex Differences in Acute Pain and Analgesic Responses: Psychosocial and Genetic Influences
ABSTRACT: Pain is one of the most costly and pervasive public health problems, with women and minorities facing increased risk for under-treated and mismanaged pain. Women, compared to men, report more frequent and intense pain and have increased prevalence of debilitating pain across a multitude of conditions. Women also represent the majority of the 40 million outpatient and ambulatory surgeries conducted each year. Acute post- operative pain and under-treatment of pain are well-documented and lead to prolonged recovery and

potentially to development of chronic long-term pain conditions. Despite incongruent findings of sex differences in analgesic efficacy, consistent reports show that women experience between 30%-75% more adverse drug reactions (ADRs) compared to men. ADRs can lead to life-threatening complications, discontinuation of pain treatment, prolonged recovery and non-compliance. Recent pharmacogenomic studies have demonstrated that genotype may contribute to sex differences in pharmacokinetic (PK) and pharmacodynamic (PD) responses to certain drugs. Genetic and nongenetic contributions to sex differences in opioid analgesia, related side effects and treatment outcome have received limited attention in the field of pain research. This study will use a common acute clinical pain model to identify and characterize psychosocial, physiological and genetic factors that contribute to sex differences in pain perception, analgesia and side effects. Aim 1 will determine sex differences in perceptual and physiological responses to acute post-operative pain and will examine how those are related to genetic, pre-operative psychophysical and psychosocial factors. Aim 2 will determine sex differences in opioid analgesia and side effects and will examine genetic, PK, PD, and psychosocial factors that explain group differences in analgesic responses. 140 male and female patients (age range 16-45) who undergo third molar extraction will be included in this study. Preoperatively, they will assess experimental pain responses and psychosocial measures. They will monitor post-operative pain levels along with PK/PD responses to the opioid fentanyl. They will examine sex differences in post-operative pain, analgesic responses and side effects immediately and for several hours post-surgery and for 3 days post-procedure. The study is designed to build a foundation for a R01 grant proposal supporting an independent line of clinically-relevant experimental pain research. This project will enhance understanding of translational research in pain as well as biopsychosocial factors that contribute to health disparities in pain and its treatment, particularly for women. Additionally, this study will provide insight into the complex genetic, PK/PD processes involved in post-operative pain and analgesic responses and will elucidate biopsychosocial contributions to sex differences in pain and side effects. The ultimate goal is to develop translational research that will reduce the increased burden of clinical pain in women through the development of tailored interventions designed to enhance the quality of life for women, consistent with priorities of the NIH Office of Research on Women's Health.

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compliance. Recent pharmacogenomic studies have demonstrated that genotype may contribute to sex differences in pharmacokinetic (PK) and pharmacodynamic (PD) responses to certain drugs. Genetic and nongenetic contributions to sex differences in opioid analgesia, related side effects and treatment outcome have received limited attention in the field of pain research. This study will use a common acute clinical pain model to identify and characterize psychosocial, physiological and genetic factors that contribute to sex differences in pain perception, analgesia and side effects. The study is designed to build a foundation for a grant proposal supporting an independent line of clinically-relevant experimental pain research. This project will enhance understanding of translational research in pain as well as biopsychosocial factors that contribute to health disparities in pain and its treatment, particularly for women. Additionally, this study will provide insight into the complex genetic, PK/PD processes involved in post- operative pain and analgesic responses and will elucidate biopsychosocial contributions to sex differences in pain and side effects. The signifiance of the application is that the study to develop translational research that will reduce the increased burden of clinical pain in women through the development of tailored interventions designed to enhance the quality of life for women.

5R21 AR055716-02
Using fMRI to evaluate CBT treatment response for patients with chronic pain
Naylor, Magdalena R.
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$112,875
This proposed study will test the hypothesis that cognitive-behavioral therapy (CBT) can modify the dysfunctional neural circuitry associated with chronic pain. Because chronic pain is considered a complex sensory and emotional experience they expect that an intervention such as CBT could alter patients' responses to both painful and emotionally provocative stimuli and thus the underlying neural circuitry tested by fMRI. They believe that their paradigm represents a valuable strategy for advancing their understanding of the neurobiology of emotional control related to pain and the effects of CBT in the group setting. The primary goal of this revised R21 application is to investigate whether a psychotherapeutic approach, group Cognitive Behavioral Therapy (CBT), modifies the dysfunctional emotional and sensory neural circuitry associated with chronic pain as examined by functional magnetic resonance imaging (fMRI). They propose to apply previously tested and accepted paradigms for symptom provocation (acute pain and negative emotional stimuli) to investigate CBT effects on neural correlates of chronic pain. Because chronic pain is not just an isolated sensory event but rather a complex sensory and emotional experience, it is reasonable to expect that an intervention which improves chronic pain such as CBT will alter responses to both painful and emotionally provocative stimuli and thus the underlying neural circuitry. The efficacy of a group CBT treatment modality for chronic pain patients has been well established. In addition, their fMRI pilot study results revealed that the exaggerated amygdala response to negative emotional stimuli in chronic pain patients was normalized after 12 weeks of group CBT, suggesting that CBT may affect at least the emotional component of the pain process. Forty subjects who meet inclusion and exclusion criteria for the fMRI study will be randomly assigned to two study conditions: 12-week group CBT Treatment Condition and Attention Control Condition. Each participant will undergo two fMRI examinations (before and after group interventions) to explore two study goals: 1) whether CBT treatment changes

the function of brain neural circuity in response to application of acute noxious stimuli and emotional (fearful) stimuli; 2) whether there is a relationship between altered activation in brain areas associated with the attentional, affective, and sensory aspects of chronic pain and quantifiable improvement in clinical measures reported at the conclusion of group CBT. Their approach is novel as there are no published studies that explore the neurobiological effects of psychotherapeutic approaches in chronic pain. By combining a noxious pain stimulation paradigm, an emotional stimulation paradigm, and brain imaging, and putting this approach into a clinical framework, they will open important, new avenues of research on chronic pain. Their approach may represent a valuable strategy for advancing their understanding of the neurobiology of emotional control related to pain and the effects of cognitive-behavioral therapy in the group setting. Measuring directly the effects of CBT on brain function could ultimately improve clinical decision making and contribute to development of the individualized treatment of patients with chronic pain.

1R21HD053510-01A2
Pain and Endometriosis: Effects on Ectopic Cyst Innervation and Axons
Bove, Geoffrey M.
$219,832
Women with endometriosis often have significant pain. Modern studies have implicated the neo-innervation of endometrial cysts as a primary source of this pain. However, the presence of nerve fibers does not necessarily specify their function and cannot determine whether, or in which situations, they are active. There has been no investigation to functionally characterize the effect of endometrial lesions on nerves or on axons. The applicant's laboratory has focused on the effects of inflammation on axons. They have shown that nerve inflammation induces ectopic mechanical sensitivity of nociceptor axons, which are not normally sensitive. Their data also indicate that nerve inflammation induces ongoing activity that arises from both the inflamed site and / or the cell body, and that sympathetic neuronal activity is decreased during nerve inflammation. Recently they adapted the model of rat endometriosis to involve the sciatic nerve. This model is very similar to the rat endometriosis model where a section of uterus is transplanted to a intraperitoneal site. Using immunohistological methods, they will determine the extent of neutrophil and macrophage invasion of the nerve-uterus complex. They will also determine if axons are damaged using ninjurin and fluoro-jade, assessing the presence in both axons and dorsal root ganglion cells. These studies will determine the function and thus the importance of the ectopic innervation of endometrial cysts, as well as the effects of the lesions on through-conducting axons. The results of this study will impacts the understanding of endometriosis pain and seed further research into the pain mechanisms of endometriosis. The significance of this proposal is that it proposes to make novel inquiries regarding the etiology of endometriosis-related pain. The information that this study will yield stands to improve diagnostic awareness and mechanistic understanding, and thus therapeutic approaches, of the treatment of the symptoms of endometriosis. As a result of this research, consideration and specific examination of nerves within the pelvis during ablative laparoscopic techniques may become an important additional diagnostic procedure for women with endometriosis.

3R01DA023513-02S1
N6F-Dependent Sensitization of Nocioceptors by Opiate

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$20,000
Opiate-induced hyperalgesia has been reported in humans and in animals. Continuous opiate administration for several days produces pronociceptive neuroplastic adaptations in both the peripheral and central nervous systems which likely underlie the observed hypersensitivity. Despite the potential clinical significance of such changes, specific mechanisms of opiate-induced hypersensitivity are unknown. Injury to tissues can result in ¿sensitization¿ of nociceptors, resulting in enhanced response to noxious and normally non-noxious stimuli (i.e., hyperalgesia and allodynia, respectively). They hypothesize that opiate-induced hyperalgesia and allodynia may result from sensitization of nociceptors. Importantly, they hypothesize that sensitization of nociceptors by opiates can occur in the absence of tissue injury. Two specific questions are addressed by the experiments proposed in this application: 1) can opiates induce nociceptor sensitization without tissue injury? 2) is opiate-induced nociceptor sensitization the result, in part, of an NGF-dependent process? Behavioral, neurochemical, immunohistochemical and electrophysiological studies will test the hypothesis that opiates (a) act at opiate receptors to produce hypersensitivity and an increase in expression of NGF in peripheral tissues; (b) increase NGF-dependent phosphorylation of p38 MAPK (pp38 MAPK) in TrkA-positive cells, (c) increase NGF-dependent and pp38 MAPK-dependent trafficking of the TRPV1 channel to the periphery, (d) upregulate CGRP and substance P (SP) expression in TrkA-positive cells in an NGF-dependent, and pp38 MAPK-dependent fashion, and (e) produce NGF-, pp38 MAPK- and TRPV1-dependent hypersensitivity. The consequences of opiate-induced neuroplasticity raise questions of whether unintended harm to patients might actually occur. Given the prevalent reliance on opiates for treatment of severe pain, understanding of the fundamental biological mechanisms associated with prolonged exposure to these drugs is essential. Additionally, mechanisms underlying possible nociceptor sensitization occurring in the absence of tissue injury may ultimately lead to insights into clinical conditions of prominent pain without apparent tissue injury including, for example fibromyalgia, IBS, CRPS-1 and perhaps migraine. The consequences of opiate-induced neuroplasticity raise questions of whether unintended harm to patients might actually occur. Given the prevalent reliance on opiates for treatment of severe pain, understanding of the fundamental biological mechanisms associated with prolonged exposure to these drugs is essential. Additionally, mechanisms underlying possible nociceptor sensitization occurring in the absence of tissue injury may ultimately lead to insights into clinical conditions of prominent pain without apparent tissue injury including, for example fibromyalgia, IBS, CRPS-1 and perhaps migraine.

