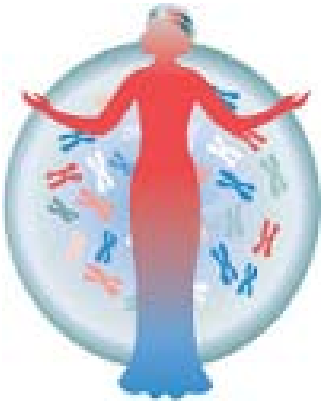

Office of Research on Women's Health (ORWH)
Research Summaries, FY 2011

Office of the Director
Division of Program Coordination, Planning, and Strategic Initiatives
National Institutes of Health

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ORWH RESEARCH SUMMARIES, FY2011

AGING

1-R21-AG-039779-01
Gonadotropins in a female model of age-induced hypertension
Sandberg, Kathryn L
Georgetown University
$230,250

This project is designed to make new discoveries into why age increases blood pressure and the prevalence of hypertension across the female lifespan. We will make these new discoveries by studying the role of the neglected gonadotropins in the age-induced increase in blood pressure that is observed in the Dahl salt-sensitive female rat maintained on a low sodium diet. Animal models of female aging are currently limited in number. Hopefully, furthering our understanding of this experimental model will lead to a greater use of this animal model in aging research on females. Furthermore, by investigating the gonadotropin hormone mechanisms responsible for the age-induced increase in blood pressure and hypertension, we may open the door to developing new therapeutic treatments for post-menopausal women and women with ovarian hormone deficiency - both of which experience marked changes in their gonadotropin profile from the ovarian hormone replete state. This project addresses the PA-10-015 by proposing to investigate the role and mechanisms of follicle stimulating hormone (FSH) and leutinizing hormone (LH) in the age-induced increase in blood pressure (BP) and body weight (BW) observed in the female Dahl salt-sensitive (DS) rat. We have previously shown that ovariectomy accelerates the age-induced increase in BP and BW in this model and that 172-estradiol (E2) prevents these effects. Aging and ovariectomy, however, also result in a marked rise in FSH and LH. Though some studies implicate these pituitary hormones in BP regulation, their mechanisms of action are poorly understood. These proposed studies will provide key insight into this experimental model of female aging and postmenopausal hypertension. Aim 1 will determine if preventing the rise in FSH & LH that occurs as a result of ovarian hormone deficiency during normal aging from 4 months old (mo) to 12 mo in the female DS rat will attenuate the age-associated increase in BP, BW, insulin insensitivity, endothelial dysfunction, renal oxidative stress and activation of the vasoconstrictor arm of the renin angiotensin system (RAS) in vascular, renal and adipose tissues. We will also investigate the E2 and progesterone (P4) dependency of these pituitary hormone effects. Aim 2 will serve as the corollary to Aim 1 and will determine if increasing FSH & LH in young (3-4 mo) female DS rats will result in an increase in BP, BW, insulin insensitivity, endothelial dysfunction, renal oxidative stress and activation of the vasoconstrictor arm of the RAS in vascular, renal and adipose tissues. The clinical significance of this research is the insight it will provide into the mechanisms underlying the marked rise in the prevalence of hypertension in women as they age and after their transition into menopause.

OD-11-301
The Science of Compassion: Future Directions in End-of-Life and Palliative Care
NINR
$2,500

This Summit brought together scientists, researchers, palliative and end-of-life care health professionals, educators, policy analysts, members of professional organizations, and members of the public. The objectives were to: examine the current status of palliative care and end-of-life research, practice, and policy; propose strategies to overcome barriers and ensure scientific and methodologic rigor in our research; delineate new action items that galvanize progress in these vital areas of science; and, envision and map pathways to ensure a future rich with scientific endeavor and achievements.

1-R01-AG-038467-01A1
A Biopsychosocial Investigation of Women's Health at Midlife
Upchurch, Dawn M
University Of California Los Angeles
$200,000

Promoting health and well-being, especially as women enter into midlife and early old age is a key public heath priority. By better understanding how social, psychological, and lifestyle factors (many of which are modifiable) contribute to health during midlife, new information relevant to clinical and programmatic interventions will become available. Midlife is a time of significant change in women's personal and professional lives. Moreover, health increasingly deteriorates, setting the stage for quality of life in later years. The purpose of the proposed research is to identify and investigate the longitudinal explanatory pathways that impact 3 important health outcomes. We target outcomes that are common and that have high personal and social costs: 1) Vasomotor Symptoms; 2) Depressive Symptoms; and 3) Allostatic Load. A distinguishing feature of this research is its use of an innovative biopsychosocial model that incorporates multiple domains of women's lives and acknowledges the multidimensionality of women's health. Specifically, we investigate the impact of: 1) Social Stressors and Social Support; 2) Psychological Factors; and 3) Lifestyle Behaviors on each health condition over a 10-year period using latent growth curve analysis, longitudinal structural equation models, and longitudinal random effects, as appropriate. In so doing, we will identify the specific pathways for both level and change over time for each woman for each health outcome. Because we propose that multiple aspects of health are linked in complex ways, we will also examine the interrelationships between the intervening variables, between the health outcomes, and investigate possible feedback between health outcomes and intervening variables. Data are from the Study of Women Across the Nation (SWAN) a community-based, 10-year longitudinal study of midlife women (aged 42-52 at baseline) designed to characterize the physiological and psychosocial changes that occur during the menopause transition. By emphasizing characteristics that are potentially modifiable, the proposed research will provide new information relevant to clinical and programmatic intervention that may serve to reduce health differentials and promote well-being among midlife women.

5R37-AG030481-04
National Social Life, Health, and Aging Project
Waite, Linda J.
National Opinion Research Center
$200,000

They propose to collect a second wave of the National Social Life, Health and Aging Project (NSHAP) to obtain data on social networks and social support, marital and cohabitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. The primary objective of the National Social Life, Health and Aging Project (NSHAP) is to establish an innovative, high-quality dataset for use by researchers studying the relationships between social processes and health among older adults. Wave I obtained questionnaire and biomeasure data on a nationally-representative sample of 3,005 community-dwelling adults ages 57-85 in 2005/6. They propose to collect a second wave in NSHAP to obtain data on social networks and social support, marital and cohabitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. They propose to revisit respondents 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.

ALCOHOL AND OTHER SUBSTANCE ABUSE

1-R21-DA-027140-01A2
Genes, Gendered Contexts, and Substance Use Outcomes
Verona, Edelyn
University of Illinois Urbana-Champaign
$184,065

Women's drug arrests have increased in the last two decades, whereas men's arrests have decreased. Thus, women's drug use has become a significant social problem. An innovative aspect of the project is the attempt to identify genetic and environmental factors that are female specific for substance use outcomes. Given important sex differences in biology, gene expression, and motives, this project can inform psychosocial and pharmacological treatments for substance use so that they are tailored to address gender-specific issues. It is becoming increasingly clear that risk factors for use and trajectories toward desistance may differ significantly for men and women (e.g., Westermeyer & Boedicker, 2000). For example, recent work has uncovered different effects of monoamine genotypes (e.g., serotonin transporter, MAO-A) on male and female psychopathology and behavior (Sjoberg et al., 2007a; Verona, Joiner, Johnson & Bender, 2006). In addition, there is evidence that pubertal onset, childhood sexual abuse, and intimate partner violence (IPV) constitute unique risk factors for antisocial behavior and drug use among women compared to men (Dick, Rose, Kaprio, & Viken, 2000) and can predict drug relapse in women many years later in adulthood (Hyman, Garcia, & Sinha, 2006). Thus, a primary goal of the present application is to identify gender differences in biological and environmental risk factors for substance use outcomes as a way of advancing nuanced conceptualizations of female drug problems. The current project intends to (1) explore various gene by environment (GxE) effects on drug use outcomes, by examining different monoamine genes (5HTT, DRD4, MAO-A) and incorporating gendered environmental risk factors that are not commonly included in studies of drug use (e.g., intimate partner violence), (2) examine the extent to which GxE effects or individual risk factors are specific to substance use outcomes in women relative to men, and (3) identify multivariate models involving GxE effects and mediators of these effects to predict substance use pathways in men and women. The goal is to examine not only GxE effects (e.g., gene-by-abuse, gene-by-IPV) that directly influence substance use outcomes, but identify potential mediators (pubertal development, internalizing symptoms) in an effort to understand nuanced pathways for female substance use. The ultimate goal is to help in the development of tailored interventions to address gender-specific manifestations and etiologies.

2-R01-AA-014441-06A1
Mechanisms For Estrogen-Dependent Myocardial Depressant Effect Of Ethanol
Abdel-Rahman, Abdel A
East Carolina University
$200,000

Given the steady rise in acute alcohol consumption by young women, the proposed research is clinically relevant because it: (i) elucidates how estrogen transforms ethanol-evoked cardio-protection into cardiodepression in females; (ii) identifies alcohol use as potential contributor to the disappointing outcomes with estrogen in clinical studies; (iii) identifies the estrogen receptor subtype(s) implicated in the higher physiological activity of the cardioprotective enzyme, myocardial mit-ALDH2 in females. Contrary to conferring cardioprotection in male animals, acute ethanol causes estrogen (E2)-dependent myocardial depression in females. Despite progress made during the previous award, the molecular mechanisms for this health related problem remain unresolved. We hypothesize that E2-mediated accumulation of ethanol-derived acetaldehyde (ACA) creates environment conducive to paradoxical transformation of E2 into a pro-inflammatory hormone. We will focus on myocardial catalase and mitochondrial aldehyde dehydrogenase 2 (mit-ALDH2) because E2 enhancement of their physiological activity confers cardioprotection and both enzymes regulate myocardial ethanol-derived ACA balance; catalase catalyzes ethanol oxidation to ACA and mit-ALDH2 detoxifies ACA. We hypothesize that E2 enhancement of myocardial catalase activity could result in higher ethanol-derived ACA. Subsequently, competition of higher ACA level with more cytotoxic substrates for mit-ALDH2 leads to accumulation of cytotoxic aldehydes (oxidative stress and myocardial dysfunction). We further hypothesize that E2 mediates these cellular effects via nongenomic estrogen receptor (ER) signaling. To test our novel hypotheses, we will employ a multidisciplinary approach that encompasses integrative, cellular, molecular and pharmacological studies to address the following specific aims. Aim 1 studies will test the hypothesis that enhancement of nongenomic rapid ER signaling mediates ethanol-evoked oxidative stress and myocardial depression in female rats. Aim 2 studies will elucidate the role of ACA generating (ADH, catalase) and aldehyde detoxifying (mit-ALDH2) enzymes in the E2-dependent oxidative stress and myocardial depression caused by ethanol. Aim 3 studies will test the novel hypothesis that ethanol/ACA- evoked eNOS/nNOS uncoupling plays pivotal role in the paradoxical transformation of E2 into proinflammatory hormone in the myocardium and vasculature. These studies will further our understanding of the molecular mechanisms for the E2-dependent myocardial dysfunction caused by acute alcohol and will allow identification of novel targets for new interventions for the treatment/prevention of cardiovascular anomalies caused by alcohol in females.

CANCER

5-R03-CA141318-02
Nuclear Pore Complex Architecture and Drug Resistance in Ovarian Carcinomas
Mount Sinai School of Medicine of NYU
$82,208

The proposed studies are concerned with a novel mechanism by which ovarian cancinoma cells acquire resistance to cisplatin. While ovarian tumors initially respond well to cisplatin and carboplatin, 70 to 80% of advanced stage ovarian cancers will develop resistance to the drug. The proposed studies will investigate the role of changes in nuclear pore architecture and patterning that may contribute to the acquisition of drug resistance by ovarian cancer cells. While ovarian carcinomas initially respond well to treatment with platinum drugs, the majority relapse and acquire resistance. In ovarian carcinomas, they have observed reductions of NUP62 in resected tumor tissue from ovarian carcinomas, and redistribution of NUP62 among subnuclear fields of nuclear pore complexes (NPCs). Further, enrichment of NUP62-depleted NPCs renders ovarian carcinoma cells resistant to cisplatin in culture. The studies suggest the hypothesis that survival advantages conferred by the enrichment of NUP62- and/or NUP214+ NPCs may be exploited by tumor cells. To advance this hypothesis, they propose: 1) To investigate alterations in the accumulation and distribution of NUP62 and NUP214 in ovarian carcinomas, and to decipher how these factors correspond to tumor parameters; and, to investigate how changes in expression or accumulation of either NUP62 or NUP214 influences distribution of the other nucleoporin among NPCs. 2) To investigate how knockdown of NUP62 confers resistance to cisplatin; specifically, to decipher how altering the distribution and prevelance of NUP62+/NUP214- and NUP62-/NUP214+ NPC populations influence survival signaling through NF-:B signaling pathways. The proposed studies impact the basic biology of epigenetic regulation and may also illuminate a new approach to improving the prognosis of ovarian carcinomas treated with platinum drugs. As the patterning and architecture of NPC populations influences the sensitivity of ovarian carcinoma cells to cisplatin, small molecules may be developed that modify NPC architecture to enhance its therapeutic effectiveness. These agents may be employed to reduce the number of cells that survive and/or become latent in response to therapy, and also to chemosensitize relapsed tumors that have acquired platinum resistance.

1-R03-CA-156648-01
Vitamin D status, Gene Polymorphism and Breast Cancer Progression/Prognosis
Dorjgochoo, Tsogzolmaa
Vanderbilt University Medical Center
$77,710

Epidemiological studies of sunlight exposure, dietary and supplemental vitamin intake, and genetic variants have mostly focused on the role of vitamin D in mitigating breast cancer (BC)

risk, and a few studies have investigated the effect of vitamin D, particularly vitamin D gene polymorphisms, and only one of circulating vitamin D, on BC prognosis or survival. Although there is some evidence that vitamin D pathway genes and circulating 25(OH)D together play a role in mitigating BC risk, no data yet exist on their combined effect on BC progression; thus, the proposed study aims to fill this research gap by evaluating the association of circulating vitamin D and its pathway gene polymorphisms with BC prognosis. The results of this study could potentially lead to the development of new preventive and therapeutic strategies that can be applied to BC patients. The association of vitamin D deficiency, or low levels of circulating vitamin D, with increased risk for cancers, including breast cancer (BC), has received extensive attention. Experimental studies have shown that vitamin D has many anti-cancer properties, including anti-proliferative, anti-angiogenic, pro-apoptotic, and immunomodulation effects. Less attention has been paid to the role of vitamin D deficiency on BC prognosis and survival outcomes. Studies have shown that circulating vitamin D and polymorphisms in genes regulating vitamin D metabolism and signaling are both associated with BC risk, however, we know less about associations with BC prognosis. A few studies have linked low circulating vitamin D levels with prognostic factors for BC outcome, such as advanced disease or metastasis. Only one study directly evaluated the association between vitamin D status and BC survival, and no study has investigated this association in relation to vitamin D polymorphisms. We propose to address these questions in a prospective cohort of Chinese women with BC and test three hypotheses: 1) Circulating vitamin D level will predict BC progression and prognosis (recurrence, metastasis, overall or disease-specific death) after cancer treatment; 2) Genetic polymorphisms in vitamin D metabolism and signaling pathway genes affect circulating vitamin D level and its bioavailability in BC survivors; and 3) Circulating vitamin D and vitamin D gene polymorphisms together affect BC progression and prognosis. The proposed study will use resources from the Shanghai Breast Cancer Survival Study (SBCSS) and the Shanghai Breast Cancer Genome-Wide Association Study (GWAS). We will include 2,073 women newly-diagnosed with invasive BC and aged 20-74 years at the time of diagnosis, who have both blood samples for assessing circulating 25(OH)D and genotype information. Information on cancer diagnosis and conventional treatment, breast cancer recurrence, and causes of death will be verified through medical chart reviews. We will evaluate the effect of circulating vitamin D level and its combined effect with polymorphisms in the vitamin D pathway genes on BC progression and prognosis using appropriate statistical methods and controlling for known prognostic factors. The Mendelian Randomization (MR) method will be used to re-assess this association. Breast cancer survivorship is recognized as a critical component of cancer- related public health programs. The proposed study aims to fill a gap in our knowledge by evaluating the associations of circulating vitamin D and vitamin D pathway gene polymorphisms with breast cancer prognosis. This study will expand our understanding of the role of "Vitamin D status" and related pathway gene polymorphisms in BC prognosis. The study results could potentially lead to the development of new preventive and therapeutic strategies that can be applied to BC patients. In addition, the research could help determine if chemoprevention clinical trials with vitamin D should be considered for BC patients at high-risk for disease progression.

1-R21-CA-143619-01A1
Videoconference CBT for Rural Breast Cancer Survivors with Cognitive Complaints
Ferguson, Robert J
Eastern Maine Medical Center
$170,338

The proposed study seeks to advance knowledge concerning the value and use of health information technology (HIT) to expand access of care to rural and underserved populations. Teleconference technology allows real-time interaction with clinicians across vast geographical distances. This makes possible the delivery of important treatments to cancer patients who otherwise may not be able to benefit from such care due to geographical distance. Cognitive dysfunction associated with cancer chemotherapies can have a dramatic effect on cancer survivor quality of life and is recognized as a growing survivorship problem. However, the etiology of chemotherapy- related cognitive change is unknown, with no current broadly validated treatment. The PI is developing a brief cognitive-behavioral therapy (CBT; Memory and Attention Adaptation Training; MAAT) designed to help cancer survivors self-manage and cope with daily memory failure. Preliminary research suggests MAAT may improve self-reported daily cognitive failures and verbal memory performance, and survivors rate it with strong satisfaction, but more research is needed. The proposed research aims to evaluate a revised and more intense version of MAAT (increase from 4 to 8 visits) delivered through videoconferencing technology to aid rural breast cancer survivors with chemotherapy-related cognitive complaints-individuals with geographic and cost barriers to survivorship services. MAAT will be compared to a videoconference supportive therapy (ST). Thus, this study seeks to evaluate feasibility of MAAT delivered through videoconference technology. Participants. 48 women treated for stage I, II, or IIIa breast cancer with chemotherapy-related cognitive complaints, 6 months past last chemotherapy and who do not have other neurologic or psychiatric histories, or untreated anxiety or mood disorders will be enrolled. Intervention. MAAT-Video (MAAT-V) will consist of 8 weekly one-hour group sessions consisting of 2-4 members each linked by videoconferencing devices at up to 6 rural outreach clinics. Multiple participants can be seen by the clinician and participants can also see each other from different sites. ST is identical in length and time of sessions (8 one-hour sessions), but is more passive and less instructional than MAAT. Design. Breast cancer survivors will be randomized to either MAAT-V or ST. Survivors will be evaluated for self-reported impact of cognitive problems on quality of life, anxiety about cognitive problems, functional wellbeing, and on brief telephone-based neuropsychological tests of memory at 3 time points: pre-treatment, post-treatment and 2-month follow-up. Statistical analyses will consist of a 2 X 3 (baseline, post-treatment and follow-up), repeated measures analysis of variance with dependent measures listed above and a planned comparison approach to reduce risk of spurious findings. Type of chemotherapy, age, education, estimated IQ, fatigue, and other factors will be evaluated as possible covariates. Clinically significant change on outcome measures will be evaluated using the reliable change index (RCI). Satisfaction will be assessed with 0-8 Likert-type ratings. A qualitative analysis of 20 randomly selected participants will be completed to assess practicality of MAAT-V. Significance. Study results will advance knowledge of the feasibility of MAAT delivered through videoconference to improve breast cancer survivor quality of life, especially in rural, underserved areas.

1-R21-CA-155932-01A1
Survivorship Care Planning and Communication for Rural Breast Cancer Survivors
Geiger, Ann M.
Wake Forest University Health Sciences
$160,950

Experts have recommended that the often difficult transition from active treatment to cancer survivorship care be eased by preparation and communication of a survivorship care plan. Our study will gather information about rural-, suburban- and urban-residing cancer survivors' needs and preferences for survivorship care planning and communication. This information will help us design and evaluate a care planning process designed specifically to accommodate the needs of rural-residing survivors while also meeting the needs of suburban- and urban-residing survivors. The Institute of Medicine and others have strongly recommended survivors exiting active treatment receive a comprehensive survivorship care plan addressing surveillance, late effects symptoms, psychosocial needs, and general health maintenance, as well as indicating which providers will handle which components of the plan. Despite this recommendation, survivorship care planning and communication are often inadequate, leaving survivors confused and uncertain about their care. In addition, little is known about communication- related barriers to survivorship care, which may be of particular concern for rural-residing survivors who often live at some distance from their oncology specialist(s) and have limited primary care access. To reduce confusion and uncertainty, and to avoid duplication of medical effort, we envision a formal planning and communication process that integrates patient preferences with recommendations from multiple providers to generate a comprehensive survivorship care plan. [We believe effective implementation of this process requires a clinically-oriented individual like a nurse, nurse practitioner, physician assistant, or physician to facilitate and coordinate communications between survivors and their primary care and oncology specialty providers.] Our goal is to generate information needed to create and evaluate a process designed specifically to accommodate the needs of rural-residing survivors while also meeting the needs of suburban and urban survivors. Thus we aim to: (1) describe breast cancer survivors' knowledge about, perceived importance of, and barriers to survivorship care planning and communication; (2) assess survivors' current and preferred communication with oncology specialists and primary care providers about their survivorship care plans; and (3) explore the relationship between current survivor and provider survivorship care planning and communication with survivors' cancer-related uncertainty and quality of life. All data will be collected via a survey relying heavily on questions drawn from previously validated instruments and administered via hard copy mail, on-line or telephone interview. Our analytic approach will include descriptive statistics, correlation, and regression modeling. Both this proposal and the resulting testable intervention of a clinical model of survivorship care planning and communication will substantially advance our understanding of cancer survivorship care, particularly for rural-residing breast cancer survivors.

1-R21-AT006376-01
Acupuncture for Aromatase Inhibitor-Related Arthralgias in Breast Cancer Patients
Hershman, Dawn
Columbia University Health Sciences
$200,000

Aromatase inhibitors have been shown to improve the survival time of women diagnosed with breast cancer. However, many women discontinue this life extending therapy due to unwanted side effect such as joint pain. This study tests will confirm the findings of a pilot randomized trial of acupuncture for decreasing aromatase inhibitor-induced joint pain. We propose a multicenter randomized, sham-controlled study of 200 breast cancer survivors. Third generation aromatase inhibitors have been shown to be superior to tamoxifen in improving disease free survival, decreasing distant and local recurrence rates and decreasing incidence of contra-lateral breast cancer in women with early stage hormone receptor positive breast cancer. However, up to 50% of women on AI report symptoms of debilitating musculoskeletal pain and joint arthralgia that can lead to noncompliance and early discontinuation, thereby impacting survival. Our previous phase II randomized study (n=40) showed that acupuncture administered twice weekly for 6 weeks compare to sham acupuncture improve AI induced joint pain/stiffness as measured by modified Brief Pain Index short form (mBPI-sf) worse pain score by 50%. The proposed phase III randomized, sham controlled, blinded, multi-centered clinical trial will look at the effects of acupuncture on joint pain/stiffness that started or increased since initiation of AI in 200 women with Stage I-III breast cancer. Women will be recruited from four institutions and randomized to either true acupuncture or sham acupuncture administered twice weekly for 6 weeks follow by maintenance weekly acupuncture or sham acupuncture for 6 weeks. True acupuncture sessions will consists of standardized full body and joint specific point prescription and the NADA auricular protocol. The sham acupuncture treatment will consist of superficial needling at full body and joint specific point prescriptions that do not correspond to any true acupuncture points. The primary hypothesis is that acupuncture administered twice weekly for 6 weeks then weekly for 6 weeks will reduce joint pain/stiffness in women with AI induced arthragia as measured by mBPI-SF scores at 6 weeks compared to sham acupuncture. Secondary endpoints will assess whether weekly maintenance true acupuncture from week 6 to week 12 will maintain the effects seen at week 6 as measured by mBPI-SF score at 12 weeks and whether true acupuncture will have a durable effect as measure by mBPI-SF score at 24 weeks, compared to sham acupuncture. Other secondary endpoint (to be evaluated at baseline, 6, 12 and 24 weeks) include 1) additional assessment of joint pain/stiffness and functional status via self administered questionnaires (Western Ontario and McMaster Universities Osteoarthritis (WOMAC), Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) and Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International criteria (OMERACT-OARSI), 2) quality of life assessment via the self administered questionnaire Functional Assessment of Cancer Therapy- Breast/Endocrine subscale (FACT-B/ES), 3) analgesic use, 4) functional testing (grip strength and "timed get up and go' for lower extremity") and 5) exploratory hormonal and inflammatory biomarkers. This study will be the first large multi-center center intervention trial looking at the effects of acupuncture on AI induced arthragia in women with breast cancer.

1-R03-CA-156626-01
Advanced Glycation End Products And Colorectal Cancer Risk In Women
Jiao, Li
Baylor College Of Medicine
$98,397

The importance of the AGEs/RAGE axis in CRC development has not been investigated in women. The findings from this study may lead to identification of potentially modifiable risk factors for CRC and biomarkers for monitoring disease progression. Advanced glycation end-products (AGEs) are sugar adducts to proteins that form and accumulate under conditions of hyperglycemia. Binding of AGEs with the receptor for AGEs (RAGE) promotes oxidative stress and inflammation and soluble RAGE can block such effects. This application sets out to examine whether AGEs increase colorectal cancer risk and soluble RAGE play a protective role in colorectal cancer development among postmenopausal women in the Women's Health Initiative Observational Study. Advanced Glycation End-products (AGEs) are a heterogeneous group of compounds formed via the nonenzymatic glycation of lipids, proteins and nucleic acids. AGEs form endogenously during normal metabolism, and exogenously from foods processed at a high temperatures and tobacco smoking. N5- (carboxymethyl)-lysine (CML)-AGE is one of the best characterized AGEs. The accumulation of AGEs in the human tissues accelerates under hyperglycemia. AGEs trigger oxidative stress and inflammation by interacting with the receptor for AGEs (RAGE). Soluble RAGE (sRAGE) neutralizes the reactions mediated by the RAGE and therefore, acts as an anti-inflammatory factor. We recently reported that levels of sRAGE significantly predicted a lower risk of colorectal cancer (CRC) in Finnish male smokers. The role of AGEs and sRAGE in CRC development has not been investigated in women. We hypothesize that AGEs contributes to CRC development while sRAGE exerts a protective effect. We propose a case-cohort study that builds upon three NIH-funded studies conducted within the Women's Health Initiative (WHI) Observational Study of a cohort 93,676 postmenopausal women. The proposed study includes 425 incident CRC cases and 791 randomly selected subcohort participants. The study has three specific aims: 1) To examine the association between baseline fasting circulating levels of CML-AGE, sRAGE, and the sRAGE/CML ratio and risk of subsequent development of CRC; 2) to examine the independent predictors of circulating levels of CML-AGE and sRAGE among the subcohort participants, including age, body mass index, alcohol use, daily average intake of nutrients (e.g., carbohydrate nutrients and fatty acids), and tobacco smoking; and 3) to explore the inter-relationships among circulating levels of CML-AGE, sRAGE and serological markers of insulin resistance, inflammation and estradiol on the risk of CRC. The availability of pre-diagnostic bio-specimens and exposure information, as well as previously measured analytes, makes this study highly feasible and efficient. The long- term goal of this research is to elucidate a modifiable pathway, AGEs/RAGE, that may connect environmental exposure (e.g., dietary intake), inflammation, and insulin resistance with CRC etiology and prognosis.

1-R21-CA-149531-01A1
Decisional Aid Intervention for Women Considering Breast Reconstruction
Manne, Sharon L
Fox Chase Cancer Center
$200,000

The decision whether to pursue breast reconstruction (BR) can be challenging. Women must weigh the importance of potential benefits of the procedure and their personal values and preferences against the risks associated with the procedure and decide what type of reconstruction to have should they pursue it. We propose to develop a web-based decision aid for women being offered BR, evaluate its usability, feasibility, and acceptability, and gather preliminary data on its impact of BR knowledge, values, decisional conflict, preparedness, BR interest, and anxiety. The decision whether to pursue breast reconstruction (BR) can be challenging. Women must weigh the importance of potential benefits of the procedure and their personal values and preferences against the risks associated with the procedure and decide what type of reconstruction to have should they pursue it. The decision is typically made in a stressful circumstance, which is immediately after the initial diagnosis of breast cancer. Complicating matters is the fact that there is evidence to suggest that there are variable rates of satisfaction with the cosmetic outcomes of BR. Outcomes may not be in line with what the patient initially expected. BR can be a difficult decision made under stressful circumstances and women may not be as well- informed about the long-term effects as they could be. When patients are faced with treatment decisions for which personal values and quality of life issue play a role and there are multiple treatment choices, decision support in the form of decision aids can be helpful to the process of making a well-informed choice. Decision support aids are a strategy used as an adjunct to practitioners' counseling to facilitate their understanding of the treatment options, the advantages and disadvantages of each option, consideration of the personal importance they attach to the benefits and risks of each alternative, and to encourage active participation with the care provider in deciding which option to pursue. We propose to develop a web-based DA for women being offered BR. We will accomplish this in three phases. Phase 1 is a developmental phase where the basic DA content is developed by the study team with input from patients who have undergone BR, were offered BR and decided against it, or are considering BR. We will include input from minority women, women over 65 years of age, and less educated women, who have less access to BR. Phase 2 consists of gathering feedback terms on the DA prototype from women who have undergone BR, women who were offered BR and chose not to have it, and women who are considering BR. Again, feedback from minority women, women over 65 years of age, and less educated women will be included. The BR Decision Aid (BRDA) will then be finalized. Phase 3 will be a usability and feasibility pilot test of the DA with a sample of women considering BR. The study has one primary aim and two secondary aims. The primary aim is to evaluate the usability and feasibility of a decisional aid to assist women with making the decision to undergo BR. The secondary aims are to examine the acceptability of the BRDA and to provide preliminary data on the impact of BRDA on BR knowledge, values, decisional conflict, preparedness, BR interest, and anxiety.

1-R03-CA-162869-01
Understanding the Cervical Cancer Health Gap for Women in Jail
Ramaswamy, Megha
University of Kansas Medical Center
$80,361

The public health impact of this study is that it will inform interventions that reduce cervical health morbidity and mortality for an already disadvantaged group, women involved in the criminal justice system. This study will tell us not only about the chasm between women's understanding of Pap events and actual medical encounters, but will also speak more generally to this population's experience with health care access, given their movement in and out of the criminal justice system. Women in the criminal justice system are four-five times as likely to have cervical cancer compared to non- incarcerated women. Some have attributed this disparity to difficulty in follow-up of abnormal Paps, but little is known empirically about why women involved in the criminal justice system have low abnormal Pap follow-up rates. The objective of this application is two-fold: to understand the interpretation of abnormal Pap events and their subsequent follow-up from the perspective of incarcerated women; second, to interpret women's abnormal Pap events and follow-ups based on a review of their medical records. The validation of women's accounts of abnormal Pap follow-up (or lack thereof) with medical chart review will provide an understanding as to why some women do not gain access to follow-up care. Thus, we will be able target interventions to address this documented gap in women's understanding of abnormal Pap events versus actual events. To meet this objective, first we will conduct focus groups and in-depth interviews with 40 women in a Kansas City county jail about abnormal Pap screening and subsequent follow-up events. Studying women's experiences with abnormal Paps and follow-up may provide clues as to their cervical cancer screening knowledge and the processes by which women actually seek out cervical cancer prevention services given their movement in and out of jails. Second, we will ask the 40 women previously interviewed for permission to access their medical records, in order to investigate whether incarcerated women's self-report of abnormal Pap and follow-up events matched actual medical records of these events. This aim will allow us to gauge women's understanding of Pap events, validate the medical barriers that women faced in trying to gain access to follow- up care, and demonstrate the feasibility of assessing health care access through medical chart review for this high-risk population. This project has significance for public health impact by providing insight into how to address the cervical cancer burden for women involved in the criminal justice system. This project is innovative in its goal of assessing incarcerated women's understanding of abnormal Pap events and validating their understanding with medical record review. Study findings will contribute to the development of an intervention that attempts to close the cervical cancer health gap between women involved in the criminal justice system and their sisters in the "free" world.

5-U19-GM-061388-12
Pharmacogenetics of Phase II Drug Metabolizing Enzymes
Weinshilboum, Richard M
Mayo Clinic
$240,292

Breast cancer is the most frequent cancer of women and depression is the most common major psychiatric illness. Drugs are available to treat both of these serious illnesses, but many patients fail to respond and some suffer serious adverse drug reactions. The Mayo Clinic Pharmacogenomics Research Network (PGRN) will apply modern pharmacogenomic techniques to help make it possible to "individualize" the drug therapy of breast cancer and depression. The Mayo PGRN is an integrated, multidisciplinary, pharmacogenomic research effort based on a decades-long focus at Mayo on the pharmacogenetics of phase II (conjugating) drug metabolizing enzymes. The Mayo PGRN began by applying a "genotype-to-phenotype" research strategy that included, sequentially, gene resequencing, functional genomic, mechanistic and translational studies. During the present funding cycle, the Mayo PGRN has also incorporated the use of genome-wide techniques and pharmacogenomic model systems, with a special emphasis on functional mechanisms responsible for genetic effects on drug response. They have used that approach to study the pharmacogenomics ofthe endocrine therapy of breast cancer and selective serotonin reuptake inhibitor (SSRI) therapy of depression - research that grew out of the contribution of phase II enzymes to the biotransformation of the estrogens that play such an important role in breast cancer and biotransformation ofthe neurotransmitters that are central to the pathophysiology and treatment of depression. Recently, they have performed pharmacogenomic genome-wide association (GWA) studies of breast cancer, and they will soon perform similar studies of the SSRI therapy of depression. They propose to continue this genome- wide focus during the next funding cycle, with both clinical and model system GWA studies of the drug therapy of breast cancer and depression, always including replication as well as functional and mechanistic studies. They also propose two "Network Resources", one designed to provide access to "Next Generation" DNA sequencing for all PGRN Centers and the other focused on pharmacogenomic ontology. In summary, the studies in this application build on Mayo PGRN strengths in DNA sequencing and functional genomics - while incorporating genome-wide techniques - to provide insight into the role of inheritance in variation in the efficacy and side effects of drugs used to treat breast cancer and depression.

1-R21-CA-160917-01
Role of the Fractalkine Signaling in Epithelial Ovarian Carcinoma (EOC)
Barbolina, Maria V
University Of Illinois At Chicago
$ (NCI funded this ANSWHR award)

Epithelial ovarian carcinoma is the deadliest gynecologic malignancy mainly due to metastasis and is an unsolved problem in public health. In this proposal we will characterize the requirement for chemokine signaling in progression of ovarian carcinoma, because 1) according to our preliminary data it could play a major role in all stages of the ovarian carcinoma metastatic cascade, and 2) chemokines and their receptors are effective drug targets proven to work in the clinic in treatments of other diseases. Epithelial ovarian carcinoma (EOC) is a leading cause of death from gynecologic malignancies. Peritoneal metastasis is an unsolved clinical problem in treatment of EOC. Currently used therapeutic approaches are not specific to EOC metastasis and are inefficient at keeping patients in remission. Thus, targeting the pro-metastatic pathways could provide improved opportunities to increase survival. In our approach to find new targets we searched among pathways that satisfy the following criteria: 1) play a major role in EOC progression; 2) have proven to be effective targets for treatments of other diseases. Chemokine signaling is essential for cancer cell migration, proliferation, adhesion, and invasion, i.e., properties that are necessary for a successful development of metastasis. In this application we will characterize fractalkine pathway as crucial for the development of metastasis in EOC and determine potential usefulness of its main players, chemokine fractalkine (CX3CL1) and its receptor, fractalkine CX3CR1, as novel targets for future therapies aimed at prevention and retardation of metastatic spread. Our preliminary data show that primary and metastatic specimens of human EOC are highly positive for CX3CR1, while normal ovarian surface epithelium in non-diseased control subjects is CX3CR1-negative. Moreover, we show that EOC cells can migrate in CX3CR1-dependent manner to CX3CL1. Furthermore, in our pilot experiments increase of CX3CR1 expression in EOC cells led to formation of more tumors of larger size in a xenograft EOC mouse model. Chemokines are promising drug targets. Moreover, chemokine receptors are the G protein coupled receptors, a class of proteins that are effective drug targets covering an estimated 30% of FDA approved drugs. Such drugs have been proven to work in the clinic, and new drugs against CX3CL1 and CX3CR1 are currently under development. CX3CL1/CX3CR1 is a uniquely suitable drug target because the interaction between the chemokine and its receptor is very specific, and there are no other chemokine ligands activating CX3CR1, in contrast to other chemokine/receptor pairs that display high cross-reactivity. Thus, drugs directed at either CX3CR1 or CX3CL1 will likely to affect only the CX3CL1/CX3CR1 axis. Based on our preliminary data and published literature our hypothesis is that CX3CL1/CX3CR1 axis is required for homing metastatic EOC cells to the peritoneum and facilitation of metastatic spread by supporting cell adhesion and migration. To test this hypothesis we propose two aims. In Aim 1 we will determine the requirement of CX3CL1/CX3CR1 in adhesion to peritoneal mesothelial cells and underlying extracellular matrix using cell culture models and previously developed by us EOC metastasis-specific culture conditions. Adhesion is one of the main initial steps of the metastatic colonization of the peritoneum. In Aim 2 we will characterize the requirement for CX3CL1/CX3CR1 in development of EOC metastasis in vivo using a xenograft mouse model.

1-R21-CA-161713-01
Confirmation Studies Of Blood Based Biomarkers Of Risk For Breast Cancer
Hanash, Samir M
Fred Hutchinson Cancer Research Center
$ (NCI funded this ANSWHR award)

There is a substantial need to identify women at increased risk for developing breast cancer. Prior studies by the applicants using in-depth quantitative technology to profile circulating proteins in the blood for potential risk markers have identified many potential markers of risk among post-menopausal women that subsequently developed breast cancer. These novel candidate risk markers for breast cancer require additional studies for their verification. The objectives of this proposal to do additional verification studies of the candidate biomarkers in an independent set of women from the Women's Health Initiative and to determine the relevance of these markers as mediators of the risk for breast cancer associated with post-menopausal hormone therapy. There is a substantial need to identify biomarkers of risk for breast cancer. An in-depth quantitative proteomics approach was applied to the analysis of plasmas that were collected prior to a diagnosis of breast cancer in search for candidate markers of risk for this disease. The samples were obtained from the Women's Health Initiative (WHI) cohort and consisted of women diagnosed with breast cancer within seven years of blood collection and controls matched for age, self-reported ethnicity, hysterectomy status and enrollment date. In parallel studies proteomic profiling was applied to blood specimens obtained at baseline and following one year of hormone therapy (HT) with conjugated equine estrogen (CEE) or CEE/MPA (medroxyprogesterone acetate). Extensive proteomic analyses identified a large subset of circulating proteins that were affected by HRT, and has also yielded a set of breast cancer risk marker candidates that merit additional validation studies. Interestingly some of the risk candidates were also affected by HRT and thus may contribute to elucidation of breast cancer risk associated with CEE/MPA therapy. In aim 1, we propose to conduct a confirmation study of risk markers identified using an independent set of WHI participants from the WHI hormone therapy trials who developed breast cancer and matched controls. Of the 14 candidates to be subjected to confirmation studies, eight have ELISAs available that would allow their assay. The remainder of the candidates would be subjected to confirmation using Multiple Reaction Monitoring mass spectrometry. A second aim consists of evaluating the identified risk markers as mediators of hormone therapy effects on breast cancer. To that effect plasmas collected at baseline and at 1-year of HT in the CEE and CEE/MPA trials will be utilized to determine changes in concentration of risk marker candidates in cases and in matched controls. The proposed project has the potential to contribute clinically relevant breast cancer biomarkers to identify women at increased risk and to clarify breast cancer risk associated with postmenopausal hormone therapy.