REPRODUCTIVE HEALTH/DEVELOPMENTAL BIOLOGY

(Please see Menopause section above for additional projects)

1R21HL093450-01A1
Compromised Microcirculation In Women With Polycystic Ovary Syndrome
Stachenfeld, Nina
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$256,203

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinopathy in young women, affecting 6-10 % of women of reproductive age. Obesity, insulin resistance, hyperandrogenism and hyperestrogenism are core functional disorders of PCOS and place women at increased risk for microvascular dysfunction. Women with PCOS have greater circulating concentrations of endothelin-1 (ET-1), a potent vasoconstrictor in the microcirculation (including that of the skin), which can increase blood pressure and lead to endothelial damage. The central hypothesis of this proposal is that testosterone effects on ET-1 mediate the peripheral microvascular dysfunction associated with PCOS. This hypothesis will be tested using a prolonged skin heating model to study peripheral microvascular responsiveness. Local skin heating has been used extensively to study mechanisms controlling peripheral microcirculation under a number of physiological conditions, including obesity, insulin resistance and hypertension. The impact of testosterone or ET-1 on microvascular responsiveness to local heating has not been studied in women with or without PCOS. This proposal seeks to provide this missing information via pursuit of two Specific Aims. Specific Aim 1 will apply dose-response curves to examine the mechanism by which ET-1 influences peripheral vasodilation. Specific Aim 2 will determine the mechanism by which testosterone affects peripheral microcirculatory responsiveness in women with and without PCOS. These studies will have broad public health implications because their findings on the effect of hyperandrogenism on endothelial function may provide insights applicable to cardiovascular health in women and men.

1R21AI083954-01
Advancing Research On The Sexually Transmitted Female 'Nuisance' Pathogen Trichom
Carlton, Jane
New York University School Of Medicine
$253,688
Trichomoniasis is the most common non-viral STD, estimated to cause ~174 million infections world-wide each year. The Trichomonas vaginalis parasite resides in the urogenital tract of both sexes and can cause vaginitis in women and urethritis and prostatitis in men. However, the disease is known more as a female 'nuisance' condition, which has resulted in a lack of scientific and medical attention and scant interest by public health officials in developing trichomoniasis control programs. Acute infections among women are associated with pelvic inflammatory disease and adverse pregnancy outcomes. Most alarming is the recognition that T. vaginalis infection appears to increase women's susceptibility to HIV-1 infection. Because of the association between T. vaginalis and risk for HIV-1 acquisition, interventions to reduce T. vaginalis infection and transmission would likely result in fewer HIV-1 infections. Completion of the T. vaginalis genome sequence in 2007 has significantly increased their knowledge concerning the biology and mechanisms of pathogenesis of the parasite, but significant gaps remain. In particular, the genetic diversity of the parasite is not known, i.e. whether the parasite is maintained as a clonal population, or whether genetic exchange occurs between parasites in the urogenital tract. The extent of genetic diversity has implications for the control of the disease, for example it determines how virulent parasites spread or how they may evade a vaccine. The focus of this R21 proposal is to examine the genetic diversity of T. vaginalis infecting women attending eight New York City Bureau of STD clinics in inner city areas, and to use some of these isolates to develop a standardized and accessible in vitro model system for the study of colonization of the vagina by the

parasite. A panel of polymorphic genetic markers - microsatellites and single copy genes - will be developed using the T. vaginalis genome sequence, and used to genotype T. vaginalis isolates identified in vaginal swabs taken from women attending the clinics. Knowledge of the genetic diversity and colonization characteristics of the parasite will provide important data points for subsequent studies, for example determining associations between T. vaginalis genotypes and the commensal microbes that make up the vaginal 'microbiome'.

1R21AI079439-01
HPV Epidemiology And Response To Screening (Hearts)
Riley, Elise D
University Of California San Francisco
$188,034
HPV vaccine development and clinical research have focused on women from the general population and little is known about HPV among indigent women, many of whom experience repeated risk for sexually transmitted infections that continues through the span of their lives. The impact of repeated exposure to HPV, as well as the impact of co-infections like HIV, HCV, gonorrhea, and Chlamydia, on the natural history of HPV infection and HPV-associated disease, is unclear in this population. Moreover, the prevalence of HPV subtypes in this population is unknown, which precludes estimates of potential vaccine effectiveness. A better understanding of HPV among indigent US women could have implications for improvement in health care delivery, particularly regarding HPV vaccine uptake and effectiveness. They propose an exploratory study to assess the prevalence and variability of cervical HPV and cervical HPV disease (cervical intraepithelial neoplasia); associations with co-infections (i.e., HIV, HCV, gonorrhea and Chlamydia) and drug use (e.g., tobacco and crack cocaine); and the feasibility of a larger randomized study among homeless and marginally housed women. Individuals will be recruited from homeless shelters, free food programs and low-income single room occupancy hotels. In this way, study participants will not be limited to individuals who visit specific institutions, thus facilitating reliable estimates from a community-based sample.

1R21HD061644-01
Physiological Reactivity To Acute Stress During Pregnancy
Christian, Lisa Michelle
Ohio State University
$181,209
Preterm delivery, an increasingly frequent occurrence in the United States, is associated with significant family burden and an estimated societal cost of at least $26 billion per year. In the U.S., the preterm birth rate is 12-13% as compared to 5-9% in other developed countries. Persistent racial disparities contribute to this discrepancy. Psychosocial stress and related physiological sequelae may contribute to preterm birth overall, as well as to racial disparities in preterm birth. The experience of chronic stress, such as that conferred by racial minority status, may sensitize physiological stress responses. Indeed, as compared to Caucasians, African-Americans exhibit greater cardiovascular reactivity to a variety of acute stressors. Importantly, blood pressure, glucocorticoid, and catecholamine responses to acute stress are attenuated during healthy pregnancy as compared to nonpregnancy. This adaptation may protect the mother and fetus from potentially detrimental effects of maternal physiological

activation. Thus, women who exhibit greater and more extended physiological reactions to everyday stressors may be at increased risk for negative perinatal outcomes. Notably, no studies of acute stress during pregnancy have examined inflammatory immune responses or mechanisms underlying blood pressure change (i.e., cardiac output, total peripheral resistance). Moreover, limited information is available regarding effects of race on physiological adaptation to pregnancy. The current study will address important gaps in the literature by examining cardiovascular, endocrine, and immune reactivity to acute stress among 40 healthy pregnant women (20 Caucasian, 20 African-American) and 40 demographically matched nonpregnant control women. This research is designed to ultimately lead to the identification of women at greater risk for negative perinatal outcomes and elucidation of mechanisms underlying increased risk, providing a basis for individualized health care services. Specific Aim #1: To utilize more comprehensive and advanced methodology to assess physiological reactivity during pregnancy versus nonpregnancy, including measures of inflammation, impedance cardiography, and glucocorticoid receptor function. Hypothesis #1: Pregnant women will show attenuated physiological responses to acute stress as compared to nonpregnant women. Specific Aim #2: To examine racial differences in physiological reactivity during pregnancy versus nonpregnancy. Hypothesis #2: As compared to Caucasian women, African-American women will exhibit greater physiological reactivity to stress during pregnancy and nonpregnancy. Specific Aim #3: To examine psychosocial correlates of physiological reactivity during pregnancy and nonpregnancy. Hypothesis #3: Women reporting greater distress will exhibit greater physiological reactivity during pregnancy and nonpregnancy. Specific Aim #4: To examine associations between physiological reactivity and length of gestation. Hypothesis #4: Greater physiological reactivity to acute stress will predict shorter gestational length.