5-R21-CA-135570-02
Estrogen and Skin Cancer
Oberyszyn, Tatiana M
Ohio State University
$ (NCI funded this ANSWHR award)

There is an increase societal pressure in the US to remain young looking. Several studies carried out in post-menopausal women demonstrate the effectiveness of topical estrogen in reversing the signs of aging including thinning, dryness and wrinkling. As a result younger pre- and peri-menopausal women are turning to topical creams containing estrogen as anti-aging lotions. Our preliminary studies using female Skh-1 hairless mice found a significant increase in the number of tumors in mice treated topically with estrogen immediately following UVB exposure compared to mice treated with vehicle control. These data indicate that increased levels of estrogen in the skin combined with UV exposure may act to enhance initiation and promotion of UV- induced skin cancers. These findings also suggest that the use of lotions and creams containing estrogenic compounds on sun exposed sites by younger women may be contributing to the increase in the number of skin tumors being diagnosed in women under the age of 40. The current studies are designed to determine the effect of topical estrogen treatment of previously UVB exposed skin on tumor development and progression from benign lesions to frank malignant squamous cell carcinomas. Americans live in a culture that glorifies youth. According to market researcher FIND/SVP, the anti- aging products market is expected to hit $56 billion by 2007. Studies in post-menopausal women have found that hormone replacement therapy is effective at reversing the dryness and wrinkling that affects aging skin. Based on these studies, there is increasing interest in the use of topical creams containing hormones such as estrogen to prevent or reverse some of the normal cutaneous aging processes in younger pre-menopausal women. While exposure to these creams may be beneficial cosmetically, the effect of applying estrogen to sun exposed sites for prolonged periods of time, on skin cancer development is not known. Our preliminary studies using female Skh-1 hairless mice found a significant increase in the number of tumors in mice treated topically with estrogen immediately following UVB exposure compared to mice treated with vehicle control. These data indicate that increased levels of estrogen in the skin combined with UV exposure may act to enhance initiation and promotion of UV-induced skin cancers. These findings also suggest that the use of lotions and creams containing estrogenic compounds on sun exposed sites by younger women may be contributing to the increase in the number of skin tumors being diagnosed in women under the age of 40. Most studies have examined the effects of topical or systemic estrogen on the skin in post-menopausal women, however the reality is that younger pre-menopausal women are applying topical estrogen containing creams on their faces previously exposed to UV light to prevent/reverse the signs of aging. Two specific aims are proposed to test the hypothesis that topical estrogen application to previously UVB exposed skin accelerates skin carcinogenesis. Studies in specific aim 1 will use the Skh-1 hairless mouse murine model of UVB induced skin carcinogenesis to determine the effects of clinically used topically applied estrogen (Estrogel(R)) on UVB induced skin tumor development in previously UVB exposed female skin of intact (pre-menopausal) and ovariectomized (post-menopausal) mice. Studies in specific aim 2 will determine the effects of topically applied estrogen (Estrogel(R)) on UVB induced skin tumor progression in female Skh-1 skin of intact and ovariectomized mice. The studies carried out in

these aims will determine whether topical estrogen increases the number of UVB induced skin tumors that develop and also whether it differentially enhances the progression of benign UVB-induced tumors to malignant squamous cell carcinomas in intact (pre-menopausal) and ovariectomized (post-menopausal) mice.

N01-CP11005
Efficacy of HPV-16/18 Vaccine Against Oral HPV Infections
Kreimer, Aimee
NCI Intramural Research Project
$50,000

With support from ORWH, we previously expanded specimen collection in our Costa Rica trial to permit the evaluation of vaccine efficacy at sites other than the cervix. It is now known that HPV causes a subset of H&N cancers, cancers of the oropharynx in particular. Given this, we are now in the process of evaluating efficacy of the vaccine to protect against HPV infections in the oral cavity. Testing of oral specimens for HPV DNA using sensitive methods is ongoing and expected to be completed in FY11. Once testing is completed, data preparation and analysis will follow. ORWH support could be used to support the analytical efforts associated with this evaluation.

N01-CP11005
Natural History and Clinical Implications of Anal HPV Infections
Kreimer, Aimee
NCI Intramural Research Project
$200,000

HPV is known to be involved in the development of the majority of anal cancers. Anal cancers are more common in women than in men, and are increasing in the United States. We previously noted that anal HPV infection is common (about 30%) among young adult women in our population in Costa Rica. Understanding of the natural history of anal HPV infections and the clinical significance of anal HPV positivity is limited. In particular, information on rates of persistent HPV given infection and the clinical implications of these persistent infections and any associated lesions is lacking. We have the opportunity to evaluate these issues within our cohort of women in Costa Rica. ORWH support could be used for activities associated with the follow-up and testing of women in our cohort previously found to have an HPV infection.

N01-CP11005
Gallbladder Cancer Pilot Study
Hsing, Ann; Koshiol Jill
NCI Intramural Research Project
$150,000

Gallbladder cancer is one of the few non-gynecological tumors known to occur with higher frequency in women than in men. The highest rates of this cancer (particularly in women) are observed in Chile. Investigators in the Infections and Immuno-epidemiology Branch (IIB) are evaluating the feasibility of conducting a case-control study of gallbladder cancer in Chile to better understand the causes of this disease. As currently envisioned, the initial pilot effort will define whether such a study would be successful at identifying and enrolling cancer cases, controls with gallstones (an important precursor for this cancer) and controls form the general population. We are working with well established investigators in the region with a proven track record of conducting epidemiological investigations to maximize the likelihood of success. A case-control study of gallbladder cancer in Chile would permit us to elucidate the role of obesity (and metabolic syndrome more generally), diet, infections, immunological responses, and genetic susceptibility factors in the etiology of this tumor. This study could have important public health implications, since cholecystectomies are currently being recommended for women for the prophylaxis of gallbladder cancer in this high risk area. A better understanding of the causes of this disease could lead to the development of better and less aggressive preventative measures against this disease.

N01-CP11005
Comparison of the Impact of Vaccination with Gardasil and Cervarix
Hildesheim, Allan
NCI Intramural Research Project
$50,000

Two vaccines are currently licensed for the prevention of HPV-infections and their associated cancers - Gardasil and Cervarix. While both vaccines are based on HPV virus-like particles, they differ with respect to the HPV types included in the vaccine, the adjuvant used, and potentially by the ability to protect against infections with HPV types other than those included in the vaccine formulation. Given these differences, it is currently unclear whether the overall impact afforded by use of these two vaccines will be similar or not, and to the extent that they differ by how much. Support from ORWH will be used for analyses aimed at addressing this question.

N01-CP11005
Immune Markers of Protection by HPV Vaccination
Safaeian, Mahboobeh; Hildesheim, Allan
NCI Intramural Research Project
$100,000

One of the stated aims of the publically-funded HPV vaccine trial in Costa Rica is to investigate potential immunological markers and mechanisms of protection by the HPV vaccine that might assist in the identification of minimal levels required for protection and also assist in the generation of second generation and/or other vaccines in the future. At the HPV Immunology Laboratory affiliated with our group, we have developed assays to help monitor vaccine immune responses after vaccination in our cohort. Support from ORWH will help activities at the laboratory to evaluate immune responses and to evaluate markers of protection against both homologous and non-homologous HPV types. It will also assist in our immunological follow-up of individuals receiving different numbers of doses, to further understand our recent finding that vaccine efficacy is observed when fewer than three doses are administered.

3-P30-CA-016058-35S1
Cancer Center Support Grant
Caligiuri, Michael A
Ohio State University
$5,000
Title: Cancer Health Disparities Research among Appalachian Women
Principal Investigators: Michael Caligiuri and Electra Paskett

Women in Appalachia Ohio suffer a disproportionate burden of cancer, including higher cancer incidence and mortality rates for cervical, colon, and lung cancer compared to cancer rates for women in Non-Appalachian region of Ohio. The proposed supplement would support a Conference to strengthen the existing community and academic infrastructure to increase community-based participatory research (CBPR) capacity within Appalachia Ohio to address the cancer health disparities among women in Appalachia Ohio. Plans for this proposed Conference have been developed in collaboration with established community partners and identified needs among women in this community. The Conference will consist of two related educational efforts: a Seminar designed to build upon our past efforts to increase knowledge about cancer health disparities among women in Appalachia, and a Workshop to support the development of joint research efforts between academic researchers and community partners to address these disparities. The Seminar will feature presentations about CBPR programs conducted to address cancer in Appalachian women by scientist/academic researchers, as well as evidence-informed interventions conducted by community partners. The agenda for the Workshop will help build academic-community partnerships through interactive sessions on the important components of CBPR and strategies to ensure academic-community partnerships effectively address cancer health disparities and cultural barrier among underserved women in Appalachia Ohio. Collectively, this conference will maximize learning, group interaction and networking among academic researchers at the Ohio State University and established community partners through the Appalachia Community Cancer Network (ACCN) to enhance joint CBPR efforts through academic-community partnerships with a goal of reducing cancer health disparities among

women in Appalachia. The proposed conference will strengthen the academic-community infrastructure at the OSUCCC to increase CBPR capacity within Appalachia to address defined cancer health disparities including elevated rates of cervical, colon and lung cancers among women in Appalachia. OSUCCC will plan, implement and evaluate this conference with a clear vision of the needs and values of this community.

3-P30-CA-047904-23S1
Cancer Center Support Grant
Davidson, Nancy E
University Of Pittsburgh
$15,000
Pilot study of somatic mutations and gene fusions in ovarian cancer
Principal Investigators:
Adrian V. Lee, Ph.D., Aleksandar Milosavljevic Ph.D. and Xiaosong Wang, M.D.

Ovarian cancer is the largest cause of death from female reproductive tract cancers. In 2010, there were an estimated 21,880 new cases and 13,850 deaths. The high rate of mortality from ovarian cancer is in part due to diagnosis at an advanced stage. Indeed, up to 70% of ovarian cancers have metastasized at diagnosis, and only 30% of women with this diagnosis can expect to live 5 years. In stark contrast, 20% of ovarian cancer is detected at an early stage (and within the ovary) resulting in an excellent 90% survival rate (2). While the last 30 years has seen dramatic reductions in mortality rates from several cancers (e.g. a 30% reduction in breast cancer mortality), the mortality rate from ovarian cancer has seen only a modest improvement. We propose a pilot analysis of ovarian cancer data publicly available from the Cancer Genome Atlas to: 1) Identify novel fusion genes which might serve as novel diagnostic, prognostic, and therapeutic targets, and 2) identify patterns of somatic mutations which may highlight novel pathways for therapy. This pilot project will involve a unique collaboration between investigators in the newly developed Women's Cancer Research Center (a collaboration between the University of Pittsburgh Cancer Institute (UPCI) and the Magee Women's Research Institute), and bioinformaticians in the Dan L Duncan Cancer Center at Baylor College of Medicine. TCGA is a rapidly providing an outstanding wealth of information on molecular alterations in many cancers (http://cancergenome.nih.gov/). However, similar to most other studies, this information (data) needs translation into knowledge, particularly the clinical relevance of the identified changes. The ovarian cancer dataset at TCGA is one of the most mature (http://tcga-data.nci.nih.gov/tcga/). 587 matched and tumor tissues have been analyzed. Assays have included expression arrays (mRNA and miRNA), DNA copy number and SNP arrays, methylation marks, and massively parallel sequencing. UPCI is a major contributor to TCGA. For ovarian cancer, UPCI provided approximately 120 matched normal and tumor tissue, and about 62 passed QC and are in the final dataset. Our goal is to perform an initial pilot analysis of molecular changes in the ovarian cancers and validate them in the index cases we have here at UCPI. Validated somatic alterations will then be examined in larger data sets and correlated with clinical features and outcomes.

3-P30-CA-072720-13S9
Cancer Center Support Grant
Dipaola, Robert S
UMDNJ-Robert Wood Johnson Medical School
$15,000
Title of project: The influence of gender on the relationship between mental health and smoking.
Principal Investigator: Cristine D. Delnevo, Ph.D.

Individuals with past-month mental health problems are approximately twice as likely to smoke as other persons and suffer a greater burden from tobacco-related morbidity and mortality, including cancer. In addition, women are overrepresented among smokers with poor mental health and preliminary data from our research team suggests that relationship between smoking and poor mental health may differ by gender. We propose analyses of three public health surveillance data systems to explore the issue of smoking and mental health by gender. The Behavioral Risk Factor Surveillance System (BRFSS), the National Survey on Drug Use and Health (NSDUH), and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) all address both tobacco use and mental health. Accordingly, we will conduct secondary data analyses to achieve these specific aims: 1) document the prevalence and demographic correlates of tobacco use and nicotine dependence among individuals with poor mental health and 2) evaluate whether there is an interaction effect by gender for smoking and poor mental health. We hypothesize that women with mental health problems, particularly certain psychiatric disorders, will be at higher risk for current smoking and nicotine dependence than men. More research is needed to examine gender disparities in the context of mental health and smoking. Thus, the significance of this proposed research is its potential to generate a better understanding of smoking and mental health by gender to inform and direct tobacco control efforts which are vital to reducing tobacco-caused cancers in women.

3-P30-CA-138313-03S1
Medical University of South Carolina - Cancer Center Support Grant
Kraft, Andrew S
Medical University Of South Carolina
$15,000
Title: Disruption of ceramide synthesis by CerS2 depletion as a tool to increase breast cancer sensitivity to taxane therapy
Principal Investigators: Stefka D. Spassieva and Lina M. Obeid

Paclitaxel is widely used for breast cancer treatment, but the success of the chemotherapy can be hindered by patients not responding or developing resistance; therefore, it is important to discover new strategies to increase sensitivity or to overcome the resistance to taxane therapy, which will improve the chances of breast cancer patients to become diseases-free. With our pilot project proposal, we address the possibility of developing such a new strategy by investigating breast cancer sensitization and resistance to paclitaxel in the context of the ceramide pathway. The potential of the ceramide pathway to sensitize to paclitaxel treatment was recently shown in a functional genomics screen . In that screen, several members of ceramide pathway are shown

to alter theresponse of chemotherapy resistant cancer cell lines (including a breast cancer cell line) to paclitaxel treatment. Of particular interest for our current study is one member of the ceramide pathway, ceramide synthase 2 (CerS2), which when down-regulated by siRNA was shown to increase the sensitivity of cancer cells to paclitaxel. Moreover, our recent study showed that depletion of CerS2 resulted in alteration of ceramide metabolism, activation of the Unfolded Protein Response (UPR), and induction of autophagy. In addition to the findings from our laboratory, the functional genomics screen showed that paclitaxel treatment of cancer cells can activated the UPR as well. Moreover, a very recent study found that the elevation of 78-kDaglucose-regulated protein (GRP78), an UPR marker, can serve as a predictor for the effectiveness of the taxane treatment in breast cancer patients. Accordingly, our working hypothesis is that aberrant ceramide synthesis in CerS2 depleted breast cancer cells disrupts ER homeostasis, which when combined with paclitaxel treatment, enhances ER stress and leads to cell death.

3-P30-CA-016359-33S1
Yale Comprehensive Cancer Center
Lynch, Thomas James
Yale University
$20,000
Title: Testing the Feasibility of a Nurse Patient Navigation Intervention in Lung Cancer
Principal Investigator: Ruth McCorkle, Ph.D., R.N.

This single blind, randomized clinical trial is designed to 1) describe the feasibility of implementing a Nurse Patient Navigation (NPN) intervention that addresses patient and caregiver questions, symptoms, psychosocial needs, and facilitates timely, coordinated care, and 2) compare the impact of the NPN Intervention with an attention control group at Smilow Cancer Hospital with newly diagnosed advanced lung cancer patients on quality of life outcomes, utilization of health care services, and perceptions of care transitions. Thirty-two women newly diagnosed with advanced lung cancer will be randomized to either the NPN intervention or attention control groups. The 14 contact NPN intervention includes provision of information, problem-solving strategies, coordination of care, and support for patients that will enhance their QOL and increase their perception of care transition. Outcome data will be collected on patient quality of life outcomes, health care utilization, and care transition at baseline, 1, and 3months post diagnosis. The primary goal of this application is to assess the feasibility of implementing a Nurse Patient Navigation (NPN) intervention for newly diagnosed advanced lung cancer patients. The intervention will be implemented and evaluated with women undergoing diagnostic and staging procedures, including surgery, at Smilow Cancer Hospital (SCH).

5-R01-CA-126841-03
Regulatory T Cell Function in Ovarian Cancer
Moysich, Kirsten B
Roswell Park Cancer Institute Corp
$15,000
Title: Single Nucleotide Polymorphisms (SNPs) in the anti-inflammatory cortisol pathway and the risk of ovarian cancer
Principal Investigator: Kirsten Moysich

Ovarian cancer remains the most lethal gynecological cancer, due to the fact that the majority of patients present with advanced disease at diagnosis. The established risk factors such as parity, use of oral contraceptive (OC) pills, use of NSAIDS, and talc exposure, suggest a role of ovulation and inflammation in the etiology of ovarian cancer. More than 90% ovarian tumors arise from the surface epithelium[1] lined by a single layer of squamous to cuboidal cells covering the entire ovarian surface[2]. This epithelium is breached during each ovulation leading to an inflammatory reaction [3-4]. Persistence of inflammation associated with ovulation can cause genetic damage and trigger carcinogenesis. Cortisol, a major anti-inflammatory steroid plays a significant role in attenuating inflammation, thereby reducing the risk of ovarian carcinogenesis. Levels of cortisol in the ovarian epithelium rise significantly prior to ovulation. Ovarian tumor cells have significantly reduced expression of genes in the cortisol pathway compared to those in normal ovarian epithelial cells [5]. We, therefore, hypothesize that single nucleotide polymorphisms (SNPs) in genes involved in the cortisol pathway are associated with the risk of ovarian cancer due to potential variation in anti-inflammatory cortisol response. SNPs in these candidate genes have not been adequately captured in a recent GWAS of ovarian cancer. Thus a thorough investigation of genetic variability in this highly biologically plausible pathway is warranted. We propose to utilize data and samples from an existing study of 800 incident epithelial ovarian cancer cases and 800 population-based controls recruited in Pennsylvania, Ohio, and New York between 2003 and 2008. Our first aim is to evaluate the association of SNPs in the cortisol pathway and the risk of ovarian cancer. We will identify functional and tag SNPs using public databases (Hapmap, Genome Variation Server, dbSNP). Logistic regression models will be used to estimate the associations between these SNPs and risk of ovarian cancer. Our second aim is to evaluate the association of SNPs in the cortisol pathway with the severity of disease (grade and stage of ovarian cancer) at diagnosis. Finally, in our exploratory aim, we propose to conduct a preliminary analysis on a subset of patients to evaluate the associations of SNPs in the cortisol pathway and disease-free and overall survival. We have substantial follow-up time (at least five years) on a large subset of the study sample. We will use Cox proportional hazards ratios and Kaplan-Meier survival probabilities to analyze the data. Dr. Moysich maintains active national and international collaborations with ovarian cancer researchers and will have access to a number of study samples for replicating significant genetic associations. The results of this study will provide a valuable insight into the etiology of ovarian cancer by uncovering an important anti-inflammatory pathway. It could also potentially help to direct therapeutic research and develop strategies to screen high risk women for prognosis

3-R01-CA-118136-05S2
Stress, Immunity & Cervical Cancer: Biobehavioral Outcomes of a Randomized Trial
Wenzel, Lari
University Of California, Irvine
$15,000

Telomeres are structures composed of repetitive DNA sequences that cap the end of chromosomes and play a critical role in preserving genomic stability and integrity. Short telomeres have been associated with hematologic and solid tumor malignancies. But more recently, in a pivotal epidemiologic study shortened telomere length was associated with development of primary malignancy and mortality after controlling for other factors typically linked with cancer , supporting an etiologic role for shortened telomeres in cancer development and progression. Telomere length in leukocytes has been documented to be responsive to a number of stimuli and in some cases can result in lengthening of telomeres . Recently, an accelerated rate of telomere loss in peripheral blood mononuclear cells (PBMCs) has been described in chronically stressed populations (3-6), begging the question can modulation of chronic stress result in changes in telomere length or rate of telomere loss? We have used archived PBMC specimens from a recently completed randomized clinical trial, in which our group demonstrated that a psychosocial telephone counseling (PTC) intervention significantly improved quality of life (QOL) and biobehavioral parameters associated with chronic stress in a cervical cancer survivor cohort (7), to establish the capacity to examine longitudinal associations between telomere length and other parameters of the psychoneuroimmune axis associated with chronic stress. We established methodologies for evaluating telomere length from PBMC subsets: T cell (CD3, CD4 and CD8), B cell (CD19) and monocyte (CD14) cellular subsets using the Flow-FISH assay. In this small sample set (n=30 subjects, for which specimens were available), a longitudinal decrease in psychological distress was associated with increased telomere length within the T cell subset population (CD3) ($r = -0.565$, $p = 0.018$). Given the previously published association between improved QOL and increased Th1 immunologic stance, it was reassuring that increased telomere length in the CD3 T cell subset was also associated with a shift toward a Th1 immune profile ($r = 0.582$; $p = 0.023$). These data provide proof of concept for the longitudinal analyses of telomere length from cryopreserved PBMCs and support telomere length as a novel component of biobehavioral paradigms, and provide preliminary data in support of exploring associations between stress response and telomere length. Thus, we propose to examine a larger sample set, over a more substantial longitudinal time frame, by conducting these analyses on PBMCs that are being collected from an ongoing larger randomized clinical study (5RO1CA118136-04 Stress, Immunity & Cervical Cancer: Biobehavioral Outcomes of a Randomized Trial) (target 250 subjects) testing biobehavioral differences between those counseled compared to those not counseled, to evaluate the downstream physiologic effects of improved QOL and decreased stress responses. This study would have provocative implications for the association between the psychoneuroimmune axis, telomere dynamics and survivorship outcomes in an underserved female population and as an area of scientific priority, directly addresses the examination of social factors, health behaviors and their interaction with biology in a testable, comprehensive interdisciplinary model of health affecting cancer treatment, control and survivorship.

OD-11-302
Characterization of Novel Viruses from Human Genitals
NCI Intramural—Center for Cancer Research
$25,000
Principal Investigators: Christopher B. Buck and Diana V. Pastrana

Next-generation sequencing projects characterizing the ribosomal genes of bacterial species have revealed that humans are stably colonized by a staggering diversity of distinct microbial species. Since viruses lack universally conserved gene products, such as ribosomal sequences, comprehensive elucidation of the diversity of the viral constitutents of the human "metagenome" has been more challenging. This proposal is aimed at developing a more detailed catalog of viral sequences chronically shed into the human genital tract. By expanding our knowledge of the human genital virome, we hope to gain insight into several diseases. For example, about a dozen known species of human papillomavirus (HPV) are thought to play a role in essentially all cases of cancer of the uterine cervix, as well as roughly 20-60% of vulvar and vaginal cancers. Several known HPV species have also been suggested as possible causal factors underlying a fraction of miscarriages. The fraction of gynecological cancers and miscarriages that are not attributable to known HPVs might theoretically be linked to previously unidentified members of the papillomavirus family or to other unidentified viruses that may commonly inhabit the female genital tract. Our laboratory has previously utilized amethod known as rolling circle amplification (RCA) to identify previously unknownHPVs and other viral families that are common constituents of skin virome of healthy human subjects. This previous work also revealed a wide variety of DNA sequences with little or no homology to any sequences available in GenBank. For the current project, we have obtained genital swab specimens from HIV infected individuals, who might be expected to harbor a higher burden of genital viral flora. Next-generation sequencing of these samples has revealed an overwhelming number of sequence fragments with no clear homologs, as well as sequence fragments with distant homology to known HPV genera. Several intriguing classes of sequence show limited resemblance to viral families that have previously only been found in plants or fungi. These preliminary data warrant continuation of the project, which will involve cloning and sequencing the complete genomes of unidentified new genera of HPVs, as well as full-length sequencing of candidate novel human virus families.

OD-11-302
Urinary Estrogens and Estrogen Metabolites in Relation to Objective Measures of Physical Activity among Controls in the NCI Polish Breast Cancer Study
Dalla, Cher; Gierach, Gretchen
NCI Intramural, Division of Cancer Epidemiology and Genetics
$15,000

The prevalence of obesity remains elevated in the United States, particularly among women. According to data from the National Health and Nutrition Examination Survey, 35% of women in the United States were classified as obese in 2007-2008 with a BMI of $\geq$ 30 kg/m2. More specifically, the prevalence of obesity among women ages 40-59 was 38.2% during this time period. This is of particular importance given the consistent association between obesity and an

increased risk of cancer among postmenopausal women, including cancers of the breast, endometrium, and colon. Additionally, numerous epidemiological studies suggest that higher levels of physical activity may reduce postmenopausal breast cancer risk . However, the mechanisms underlying these observed associations and the relationship between energy balance and biomarkers, such as estrogens and their metabolites, remain unclear. Promoting physical activity may have important implications for reducing breast cancer risk and other cancers, but to date, our understanding of the underlying mechanisms is limited in several respects: 1) lack of objective measures of physical activity in studies of sex steroid hormones; 2) incomplete assessment of estrogen metabolites, which are suggested to differentially contribute to breast cancer risk and 3) small sample sizes and limited covariate information in previous studies. We aim to better define relationships between physical activity and estrogen metabolites among postmenopausal women by leveraging the existing resources of the population-based NCI Polish Breast Cancer Study. We propose a novel approach to examine the association between accelerometer measured physical activity and a more comprehensive estrogen hormone profile among population-based controls (n=685) from the Warsaw site of the Polish Breast Cancer Study. Objective physical activity measures, collected through the use of an accelerometer, quantify the duration and intensity of activity on a minute-by-minute basis, without the limitation of self-report bias. This study addresses health behaviors and their interaction with biology and their role in cancer prevention, two areas of scientific priority outlined by the Institute of Medicine (IOM). Findings from this study will extend our biological understanding of the effects of physical activity, a modifiable health behavior, on estrogen metabolism and may contribute to translational efforts to improve cancer prevention and risk prediction for women.

OD-11-302
Symposium: Opportunities and Changes in Cancer Research among Women in Developing Countries
Ji, Bu-Tian; Chow, Wong Ho
NCI Intramural, Division of Cancer Epidemiology and Genetics
$5,000

Studies of cancer risks and survival in different populations with diverse exposures, cancer surveillance and care, and varying incidence and mortality patterns broaden the opportunities for discoveries of cancer causes and prognostic factors. With rapid changes in economic conditions and industrial development in Asia, particularly in countries such as China, South Korea, and Japan, lifestyle and environmental exposures in this region have also undergone substantial changes over the past few decades. These changes are reflected in the cancer incidence patterns of these countries. For instance, in Shanghai, China, incidence rates of cancers that are traditionally high in developing countries, such as esophageal squamous cell carcinoma, and cancers of the stomach and liver, have declined precipitously over the past few decades. In contrast, cancers of the colon and breast have increased substantially. In fact, among women under age 50 years, breast cancer is the most rapidly rising malignancy in Shanghai. Similar cancer incidence patterns are being reported in other areas of Asia. Changes in lifestyle such as fewer number of children and later age at first child birth, decreased physical activity both at work and at home, and increasing intake of meat, fat, and processed foods are believed to have contributed to the upward trends of colon cancer and breast cancer among women in Shanghai

and some other areas in Asia. Likewise, the relatively high and perhaps worsening air pollution in many Chinese cities have kept the lung cancer incidence rates relatively high among women in these areas, despite an extremely low rate (<5%) of cigarette smoking among Chinese women. Occupational exposure to industrial agents also tends to be higher than similar industries in the United States. Furthermore, almost all women have held jobs outside the home, with the majority being employed in blue collar jobs with greater chance for exposure to industrial carcinogens. The changing environment and cancer occurrence in Asia provide an unparalleled opportunity for collaborative research into cancer causes and gene-environment interaction in cancer development. Since the early 1980s, the pioneering efforts of several investigators in DCEG and other NCI Divisions have led to many fruitful collaborations in China. With more rapid changes in recent years in China and other parts of Asia, there are enhanced opportunities for further collaboration. The purpose of the proposed workshop is to review current status of collaborative cancer research, to discuss research ideas and identify new opportunities for research, and to plan future collaborative research directions. The proposed workshop will invite investigators from the U.S., China, and other Asian countries who have conducted collaborative research in Asia to share their research results, with the goal of identifying gaps and opportunities for further collaboration. The proposed location for this one-day workshop is Shanghai, China, in order to minimize travel by most invited investigators from Asia. The workshop is tentatively planned for June 28, 2011, and will be opened to local academic participants. The workshop is to be jointly sponsored by the NCI and the Shanghai Cancer Institute. The requested funding from the Office of Science Planning and Assessment will support meeting arrangements (i.e., meeting site, technical support, and refreshments) and travel for a limited number of invitees from Asia. A summary report and abstract of presentations will be delivered after the workshop. However, the ultimate achievement will be the continuing dialogue and new research collaborations among some meeting participants.

OD-11-302
Workshop: Postpartum Breast Remodeling, Lactation and Breast Cancer Risk: Towards Improved Assessment and Prevention
Sherman, Mark
NCI Intramural, Division of Cancer Epidemiology and Genetics
$5,000

The goal of this workshop is to critically assess key questions related to postpartum events and the pathogenesis of breast cancer. The postpartum period is an important focus of research related to promoting child health. In contrast, comparatively few studies have taken advantage of the repeated medical contacts during this period to conduct research on maternal health, and in particular, to develop strategies for reducing breast cancer mortality. The postpartum period is temporally related to pregnancy and breastfeeding, two poorly understood factors related to breast cancer risk. In addition, this window offers the unique opportunity to collect and analyze breast milk, which may enable non-invasive analyses of breast cells and fluids among young healthy women. Therefore, this time in the life course represents a promising interval for investigating the pathogenesis of early onset breast cancer and for developing strategies for risk assessment and prevention of these tumors. Accordingly, the objective of this workshop is to assemble experts to critically assess our current understanding of postpartum re-modeling of the

breast, lactation, and breast cancer and to identify gaps in knowledge and resources that would be required to advance research on this topic. A recent comprehensive review of breastfeeding in developed countries produced by the AHRQ (Ip et al Breastfeeding Medicine (2009) concluded that breastfeeding reduces maternal risks for breast cancer and for type 2 diabetes mellitus, which elevates breast cancer risk. Risk stratification of young women may allow the development of evidence-based screening intervals at later ages or identification of candidates for prevention interventions.

CARDIOVASCULAR DISEASE

Y2-OD-1456-01:
Role of Androgen and Estrogen Receptor Signaling in Pulmonary Arterial Hypertension (Bench to Bedside)
Danner, Robert;
Clinical Center/NIH; NIDDK; University of Pennsylvania
$110,000

Idiopathic pulmonary arterial hypertension (IPAH), a subtype of plexogenic pulmonary arteriopathy (PAH), is a rare disorder associated with poor survival. Despite consistent epidemiological evidence demonstrating a 2 to 4 fold female predominance in IPAH, the underlying mechanisms for this imbalance are unclear. Endothelial dysfunction resulting from 1) genetic susceptibility, and 2) a triggering stimulus that initiates pulmonary vascular injury, the so-called two-hit hypothesis, appears to play a central role both in the pathogenesis and progression of PAH. Inflammation may drive this dysfunctional endothelial phenotype, propagating cycles of injury and repair in genetically susceptible patients with IPAH and patients with disease associated PAH (e.g. scleroderma, HIV, and sickle cell disease). Histologic specimens from patients with IPAH reveal the presence of inflammatory cells, including macrophages and T- and B-lymphocytes, within classic plexiform lesions that are the hallmark of PAH. Pulmonary artery endothelial cells (PAECs) in PAH orchestrate the recruitment of inflammatory cells as well as secreting pro-inflammatory and pro-coagulant cytokines into the circulation. Patients with IPAH have higher levels of circulating IL-1β, IL-6, P-selectin and E-selectin in comparison to healthy controls. Therefore, targeting PAEC inflammation may interrupt the cycles of injury/inflammation and repair that contribute to progressive increases in pulmonary vascular resistance in patients with PAH, and thereby delay or prevent right ventricular failure and death. Both estrogen and testosterone promote vasodilatation and affect vascular inflammation through binding to estrogen (ER) and androgen receptors (AR), respectively, members of the nuclear receptor (NR) family of transcription factors. However, the interaction between sex hormone signaling and IPAH-associated vascular injury/inflammation is not understood. Many NRs inhibit inflammation through a trans-repression mechanism that recruits co-repressor proteins to promoter NFκB and AP-1 binding sites in a tissue and target gene specific manner. Using an in silico bioinformatics approach, we found that the androgen receptor (AR) is relatively over-expressed in primary human endothelial cells compared to phagocytic leukocytes. Initial work in our laboratory using EA.hy926 cells, a human endothelial

line, demonstrates that dihydrotestosterone (DHT) can suppress TNFα-induced VCAM1 mRNA expression, while spironolactone, a mixed mineralocorticoid receptor and AR antagonist currently used in PAH for advanced right heart failure, was found to inhibit NFκB signaling. We hypothesize that AR and ER differentially modulate endothelial inflammation in IPAH and this may in part explain the female predominance of this disease. Here, the effects of AR and ER signaling on endothelial dysfunction and inflammation will be investigated in cell culture models. Patients with PAH will be recruited to the NIH to investigate novel MRI-based methods to improve clinical phenotyping and as part of a pilot feasibility study on the effects of early spironolactone on endothelial inflammation in vivo.

3-R01-HL-089847-03S1
Endogenous Cardiac Repair in Humans
Margulies, Kenneth
University Of Pennsylvania
$40,000

In recent successful experiments, we have isolated resident stem/progenitor cells from human hearts and induced their in vitro differentiation into contracting cardiac myocytes. Building on these findings, this research is focused on characterizing selected subpopulations of these stem/progenitor cells with an emphasis on elucidating their capacity for replication and differentiation into functioning cardiac myocytes. We contend that insights into the cardiomyogenic potential of endogenous cardiac stem/progenitor cells will promote progress towards therapeutic cardiac regeneration with or without cell therapy per se. Until recently, the heart has been viewed as a terminally differentiated organ with no capacity for new cardiac myocyte (CM) formation. This view appears to be incorrect, in that we and others have been able to isolate cardiac-derived progenitor cells (CDPCs) from human myocardium. Extending these results, our recent studies indicate that cells expressing the stem cell surface marker c-kit can be isolated from human hearts immediately after explantation and subsequently induced to differentiate into CM via short-term co-culture with neonatal rat ventricular myocytes (RVMs). Though we typically find more c-kit+ cells usually in failing vs. nonfailing hearts, the need to replace these failing hearts via transplantation highlights the inadequacy of native cardiac repair mechanisms. Based on these findings, our broad working hypothesis is that increased c-kit+ CDPCs in failing human hearts include both lineage-negative c-kit+ and c-kit+/CD45(dim-moderate) cells that are each capable of new myocyte formation in vitro. In this context, the objective of this proposal is to quantify and characterize these distinct subpopulations of stem/progenitor cells within human hearts with an emphasis on elucidating their functional capacity for replication and CM differentiation. Our first aim is to identify what types of stem/progenitor cells are present in normal and failing human hearts. We will define distinct stem/progenitor subpopulations based on immunotyping of disaggregated myocardial cells with fluorescence microscopy and flow cytometry and perform complementary studies in tissue sections from the same hearts to define their distribution. Our second aim is to characterize replicative capacity of the selected CDPC subpopulations based on a combination of static assays (telomere length, telomerase activity and and p16INK4a expression) and functional assessment of proliferation rates. Our third aim is to characterize the cardiac myogenic potential of selected CDPC subpopulations derived from human hearts. These studies will define the rates and

frequency of CM differentiation for sorted subpopulations under stardardized co-culture conditions, define whether cell contact is required for induction of CM differentiation by neonatal rat myocytes and identify secreted factors (chemokines or growth factors) that promote or augment rates of in vitro CM diffentiation in selected CDPC subpopulations. The clinical/therapeutic significance of this proposal is based on the premise that insights into the proliferative and cardiomyogenic potential of endogenous cardiac stem/progenitor cell subpopulations will promote progress towards therapeutic cardiac regeneration with or without cell therapy per se.

3-R01-HL-060666-11
Metabolism During Mechanical Circulatory Support in the Developing Heart
Portman, Michael A
Seattle Children's Hospital
$20,000

Infants and children are often supported by a bypass pump during or after heart repair. This study will determine hormone and nutritional strategies to support the immature heart while supported by this type of mechanical circulation. In particular, we will examine how thyroid hormone influences how the heart generates and uses important energy molecules. Extracorporeal membrane oxygenation (ECMO) remains the primary method of long term support after myocardial stunning caused by cardiac surgery in infants and children. ECMO often provides a bridge to recovery in these young patients. However, ventricular unloading as occurs with ECMO also promotes cardiac atrophy. Therefore, this therapy can be counterproductive in initiating reparative processes leading to restoration of normal cardiac function. Substantial abnormalities in hormonal homeostasis, such as decreases in circulating levels of thyroid hormones, occur during both shorter term cardiopulmonary bypass (CPB) and longer term ECMO. Disruptions in thyroid hormone homeostasis can alter substrate utilization, deplete citric acid cycle intermediates, possibly effecting net protein turnover. Additionally, we have noted that pyruvate supplementation can improve cardiac function after CPB in immature pigs. Thyroid hormone supplementation promotes pyruvate entry into the citric acid cycle, and promotes citric acid cycle intermediate conversion to amino acids. These findings suggest that appropriate substrate supplementation can improve protein synthesis and functional recovery after protracted mechanical circulatory support. We will study a prolonged period of mechanical circulatory support (ECMO) in the immature pig, an appropriate translational model for children undergoing these procedures. We will test the primary hypothesis: in the developing heart cardiac dysfunction due to ventricular unloading (ECMO)-is a consequence of impaired substrate utilization due at least in part to disruptions of thyroid hormone homeostasis. Targeted metabolic interventions in combination with thyroid hormone supplementation will minimize the adverse effects of ECMO and thereby improve longer term functional recovery and survival. Using NMR and GC-MS, we will determine if metabolic abnormalities, which lead to cardiac dysfunction and atrophy can be treated by supplementing the citric acid cycle with pyruvate. We will determine if pyruvate combined with thyroid hormone supplementation (T3) a) accelerates pyruvate flux, b) reduces oxidation of amino acids, c) stimulates transamination to amino acids and d) improves cardiac function and protein synthesis after a prolonged period of ventricular

unloading. We will also determine if supplementation of medium chain fatty acids with and/or without thyroid hormone similarly supports the heart.