1R21HD059074-01A1
A Study Of The Factors Influencing Women's Decision About Childbirth
Regan, Mary J
University Of Maryland Baltimore
$238,251
Cesarean section (CS) is currently used at over twice the rate recommended by the World Health Organization (CDC, 2006); use of the procedure has almost doubled in the last two decades for reasons that are as yet poorly understood. Overutilization results in avoidable morbidity and mortality and higher health costs related to childbirth. Many causes for the increased use of CS have been suggested, including growth in the number of 'maternal requests' -- healthy women asking for CS in the absence of medical indications. An NIH expert panel explored maternal request CS and concluded that at this time there is insufficient evidence to warrant CS on maternal demand without medical indications and recommended 'increased research devoted to strategies to predict and influence the likelihood of successful vaginal birth' (NIH, 2006, p. 20). Using the same data, the American College of Obstetrics and Gynecologists (ACOG) concluded that there is no reason to deny a surgical birth to a healthy mother as long as she is well-informed (ACOG, 2003). The divergence between these positions points to a critical gap in knowledge about the factors that drive CS rates, including the influence of maternal demand on the use of CS. Despite this recent focus on maternal demand, there is scant research on what women want from their birthing experience, including their reasons for choosing one mode of childbirth over another. The purpose of their

proposed research is to answer the question: what factors influence women's decisions about how their babies will be born? Women's hopes and desires for their first birth experience are influenced by what they know - both consciously and unconsciously. Because people are only partly aware of the attitudes and beliefs that inform their hopes and desires, this proposal will use three methods of data collection. The first is a projective method commonly used in the social sciences to access knowledge that exists outside of consciousness. The second is a focus group method that provides a venue for birthing women to articulate the conscious basis for their ideas about childbirth and allow participants to compare their ideas with others. Third, all women will be interviewed after the baby is born to build understanding about how their experiences influence future birthing choices the women make. Participants will be 50 primigravid women with uncomplicated pregnancies aged 21 or older. This proposal builds on the researchers' previous work related to the use of CS. It is one step in a defined program of research directed towards improving the health of mothers and their children by optimizing care during pregnancy, labor and birth.

1R21ES016846-01A1
Modulation Of PAH Ovarian Toxicity By Biotransformation Enzyme Polymorphisms
Luderer, Ulrike
University Of California Irvine
$229,745
Infertility or impaired fecundity affects 12% of American women. Ovarian dysfunction, including premature ovarian failure is a major cause of infertility. It is likely that exposure to environmental toxicants is responsible for many more cases of impaired ovarian function than is currently appreciated. Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants, which are known to impair ovarian function and cause ovarian failure in rodents and are probable ovarian toxicants in women. Tobacco smoke, foods, and air pollution are among the sources of exposure to PAHs. The mechanistic basis for interindividual variation in susceptibility to PAH ovarian toxicity is not understood, but polymorphisms in enzymes that metabolize PAHs likely play an important role. The work outlined in this proposal will demonstrate the feasibility of a larger study to test the hypothesis that genetic variations in Phase 1 and Phase 2 biotransformation enzymes involved in metabolizing PAHs modulate the ovarian toxicity of PAHs in women. Specific Aim 1: To test the feasibility of prospectively measuring time to pregnancy and PAH exposure and of using genomewide genotyping methods to determine PAH biotransformation enzyme polymorphisms for a study analyzing the associations between PAH exposure and biotransformation enzyme polymorphisms and fecundability (time to pregnancy). Specific Aim 2: To test the feasibility of using microelectronic dipstick monitors to measure daily urinary reproductive hormone concentrations over multiple menstrual cycles for study of the associations between PAH metabolizing enzyme polymorphisms and PAH exposure and menstrual cycle abnormalities. Specific Aim 3: To pilot test serum anti-M|llerian hormone, follicle stimulating hormone, and inhibin B concentrations as markers of ovarian reserve for study of the associations between PAH exposure and diminished ovarian reserve.

1R03NS063233-01A1
Neuroactive Steroids And Seizure Control During Pregnancy In Women With Epilepsy
Pennell, Page Buckhannan

Brigham And Women's Hospital
$102,626
Epilepsy is a common disorder, affecting approximately 1.3 million women of child-bearing age in the United States. Seizures during pregnancy can cause increased risks to both the mother and fetus. These risks have to be balanced against the known teratogenic effects of antiepileptic drugs (AEDs). During pregnancy, the sex steroid hormones estradiol and progesterone increase dramatically. Sex steroid hormones and the metabolic byproducts that are capable of modifying neural activity are classified as neuroactive steroids (NAS). Animal models demonstrate modulation of seizure activity by the NAS 17¿-estradiol (EST), progesterone (PROG), and allopregnanolone (ALLO). In women, fluctuations in these NAS have been implicated in seizure control in the non-pregnant state, with worsening seizures at certain times of the menstrual cycle (catamenial epilepsy). Human studies have demonstrated an increase in seizure frequency with elevated EST/PROG ratios and with declining or low PROG levels. This has not been studied during pregnancy in women with epilepsy. This proposed study will utilize serum samples (n=810 samples) already collected from 135 women with epilepsy during different stages of pregnancy during a Specialized Center of Research in Women and Gender Issues program project grant. These women were enrolled prospectively with tracking of seizures and medications. Collection of plasma samples occurred at multiple points in each trimester. Based on variable points of enrollment (< 20 weeks gestation), they have increased observations/samples in the later trimesters of pregnancy. Seizure frequency will be analyzed during the second and third trimesters of pregnancy and compared to the nonpregnant baseline for each subject. Consistent with the R03 mechanism, the current application will extend the analysis of these existing data/samples via measurement of the neuroactive steroids EST, PROG, and ALLO. The working hypotheses are 1) during pregnancy, changing concentrations of EST and PROG influence seizure control; 2) the progesterone metabolite, ALLO, mediates the seizure-reducing effect of PROG. The following will be analyzed in relationship to change in seizure frequency during pregnancy: EST/PROG ratio, the rate of rise of PROG, and the rate of rise of ALLO. Additionally, given that labor and delivery is a particularly vulnerable time for increased seizures; ALLO and PROG levels will be compared between women who had peripartum seizures and those who did not. This study can ultimately lead to a better understanding of the NAS regulation of seizure control during pregnancy. Insights gained from this study could provide the impetus for further development of NAS analogs, with treatment benefits extending to both genders and across all ages. During pregnancy, treatment with supplemental progesterone could allow for decreased levels of fetal exposure to AEDs in utero, with improved seizure control and reduced anatomical and neurodevelopmental teratogenicity.

1R21AI083954-01
Advancing Research on the Sexually Transmitted Female 'Nuisance' Pathogen Trichomoniasis
Carlton, Jane
New York University School of Medicine
$253,688
Trichomoniasis is the most common non-viral STD, estimated to cause ~174 million infections world-wide each year. The Trichomonas vaginalis parasite resides in the urogenital

tract of both sexes and can cause vaginitis in women and urethritis and prostatitis in men. However, the disease is known more as a female 'nuisance' condition, which has resulted in a lack of scientific and medical attention and scant interest by public health officials in developing trichomoniasis control programs. Acute infections among women are associated with pelvic inflammatory disease and adverse pregnancy outcomes. Most alarming is the recognition that T. vaginalis infection appears to increase women's susceptibility to HIV-1 infection. Because of the association between T. vaginalis and risk for HIV-1 acquisition, interventions to reduce T. vaginalis infection and transmission would likely result in fewer HIV-1 infections. Completion of the T. vaginalis genome sequence in 2007 has significantly increased their knowledge concerning the biology and mechanisms of pathogenesis of the parasite, but significant gaps remain. In particular, the genetic diversity of the parasite is not known, i.e. whether the parasite is maintained as a clonal population, or whether genetic exchange occurs between parasites in the urogenital tract. The extent of genetic diversity has implications for the control of the disease, for example it determines how virulent parasites spread or how they may evade a vaccine. The focus of this proposal is to examine the genetic diversity of T. vaginalis infecting women attending eight New York City Bureau of STD clinics in inner city areas, and to use some of these isolates to develop a standardized and accessible in vitro model system for the study of colonization of the vagina by the parasite. A panel of polymorphic genetic markers - microsatellites and single copy genes - will be developed using the T. vaginalis genome sequence, and used to genotype T. vaginalis isolates identified in vaginal swabs taken from women attending the clinics. Knowledge of the genetic diversity and colonization characteristics of the parasite will provide important data points for subsequent studies, for example determining associations between T. vaginalis genotypes and the commensal microbes that make up the vaginal 'microbiome'. The significance of this project is that it proposes to determine the genetic diversity of the parasite in women attending STD clinics in New York City, and to use these extant isolates in the development of a model system for the study of colonization of the vagina.

1R21ES016846-01A1
Modulation of PAH Ovarian Toxicity by Biotransformation Enzyme Polymorphisms
Luderer, Ulrike
University of California Irvine
$229,745
Infertility or impaired fecundity affects 12% of American women. Ovarian dysfunction, including premature ovarian failure is a major cause of infertility. It is likely that exposure to environmental toxicants is responsible for many more cases of impaired ovarian function than is currently appreciated. Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants, which are known to impair ovarian function and cause ovarian failure in rodents and are probable ovarian toxicants in women. Tobacco smoke, foods, and air pollution are among the sources of exposure to PAHs. The mechanistic basis for interindividual variation in susceptibility to PAH ovarian toxicity is not understood, but polymorphisms in enzymes that metabolize PAHs likely play an important role. The work outlined in this proposal will demonstrate the feasibility of a larger study to test the hypothesis that genetic variations in Phase 1 and Phase 2 biotransformation enzymes involved in metabolizing PAHs modulate the ovarian toxicity of PAHs in women. Specific Aim 1: To test the feasibility of prospectively measuring time to pregnancy and PAH exposure and of using

genomewide genotyping methods to determine PAH biotransformation enzyme polymorphisms for a study analyzing the associations between PAH exposure and biotransformation enzyme polymorphisms and fecundability (time to pregnancy). Specific Aim 2: To test the feasibility of using microelectronic dipstick monitors to measure daily urinary reproductive hormone concentrations over multiple menstrual cycles for study of the associations between PAH metabolizing enzyme polymorphisms and PAH exposure and menstrual cycle abnormalities. Specific Aim 3: To pilot test serum anti-M|llerian hormone, follicle stimulating hormone, and inhibin B concentrations as markers of ovarian reserve for study of the associations between PAH exposure and diminished ovarian reserve. The signifiance of the application is that the research is to understand how toxicants cause ovarian dysfunction so that they can prevent it. These studies will provide insights that will help us to understand why some women are more sensitive to ovarian toxicants than other women. In so doing, they will also lay the groundwork for possible interventions to protect against ovarian dysfunction.