OD-11-287
Clinical research united in successful enrollment – workshop on clinical trials.
NHLBI
$9,964

As our health care system moves to expand access, evidence based-medicine and the need for well designed and conducted clinical trials become paramount. The goal of this workshop was to provide recommendations to NHLBI and co-sponsors in three key areas that impact clinical trial enrollment: 1) Public and professional awareness and acceptance of clinical trials, 2) Human subject research policies, guidelines, and reimbursement, and 3) clinical trial enrollment experience and practice, in order to optimize enrollment in clinical trials.

1-R21-HL-093631-01A1
Sex Differences in Molecular Heterogeneity of Cardiac Repolarization
Bett, Glenna C L
State University of New York At Buffalo
$ (NHLBI funded this ANSWHR award)

This proposal seeks to understand the basis of sex-differences in the electrical activity and pharmacological sensitivity of the heart. Sex is an often overlooked fundamental clinical variable, which can have a significant impact on health outcome. Understanding the basis of cardiac sex differences offers the opportunity for translational advances in the identification of therapeutic targets with the potential to improve patient outcomes and improve healthcare for both men and women. This proposal is a revised application in response to an RFA for R21 applications to advance Novel Science in Women's Health Research. Although heart disease is the #1 killer of both Men and Women in the US, only 27% of participants in cardiac clinical trials are women. In basic research, most experiments are performed on male animals only. It is therefore not surprising that little is known about the basic molecular mechanisms even for such clinically important fundamental factors such as why female cardiac action potentials are longer than male action potentials. Even less is known about why 70% of congenital Long QT syndrome patients are women, and why women are at particular risk for drug induced arrhythmias. This application proposes to advance science in women's health research by determining the molecular basis for sex dependence and hormonal regulation of IKr and IKs, the two major repolarizing currents in heart. This research is strongly hypothesis driven, and the overall guiding hypothesis is that differences in the electrophysiological and pharmacological profile of IKr and IKs are responsible for sex differences in cardiac repolarization. This is a departure from the current concept that it is purely the action potential duration that is the key determinant of arrhythmia susceptibility. We are proposing that the important factor is not the absolute action potential length, but the relative contribution of IKr and IKs, combined with their pharmacological sensitivities that are a critical factor in arrhythmogenesis. The alpha subunits of IKr and IKs are HERG and KCNQ1 respectively. However, their relative expression, electrophysiological and pharmacological profiles are determined by the presence of KCNE

ancillary subunits. Our hypothesis is that hormonal regulation of these subunits is the major factor in determining differences between male and female myocytes. We will test this hypothesis by determining IKr and IKs electrophysiological profile in human cardiomyocytes derived from male and female induced Pluripotent Stem Cells (iPSCs) from skin cells, as well as ventricular myocytes from male, female and ovariectomized (OVX) guinea pigs. We will also expose myocytes to estradiol and testosterone to test the direct effects of hormones on currents and use molecular interventions to determine subunit specificity. We will use the experimental data to develop mathematical models of human and guinea-pig action potentials which contain hormonal regulation of IKr and IKs. We will use these models to make predictions about the dynamic behavior of repolarization (e.g., restitution, QT prolongation and pharmacological sensitivity) which can be tested in our experimental human and guinea pig models. These innovative simulation studies will provide testable hypotheses which are readily applicable to electrophysiological studies in humans.

1-R21-HL-109527-01
Cardiovascular Disease Biomarkers and Mediation of Hormone Therapy Effects
Prentice, Ross L
Fred Hutchinson Cancer Research Center
$ (NHLBI funded this ANSWHR award)

This project will evaluate novel blood proteins as potential risk markers for coronary heart disease and stroke in postmenopausal women, and will evaluate the extent to which changes in these biomarkers as a result of postmenopausal hormone therapy can help to explain the observed effects of postmenopausal estrogen and estrogen plus progestin on the risk for these major diseases. Confirmatory analyses of novel plasma protein associations with the risk of coronary heart disease and stroke will be carried out by applying enzyme-linked immunosorbent assays to baseline plasma specimens from cases and controls in the Women's Health Initiative postmenopausal hormone therapy trials. Candidate proteins were highly ranked in recent in-depth proteomic discovery research. For CHD these are alpha-1-acid glycoprotein 1, thrombospondin 1, complement factor D preprotein, glutathione peroxidase 3, and insulin-like binding protein 1 (IGFBP1). For stroke the candidate biomarkers are IGFBP2, IGFBP6, insulin-like growth factor 2, hemopexin, and beta 2 microglobulin. Specimen analyses will be carried out for 349 CHD cases and for 1-1 matched controls, and for 326 stroke cases and matched controls. Data analyses will control for traditional cardiovascular disease risk factors, and for available biomarkers of inflammation, thrombosis, and lipids. Women developing CHD or stroke following their first year of hormone therapy trial enrollment, and their matched controls, will also have plasma concentrations assessed in 1-year blood specimens for the subset of these proteins found to be affected by estrogen-alone or by estrogen plus progestin in discovery work using the same proteomic platform. The baseline and 1-year protein concentrations will be jointly analyzed to assess the extent to which treatment-related changes in these protein concentrations can mediate hormone therapy effects on CHD and stroke. These analyses will incorporate a novel correction for biomarker measurement error. The project has a high probability of confirming some new biomarkers of CHD and stroke risk, and for providing additional insight into observed hormone therapy effects on these diseases.

1-R21-HL-109822-01
Phytoestrogens, insulin resistance and endothelial function
Stachenfeld, Nina
Yale University School of Medicine
$ (NHLBI funded this ANSWHR award)

With the goal of reducing vasomotor symptoms and protection against the age-associated increase in cardiovascular disease risk, women are increasingly choosing over the counter phytoestrogens (such as genistein) in favor of estrogens prescribed by their physicians. Genistein may improve vascular function but not carry with it the increased breast cancer risks that have been associated with estrogen exposure. Insulin resistance increases cardiovascular disease risk, and may also interfere with the actions of genistein on cardiovascular function. Therefore, these studies have broad public health implications because it is important that women not have a false sense of cardiovascular protection while taking genistein. Genistein is the best studied and most common of the soy-derived phytoestrogens. Genistein is structurally similar to 172-estradiol and has high affinity for the ER2 receptor present in the human vasculature, but low affinity for the ER1 receptor present in reproductive organs. Studies support beneficial effects of soy-derived phytoestrogens on vascular reactivity and endothelial function. However, during genistein treatment the expected improvement in endothelial dependent dilation is attenuated in individuals with insulin resistance. This project is designed to study the impact of genistein on microvascular reactivity both in healthy women and in women with insulin resistance. Our general hypothesis is that genistein improves endothelial function through a nitric oxide mechanism in healthy women, but that this mechanism is ineffective in women with insulin resistance. We will use the cutaneous vasculature as a model to study endothelial function, and will infuse estradiol and genistein directly into the skin using microdialysis while measuring microvascular blood flow with laser Doppler flowmetry. Our first Aim will use dose-response curves to determine the 172-estradiol and genistein effects on the peripheral microvasculature in women with and without insulin resistance. We hypothesize that both hormone infusions will increase blood flow in both groups of women, but the vasodilation will be attenuated in women with insulin resistance. Our second Aim tests the hypothesis that nitric oxide mediates the estradiol and genistein-induced vasodilation in healthy women, but is not a factor in the more moderate vasodilation seen in women with insulin resistance. Women take genistein and other phytoestrogens assuming a level of cardiovascular protection, but data have not definitively demonstrated these benefits. Our studies will directly assess the extent to which genistein impacts vasodilation and examine the mechanism for its effects. Moreover, our findings will provide a basis to study the impact of genistein and other phytoestrogens on other conditions associated with compromised peripheral circulation such as Reynaud's disease and hypertension. The proposed studies will not only provide mechanistic information on the interaction between estradiol, genistein, insulin resistance and endothelial function, but will serve as a basis for future studies in older women and men with insulin resistance.

CHRONIC FATIGUE SYNDROME

5-R01-AR-053821-05
HERV-K18 as a Risk Factor for CFIDS
Huber, Brigitte T.
Tufts University Boston
$164, 058

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 are that they provide genetic evidence for the unique etiology of at least one group of CFS patients. Thus, it may be possible to delineate different subtypes of CFS, depending on the clinical history of the patients. It is now proposed to substantiate these pilot results, using a much larger cohort of 400 CFS patients associated with EBV that has been assembled by the co-investigator, Dr. Renee Taylor. Dr. Ben Katz, board certified in both Pediatrics and Pediatric Infectious Diseases, will clinically evaluate the patient cohort, and Dr. Inga Peter, a genetic epidemiologist and biostatistician, will oversee the statistical analyses. In addition, the expression pattern of the HERV-K18 SAg during active disease versus intermission will be measured. Furthermore, T cell stimulatory activity of this SAg, expressed on peripheral blood lymphocytes of patients during the course of the disease, will be tested ex vivo, using a T cell hybridoma reporter assay that has been developed in their lab. Since SAg-activated T cells produce massive quantities of chemokines, lymphokines and neurokines, the expression of the HERV-K18 SAg could influence not only the immune system, but other organs as well. A positive association between CFS and either HERV-K18 alleles or expression patterns would open new avenues for the development of clinical treatments of this chronic disease. CFS is a disease that affects a significant number of people worldwide, yet the underlying mechanism(s) of pathogenesis remains unclear. The 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.

1-R21-NS-075653-01
Neuropathologic Abnormalities Define A Subgroup of Patients with CFS
Natelson, Benjamin
Beth Israel Medical Center
$189,405

Chronic fatigue syndrome (CFS) is a medically unexplained debilitating disease that is diagnosed by the presence of a set of predefined symptoms. Because there are no validated diagnostic tests for the illness, progress in understanding its causes has been slow. From a series of studies by our group and others there has emerged strong preliminary evidence that supports the existence of a subgroup of CFS patients whose illness appears to be due to specific biological abnormalities in the brain. The purpose of this Exploratory/Developmental grant proposal is to conduct carefully controlled studies that will seek to confirm the existence of such a subgroup of CFS patients. If successfully completed, this study could validate an approach for selecting more homogeneous CFS patient populations in future research studies to enable them to focus better on understanding the exact cause of CFS and developing effective treatments for the illness. Chronic fatigue syndrome (CFS) is a debilitating multi-symptom disorder characterized by unexplained and prolonged fatigue, whose diagnosis is currently based on a relatively broad clinical case definition. Consequently, the pool of CFS patients included in clinical studies of the illness is greatly heterogeneous - a fact that might have impeded research progress to date. A major step forward in understanding the pathophysiology of CFS would involve reducing this heterogeneity by identifying one or more subgroups of patients with different pathophysiological causes of their illness, and then selecting one of these subgroups for inclusion into research studies. Over the past few years, we and others have provided substantial data supporting the existence of a subgroup of patients with a neurobiological cause for their illness, based on stratifying the sample according to the absence or presence of comorbid Axis I psychopathology (CFS-no psych or CFS-NP and CFS-psych or CFS-P, respectively). Compared to CFS-P patients, the CFS-NP patients had more cognitive dysfunction, a higher rate of abnormal cerebrospinal fluid (CSF) findings, lower regional cerebral blood flow (rCBF), and higher ventricular CSF lactate values. A further complication and limitation of these studies is that each had investigated only one brain-related variable, whose utility in separating CFS patients into subgroups was limited. The purpose of the present Exploratory/Developmental Research Grant (R21) proposal is to rigorously assess and confirm whether patients in the CFS- NP group have consistent abnormalities across several different neuropathological variables - an outcome that would be expected if this group, in fact, does have distinct neurobiological underpinnings. Specifically, in the same subjects, we will (a) assess cognitive function using objective neuropsychological testing; (b) conduct biochemical analysis of spinal fluid samples obtained by lumbar puncture; and (c) measure rCBF and ventricular lactate using magnetic resonance imaging and spectroscopy, respectively, in CFS-P and CFS-NP patients. This will allow us to test the hypothesis that CFS-NP patients have more abnormalities in these outcome variables than CFS-P patients. Our second Aim will use the results from the first Aim in a cluster analysis to attempt objective, data-driven classification of the CFS subjects into subtypes, and then compare the resulting subgroups based on membership into CFS-NP or CFS-P groups. This aim will test the hypothesis that the results of the cluster analysis will identify a group with

abnormalities across the multiple brain-based variables studied, and this group will be constituted of significantly more CFS-NP patients than in other groups.

CRANIOFACIAL

N01-DE32636-23-0-1
International Research Registry Network for Sjogren's Syndrome
Shiboski, Caroline
University of California San Francisco
$150,000

The purpose of this contract is to develop an International Research Registry Network for Sjogren's Syndrome. Specific aims are: 1. To develop standardized diagnostic criteria for Sjogren's Syndrome (SS) through a prospective cohort study design and based on analysis of existing criteria and their current usage; adoption of a new objective "working standard" (in lieu of a "gold standard"); and measurements of the sensitivity, specificity and accuracy of many combinations of diagnostic tests based on that standard. 2. To collect, process and store clinical data and biospecimens from patients diagnosed using these new criteria and controls. 3. To develop a data and biospecimen bank.

DIABETES

5-U01-DK-057136-13
Look AHEAD: Action for Health in Diabetes
Espeland, Mark
Wake Forest University Health Sciences
$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.

5-U01-DK-048489-18
Diabetes Prevention Program Outcomes Study
Fowler, Sarah E.
George Washington University
$900,000

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.

DIETARY SUPPLEMENTS/ CAM

5-R21-AT-005377-02
Identification of novel phytoprogestins from hops and red clover
Burdette, Joanna E
University of Illinois at Chicago
$194,287

Women are already taking phytoestrogens in botanical extracts for menopausal symptoms, and the incorporation of progestins may prevent hyperplasia and cancer of the uterus. As women search for more potent alternative estrogens to satisfy the need for menopausal symptom alleviation, the chance for hyperplasia in the uterus increases and makes the characterization of novel phytoprogestins crucial. Hormone replacement therapy (HRT) is the most commonly prescribed medication for the alleviation of menopausal symptoms. Unopposed estrogen replacement therapy increases the risk of developing endometrial cancer by 120% for every 5 years of use. To eliminate this risk in women with a uterus, the addition of progesterone to HRT in the form of combined estrogen/progesterone replacement has been implemented. Considerable evidence now indicates that the addition of synthetic progestins to HRT increases the risk of breast cancer as well as many other deleterious side effects. In response to the problems associated with HRT, millions of women are exploring the use of botanicals and dietary supplements for the alleviation of climacteric symptoms. However, the use of botanicals with only plant-derived estrogens in the absence of progestins might increase the risk for developing endometrial cancer similar to estrogen alone. Two common supplements, hops and red clover, contain phytoestrogens that bind and activate estrogen receptors. Interestingly, when hops and red clover are given orally to ovariectomized rats, uterine weights are not significantly increased in animals treated with a crude extract but are significantly increased in animals given an equivalent dose of the pure phytoestrogen. The hypothesis of this grant proposal is that selective natural progesterone compounds can be identified from botanical extracts to generate a combined phytoestrogen-phytoprogestin alternative to traditional hormone replacement therapy. The presence of both estrogen and progesterone receptor agonists in one botanical extract may provide both the benefits of estrogens for alleviation of menopausal symptoms and the progesterone necessary to combat formation of uterine cancers. Selective and safer progestins might also be identified from botanical sources improving the overall behavior of the progestin used in HRT. In order to provide support for this hypothesis the following specific aims are proposed: Aim 1. Do botanical extracts contain phytoprogestins and what are the pure compounds responsible for the progesterone-like activity? Aim 2. Are phytoprogestins specific and selective for uterine progesterone receptors? Aim 3. Are phytoprogestins protective against uterine hyperplasia in an ovariectomized rat model? These studies will provide a clear justification for the use of botanicals that have the possibility of providing both estrogen and progestin-like activity but with more selective and safer profiles for the treatment of menopausal symptoms. Women are already taking phytoestrogens for menopausal symptoms, and incorporation of progestins may prevent hyperplasia and cancer of the uterus.

GENITOURINARY

5-U01-DK058229-11
Urinary Incontinence Treatment Network
Tennstedt, Sharon L
New England Research Institutes, Inc
$100,000

This proposal is submitted in response to RFA-DK-06-501 for continuation of the Urinary Incontinence Treatment Network (UITN) Data Coordinating Center (DCC) at New England Research Institutes, Inc. 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.

1-R21-HD-069962-01
Tailored Outcomes for Female Urinary Incontinence
Sung, Vivian W
Women & Infants Hospital, Providence RI
$ (NICHD funded this ANSWHR award)

With the aging population, the number of women seeking care for urinary incontinence (UI) will increase. High- quality, patient-important outcomes that can be tailored, are efficient and monitor treatment outcomes from the patient perspective are critical to improving scientific knowledge and the care of women who suffer from UI. Urinary incontinence (UI) disproportionately affects women over men and is associated with embarrassment, social and functional decline. Treatments are primarily aimed at improving aspects of a woman's quality of life and function; therefore, high quality patient-reported outcomes (PRO) that cover multiple dimensions are paramount to inform treatment progress. Limitations of existing UI PRO measures include their inflexibility, significant respondent burden, and inability to be personalized. The overarching goal of this proposal is to make a major advance in UI PRO measures by developing an innovative measurement system that is multi- dimensional, flexible, and efficient, can be tailored to individuals, yet also decreases respondent burden. Such a system is likely to be accepted by patients, clinicians, researchers, and industry for evaluating treatment outcomes from the patient perspective and can streamline research findings and patient care. Using item response theory and computerized adaptive testing, The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) has developed core PRO item banks relevant to a wide range of chronic diseases. As comprehensive as PROMIS is, it does not fully address the needs of women with UI. To fill this need, we will build on our previous work to continue validation and calibration of UI-specific item banks based on an expanded PROMIS conceptual framework that is sensitive to the outcomes valued by women with UI. Specifically, our aims are to: 1) confirm face and content validity of our UI item banks and conceptual framework through cognitive-based interviews and expert review; 2) calibrate and field-test the item banks using item response theory in 700 women with UI recruited across two hospital settings; and 3) develop and pilot-test a web-based UI-computerized adaptive test prototype (UI-CAT). We will evaluate item/model/person fit, compare item discrimination power, and assess differential item functioning across demographic variables, UI severity and type, and co-existing pelvic floor disorders. We have convened an interdisciplinary team of experts in female UI, PRO development, PROMIS methodology, item response theory, computerized adaptive testing, and informatics. The application of modern psychometrics and computerized adaptive technology can dramatically improve our PRO measurement capabilities in female UI and women's health. The UI-CAT can be used to help tailor our treatments to the needs and values of women with UI, improve the specificity of our treatments, and improve the delivery of personalized care to women.

1-R24-DK-094575-01
Microbiomes of Interstitial Cystitis
Schaeffer, Anthony J
Northwestern University
$50,000

Interstitial cystitis/painful bladder syndrome (IC) is a debilitating chronic bladder condition without known cause or effective treatments. This study will develop an interdisciplinary team to explore the novel question of whether alterations in the large bacterial communities that populate the gastrointestinal and reproductive tracts play a causal role in IC. Interstitial cystitis/painful bladder syndrome (IC) is a devastating condition characterized by severe pelvic pain and voiding dysfunction. Despite years of investigation, no etiology or widely effective therapies exist for IC, indicating the needto consider new ideas and approaches. Based on several lines of evidence, the "microbiome" is an emerging field of study that has the potential to play a significant role in our understanding of I. First, many IC patients exhibit Gl or reproductive tract co-morbidities. Second, it is established that crosstalk exists among the bladder, Gl tract, and reproductive tract. Third, we find that bacteria can mediate a range of pelvic pain responses, from pain suppression to causing chronic pain. Fourth, microbial flora densely populate certain body sites, indeed outnumbering human cells, and new findings demonstrate that altered microbiomes can drive complex diseases. We therefore will develop an interdisciplinary team to address this novel question: is an altered gastrointestinal and/or reproductive tract microbiome associated with IC? Our team will bring together clinical expertise in IC, methodologic and biologic expertise in defining microbiomes of the Gl and reproductive tracts, and expertise in the microbial basis of pelvic pain. Our team will exploit the synergies from these key fields to develop specific hypotheses and strategies for defining associations between microbiomes and IC. Moreover, clinically relevant murine models will be developed to establish a causal link between altered microbiomes and modulation of pelvic pain. Defining IC microbiomes has potentially major significance for understanding IC etiology, mechanisms, and treatments. IC patients often have a history of antibiotic treatments for urinary tract infection, yet antibiotics can shift microbial diversity and thereby cause disease. Altered IC microbiomes could result in dysfunctional modulation of pelvic pain via organ crosstalk or expanded reservoirs of uropathogens. Finally, manipulation of microbiomes is proving efficacious in other clinical specialties, suggesting the possibility of possibility of convenient probiotic therapies for IC.

1-R24-DK-094583-01
Sensory Sensitivity and Urinary Symptoms in the Female Population
Clemens, J. Quentin
University Of Michigan
$50,000

Bladder symptoms such as pain and urgency are very common, and treatments are poorly effective. These studies will examine for clinical evidence of global pain hypersensitivity in these patients. If a global pain abnormality is identified, additioal studies can be done to examine the etiology of these symptoms and design novel treatments that are focused on central, rather than peripheral, pathophysiology. Bladder pain and discomfort, as well as urinary urgency and

frequency, are common and bothersome symptoms seen in the general population. Clinical diagnostic terms used to describe these symptoms include interstitial cystitis (IC), painful bladder syndrome (PBS), chronic prostatitis, and overactive bladder (OAB), but there is tremendous overlap between these entities, and the distinction between them is based more on imminence than evidence. Pain and/or sensory sensitivity have been suspected to play a role in the pathogenesis of both bladder pain and urinary urgency/frequency. However, there has never been a study to determine whether entities such as IC/PBS and OAB might merely represent different points in a continuum of bladder sensory sensitivity. Moreover, we know of no studies that have directly compared whether sensory sensitivity in the bladder is related to global (i.e. CNS-mediated) sensory sensitivity. In the proposed study, a team of investigators with complementary expertise will perform a population-based study assessing bladder and overall sensory sensitivity, in a cohort of women chosen to be representative of the general population with respect to the entire continuum of bladder pain (from none to severe), and symptoms of urgency/frequency. These individuals will undergo urodynamics to measure sensory sensitivity in the bladder, as well as pressure pain and auditory loudness thresholds. Our Specific Aims are to demonstrate that in the population, 1) sensory sensitivity in the bladder is related to sensory sensitivity elsewhere in the body, suggesting that this is a CNS-driven mechanism, and 2) those individuals in the population that have more pronounced global sensory sensitivity will display: a) more bladder pain, b) more urgency/frequency, and c) more other symptoms of centrally-mediated pain states, such as pain elsewhere, fatigue, and insomnia. We feel that these studies are crucial to better understand the relationship between sensory sensitivity and urinary symptoms, and to add to the evidence necessary to appropriately diagnose and treat these symptoms and individuals.

GLOBAL HEALTH

3-D43-TW-008438-03S2
QUIPU: The Andrean Global Health Informatics Research and Training Center
Garcia, Patricia Jannet
Universidad Peruana Cayetano Heredia, Lima, Peru
$10,000

Within South America, the Andean Region (AR) is the most disadvantaged. However, modern technology such as computers, cellular phones, and other information and communications technologies (ICT) are becoming more widely available in the region. The fields of informatics and global public health are both growing, but we lack an institutionalized effort to train professionals to apply ICT to global health issues in the context of regional needs and to develop health information technology experts capable of linking informatics with health research. The overarching goal of this proposal is to establish the "QUIPU: Andean Global Health Informatics Research and Training Center," a center of excellence for training and research in global health informatics (GHI) to serve as a hub for addressing the national and regional needs for high-quality training in the Andean Region (AR) at a fraction of the cost of similar training programs

in the U.S. The specific aims of the proposal are: 1. To develop and implement short-term and long-term training opportunities in GHI within the AR; 2. To engage emerging investigators in regionally pertinent research in health informatics and bioinformatics; and 3. To expand and consolidate a research network to link researchers in the AR, promoting south^south collaborations, as well as with colleagues from partner universities in the U.S. and other institutions. The Center will expand from the Universidad Peruana Cayetano Heredia (UPCH) and the U.S. Naval Medical Research Center Detachment (NMRCD) in Lima, Peru, two universities from the AR, the Universidad del Cauca (UCA) in Colombia and the Universidad Andina Simon Bolivar (UASB) in Ecuador, and the University of Washington (UW); who will work together as a Consortium to collaboratively implement QUIPU. The proposed program builds on existing and emerging collaborations between the four institutions, as well as a long-standing training-centered collaboration between UPCH and UW through NIH-Fogarty funded programs which allowed the development of a critical mass of trained researchers at UPCH and in Peru. We envision GHI as an umbrella for integrating health informatics and bioinformatics into clinical, biomedical and behavioral research issues that are key to advancing the health of populations in the AR and around the globe. The proposed program includes training and a research component. The training component will offer courses, two Certificate programs (health informatics and bioinformatics), as well as Masters and PhD programs for advanced students. We plan to offer 12 scholarships for short courses, 11 for Certificates, 14 for Masters and 2 for PhD degrees during the 5-year grant. Candidates will be selected from Andean countries with a focus on Colombia, Ecuador and Peru. Video conferences and internet-based courses will be used to expand availability to a broader pool of students. The component for research in health informatics will strengthen NIH and non-NIH funded research conducted in the region, by providing competitive research awards, opportunities within already established research projects, and links to other researchers within the networks of collaborating institutions, including a regional research conference.

3-R01-HD-061115-03S1
Gender Equity-Focused, Male-Centered Family Planning for Rural India
Saggurti, Niranjan
Boston University
$60,573

The major barrier to India meeting its national goal of replacement fertility is the huge discrepancy between urban and rural family planning, with rural young women at highest risk for unplanned and unspaced pregnancies. These concerns are considered to drive the persistent and unacceptably high rates of maternal and infant mortality in India. Major impediments to these young wives' acquisition of family planning services include high male partner control over reproductive decision-making, low mobility, and very low access to family planning services in villages. Such findings document the need for male-centered family planning efforts available at the village level, to better meet the needs of rural young wives. These male-centered efforts must address male gender role and gender inequity ideologies and norms (e.g., son preference, wife abuse) and marital communication, as these factors are associated with lower likelihood of contraceptive use in rural young Indian couples. Hence, the proposed study involves development and testing of the CHARM Program, a gender equity (GE)-focused, male-centered

family planning (FP) program delivered by private village health providers (VHPs), via a public-private partnership with primary health centers (PHCs) serving rural India. In Phase 1 we will conduct formative research including health care resource mapping of Vasai within the Thane district of Maharashtra to identify villages and VHPs for inclusion in subsequent research and intervention. We will also conduct in-depth interviews with rural young husbands (n=30), rural young wives (n=20), and health care providers (n=12), as well as focus groups with mothers' of rural young husbands (n=40). These data will be used to develop the CHARM program and efficacy trial. Phase 2 will involve development and pilot testing of CHARM protocols and training of VHPs for their role in the intervention trial (Phase 3). The CHARM intervention will involve VHP-delivered GE and FP counseling and services, delivered over 3 intervention sessions + 2 booster sessions. Phase 3 will involve evaluation of CHARM, using a two-armed randomized controlled trial design. Villages (N=50) will be randomized to receive either CHARM or the control program (standard FP referral to government public health centers [PHCs] located outside of villages), to assess treatment impact on spacing contraceptive use, pregnancy, and unmet family planning need. Intervention effects will be assessed via behavioral surveys collected on hand-held computers (PDAs) with rural young husbands (18-30 years) and their wives (N=1500 couples, 30 couples per village) at baseline and 6,12, and 18 month follow-up, as well as pregnancy tests from wives, conducted at baseline and 18 month follow-up. A process evaluation will be undertaken via interviews with study participants and VHPs, as well as through VHP observations and clinical record review, to assess program adherence, participation rates, response to program, and ease of delivery. In-depth interviews will also be conducted with key informants from the village and public and rural health systems to assess sustainability and institutionalization of the model.

3-D43-HD-065249-03S1
Interdisciplinary Research Training: NCD Epidemiology And Prevention In India
Tandon, Nikhil
Centre For Chronic Disease Control, New Delhi, India
$50,240

NCDs are a large, growing, and costly problem for India. Over the next decade, the country is projected to lose $237 billion in national income due to heart disease, stroke, and diabetes, and to account for 40-60% of the global CVD burden. Despite these projections, research infrastructure is lacking, and building research capacity at post-doctoral and junior faculty levels is clearly identified as a priority by the Government of India and health organizations. There is an acute shortage of post-doctoral and junior faculty research capacity in India, with no postdoctoral programs in epidemiology and prevention of non-communicable diseases (NCDs). The proposed interdisciplinary training program will focus on the epidemiology and prevention of NCD across the life-course, in cross-connecting subject areas (child health; nutrition and lifestyle, environmental health, obesity and diabetes, stroke and other vascular diseases) and population science disciplines (epidemiology and biostatistics; clinical trials; translation research, social sciences, and economics). This effort will leverage an established network of research collaborations involving partners in India and the US (Ovations Center for Excellence in Chronic Diseases, New Delhi). The program will have two components: (1) Short-term training in year 1: Eight junior faculty researchers will receive four months of training at Emory to acquire specific

and focused mentoring and research skills. (2) Long-term training in years 2-5: A total of ten post-doctoral fellows (one batch of five in years 2-3 and one batch in years 4-5) will receive 24 months of training (four months at Emory in the first year, six weeks at Emory in the second year, and the remaining 18.5 months in India). Training components include mentored research, coursework, professional development (ethics, grants-writing, communication skills), and an emphasis on context-specific innovation in health programs and research. Collaboration with Emory will compliment India-based mentoring and training, and permit transfer of skills and expertise in specific areas. The program will build a critical mass of NCD researchers and incorporate them within integrated NCD research programs in India. An important innovation of our program is the emphasis on retaining talented young scientists in India, enabling them to develop world-class research skills in an Indian-based training program, facilitating international collaborations, and providing end-of-training grants to promote in-country research projects. We expect the program to have a cascade effect, as each of the 18 trainees will serve as a resource upon completion of the program, disseminating knowledge and skills to other researchers at in-country institutions.

3-D43-TW-008652-02S1
Training Program on Operational and Health Services Research for Malaria in Mali
Doumbia, Seydou
Johns Hopkins University
$45,172

Lack of sound operational research to accompany past efforts to implement large-scale malaria control programs has been cited as one reason for their ultimate failure. Mali is particularly in need of such a training program because it is a challenging environment for implementation of malaria interventions (low population densities, low literacy), and there are few researchers trained in operational research in Mali. The training program's main aim will be to strengthen current malaria prevention and control efforts in Mali by providing training in Mali in relevant research and evaluation skills. A secondary aim will be to support public health graduate training in Mali at both the masters and doctoral levels. Each year during the first three years of the training program, two trainers will spend two months at the JHSPH, take two or three courses, and develop the detailed training curriculum for a course they will offer upon their return to Mali. One 5 to 10 day course on malaria prevention and control will be organized each year for approximately 25 participants. Participants will be drawn from Ministry of Health personnel and personnel working in control projects implemented by UNICEF, NGOs or other organizations. The Department of Public Health of the University of Bamako is initiating a 2-year Masters in Public Health Program during the 2009-2010 academic years. This training grant will support a first cohort of 5 students then 3 subsequent cohorts of 3 students per year. On-going collaboration with the Malaria Research and Training Center provides opportunities for students to be exposed to malaria research, and to carry out their field placements at MRTC field sites and laboratories. Two students will be supported to carry out doctoral studies at DPH during Years 3 to 5 of the training grants. Students will be recruited from among the first 5 students to complete the MPH, and students with MPH from other universities. During the fourth and fifth years of the training grant, the students will spend one term each year at JHSPH taking additional courses not offered at DPH and getting input from JHSPH faculty on their dissertation research.

3-D43-TW-009101-01S1
China-Rochester Suicide Research Training Program (CRSRT)
Caine, Eric D
University of Rochester
$10,000

This D43 NCD-LIFESPAN application is entitled the China-Rochester Suicide Research Training Program (CRSRT). It is built upon the International Clinical, Operational and Health Services Research Training Award ("ICOHRTA") program that has been funded since 2001 (D43TW005814). The current proposal is written in response to PAR-10-257 for a Chronic, Non-Communicable Diseases and Disorders Across the Lifespan: Fogarty International Research Training Award (NCD-LIFESPAN). Suicide is a major public health problem in China. It is the fifth leading cause of death overall, and the leading cause of death for individuals in the 15- 34 year old age range. It has a national rate of approximately 23 deaths per 100,000; during 1995-1999, approximately 287,000 died by suicide. In response, we now are systematically growing the CRSRT to encompass multiple complementary settings that serve to diversify the academic breath and geographical distribution of our initiatives, increase our committed mentors, and widen the pool of applicants. Our high rate of positive outcomes during the past decade reinforces the rewarding nature of our high-intensity mentoring strategy. The CRSRT involves the Center for the Study and Prevention of Suicide (CSPS) of the University of Rochester Medical Center (URMC), and six key collaborators in China who bring a diversity of skills and leadership to our growing collaborative efforts, with centers in Beijing, Shanghai, Chengdu, and Changsha. Our proposal reflects an ongoing, self-scrutinizing process that has informed our efforts to: 1) build training and research infrastructure, focusing primarily on public health and population-oriented research and prevention efforts; 2) identify and train excellent future scientists; and 3) develop new research findings that will inform efforts to prevent suicide in China during the coming decades. The CRSRT involves a year of intensive training in the CSPS, followed by two further years of mentored research in China. We provide trainees with the skills to emerge as independent investigators through intensive one-to-one mentoring and engagement in a variety of peer-oriented training experiences. We will continue to systematically evaluate the effectiveness of our recruiting, training, and research efforts.

5-R01-AI-083563-02
Congenital Transmission of Lineages I and II of Trypanasoma cruzi
Buekens, Pierre
Tulane University
$10,000

A better understanding of the epidemiology of Trypanasoma cruzi (TcI) congenital infection is a crucial step toward the potential development of screening and early treatment programs in Mexico and Central America, as well as in the United States, where large immigrant populations come from countries where TcI predominates. Thus, the proposed research project is highly relevant to public health. T. cruzi has been divided into two main lineages: T. cruzi I (TcI) and T. cruzi II (TcII). TcI is predominant in Mexico and Central America, while TcII is predominant

in most of South America, including Argentina. In recent studies from Argentina, the risk of congenital transmission has been estimated to vary between 2.6 percent and 7.9 percent. By contrast, we know very little about the congenital transmission of TcI. It has been suggested that congenital transmission of T. cruzi is strain related, and there is an urgent need to know if TcI transmits differently than TcII. Our primary hypothesis is that congenital transmission rates are different for TcI versus TcII. Our secondary hypothesis is that the characteristics of T. cruzi infected mothers (e.g., age, parity, transmission in previous pregnancies) and their exposure to vectors are different in regions where TcI is predominant versus regions where TcII is predominant. To test these hypotheses, we propose to conduct a prospective study to enroll at delivery 10,000 women in Mexico, 5,000 women in Honduras, and 5,000 women in Argentina. We will measure transmitted maternal T. cruzi antibodies in cord blood, and, if the results are positive, we will identify infants who are congenitally infected by performing parasitological examinations on cord blood and at 4-8 weeks, and serological follow-up at 10 months. We will also perform standard PCR, real-time quantitative PCR, and T. cruzi genotyping on maternal blood, standard PCR and T. cruzi genotyping on the cord blood of congenitally infected newborns, and serological examinations on siblings. We will estimate the exposure to vectors in the household. In addition, we will measure prenatal outcomes among infected and uninfected infants with seropositive mothers, and the birth weight of their siblings. The specific aims of this study are: 1) To determine the rate of congenital transmission of TcI compared to TcII; 2) To compare the T. cruzi infected mothers' characteristics and exposure to vectors in regions where TcI is predominant and regions where TcII is predominant; and 3) To describe the birth outcomes of infected and uninfected infants born to TcI and TcII seropositive women.

3-R01-HD-041455-06S1
India Human Development Survey
Desai, Sonalde B.
University of Maryland
$42,600

As Indian economy grows, health profile of the Indian society is changing along with the mechanisms for financing health care. The proposed study will collect data that will facilitate research on a variety of topics associated with public health and child development in India. Data from India Human Development Survey I and II will be premier public resource for all researchers. Researchers from the University of Maryland, the National Council of Applied Economic Research, and AMS Consulting, together with an interdisciplinary team of collaborators, propose to field the second round of the India Human Development Survey (IHDS-II), a nationally representative survey of 41,554 households who were surveyed in 2004-2005 under NIH grants R01HD041455 and R01HD046166. This survey is designed to be a premiere public resource for researchers interested in studying different dimensions of human development in India. The proposed project has two specific aims: A. Resurvey the households initially surveyed in 2004-5 once again in 2011-12. Given the vast changes in India since 2005, IHDS-II will provide a multi-topic, multi-purpose source of data for international and Indian research on health, education, income, employment, gender and social inequality. Panel data will allow an exploration of lagged effects as well as better estimation of causal relationships. IHDS-II will permit the analysis of two major government programs initiated since 2005 - the National

Rural Employment Guarantee Scheme and the National Rural (and now Urban) Health Mission. These programs introduce exogenous changes in the male/female wage gap and provide cash incentives for hospital deliveries. Panel analyses of these changes create new opportunities to investigate the determinants of gender gaps in employment, education, and health. B. Expand the range of data collected. Data collection will be expanded in two principal ways: 7 Some questions from IHDS-I will be revised and extended based on our field experience, analysis results, and user feedback. 7 New modules will be added to study the mechanisms through which spatial disparities in health and education emerge. Research conducted under the parent grant has highlighted the importance of spatial disparities in health, education, income, and employment as well as caste and gender differences in these outcomes. Analyses of IHDS-I have showed us that these large regional differences persist in spite of a wide range of controls for individual level factors. In this renewal, we seek to measure a broader range of mechanisms through which these spatial disparities emerge. New efforts focus on supplementing the household surveys with expanded geographic data and institutional surveys.