1R21HD061644-01
Physiological Reactivity to Acute Stress during Pregnancy
Christian, Lisa Michelle
Ohio State University
$181,209
Preterm delivery, an increasingly frequent occurrence in the United States, is associated with significant family burden and an estimated societal cost of at least $26 billion per year. In the U.S., the preterm birth rate is 12-13% as compared to 5-9% in other developed countries. Persistent racial disparities contribute to this discrepancy. Psychosocial stress and related physiological sequelae may contribute to preterm birth overall, as well as to racial disparities in preterm birth. The experience of chronic stress, such as that conferred by racial minority status, may sensitize physiological stress responses. Indeed, as compared to Caucasians, African-Americans exhibit greater cardiovascular reactivity to a variety of acute stressors. Importantly, blood pressure, glucocorticoid, and catecholamine responses to acute stress are attenuated during healthy pregnancy as compared to nonpregnancy. This adaptation may protect the mother and fetus from potentially detrimental effects of maternal physiological activation. Thus, women who exhibit greater and more extended physiological reactions to everyday stressors may be at increased risk for negative perinatal outcomes. Notably, no studies of acute stress during pregnancy have examined inflammatory immune responses or mechanisms underlying blood pressure change (i.e., cardiac output, total peripheral resistance). Moreover, limited information is available regarding effects of race on physiological adaptation to pregnancy. The current study will address important gaps in the literature by examining cardiovascular, endocrine, and immune reactivity to acute stress among 40 healthy pregnant women (20 Caucasian, 20 African-American) and 40 demographically matched nonpregnant control women. This research is designed to ultimately lead to the identification of women at greater risk for negative perinatal outcomes and elucidation of mechanisms underlying increased risk, providing a basis for individualized health care services. Significance of The Application: This study will fill important gaps in their knowledge regarding physiological adaption during pregnancy and effects of race on such adaptation. Information gained from this study will provide the groundwork for the following: 1) identification of women at greater risk of negative perinatal outcomes; 2)

describing physiological mechanisms underlying the link between stress and risk of preterm delivery; and 3) providing interventions designed to reduce the effects of stress and promote healthy pregnancy and fetal development.

1 S06GM087165-01
Research to Improve Preconception Health of Adolescent Women
Jumping Eagle, Sara
Oglala Lakota Oyate, Pine Ridge, SD
$121,622
The Oglala Sioux Tribe, in partnership with Stanford Research/University of South Dakota School of Medicine and the Oglala Lakota College, will be addressing priority health issues identified by the tribe and to support and expand the research capacity and infrastructure that will build on the research foundation that has been developed within the tribe over the past decade.

1R21HD059074-01A1
A Study of the Factors Influencing Women's Decision about Childbirth
Regan, Mary J.
University of Maryland Baltimore
$238,251
Cesarean section (CS) is currently used at over twice the rate recommended by the World Health Organization (CDC, 2006); use of the procedure has almost doubled in the last two decades for reasons that are as yet poorly understood. Overutilization results in avoidable morbidity and mortality and higher health costs related to childbirth. Many causes for the increased use of CS have been suggested, including growth in the number of 'maternal requests' -- healthy women asking for CS in the absence of medical indications. An NIH expert panel explored maternal request CS and concluded that at this time there is insufficient evidence to warrant CS on maternal demand without medical indications and recommended 'increased research devoted to strategies to predict and influence the likelihood of successful vaginal birth' (NIH, 2006, p. 20). Using the same data, the American College of Obstetrics and Gynecologists (ACOG) concluded that there is no reason to deny a surgical birth to a healthy mother as long as she is well-informed (ACOG, 2003). The divergence between these positions points to a critical gap in knowledge about the factors that drive CS rates, including the influence of maternal demand on the use of CS. Despite this recent focus on maternal demand, there is scant research on what women want from their birthing experience, including their reasons for choosing one mode of childbirth over another. The purpose of the grant application is to answer the question: what factors influence women's decisions about how their babies will be born? Women's hopes and desires for their first birth experience are influenced by what they know - both consciously and unconsciously. Because people are only partly aware of the attitudes and beliefs that inform their hopes and desires, this proposal will use three methods of data collection. Participants will be 50 primigravid women with uncomplicated pregnancies aged 21 or older. This proposal builds on the researchers' previous work related to the use of CS. It is one step in a defined program of research directed towards improving the health of mothers and their children by optimizing care during pregnancy, labor and birth. Significance Of The Application: This project in focused on building knowledge about what women want from their birthing experience and what informs their choices about

mode of birth. This knowledge is essential if they are to understand the role of maternal demand in use of CS. The outcome of the research data will inform public health policy concerned with both supporting maternal choice and ensuring long term maternal- child health by reducing the risks associated with childbirth. This study is part of a systematic program of research dedicated to improving women's health and satisfaction with their birthing experience.

1R21HL093450-01A1
Compromised Microcirculation in Women with Polycystic Ovary Syndrome
Stachenfeld, Nina
John B. Pierce Laboratory, Inc., New Haven, CT
$256,203
Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinopathy in young women, affecting 6-10 % of women of reproductive age. Obesity, insulin resistance, hyperandrogenism and hyperestrogenism are core functional disorders of PCOS and place women at increased risk for microvascular dysfunction. Women with PCOS have greater circulating concentrations of endothelin-1 (ET-1), a potent vasoconstrictor in the microcirculation (including that of the skin), which can increase blood pressure and lead to endothelial damage. The central hypothesis of this proposal is that testosterone effects on ET-1 mediate the peripheral microvascular dysfunction associated with PCOS. This hypothesis will be tested using a prolonged skin heating model to study peripheral microvascular responsiveness. Local skin heating has been used extensively to study mechanisms controlling peripheral microcirculation under a number of physiological conditions, including obesity, insulin resistance and hypertension. The impact of testosterone or ET-1 on microvascular responsiveness to local heating has not been studied in women with or without PCOS. This proposal seeks to provide this missing information. Significance of The Application: Women with Polycystic Ovary Syndrome (PCOS) have greater risk for cardiovascular disease, in particular dysfunction of the peripheral circulation that can lead to hypertension and comprised glucose disposal. This research will determine the role of hyperandrogenism in microvascular responsiveness in women with PCOS, and the mechanisms by which testosterone may impact endothelial function. These studies also have broad public health implications because their findings on the effect of hyperandrogenism on endothelial function may provide insights that can improve cardiovascular health of all obese women and men.

1P01 HD057877-01A2
Uterine Leiomyoma Research Center Program
Bulun, Serdar E.
Northwestern University, Chicago IL
$250,000
Uterine leiomyomata (fibroids) represent the most prevalent benign gynecologic disorder in the US. The cellular and molecular mechanisms regulating the development and growth of leiomyoma are not well understood. Their multidisciplinary team has designed 3 well-integrated projects focusing on Interactions between biologically critical hormonal pathways in uterine leiomyoma involving the transcription factors progesterone receptor (PR) and FOXO, the signaling pathway PI3K/AKT and the pro-fibrotic factor TGF-beta. Project I (Bulun) will be pursued to understand the mechanisms as to how antl-progestins such as

RU486 reduce tumor size. They hypothesize that progesterone regulates a number of critical genes, that favors increased proliferation and decreased apoptosis of leiomyoma smooth muscle cells, whereas anti-progestins reverse this effect by enhancing apoptosis and decreasing proliferation. Project II (Kim/Chakravarti) will determine the role of the PI3K/AKT/F0X0 signaling pathway regulating leiomyoma cell growth and survival in response to progesterone. They hypothesize that progesterone Induces proliferation of leiomyoma cells through activation of the PI3K/AKT/F0X0 signaling pathway and that Inhibitors of the AKT pathway should override the proliferative effects of progesterone and promote apoptosis. Project III (Nowak) will define the mechanisms as to how antifibrotic drugs regulate leiomyoma growth. They hypothesize that the increased proliferation exhibited by leiomyoma smooth muscle cells Is due to a major shift in the extracellular matrix environment caused by increased synthesis of new, monomeric collagen type I by these cells. They will determine whether antifibrotic drugs may be an effective new treatment for leiomyomas. These projects are supported by an Administrative Core (Bulun) and Tissue Procurement and Cell Culture Core (Kurita). Overall, as part of their long range goal, all projects investigate local hormonal signaling regulating apoptosis and proliferation as biologic endpoints and test existing and upcoming pharmaceutical compounds that target these pathways in uterine leiomyomata. RELEVANCE (See instructions): Symptomatic uterine leiomyomata affect millions of US women and cause irregular uterine bleeding, anemia, recurrent pregnancy loss leading to more than 200,000 hysterectomies per year. Available treatments are limited due in large part to the fact that the mechanisms regulating the development and growth of these tumors are unclear. They propose integrated molecular, cellular and translational studies that should lead to a better understanding and future development of novel therapeutics for uterine leiomyomata.

5R21 HD059015-02
The Role of GPR54 Signaling in Pubertal Disorders
Bianco, Suzy; Drumond Carvalho
University of Miami School of Medicine, Coral Gables, FL
$20,000
The long term goal of this project is to identify factors that regulate the timing of pubertal onset and reproductive maturation. The identification of GPR54, a G-protein coupled receptor, and its ligand, kisspeptin, as upstream regulators of GnRH secretion has led to intense research to elucidate their roles in the regulation of the reproductive axis. Inactivating mutations in GPR54 cause failure to undergo puberty and infertility. In contrast, early stimulation of this receptor triggers precocious puberty in mice. Preliminary results indicate that GPR54 is desensitized and internalized in response to continuous kisspeptin stimulation, and that a GPR54 amino acid substitution identified in a female patient with central precocious puberty (a disorder with disproportionately high female incidence) increases GPR54 responsiveness by delaying the desensitization of the receptor. The hypothesis is that the timing of signaling and desensitization of GPR54 is critical for its role in controlling puberty and reproduction, and that amino acid substitutions in GPR54 may affect its responsiveness by interfering with signaling or desensitization, thereby contributing to the clinical presentation. Although G-protein coupled receptor desensitization is generally strongly regulated, no data have been published on GPR54 desensitization. The short term goal of this project is to define the mechanisms underlying GPR54 desensitization, in order to

understand how genetic mutations of this receptor affect these mechanisms and hence the timing of pubertal onset and sexual maturation. A thorough understanding of the mechanisms underlying GPR54 signaling may uncover the basis of gender differences in normal and abnormal pubertal development, as well as reveal a new array of potential targets of pharmacological manipulation for the treatment and prevention of abnormal pubertal development and possibly other reproductive disorders.

5U10 HD047891-05S2
Obstetric-Fetal Pharmacology Research Units Network
Hankins, Gary D.
University of Texas Medical Br Galveston
$235,025
The University of Texas Medical Branch (UTMB) has the capability to participate actively as a member of the Obstetric-Fetal Pharmacology Research Units (OPRU) Network. Gary Hankins, MD, as PI, is responsible for the proposed clinical trial on the use of hypoglycemic drugs in the treatment of diabetes during pregnancy. He has extensive experience within several NIH multicenter trials, eg, First and Second Trimester Evaluation of Risk of Aneuploidy (FASTER), Beneficial Effects of Antenatal Magnesium Sulfate Study (BEAM), and the Vaginal Ultrasound Cerclage Trial. Dr. Hankins has achieved successful patient recruitment and retention by involvement with UTMB's Regional Maternal & Child Health Program (RMCHP). All RMCHP clinics follow protocols established by the Maternal-Fetal Medicine division, headed by Dr. Hankins. Over 12,000 pregnant women are cared for annually within the RMCHP clinic system, approximately 7,000 of whom deliver at UTMB. The Pharmacology/Pharmacokinetics (PK) Co-Investigator, Mahmoud S. Ahmed, PhD, has over 25 years of expertise in utilizing human placenta and derived preparations in his investigations. Dr. Ahmed is a laboratory-pioneered investigator in placental receptors, their natural ligands and mediated responses, as well as the mechanism of hCG release from trophoblast tissue. They investigated the effects of in vitro and in vivo chronic administration of opiates on placental physiology and maternal-neonatal outcome. Utilizing dual perfusion of placental lobule, they demonstrated the influence of efflux protein and placental metabolic [enzymes on the PK for placental transfer of opiates. They identified placental aromatase as a drug-metabolizing enzyme and are investigating its polymorphism. Kenneth D. Carey, DVM, PhD, as Animal Model Co-Investigator, is responsible for coordinating the baboon studies to be conducted at the Southwest National Primate Research Center (SNPRC) in San Antonio. A population of normal and diabetic baboons will be studied. Dr. Hankins is an adjunct investigator at the SNPRC and has had extensive involvement with the Primate research staff. The Department of Ob/Gyn has well-funded scientists with expertise in areas relevant to this RFA including infection, vascular physiology, and placental functions. Clinical PK Co-Investigators Susan Abdel-Rahman, Pharm D., and Wayne Snodgrass, MD, PhD, have over 30 years of combined experience in the development of protocols for PK studies, evaluation of data obtained, and PK/PD modeling. The Division of Neonatology, the GCRC, and other departments at UTMB will provide support for this project.

5G13 LM009242-02
The History of Emergency Contraception
Prescott, Heather M

Central Connecticut State University, New Britain, CT
$75,530
The National Library of Medicine Grant for Scholarly Works in Biomedicine and Health will be used to research and write a book-length project on the history of emergency contraception from the 1960s until the present. Postcoital methods of contraception were first developed in the early 1960s as part of larger movement to provide reproductive health care to adolescent and young adult women. This project will explore the multiple constituencies involved in the development and marketing of emergency contraceptives since the 1960s. It will draw upon the personal papers of major reproductive scientists, gynecologists, population groups, and feminist activists. This study will emulate the method used by social historians of medicine, which views the history of medicine as a negotiated process between experts and clients. Therefore, a major focus of the project will be the role women patients played in the dissemination of this technology. This project will show women not only as test subjects for this new method of birth control but also as active health care consumers.

Z01 HD008737-09
ORWH-NICHD Leiomyoma Tissue Bank
Segars, James
NICHD Intramural program
$85,000
The health of 30-50% of women in the U.S. is adversely affected by uterine leiomyoma (fibroids). Uterine fibroids are a health disparity issue that disproportionately affects African American women. Research into causes and treatment has lagged behind other disciplines, in part due to lack of available tissues, since surgical samples are often not made available to scientists. To address the problem of tissue availability, and promote research on this condition, this project proposes to establish a fibroid tissue bank as an initiative in the intramural program of NICHD. This tissue bank will provide samples to NIH-funded investigators and DoD-funded investigators to support work on this condition. The Leiomyoma Tissue Bank (LTB) will be physically located in space assigned to Dr. Segars of NICHD. The LTB will be structured after RStaR-banks for endometrium and ovary established by the Specialized Cooperative Program in Reproductive Research. Computerization of sample inventory will be performed with software provided by NICHD.

1 K99 HD055357-01A2
Activin Target Genes in the Ovary: Regulation of Ovarian Follicle Development
Kipp, Jingjing
Northwestern University
$83,333
These proposed studies will increase their understanding on the mechanisms of activin regulation of normal ovarian follicle development, and provide new insights into this important reproductive process and hence fertility control, infertility treatment and human health related diseases including cancer. Normal development of ovarian follicles is critical for female reproduction and endocrine function, as it prepares and provides healthy and fertilizable eggs and ensures normal production of steroid and peptide hormones. This process is finely regulated by various intrinsic and endocrine factors. Factors produced by granulosa cells include the TGF-beta superfamily member activin and the steroid hormone estrogen,

both of which have been demonstrated to play an intra-ovarian role in regulating ovarian follicle development. I have revealed a linkage between activin and estrogen signaling pathways in the ovary. Mice treated neonatally with activin show an increase in follicle formation and activin stimulates mouse granulosa cell proliferation in vitro. The mechanisms that mediate these events are not known. I have identified Cyp26b1 as the gene that was most significantly suppressed by activin and confirmed its expression in the postnatal ovary. Cyp26b1 degrades the potent morphogen retinoic acid which has been suggested to regulate ovary development. Therefore, the central hypothesis of this proposal is that activin modulates ovarian follicle development through regulation of gene expression profiles of a subset of targets including ERa, ERP and Cyp26b1. The studies proposed will test this hypothesis through three specific aims. Aim 1 will investigate the mechanism(s) underlying activin regulation of ER expression. This will be accomplished by examining involvement of the activin signaling proteins Smad2/3 in activin stimulation of ER expression, and identifying binding site(s) of Smad protein complexes to the ER promoter and determining their functional importance. Aim 2 will identify novel activin regulated genes in the ovary. This will be accomplished by microarray gene expression profiling using neonatal whole ovary cultures and by further verification of the results with real time RT-PCR. Aim 3 will investigate the roles of C3T326b1 and activin in regulating RA environment in the ovary and how Cyp26b1 and RA may affect ovarian follicle formation and development. Together with these experimental studies, the proposal includes a logical plan for further training and mentoring of the applicant, leading to a successful transition to an independent academic career.

1 K24 HD057086-01A1
Improving Contraceptive Use in High-Risk Women
Raine-Bennett, Tina
University of California, San Francisco
$144,892
Little is known about interventions that work to improve contraceptive use and decrease unintended pregnancy. Information that can be obtained from high-quality clinical trials will be generalizable and provide evidence based guidance for providers in public clinic settings. It is important to mentor the next generation of obstetricians and gynecologist trained in epidemiologic research and clinical trials methodology. Early unintended pregnancies have significant consequences and occur at disproportionately higher rates in young, poor, uneducated, and minority women. The overall goals of this proposal are to: 1) To lay the ground work for conducting a high-quality, large-scale, theory driven intervention to improve contraceptive use and reduce unintended pregnancy rates among young, low-income, and minority women receiving care at family planning clinics; and 2) Engage fellows and junior faculty in the development of patient oriented research to improve contraceptive use behavior among women at high-risk for unintended pregnancy. Formal training in health services research methods through a Robert Wood Johnson (RWJ) Clinical Scholars post-doctoral fellowship and a Mentored Minority Medical Faculty Development Award provided skills and experience to become an independent investigator and build a productive research agenda in patient-oriented research. Principal findings from the analysis of data from my current NICHD-funded longitudinal cohort study of teens and young women who initiate hormonal contraceptives will provide the guiding concepts that will determine the content of a multi-

component, clinic-based intervention aimed at multiple relevant modifiable factors. The dataset will form the basis of the qualitative analyses in the research plan and will serve as a key teaching tool for fellows needing to learn epidemiological research skills. They will perform primary and secondary analyses examining individual-level data (demographic, personal, and reproductive characteristics) as well as a wide range of information on contextual factors such as relationships, family, peer and community norms that influence contraceptive method choice and continuation. This will be followed by formative qualitative work and pilot studies to develop a relevant and operationally feasible intervention. The work in this proposal is intended to bridge the gap between collecting observational behavioral data and implementing theory driven patient oriented research to modify behaviors. The K24 award will strengthen my scholarly potential and contribution by expanding the scope of my current patient oriented research and allowing me to focus more explicitly and directly on mentoring and developing beginning investigators in patient-oriented research in family planning.