3-R21-HD-062821-02S1
Empowering Daughters and Mother-in-laws to Mitigate Gender-based Violence and Promote Women's Health in India
Krishnan, Suneeta
Research Triangle Institute, Research Triangle, NC
$50,438

A growing body of research indicates that gender-based violence (GBV) is a major global public health challenge. Yet, there is a dearth of evidence to guide program planning and policy-making efforts to reduce GBV. Our study will evaluate the feasibility, safety, and potential effectiveness of an innovative women's empowerment intervention to reduce GBV and related adverse health outcomes. It is expected that the study findings will provide evidence to determine if a phase 3 effectiveness trial is merited and advance the science underlying GBV prevention. A growing body of research indicates that gender-based violence (GBV) is a major global public health challenge. Yet, there is a dearth of evidence to guide program planning and policy-making efforts to reduce GBV. Our study will evaluate the feasibility, safety, and potential effectiveness of an innovative women's empowerment intervention to reduce GBV and related adverse health outcomes. It is expected that the study findings will provide evidence to determine if a phase 3 effectiveness trial is merited and advance the science underlying GBV prevention. The prevalence of physical, psychological, and sexual gender-based violence (GBV) is staggeringly high among young, married women in India. However, few GBV prevention interventions have been implemented, and none of these interventions has been rigorously evaluated. We aim to fill this gap by conducting exploratory research on an innovative women's empowerment-based GBV prevention intervention. The proposed study builds on our previous research in urban poor communities in Bangalore, India, which revealed that efforts to enhance young, married women's power and to mitigate GBV will be limited if the broader context of their lives, which is shaped mainly by the marital family, is unaddressed. Previous research suggests that mothers-in-law (MILs) are a strategic familial entry point and that it may be possible to redirect the power they wield in the family toward reducing GBV against daughters-in-law (DILs). Based on this

evidence and women's empowerment approaches that have successfully reduced GBV elsewhere, we developed the intervention Dil Mil (meaning "Hearts Together" in India's national language, Hindi). Guided by the Social Cognitive Theory and Heise's social-ecological framework of GBV, Dil Mil aims to empower DIL-MIL dyads with knowledge, skills, and social support critical to the mitigation of GBV and related adverse health outcomes among DILs. We chose antenatal care as the context for implementing this intervention because of women's nearly universal use of antenatal care in urban India. A phase 1 pilot study demonstrated that our approach is acceptable and likely to be safe. The aim of this R21 is to conduct a phase 2 trial to examine the feasibility, safety, and potential effectiveness of Dil Mil in order to determine if a phase 3 effectiveness trial is merited. The proposed study is a randomized controlled trial with 140 dyads comprising pregnant DILs (aged 18 to 30 years, in their first or second trimester of pregnancy, with a history of GBV) and their MILs. Recruitment will take place at four primary health centers serving poor communities in Bangalore. Dyads will be offered standard care or standard care plus the Dil Mil intervention, and evaluations will be conducted at 3 months and 6 months postpartum. We will characterize the study population using descriptive statistics and assess feasibility and safety of the intervention using qualitative and quantitative data (Aim 1). Data on the effect of the intervention on intermediary outcomes-the empowerment of DILs and MILs (Aim 2)-and on the incidence of GBV among DILs during the first 6 months postpartum, DILs' perceived quality of life and psychosocial status, and maternal and infant health outcomes (Aim 3) will be analyzed using the intention-to-treat principle. Based on this evidence, we will determine if a phase 3 trial is merited. In conclusion, this study will generate important insights on a novel, urgently needed response to GBV in a high prevalence setting and is highly likely to have a significant public health impact.

5-R01-TW-008151-03
Molecular epidemiology of drug resistance and population genetic structure of *Plasmodium falciparum* and *P. vivax* in Yunnan and Hainan, China
Lu, Fangli
Sun Yat-sen University, Guangzhou, PR China
$50,000

The 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, our 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 we 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

5-R01-TW-008288-03
Weight, Diet, Genes and CVD Risk Factors (Hypertension and Diabetes)
Lee, Nanette Requintina
University Of San Carlos, Cebu City, 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 we 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.

5-R24-TW-008881-02
Novel Education Clinical Trainees and Researchers (NECTAR) Program
Campbell, Thomas B.
University Of Zimbabwe
$60,000

This application for a MEPI Programmatic Award will establish the Novel Education Clinical Trainees and Researchers (NECTAR) program at the University of Zimbabwe College of Health Sciences (UZCHS). UZCHS is the centre of medical research and education for Zimbabwe. NECTAR will be a consortium of investigators based on the long history of strong and productive collaborations in education and research between faculty at UZCHS and faculty at Stanford University and the University of Colorado Denver. The NECTAR consortium will consolidate the unique education and research training experience and expertise available in each of the consortium institutions. UZCHS, is the applicant institution and the site of most NECTAR activities. The strategy of NECTAR is that improvements in the approach to medical education at the medical student and post graduate levels, coupled with programs to improve faculty training and support and investments in novel educational models and technologies, will lead to improved capacity of UZCHS to meet the healthcare training and research capacity needs of Zimbabwe. The goals of NECTAR are to: (1) Increase the number and improve the proficiency of UZCHS medical graduates in PEPFAR priority areas. (2) Improve the retention of UZCHS graduates in Zimbabwe and increase the proportion of recent graduates who practice in Zimbabwe, serve as faculty at UZCHS, conduct research and are engaged in PEPFAR health priority areas. (3) Improve the recruitment and retention of academic faculty at UZCHS by transforming the UZCHS academic environment, creating new and sustainable educational and clinical partnerships and research opportunities.

5-R24-TW-008863-02
Enhancing, Training, Research Capacity And Expertise In HIV Care-ENTREE
Lalloo, Umesh G.
University Of Kwazulu-Natal
$60,000

This medical education partnership initiative project will enhance the competency and number of doctors, nurses and pharmacists in HIV/AIDS care in KwaZulu-Natal, South Africa which has numerous PEPFAR treatment sites. It will contribute to the goal of increasing the quality and numbers of patients receiving care. This will be achieved through its HIV/AIDS focused programs of undergraduate and postgraduate medical education and academic support for HIV treatment platforms and will promote the development of women. The broad aim of the Enhancing Training, Research Capacity and Expertise in HIV Care (ENTREE) program is to address the shortage of competent health care personnel to manage the increasing burden of HIV/AIDS in the Province of KwaZulu Natal that has numerous PEPFAR treatment programs. The specific aims are to: increase the competency of medical, nursing and pharmacy students in the management of HIV/AIDS through enhancement of undergraduate training and infusion of the curriculum with a program of a continuum of care approach to HIV/AIDS and improved clinical preceptorship; scaling up of an innovative parallel training track for selected undergraduate medical students in HIV towards a certificate / diploma / masters program; increase the competency of medical interns / house-officers through the development of a program that will create a cadre of master trainers to support and enhance the internship experience; create a supportive learning environment and in so doing attract medical trainees to return to these centers that include both urban and rural internship and academic and non-academic clinical service centers; develop and support a program of research to enhance skills, among undergraduates and faculty, in research methodology and research implementation with particular emphasis on HIV and related complications including individuals selected from Southern African Development Community (SADC) countries; develop a program to promote retention of academic and research staff by providing a research career pathway and research support; and develop a postgraduate medical resource center unit within the Nelson R Mandela School of Medicine (NMSM) with seed funding support from the Department of Health training grant. At least 50% of the beneficiaries of the program will be women. The program will use and expand an established telehealth program and set up academic resource centers in HIV care sites in KwaZulu Natal. The project will harness the resources of the academic departments of the Nelson R Mandela School of Medicine, the Schools of Nursing and Pharmacy and the established HIV/AIDS research units in the University KwaZulu- Natal. The University of Columbia is the US partner in this project.

5-R24-TW-008873-02
Programmatic: Expanding Innovative Multidisciplinary Medical Education in Zambia
Mulla, Yakub F
University Of Zambia
$60,000

The people of sub-Saharan Africa are the most heavily affected by the HIV epidemic. The Zambian programmes for expansion of HIV therapy and prevention services has been very impressive but can only be sustained if more health care workers are trained. The single center for most advanced health care worker training in Zambia is the University of Zambia (UNZA). We propose to enhance the training programs at UNZA to improve the quality of training allowing for training many more HCW throughout Zambia. Zambia is one of the countries in the world most heavily impacted by the HIV epidemic with an estimated adult prevalence of 14.3%. While recent indicators suggest progress in the national HIV prevention and management response, this is not sustainable without substantial increases in health manpower. Health care worker (HCW) training will require investments at many levels, starting with the expansion of the capacity and quality of pre-service training programs. The University of Zambia (UNZA) is the sole training institution in Zambia for Medical Officers and other health care professionals including bachelors degree programs in Nursing, Pharmacy, Biomedical Sciences, and Physiotherapy, Masters in Public Health and Nursing, and Masters in Medicine for clinical subspecialties. UNZA also has active affiliation agreements with the only Clinical Officer training program at Chainama College of Health Sciences and with other training institutions for nursing and HCW training institutions throughout Zambia. UNZA is thus critical for addressing the needs to expand HCW training in Zambia. Critical shortages of faculty and instructors must be addressed in order to meet these targets. The overall goal of this programmatic application is to strengthen both the quality and quantity of HCW education across selected high-priority training programs at UNZA and its partner institutions. Expanding and retaining faculty will be critical to these goals long-term. To accomplish this goal, our Specific Aims are: Specific Aim 1: Improve substantially the capacity of UNZA to train more HCWs at the UNZA School of Medicine (SOM) and affiliated institutions. Specific Aim 2: Improve the overall quality of HCW training, emphasizing integrated HIV specific training at UNZA. Specific Aim 3: Enhance the MMed degree program for physicians to ensure that graduates have the capacity to conduct evidence-based research and program evaluation. Specific Aim 4: Enhance the academic environment at UNZA to better retain faculty.

5-R24-TW-008908-02
The Universidade Eduardo Mondlane/UCSD Medical Education Partnership
Noormahomed, Emilia
Universidade Eduardo Mondlane, Maputo Mozambique
$60,000

Although the development of new curriculum and of new educational approaches has had a profound impact on medical education around the world, the biggest challenge to medical education in many sub-Saharan Africa countries continues to be that there are too few medical educators and that the institutions in which they teach are so poorly supported that they cannot fully apply their considerable skills and energy to medical education. Thus, the overriding goal of the Universidade Eduardo Mondlane-UCSD Medical Education Partnership is substantially increase the number of highly skilled medical school faculty in Mozambique. We will emphasize the development of a powerful but locally sustainable biomedical informatics infrastructure to enhance both teaching and learning. By strengthening the infrastructure for clinical, operational and epidemiological research we will both provide additional avenues for faculty development

and greatly enhance institutional stability. A major priority of this collaboration is to recruit trainees and junior faculty into lifelong careers in medical education and to provide them with the skills to make these careers sustainable. To this end, we will develop early and mid-career mentoring programs that are tailored to the goals of individual Mozambican faculty and trainees as well as to the needs of the UEM Faculty of Medicine. Although the partnership will be anchored in Mozambique by the Universidade Eduardo Mondlane, as the program develops we will provide active assistance to Mozambique's two new medical schools in Nampula and Tete to create a network of all three of Mozambique's publicly funded Faculties of Medicine in order to extend the impact of this MEPI to all of Mozambique. By substantially strengthening Mozambique's medical education infrastructure, we expect that our partnership will have a profound effect on Mozambique's ability to deliver better medical care to all of its citizens for the next several decades.

5-R24-TW-008886-02
Medical Education for Services to All Ugandans (MESAU)
Sewankambo, Nelson K
Makerere University, Kampala, Uganda
$60,000

Improving medical education in resource-limited settings through Innovative curricula will result in a larger number of high quality health care workers with the competencies to address Ugandan health care priorities such as HIV/AIDS and non-communicable disease such as cardiovascular disease and cancer. In Africa, HIV, infectious diseases and other severe health problems compounded by critical shortages of health workforce compromise effective health care delivery. In order to train the necessary number of medical doctors in Africa, medical schools need to produce more high quality doctors. This proposal assembles a 5 Ugandan medical school consortium with JHU to catalyze capacity building and performance enhancements in medical education, research, and environment geared towards improved service delivery. Funding this proposal will facilitate Ugandan universities to strengthen countrywide south-south institutional collaboration as a strategy to enhance quality in medical education with an increase in the number of health workers trained and retained in the country, especially in rural areas. This funding will strengthen the capacity of the Ugandan medical schools consortium to realize their joint mission "to ensure the transformative innovative medical education built on strong sustainable systems to produce more health workers of consistently high quality to address health priorities like HIV/AIDS through service and research to improve health outcomes for Uganda." The specific aims of the proposal are to improve the quality and relevance of medical education and service training by developing learner-centered curricula to be implemented at standardized community-based platforms for education, service, and research which geographically cover the entire country. Well-trained on-site supervisors will teach competencies necessary to deliver locally relevant services in resource-limited environments. Next, incentives and support will be provided to faculty and students to undertake transdisciplinary research at the community-based sites. A series of grants will be offered that will give students the opportunity to initiate operational research at community sites, will increase the pipeline of basic science and family medicine advanced degrees, and encourage faculty development and retention through research

grants with "twinning" opportunities with JHU faculty. Finally, support systems capacity building will be emphasized to facilitate the efficient conduct of education and research.

HIV

5-R21-AI-082689-02
Development of Antimicrobial Peptides as Topical Microbicides
Buckheit, Robert W
ImQuest BioSciences
$21,428

We hypothesize that novel anti-HIV and anti-STI topical microbicides based on natural antimicrobial peptides collected in the Antimicrobial Peptide Database developed by the co-PI's laboratory (http://aps.unmc.due/AP/main.html) can be discovered and improved through peptide engineering technology. During the R21 phase, we will methodically screen peptides from the database and define specific inhibitors of HIV and HSV-2 as well as broad based inhibitory peptides. These active agents will be further developed in order to understand their range and mechanism of anti-HIV action. Superior peptides identified in SA1 will be characterized in SA2 to provide a rationale for continued development in SA3 using various molecular strategies which will result in the improvement of the therapeutic index of the peptide agents, with and without other small molecule microbicides, in order to begin development of an effective microbicide product. This product will be formulated and evaluated in animal models and safety assessment studies in the R33 portion of the project. Our goal is to produce a female controlled preventative agent which can be utilized to prevent the sexual transmission of viral, bacterial and fungal organisms with a focus on inhibiting the transmission of HIV. The research data will be entered into the existing antimicrobial peptide database to facilitate the use by funding agencies, other researchers, students and the public.

5-R21-AI-088601-02
Targeted siRNA Delivery As An Anti-HIV Microbicide
Dykxhoorn, Derek Michael
University of Miami School of Medicine
$21,428

Human immunodeficiency virus (HIV) is a highly lethal lentivirus which over a protracted course destroys the host's adaptive immune system leaving them vulnerable to numerous opportunistic infections. Unlike most viruses whose genome replicates independently of the host cell's genome, the HIV-1 genome integrates into and is replicated with the host genetic material. Therefore, even if therapeutic approaches can inhibit new virus production, the viral genome remains intact and competent. Therefore, strategies that can prevent the uptake and integration of the virus would be of tremendous clinical value. The vast majority of HIV infections occur as a consequence of viral transmission through mucosal surfaces, such as the vaginal mucosa. The delivery of siRNAs that specifically silence host factors required for early events in the HIV life

cycle to lymphocytes in the vaginal mucosa could prove to be an effective means of protecting individuals from HIV infection and serve as a potential microbicide. One of the main challenges facing the clinical application of siRNAs as a genetic therapy is the ability to delivery siRNAs to the cytoplasm of the appropriate target cell types. We have recently developed a novel lipid nanoparticle that is coated with an antibody recognizing the integrin molecule LFA-1 which is broadly expressed on lymphocytes. These immuno-nanoparticles will be used to deliver siRNAs to lymphocytes present in the vaginal mucosa of humanized mouse models of HIV. Given the high level of sequence heterogeneity, the propensity of HIV-1 to mutate and the inability of anti-HIV siRNAs to target the incoming viral RNA genome and prevent integration, alternative therapeutic targets are required to prevent the transmission of HIV. Host factors that are necessary for early events in the HIV lifecycle but are dispensable for cellular functioning could prove to be an effective therapeutic alternative. Using a high-throughput RNA interference-based screening platform, we have identified a large number of potential therapeutic targets that could serve to inhibit HIV integration when silenced. However, these factors require extensive analysis and characterization to ensure their safety and efficacy. We will be combining the LFA-1-mediated cell-type specific vehicle to introduce siRNAs targeting therapeutically relevant host factors as a potential means to inhibit viral infection in humanized mouse models of HIV. These experiments will provide the preclinical groundwork necessary for the development of an effective RNAi-based anti-HIV microbicide. Heterosexual transmission is the leading cause of new HIV infections in the world. A microbicide providing true intracellular immunity would make a significant contribution to controlling the spread of this deadly virus.

5-R21-AI-088586-02
Development of a novel nanoparticle pyrimidinedione vaginal polymeric film as an anti-HIV microbicide
Ham, Anthony Sang Won
ImQuest BioSciences
$21,428

Pyrimidinediones (PYD) are highly potent small molecule inhibitors that have a dual anti-HIV mechanism of action: viral entry inhibition and non-nucleoside reverse transcriptase inhibition (NNRTI). The PYD compounds have shown in vitro subnanomolar levels of activity as an NNRTI and nanomolar levels of activity as inhibitors of entry occurring prior to chemokine receptor binding and fusion. However, as microbicides compounds are being developed, delivery issues that are part of the formulation of the compound have lagged behind causing a critical delay in product development. Due to low solubility and poor penetration through the mucosa to the target site of action, Pyrimidinediones face significant obstacles as microbicides. Strategic drug delivery design is essential for Pyrimidinediones to advance as viable microbicide products. We propose a combination of innovative drug delivery strategies to enhance PYD anti-HIV efficacy through polymer biochemistry formulations. Specifically, nanoparticle encapsulation has been used to overcome many of the challenges presented when using hydrophobic drug molecules; however, its use as a vaginal drug delivery system has not been investigated. In the R21 phase of this project, we propose to develop nanoparticle encapsulation of PYD as a novel drug delivery method to improve the potency of HIV inhibition activity by increasing long term drug release, protecting against enzymatic degradation, enhancing submucosal tissue penetration

and cell localization. Additionally, we propose to further formulate the nanoparticle PYD formulation into a vaginally delivery polymer film dosage form. Such "quick dissolving" solid dosage forms have recently been proposed as a innovative alternative to address several acceptability and compliance issues observed in more traditional vaginal delivery systems (gels, creams, intra-vaginal rings). Our nanoparticle PYD film delivery approach offers several innovative advantages in microbicide development by suggesting enhanced apparent activity without active pharmaceutical ingredient (API) reformulation, conferring HIV protection over long periods of time through controlled drug release, making such a microbicide coitally-independent, and introducing a novel drug delivery method through vaginal films that addresses many of the acceptability issues with gels and other semi-solid dosage forms. Biological characterization and evaluation will be preformed to confirm the efficacy of PYD nanoparticles in biologically relevant conditions. The encapsulation of PYD into biodegradable nanoparticles will be characterized and evaluated in specifically designed in vitro assays to determine drug targeting and release. Additionally, the anti-HIV efficacy of the nanoparticle PYD will be compared to unformulated PYD in biologically relevant in vitro assays to determine the optimal formulation. Finally, the formulation will be introduced into a solid vaginal film dosage form to evaluate its biological properties in HIV prevention.