1 R01 HD057941-01A2
Malaria in Pregnancy: Nutrition and Immunologic Effects
Fawzi, Wafaie
Harvard University School of Public Health
$200,000
Vitamin A and zinc supplementation during pregnancy have the potential to boost the immune response to prevent placental malaria and/or avoid clinical complications associated with it such as maternal anemia and low birth weight in the infants. However, the safety and efficacy of such supplements in pregnant women has not been examined. The proposed study will address this research question and will provide evidence that may lead to an optimization of international guidelines on vitamin A and zinc supplementation in pregnant women that will be important for more than 25 million women becoming pregnant in malaria-endemic regions in Africa every year. Malaria in pregnancy is a major public health problem in Tanzania and many other countries in sub-Saharan Africa. Malaria is associated with tremendous morbidity in the mother including severe anemia, and in the fetus in the form of low birth weight and fetal loss. Vitamin A and zinc deficiencies are specific factors which can modulate the clinical course of malaria and exacerbate associated complications. The published literature suggests that these two micronutrients favor a reduction in risk of placental malaria and related clinical outcomes including malaria and anemia among women, and low birth weight. They propose to study the efficacy of zinc and/or vitamin A supplementation in reducing the risk of placental malaria and other maternal/fetal outcomes. They will recruit 9,000 women of reproductive age and follow them up on monthly basis for pregnancy status, and identify and randomize their target sample of 2500 pregnant women. Subjects eligible for randomization will be HIV-negative women who are at or before 8 weeks of gestation. Women will be enrolled using a factorial design and assigned to receive zinc alone, vitamin A alone, both zinc and vitamin A, or placebo. All women will receive daily folate and iron supplements as per standard prenatal care. Women, and after delivery babies, will be followed up until 6 weeks after delivery. Compliance with supplement use will be assessed by direct questioning of women and pill count at monthly clinic visits. Biochemical assessment of compliance will also be assessed measuring the plasma concentration of vitamin A and zinc in a random subsample of 400 women at randomization, at 30 weeks of gestation, and at delivery. The

primary endpoint is placental malaria, and secondary endpoints include maternal malaria, maternal anemia, and low birth weight. They propose to examine key aspects of the humoral and cell-mediated immune response to malaria in a sub-study. The program will be carried out by Harvard School of Public Health in collaboration with Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania.

1 K24 HD060687-01
Midcareer Investigator Award in Patient-Oriented Research
Barnhart, Kurtt
University of Pennsylvania
$187,466
Recruitment and retention of productive junior investigators is a priority of academic medical institutions and the research community, and a strong mentoring relationship will increase the likelihood of success. The purpose of this Mid-career Investigator Award In Patient-Oriented Research is to provide support for Kurt Barnhart, MD, MSCE, a reproductive endocrinologist and epidemiologist at the University of Pennsylvania. Dr. Barnhart is an accomplished clinical investigator with continuous NIH support since he joined the faculty at Penn in 1996. He has also been recognized as an outstanding mentor. The candidate's immediate and long-term career goals center on his desire and intention to continue to evolve and mature as a patient-oriented researcher, teacher, and mentor. In doing so, he needs to be able to enhance and focus his efforts on conducting patient-oriented research (POR), and building a clear training and mentoring path for those interested in POR in women's health. This award will allow him to achieve these goals by protecting 50% of his time through a reduction in his clinical and administrative duties. He will also reduce effort on some of his funded projects while concomitantly increasing the effort of junior faculty he currently mentors. Mentoring: Dr. Barnhart will focus his mentoring on scholars enrolled in the Masters of Science in Clinical Epidemiology (MSCE) supported by the NIH T32 Reproductive Epidemiology training grant. Candidates for this program include fellows in sub-specialties in women's health, family medicine and pediatrics. Dr. Barnhart was one of the first trainees of this grant and is currently the co-PI. Other mentees will include junior faculty, fellows in Reproductive Endocrinology and Infertility, residents in Ob/Gyn and medical students. He plans to serve as primary thesis mentor for some, a research mentor for others, and will direct the Ob/Gyn resident research program at Penn. Dr. Barnhart is committed to the career development of clinician investigators. Research Plan: The specific aims proposed in this application will evaluate the short and long term consequences of assisted reproductive technology (ART), a priority area of research for NIH. The three specific aims which investigate the association of ART with short term perinatal morbidity and childhood development provide the perfect opportunity to mentor young investigators on the design and conduct of a hypothesis-driven clinical research that will serve as the basis for future studies. Complementary and diverse research methods have been proposed to address this important research area. Aim # 1 will use the national SART database to test the hypothesis that supra-physiologic conditions associated with a fresh IVF cycle may be associated with perinatal morbidity. Aim #2 will use a three arm cohort study assessing childhood development in children conceived with IVF, superovulation or without medical assistance. Aim #3 will use a large administrative dataset to link mothers and children and assess for autism spectrum disorder in a true population setting. These aims not only address an important question but also are designed to advance

the skills of the PI, enhance multidisciplinary research and provide optimal opportunity for training and mentorship. Finally, these aims will likely provide evidence to be used to design larger trials, hopefully by the growing cadre of reproductive epidemiologists and POR researchers in women's health nationwide, many of whom will have been mentored by Dr. Barnhart.

1 R01 HD061821-01
Identification of Genes Predisposing to Pelvic Floor Disorders
Cannon Albright, Lisa A.
University Of Utah
$66,667
This research has a major potential to affect public health in the prevention of PFDs: they may be able to identify high risk populations who can be identified at a young age, studied and possibly targeted for prevention; and at a later stage in the development of PFDs, special interventions can be studied and possibly implemented in women at risk for recurrence of their condition. Someday, identification of these high risk populations may be as general as familial risk, or as specific as specific gene screening. The investigators propose a unique and powerful collaboration between basic and clinical scientists in Utah to identify genes affecting predisposition to pelvic organ prolapse (POP). The co-PIs both have significant experience, Dr. Norton in Pelvic Floor Disorder (PFD) genetics and Dr. Cannon-Albright in predisposition gene identification. The investigators will access the Utah Population Database, a computerized genealogy of Utah combined with decades of medical data from the two largest healthcare systems in Utah (serving 90% of the state), to identify and recruit surgically treated cases of POP (1,250 cases in 5 years). All POP cases sampled will be genotyped with the Illumina 610Q SNP marker set. The PIs will apply multiple different genetic analyses to this resource of genotyped POP cases to aid in the identification of predisposition genes. The record linkage of medical procedure codes (identifying surgeries performed on each patient) to individual genealogy data allows us to identify all genetic relationships among the POP cases. They will perform genome-wide association analysis, using software they have developed which allows inclusion of both independent and related cases. They will identify all genetic relationships between the sampled POP cases and perform linkage analysis in informative, high-risk POP pedigrees. They will identify chromosomal regions shared Identical by Descent (IBD) in very distantly related cases in these pedigrees, and they will identify IBD sharing within the small subset of POP cases (2%) who are inbred. Initial collaborative analysis of data obtained by Dr. Norton's NIH funded study of affected PFD sib-ships has already provided significant evidence for a predisposition gene localization on chromosome arm 9q, and suggestive evidence for at least one other locus on chromosome 1. In summary, they will create a population-based resource of surgically treated POP cases, they will pursue established and new methods to identify and localize predisposition genes affecting POP, and they will begin a detailed search for the chromosome 9 gene they have localized.

1 R01 HD061811-01
Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team
Moalli, Pamela A.
Magee-Women's Res Inst And Foundation, Pittsburgh, PA

$66,666

Prolapse (i.e., abnormal descent) of the pelvic organs is a common costly condition that negatively impacts the lives of millions of women world-wide. Biologic and synthetic meshes are often used in the surgical repair of prolapse due to improved anatomical outcomes over native tissue repairs; but with little scientific data on which to base the selection of a particular product. Unfortunately, the complications associated with certain meshes cause unacceptably high rates of morbidity including infection, tissue contraction, vaginal discharge, and pain. In this proposal, they aim to establish a comprehensive mesh testing center in which previously or newly marketed prolapse meshes can be objectively tested and the next generation of prolapse meshes can be developed based on specific scientific criteria. Each year roughly 200,000 U.S. women undergo a surgery to repair pelvic organ prolapse. Biologic and synthetic meshes are widely used in prolapse repairs to improve anatomical outcomes over native tissue repairs which currently have a failure rate of over 30%. To date, however, there is little scientific data to guide surgeons in the selection of a particular product. As a result, meshes are used based on the recommendations of a local vendor and consequently, are placed in women on a trial and error basis. There is growing evidence, however, that the complications associated with prolapse meshes cause unacceptably high rates of morbidity including infection, mesh shrinkage, mesh erosion, mesh exposure, pelvic, rectal and bladder pain and dyspareunia. Such complications have become significant enough for the FDA to recently release a warning about mesh use, especially when it is placed transvaginally. In this proposal, they therefore, aim to establish an interdisciplinary team of scientists dedicated to the comprehensive testing of previously or newly marketed prolapse meshes and for the development of the next generation of graft materials based on specific scientific criteria. In the first phase of the study, they determine how biochemical and structural changes in the prolapsed vagina impact passive and active mechanical behavior so as to develop a mesh in which these deficiencies are repaired or compensated for, allowing us to restore the prolapsed vagina to the nonprolapsed condition. In the second phase, they hypothesize that the shortcoming of current prolapse meshes is that they are too stiff. While this results in a repair with increased tensile strength, it occurs at the expense of tissue function with accelerated tissue contraction, decreased elasticity and compliance, and deterioration of smooth muscle function. To test their hypothesis, they implant commonly used synthetic prolapse meshes into the vagina of nonhuman primates with prolapse using the gold standard surgical procedure (the abdominal sacrocolpopexy) and then define the cellular, biochemical and biomechanical impact on the vagina at 6 months post implantation. Eventually, they will implant meshes transvaginally to characterize the distinct host response to this surgical approach. In the third phase, they explore the development of future grafts for prolapse surgery. They hypothesize that because of its bioinductive effects, a combined biologic/synthetic mesh will be superior to a synthetic mesh alone in restoring vaginal structure and function. They propose that a key yet poorly developed component of prolapse repairs is the re-establishment of smooth muscle reactivity and therefore, test the use of a temporary biologically active scaffold in achieving this process. In this way, this grant proposal provides a mechanism to establish the first team of scientists dedicated to the comprehensive unbiased evaluation of prolapse meshes as a means of educating both current and future prolapse surgeons, and the public regarding potential problems associated with certain materials. Indeed, the development of such a group is imperative for protecting the health of women.

1 R01 HD061787-01
Wireless Remote Abdominal Pressure System: Developing A More Comprehensive Understanding Of Physical Activity And Its Association With Incidence, Progression And Recurrence Of Pelvic Floor Disorders
Nygaard, Ingrid E.
$66,667
The effect of strenuous physical activity on new or recurrent pelvic floor disorders is unknown. They developed an intravaginal pressure sensor to measure intraabdominal pressure. They will perfect the wireless technology needed to use the sensor remotely so that they can understand how different activities done during real world settings affect intraabdominal pressures and pelvic floor disorders. Pelvic floor disorders affect one in four American women. Few modifiable risk factors have been identified that might reduce the incidence or progression of pelvic floor disorders. Popular wisdom and scant clinical data suggest that strenuous activity causes or promotes pelvic floor disorders. Given the health benefits of activity, women should be encouraged to be maximally active unless there is scientific evidence to the contrary. Existing physical activity instruments are largely designed to assess cardiovascular exertion and are validated using activity diaries, accelerometers, and step counters. Such measures may not accurately measure activities that increase loading on the pelvic floor (such as lifting). After researching available technologies, they concluded that a tool to understand how physical activities impact abdominal pressure in the real world does not exist. Over the past 18 months, their interdisciplinary team of bioengineers, urogynecologists, electrical engineers, and exercise scientists developed and validated the performance of a prototype for an intravaginal abdominal pressure sensor that accurately measures pressure in the upper vagina, an easily accessible space that records pressures similar to the true intraabdominal pressure. In this proposal, they plan first to further develop an integrated system (the "WRAPS", Wireless Remote Abdominal Pressure System) to monitor intraabdominal pressure outside of the clinical setting. This system will consist of three key elements: an intravaginal pressure sensor with wireless data transmission capability, a small portable data monitoring and storage unit, and computer based data translation software for downloading and managing the pressure data. In a controlled exercise laboratory setting, they will then use intraabdominal pressure data generated by the WRAPS to determine the reproducibility of intraabdominal pressures measured during specific types of physical activity and will finalize development of a valid questionnaire that categorizes the magnitude of intraabdominal pressures during activities. Finally, in a real-world setting in which participants wear the intravaginal sensor during waking hours for four 1-week periods over the course of a year, they will characterize intraabdominal pressures experienced by women of varying degrees of habitual physical activity and, using WRAPS data as the gold standard, determine whether activity can be appropriately categorized in terms of pelvic loading by means of self-administered questionnaires, the current standard. Obtaining future evidence about the impact of physical stressors on pelvic floor disorders relies on their ability to measure the risk factor in question. This innovative translational collaboration will remove a critical barrier to progress in understanding the etiology of pelvic floor disorders in women.

5U10HD054215-04
The Cleveland Clinic Clinical Site

Barber, Matthew
Cleveland Clinic, Cleveland, OH
$25,000
Pelvic floor disorders (PFD) including urinary incontinence, pelvic organ prolapse (POP), and fecal incontinence affect a substantial proportion of women in the U.S. PFD result in significant psychosocial costs to an individual and their aggregate social and economic costs to society are enormous. Despite their substantial health impact, the quality of the evidence supporting most of the commonly used treatments, especially surgical interventions, is limited by the lack of standardization of diagnostic and therapeutic interventions, use of non-standardized and non-validated outcome measures, poor quality research designs, and inadequate power to detect clinically meaningful differences. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with PFD using the highest quality research methods available. The specific aims of this application are: 1) to demonstrate that the Cleveland Clinic Foundation (CCF) possesses the personnel, patient, clinical, and administrative resources needed for successful participation as a Clinical Site in the PFDN; and that their participation would be advantageous to the successful attainment of the Network's scientific goals and 2) to present a concept application for potential conduct by the PFDN. The broad, long-term objectives of their concept application are 1) to compare sacrospinous ligament fixation (SSLF) to uterosacral vaginal vault fixation (USWS) and 2) to assess the role of perioperative pelvic floor physiotherapy (PFPT) in women undergoing transvaginal surgery for apical or uterine POP. Their Specific aims are to: 1) compare the anatomic outcomes of SSLF to USWS in women undergoing transvaginal surgery for Stage 2-4 POP involving the vaginal apex or uterus 3 years after surgery;2) compare functional, sexual, and health-related quality of life (HRQOL) outcomes of SSLF to USWS in the same women 3 years after surgery; 3) assess whether short-term functional, sexual, and HRQOL outcomes improve in women receiving PFPT perioperatively compared to those who receive surgery alone; 4) assess whether perioperative PFPT improves anatomic, functional, sexual and HRQOL outcomes 3 years after surgery (long-term) compared to surgery alone and 5) determine the incremental cost-effectiveness of perioperative PFPT at the time of transvaginal surgery for POP. They present a collaborative multi-centered randomized trial comparing SSLF to USSVS with or without perioperative PFPT using a 2x2 factorial study design. A standardized common protocol for enrollment, treatment and data collection will be employed by 6-8 Clinical Sites within the PFDN coordinated by the data coordinating center.

5U10HD041250-09
The Pelvic Floor Disorders Network
Brubaker, Linda
Loyola University, Chicago, IL
$25000
Loyola is a productive, innovative clinical research institution that has contributed to the first cycle of the Pelvic Floor Disorders Network and they are eager to build on the PFDN's excellent start. Their application documents: I. The Qualifications and Commitment of Institution and Key Personnel at Loyola A qualified and committed institution with a multidisciplinary faculty with experience in clinical trials design and conduct. A highly qualified and committed research team Lead by the same PI, Dr. Brubaker, this research team

contains urogynecologists and urologists. Two of the faculty members received Master's Degrees in Clinical Research Design and Statistical Analysis and one is currently in this degree program. A cadre of study coordinators are cross-trained to meet the needs of the PFDN study roster. The team has a excellent collaborations within the Loyola faculty. II. Loyola's Participation in PFDN Protocols and Procedures High quality participation in PFDN protocols with excellent and consistent recruitment. They also demonstrate their consistent contributions in PFDN work, including dissemination of PFDN scientific findings. Loyola has been productive and has worked well with the PFDN team. Their first cycle application proposed the essence of the CARE trial, which was completed ahead of schedule and is under consideration for publication. III. A Feasible, Scientifically Relevant Concept Protocol (Randomized Surgical Trial): They believe they have demonstrated their ability to design and conduct high quality clinical trials. This application also describes a randomized surgical trial for women who select vaginal apical reconstruction. A comparison of the two most common techniques may inform a future study which seeks to determine which route of surgery (abdominal vs. vaginal) is best suited for an individual woman. This trial is a feasible, scientifically relevant randomized surgical trial. The draft protocol is suitable for PFDN Steering Committee discussion and revision, prior to implementation.

5U10HD054214-04
Pelvic Floor Disorders Network
Nager, Charles William
University of California San Diego
$25,000
The objectives and aims of this application are for San Diego to become the first western United States clinical site in the Pelvic Floor Disorders Network (PFDN). The San Diego Clinical Site is a collaboration of three medical centers: 1) the University of California, San Diego (UCSD), 2) Kaiser Permanente, San Diego (Kaiser) and the 3) Naval Medical Center, San Diego (NMCSD). This same collaboration in the Urinary Incontinence Treatment Network (UITN) led all sites in patient recruitment for the UITN SISTEr (Stress Incontinence Surgery Treatment Efficacy) trial. The efficiency of the San Diego Clinical Site's efforts was recognized by the PFDN and they were asked to become a subcontract site for the University of Alabama for the Colpopexy and Reduction Efforts (CARE) study. In the brief nine months available before the CARE study ended, San Diego (UCSD and Kaiser only) recruited 19 patients to CARE. This total was more than all but one center during those nine months. They were the third UITN site to reach recruitment goals in the UlTN's BE-DRI (Behavior Enhances Drug Reduction Incontinence) study. Additionally in the UITN, their site has led efforts in the design, protocol development, and workgroup leadership for the UlTN's current study, TOMUS (Trial Of Mid-Urethral Slings). Urodynamic studies are commonly performed in the United States at an annual cost of approximately 400 million dollars. These urodynamic studies are routine preoperative investigations in most centers that have urodynamic capability, yet they do not have evidence that these tests improve outcomes. Their concept proposal is a randomized trial of preoperative urodynamic studies in women with predominant stress urinary incontinence. The primary aim is to determine if preoperative urodynamic studies improve treatment success rates in all women considered candidates for SUI surgery after an office evaluation. They believe that this proposed urodynamics study requires a multi-center randomized clinical trial and has significant relevance to the

appropriate evaluation and care of women with pelvic floor disorders, namely urinary incontinence. The proposed study also has potential significant importance for national health care resource allocation and expenditures. The work that the San Diego investigators have done for the UITN in the last five years to develop standardized, quality urodynamic studies make them the ideal investigators to lead this effort. They believe that the PFDN will benefit greatly by the proven ability of the San Diego Clinical Site's demonstrated energy, skills, and leadership.

5U10HD054136-04
Utah Pelvic Floor Disorders Network
Nygaard, Ingrid E.
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$25,000
Pelvic floor disorders are common, bothersome, and inadequately treated. The overarching aim of the investigators from the proposed University of Utah Pelvic Floor Disorders Clinical Site is to improve women's health in the area of pelvic floor dysfunction. To this end, site specific aims include: 1) Identifying priority areas of research, 2) Developing assessment tools, 3) Developing and implementing PFDN protocols, 4) Recruiting and enrolling subjects in PFDN protocols, 5) Achieving on-target recruitment goals and high subject retention, 6) Ensuring high-quality data, 7) Transmitting data accurately to the Data Coordinating Center, 8) Participating in data analysis, 9) Disseminating results to the research community, and 10) Producing high-quality publications. The broad scientific aim for the randomized clinical trial outlined in this proposal is to evaluate whether post- operative pelvic floor muscle training following surgery for pelvic organ prolapse and/or stress urinary incontinence improves post-operative outcomes (anatomic, symptomatic and quality of life outcomes) at 3 months, 1 year and 2 years post-operatively.

5U10HD041261-09
Perioperative Pelvic Floor Rehab: A Randomized Trial
Richter, Holly E.
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$25,000
Surgical techniques for the treatment of stress incontinence (SUI) have significantly evolved over the last 100 years. The gold standard Burch urethropexy and pubovaginal sling procedures are now being performed less frequently, with the increased use of the newer minimally invasive mid-urethral sling procedures, the most common being the tension-free vaginal tape procedure (TVT). The TVT procedure is comparable in efficacy to the open Burch procedure with low morbidity and fewer complications. Because the sling is placed at the level of the mid-urethra under no tension, it was thought that the TVT would yield fewer postoperative lower urinary tract symptoms. However, a review of the literature has not borne this out, with postoperative storage symptoms reported in up to 42% of women. The primary purpose of the proposed randomized clinical trial is to test whether a perioperative behavioral/pelvic floor muscle training program can reduce the occurrence of these postoperative storage symptoms and voiding dysfunction in women undergoing a TVT procedure for SUI. Behavioral interventions are known to be effective for treating urge incontinence and voiding dysfunction unrelated to surgery, but have not been tested as a

preventive adjunctive strategy. Approximately 400 subjects will be randomized to a perioperative behavioral program or usual care. The intervention will be implemented 2 weeks preoperatively, and reinforced before leaving the hospital and two weeks postoperatively. The primary outcome will be complaints of urgency, frequency, nocturia and urge incontinence using the overactive bladder questionnaire (OABq). Evaluations will be performed at 2 and 6 weeks, 3, 6, and 12 months postop, and will include the OABq, questionnaire for urinary diagnosis (QUID), urogenital distress inventory (UDI), pelvic organ prolapse/urinary incontinence sexual function questionnaire (PISQ), patient global impression of severity (PGI-S) and SF-36. Subjects will also complete a 7-day bladder diary to assess frequency of storage symptoms. Secondary aims are to determine whether this intervention reduces time to voiding and symptoms of voiding dysfunction, whether it impacts on patient satisfaction and quality of life, and to identify predictors of postoperative storage symptoms and voiding dysfunction symptoms. This type of information will allow physicians to more effectively counsel and treat their incontinent female patients to further enhance long-term quality of life.

5U10HD054241-04
Nichd Pelvic Floor Disorders Network
Schaffer, Joseph I.
University of Texas SW Med Ctr/Dallas
$25,000
This application describes the qualifications and experience of the urogynecology and urology faculty and research teams at the University of Texas Southwestern (UT Southwestern) Medical Center and Parkland Hospital and the facilities and patient population available to carry out clinical protocols sponsored by the Pelvic Floor Disorders Network. In 2004, there were more than 2,100 women with pelvic floor disorders seen in their clinics and 617 women underwent surgical procedures for correction of pelvic floor disorders. The Departments of Obstetrics and Gynecology and Urology have increasingly collaborated since 1997 to offer comprehensive care of women with pelvic floor disorders. In addition to urogynecology and urology, collaboration includes faculty from colorectal surgery, radiology, physical therapy, and maternal-fetal medicine. The clinical research teams described in this application have successful prior as well as on-going experience in NIH sponsored national multi-center trials. Centerpieces in this application are two existing research clinics, one targeted at private patients (operated by the Urology Department) and the other focused on medically indigent patients (operated by the Obstetrics and Gynecology Department). Also included in this application is a concept application for a randomized trial designed to assess the efficacy of end-to-end versus overlapping repair of the external anal sphincter lacerated during childbirth. The primary outcome is anal incontinence which is a significant consequence of such lacerations. This trial would permit accurate evaluation of the outcome of specific surgical procedures which is one of the prime areas of interest leading to creation of the Pelvic Floor Disorders Network. They are of the view that along with strategies for prevention of anal sphincter laceration during childbirth, optimal management of the torn sphincter should also be studied since more than 200,000 women sustain such pelvic floor injuries each year in the United States.

5U01HD041249-09

Pelvic Floor Disorders Network-Data Coordinating Center
Spino, Catherine A.
University of Michigan at Ann Arbor
$25,000
Pelvic floor disorders, such as urinary incontinence, pelvic organ prolapse, and fecal incontinence, are common and significant health-related problems for women in the United States. Outcomes following surgical and non-surgical intervention for pelvic floor disorders have not been adequately evaluated. As a result, data necessary to fully inform patients and to make important policy decisions are unavailable. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to systematically evaluate these outcomes. This application to be the Data Coordinating Center (DCC) for the pelvic floor disorders network brings together experienced investigators from biostatistics, urogynecology, urology, quality of life and health services research to prospectively assess the outcomes from various surgical interventions for female pelvic floor disorders. The specific aims of the DCC are to: 1. Assist in protocol development by providing expertise in the design, conduct and analysis of clinical trials conducted by the PFDN. 2. Provide expertise in measurement of quality of life and in the selection of the appropriate instruments to assess treatment outcomes and, when appropriate, to perform the interviews. 3. Coordinate the implementation of the study protocols approved by the Steering Committee, including design of the case report forms and interviewing protocols, development of a manual of operations, centralized database management with either centralized or remote data entry, submission of an IND to the FDA when necessary, and by organizing training and certification sessions, as needed. 4. Establish a database for each study conducted by the PFDN. 5. Implement either centralized or web-based data entry and verification. 6. Monitor the clinical sites with respect to data quality. 7. Provide infrastructure for monitoring adverse events and regulatory oversight for the network. 8. Provide logistical support for the Steering Committee, Advisory Board and DSMB, for both face-to-face meetings and teleconferences. 9. Maintain a website for the PFDN that includes web pages with content for the public, and a password- protected site with all study documentation and databases. 10. Manage and distribute protocol funds to the Clinical Centers. To illustrate the work of the DCC, a randomized clinical trial is proposed to compare surgical procedures for pelvic organ prolapse using a vaginal approach.

5U10HD041267-10
Pelvic Floor Disorders Network
Visco, Anthony G.
Duke University, Durham, NC
$25,000
Women's health research at the University of North Carolina (UNC) is sophisticated and widespread with many committed investigators addressing issues of fundamental importance to women. UNC has a tradition of excellence in clinical care, training and research in_pelvic floor disorders and includes one of the nation's first accredited fellowship programs in the Division of Urogynecology and Reconstructive Pelvic Surgery. They offer comprehensive evaluation and treatment options in a high-volume care setting that serves as a tertiary referral center for women from across the state. Women sought consultation or treatment for more than 2700 pelvic floor disorders by Urogynecologists at UNC in the previous two years. Seventy-eight percent of the women were Caucasion and 15% were African American,

predominantly from rural and suburban communities with stable care and follow-up patterns. Approximately 427 women had multi-channel urodynamic studies annually. UNC providers have extensive expertise in both surgical and non-surgical management of urinary incontinence, pelvic organ prolapse and defecatory dysfunction. The Division of Urogynecology performs an average of 106 surgical procedures for the primary indication of urinary incontinence, 300 for prolapse and provides medical management for over 1,464 women with these conditions each year. The UNC Pelvic Floor Disorders Research Collaborative, led by the Division of Urogynecology is a multidisciplinary team of outstanding investigators in Urogynecology, urology, gastroenterology, radiology, maternal-fetal medicine and clinical research methodology. They have a history of strong clinical ties and dedication to interdisciplinary research. Diagnostic resources include muti-channel urodynamic testing, cystoscopy, defecography, pelvic MRI, 360-degree endoanal ultrasound, anal manometry and needle electromyography. Clinical services include surgical treatment of complex pelvic floor disorders and a wide range of non-surgical options. As an active PFDN clinical network site, UNC has an established research infrastructure with the proven ability to support large-scale, multi-centered clinical research. The collaborative is well-equiped and uniquely qualified to continue as a valuable member of the Pelvic Floor Disorders Network. Given the exceptional quality of the research opportunities and resources available at UNC, the stable and diverse patient population, the strength of the investigator pool, their proven high-level recruitment and the commitment of the institution to the stated goals of this RFA, they look forward to continuing to make substantial contributions to advancing women's health related to pelvic floor disorders.