5-R21-AI-082680-02
Phosphorothioate Oligonucleotides as Microbicides against HIV Transmission
Katsikis, Peter D
Drexel University
$21,428

Developing interventions that inhibit the transmission of HIV infection are critical for halting the HIV epidemic. Topical prevention strategies usually termed microbicides have been proposed as one strategy to halt or slow down the HIV epidemic. We have identified novel lead microbicides that potently inhibit HIV and SIV infection/replication in vitro. During our previous submission we reported an oligonucleotide with a phosphorothioate backbone (OPB) that could inhibit HIVBaL or SIVmac251 infection and/or replication in human or simian PBMC, respectively. OPB also inhibited infection/replication in cell-free infections of P4-R5 MAGI cells by HIVBaL and HIVIIIB. OPB exhibited no toxicity against PBMC or P4-R5 MAGI cells after 24h continuous exposure. Preliminary data suggested that OPB may also inhibit other viruses as it was also effective against influenza type A virus. Thus, our first generation OPB may be a potent microbicide against HIV that prevents infection at mucosal sites when topically applied. Our preliminary studies were carried out with a 13mer Poly T or Poly A oligonucleotide of OPB and this suggested that the effect was sequence independent and may even be mediated by the phosphorothioate deoxyribose sugar backbone. Indeed in our current re-submission we present data on our next generation compound, a baseless phosphorothioate 2' deoxyribose backbone (PDB) that has more potent HIV inhibitory activity than OPB. A 14mer PDB we show here has no toxicity, is a potent inhibitor of HIV and has the advantage of being a TLR7/9 antagonist that inhibits HIV-induced IFN¿ production. This later property is important as the establishment of HIV infection may depend on HIV-induced mucosal inflammation triggered by TLR. Importantly, we show that PDB is active when formulated in hydroxyethylcellulose (HEC) gel at pH 4.4, survives pH transition to a neutral pH, and in retains its activity in HEC for long periods.

We hypothesize that PDB binds enveloped viruses and inhibits their infectivity by acting as a "chemical lectin". We further hypothesize that PDB can act as a microbicide against HIV and can prevent SIV vaginal infection of rhesus macaques. The studies planned in the R21 phase will further optimize and characterize the safety and effectiveness of PDB in vitro and its safety in the Swiss Webster mouse vaginal/cervical model of irritation. They will determine the optimal size and composition that remains effective against HIV and exhibits no toxicity. Finally, the mechanism of action of PDB will be investigated, the effect of inclusion into hydroxyethylcellulose gel will be tested and PDB's effect on the growth of commensal lactobacilli will be determined. Five specific milestones have been set for the progression from the R21 Phase to the R33 Phase. The R33 phase will test the effectiveness of PDB in preventing vaginal SIV infection, investigate the effect of seminal plasma and pH transition on the efficacy of OPB, determine its safety with human genital epithelial tissue, and investigate its effectiveness against HSV-2. The current application will allow for an extensive evaluation of PDB as possible novel microbicide candidates. The studies proposed here address the important public health problem of developing treatments that inhibit the transmission of HIV infection. The current application investigates a novel chemical that may be used to inhibit infection with HIV.

5-R21-AI-088585-02
Plant-produced Actinohivin as a Candidate HIV Microbicide
Matoba, Nobuyuki
University of Louisville
$21,428

Safe, effective, and inexpensive topical microbicides are urgently needed to curb the global human immunodeficiency virus type-1 (HIV-1) epidemic. Actinohivin (AH) is an actinomycete-derived lectin. This lectin specifically binds to high-mannose clusters uniquely found on the HIV-1 envelope (Env), thereby eliciting nanomolar antiviral activity against multiple HIV strains. Preliminary analyses revealed that AH has a high safety profile in human peripheral blood mononuclear cells (PBMCs) and in the rabbit vaginal irritation assay. Meanwhile, a translational AH-AH fusion protein (recombinant dimer [rd] AH) was suggested to have stronger and broader anti-HIV-1 activity than the original monomer. Given these high potentials, we hypothesize that rAH and/or rdAH (r/rdAH) are excellent HIV-1 microbicide candidates. This project's goal is to reveal the feasibilities of r/rdAH in terms of manufacture, antiviral efficacy, and safety upon use as a vaginal microbicide. In the R21 phase, we will initially focus on developing a highly efficient, scalable production system for r/rdAH that allows for extensive efficacy and safety studies and possible global use. We will utilize recombinant plant virus-based expression systems and various molecular biological approaches for rapid and high-level expression of high-quality r/rdAH. Upon obtaining bulk r/rdAH active pharmaceutical ingredients with high purity standards, we will analyze HIV-1 neutralization effects against selected R5-type viruses in two in vitro HIV neutralization assays based on Env-pseudotyped virus-reporter gene expression and primary isolate- PBMC infection systems. Next, r/rdAH' cytotoxic, mitogenic, and inflammatory potentials will be tested in PBMCs and/or human cervicovaginal (CV) epithelial cell lines to establish the minimal safety profile. Our success criteria in the R21 phase are: (1) establishing the bulk preparation procedure; (2) demonstrating

cross- clade antiviral effects to R5 viruses; and (3) demonstrating no apparent in vitro cytotoxicity, mitogenic activity, or inflammatory potential at >100 times above an average anti-HIV IC50, for plant-made r/rdAH. Upon approval of our transition to the R33 phase, we will comprehensively analyze anti-HIV-1 efficacy of r/rdAH for various modes of HIV-1 infection and transmission, using various in vitro assay systems. In addition, we will investigate potential overlap, complementation, synergy, and antagonism of anti-HIV activities between r/rdAH and other inhibitors toward potential microbicide combination strategies. Finally, we will perform extensive evaluations of r/rdAH upon vaginal application in rabbit and mouse models. We will thoroughly evaluate r/rdAH' vaginal toxicity, inflammatory potential, and stability. Upon determining the maximal tolerated dose of r/rdAH, we will examine their potential immunogenicity and toxicity after a long-term exposure. Potential toxicity to the symbiotic vaginal commensal bacteria, the Lactobacillus species, will be examined. In summary, the proposed studies should answer the question of whether r/rdAH is justified for advanced next-stage preclinical studies. . The proposed studies will analyze the feasibilities of the novel HIV-1-binding lectin Actinohivin and its derivative recombinant dimer, as a candidate vaginal HIV-1 microbicide. The proposed studies should generate a comprehensive data set that will reveal their large-scale producibility, anti-HIV-1 efficacy, and broad toxicity profile upon vaginal application, thereby providing criteria of whether Actinohivin and its derivative are justified for further extensive preclinical and clinical studies.

5-R21-AI-088597-02
Engineering Antiviral Innate Immunity For Safe And Effective Microbicides
Shen, Hong
University of Washington
$21,428

HIV infections afflict millions of people and cause tremendous health and economic burdens. One of the major risk factors for HIV-1 transmission is the pre-existing infections caused by sexually transmitted agents such as herpes simplex virus type 2 (HSV-2). Therefore, a rational prevention strategy to halt HIV spread is to target HSV-2 infection and control its spread. In the absence of vaccines against HSV-2, a more practical and effective intervention for HSV-2 is the utilization of microbicides. A promising microbicidal approach is to potentiate antiviral innate immunity effective against a broad range of viruses at the site of viral encounters. The toll-like receptor (TLR)-based innate immunity have been shown to be crucial in initiating a cascade of antiviral activities mediated by type I interferons (IFNs). Both TLR3 and TLR9 agonists, polyinosinic: polycytidylic acid (poly IC) and CpG oligonucleotides (ODNs) are effective in protection against HSV-2 infections. However, undesirable inflammatory responses and autoimmunity accompanying the non-specific stimulation of TLRs are of major concern, which could severely limit the use of TLR agonists as microbicides. Thus, the key to developing TLR agonists as microbicides is to target them to relevant cell types at the potential sites of viral exposure and to elicit IFN responses in a regulated fashion. We propose to develop localized, controlled-release, and cell-targeted delivery systems to regulate the stimulation of TLR-based innate antiviral immunity. In the R21 Phase, three aims will be accomplished: Aim 1: to design and characterize cell-targeted delivery systems based on poly (lactide-co-glycolide) (PLGA) nanoparticles to specifically and locally target pDCs and epithelial cells with TLR agonists; Aim

2: to evaluate the effectiveness against genital HSV-2 infections by locally and selectively targeting CpG ODNs and/or poly ICs to pDCs and epithelial cells with cell-targeted nanoparticles; Aim 3: to evaluate toxicity by locally and selectively targeting CpG ODNs and/or poly ICs to pDCs and epithelial cells with cell-targeted nanoparticles. Built upon the results from the R21 phase, in the R33 phase, we will accomplish: Aim 4: to design and characterize delivery systems for sustained release of TLR agonists; Aim 5: to evaluate the effectiveness against genital HSV-2 infection and toxicity by localized, sustained-release and cell-targeted nanoparticles loaded with CpG ODNs and/or poly IC; Aim 6: to evaluate the adaptive immunity against genital HSV-2 infection mediated by localized, sustained-release and cell targeted nanoparticles loaded with CpG ODNs and/or poly IC. This application will enable the translation of TLR-based antiviral innate immunity to effective and safe microbicides.

2-R21-AI-088595-02
Exploring the Role of Vif Antagonists in Preventing Sexual HIV Transmission
Stevenson, Mario
University of Massachusetts Medical School
$21,428

Since it has proven difficult to develop a vaccine against HIV-1, the major cause of the AIDS pandemic, the research community has shifted some of its focus to the development of topical microbicides. Since both the vaginal and rectal tract are portals of HIV-1 entry, topical microbicides suitable to protect both sites need to be developed. In this grant, we focus on a novel mechanism that has not previously been explored for HIV prevention. In 2002, it was found that the cellular target of the HIV-1 protein Vif is APOBEC3G (A3G). A3G is an enzyme of the AID/APOBEC family, characterized by the targeted deamination of cytosine to generate uracil within DNA. APOBEC3G plays an important role in retroviral defense by acting on viral reverse transcripts and mediates numerous critical immune responses. We believe that A3G is an important innate retroviral defense mechanism in the vaginal and rectal tract. By using inhibitors of the viral protein Vif, the Vif-APOBEC3G interaction is blocked and APOBEC3G is not degraded by the proteosome. As a consequence, fatal hypermutations are introduced into the viral cDNA transcripts and HIV is rendered incompetent for replication. Our grant has four specific aims: Specific Aim 1: Explore the role of the restriction factor A3G in mucosal tissues of the vaginal and rectal tract Specific Aim 2: Examine whether RN18 and its analogs are active in microbicide cell-based assays and ex vivo explant HIV transmission models Specific Aim 3: Vaginal humanized BLT mouse model testing of promising Vif inhibitor candidates Specific Aim 4: Macaque microbicide model testing of promising Vif inhibitor candidates It is expected that these studies will define the role of A3G in the vaginal and rectal tract and whether inhibitors of the viral Vif protein can prevent sexual transmission of HIV.

5-D43-TW-001039-12
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.

5-D43-TW-001042-12
Emory AIDS International Training and Research Program
Del Rio, Carlos
Emory University
$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.

5-D43-TW001038-12
AIDS international Training and Research Program
Harrison, Lee H.
University of Pittsburgh
$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.

5-U2R-TW-006896-08
Haiti AIDS Research Training: Models to Implementation
Pape, Jean William
Gheskio Center, Port-Au-Prince, Haiti
$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.

5-D43-TW-001035-12
Vanderbilt University-CIDRZ AIDS International Training And Research Program
Vermund, Sten H
Vanderbilt University
$20,000

The Vanderbilt University (VU)- Center for Infectious Disease Research in Zambia (CIDRZ) training partnership with their international collaborators is designed to strengthen both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care in developing countries. The VU-CIDRZ 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.

1-R21-AI-094412-01
Nanoparticle Microbicides For Delivery Of Combination Antiretroviral Drugs
Woodrow, Kim A.
University of Washington
$18,750

Women are disproportionately impacted by the HIV epidemic and access to female-controlled prevention methods such as an effective topical microbicide is critical. To overcome challenges associated with formulating multiple anti-HIV compounds in a topical gel, we propose a single topical strategy that uses particulate-based microbicides to encapsulate individual agents that are delivered in combination. This approach will empower and provide women with an effective means of protecting themselves against sexual HIV-1 infection. Sexual transmission through the genital tract or rectal mucosa is the most common route for acquiring new HIV infections and accounted for ~70% of the 2.7 million people worldwide who became newly infected in 2007. A cure or effective vaccine that would contain the global spread of this epidemic is not expected in the near term, and new HIV infections continue to outpace advances made in treatment with antiretroviral drugs. There is consequently an urgent need to develop agents that can be applied topically to mucosal surfaces to prevent the sexual transmission of HIV. However, several large-scale clinical trials testing the efficacy of agents that disrupt the integrity of the viral envelope (detergents) or prevent adsorption or fusion of the virus with its target cells (polyanions) have failed to protect against HIV infection. The success of highly active antiretroviral therapy (HAART) provides a paradigm for developing the next generation of microbicides, raising the possibility that a combination of potent and broadly active inhibitors that exhibit multiple and complementary mechanisms of action may be vastly superior to the delivery of single compounds. To fully realize the potential of these potent antiretroviral (ARV) drugs, the challenges of formulating and delivering compounds with markedly different chemical stability and aqueous solubility in a topical combination product must be overcome. This research plan is designed to evaluate nanoparticle-based vaginal drug delivery systems for HIV prevention. The experimental focus is to achieve protection against vaginal transmission of HIV-1 by topical delivery of a combination of antiretroviral drugs using mucus- and tissue-diffusing nanoparticle microbicides. This research would be the first to control the temporal and spatial co-delivery of a combination of antiretroviral agents that have different mechanisms of action against HIV-1 (Aim 1). If successful, our studies would be the first to determine the size range and penetration depth accessible for nanoparticulate drug delivery systems in the vaginal mucosa (Aim 2). Our proposed research will also provide valuable data on the transport, biodistribution, and pharmacokinetics of encapsulated and released antiretroviral agents that are administered topically to the vaginal mucosa using nanoparticle microbicides (Aim 3). Finally, we will conduct preclinical safety and anti-HIV efficacy studies to rapidly advance our nanoparticle-based microbicides to human safety and efficacy trials (Aim 4). The outcomes from our proposed research may highly impact the field of microbicide research for HIV and other sexually-transmitted infections.

1-R21-AI-094508-01
Thermostable Vaginal Probiotic Microbicide
Bronshtein, Victor
Universal Stabilization Technologies, San Diego, CA
$18,750

As the number of individuals living with HIV continues to rise and a feminization of the epidemic is occurring. At the end of 2007 women accounted for 50% of all adults living with HIV worldwide and 61% in sub-Saharan Africa. Of new HIV cases at least half are in individuals less than 25 years of age and of those aged 13-19 54% are teenage girls. For this reason there is a desperate need for the development of an effective female controlled microbicide product to protect against acquisition of HIV. The innate vaginal flora provide a natural defensive barrier to infection hence a probiotic microbicide provides a promising strategy for prevention. This project serves to evaluate a strategy to overcome two barriers to its successful application, long term bacterial preservation at relevant environmental conditions and a user acceptable stable delivery system for vaginal administration. The innovative combination of preservation by vaporization and thin film dosage forms with use of multi-strain formulations provides a unique technology which can serve to overcome existing barriers to provide a safe and effective probiotic microbicide product to protect women from acquisition of HIV. Recently revised statistics show the number of individuals living with HIV at over 33 million worldwide, with 68% being in sub-Saharan Africa. Current HIV prevention methods, such as condom use, monogamy and abstinence, are not always feasible. The need for improved HIV preventative technologies remains urgent. The development of topical microbicides represents a new and exciting field in the prevention of sexually transmitted diseases. Of these, application of live probiotic bacterial microbicides (PBM) represents a promising preventative method. Our ultimate goal is to develop potent optimized multistrain thermostable and easily deliverable probiotic vaginal topical microbicides. To achieve this goal we will stabilize vaginal probiotics for long-term storage at high ambient temperatures and short term survival at temperatures required for quick dissolve film manufacturing (60C and above). The cornerstones of this proposal are: 1) Preservation by Vaporization" (PBV) - an innovative, patent pending method of dry-stabilizing probiotics bacteria and other fragile biologicals at high ambient temperatures, and 2) Quick-dissolve thin film technology that is being optimized to deliver conventional vaginal microbicides. The strategy can be described briefly as, to occupy the vaginal epithelium and provide a long lasting protective environment against HIV, BV, and STI acquisition small glassy sugar particles containing PBV vaginal probiotic bacteria will be formulated into thin films which utilize a water soluble polymer base. Thin films offer a unique delivery platform which has a number of advantages over other dosage forms. In a recent study comparing women's preference between films, tablets and ovules, the film dosage form was shown to have greatest acceptability among women studied. We believe that women will prefer using a vaginal film over other potential methods of probiotic microbicide delivery especially if a long-acting effect of the bacteria colonizing vaginal epithelium allows for less frequent use. Biologic properties of PBM after long-term storage at ambient temperatures will be characterized using cell culture models of vaginal and cervical epithelium.

1-R21-AI-094511-01
The Semen Enhancer of HIV Infection as a Novel Microbicide Target
Dewhurst, Stephen
University of Rochester
$18,750

New approaches to prevent the transmission of human immunodeficiency virus type-1 (HIV-1) are urgently needed. This application seeks to develop a new class of microbicidal agents that are targeted not to the virus itself, but to a host protein found in semen that strongly enhances HIV-1 infection. This high risk, high reward approach is fundamentally different from traditional microbicidal strategies that target the virus, and is expected to be highly complementary with direct antiviral approaches. Human semen contains cationic amyloid fibrils, termed the "Semen Enhancer of Virus Infection" (SEVI), which strongly enhance HIV-1 infection and may play an important role in viral transmission. Our preliminary data show that amyloid-binding molecules bind to SEVI, and block semen-mediated enhancement of HIV-1 infection. This suggests that (i) SEVI is responsible for semen-mediated enhancement of HIV infection and (ii) SEVI represents a novel microbicide target. We therefore propose to explore a novel, innovative approach to HIV-1 microbicide development, using agents that selectively target SEVI. This high-risk/high-reward approach is fundamentally different from traditional microbicidal strategies that target the virus itself, and is expected to be highly complementary with direct antiviral approaches. Indeed, our long-term goal is to use SEVI-targeting agents in combination with traditional microbicides, to achieve optimal antiviral effectiveness. In the R21 phase, we will test whether novel amyloid-binding small molecules inhibit semen-mediated enhancement of HIV infection. The feasibility of this approach has been established using two amyloid-binding small molecules which contain "shielding" oligo-ethylene glycol (EG) moieties: BTA-EG4 and -EG6. These agents efficiently inhibit SEVI- and semen-mediated enhancement of HIV infection. In Aim 1, we will generate and test novel derivatives of these and other amyloid-binding molecules, including oligovalent molecules that are expected to possess increased SEVI binding affinity. We will then test their ability to inhibit SEVI- and semen- mediated enhancement of HIV infection using a panel of R5 virus strains (including different clades and transmitted strains). In Aim 2, we will examine the interaction between novel amyloid-binding small molecules and cells from the female reproductive tract. We will evaluate whether our compounds are toxic to human cervicovaginal epithelial cells (HCEC), and we will test whether they inhibit SEVI-enhanced binding of HIV-1 to HCEC and/or SEVI-enhanced trans-infection of PBMC by HCEC exposed to HIV-1 virions. The R33 phase will be undertaken only if well-defined milestones are achieved. In Aim 3, we will use structure-activity relationship (SAR) data to refine our chemical compositions. We will also test whether our lead molecules have efficacy in a cervical explant model for HIV-1 infection, and whether they have a synergistic or additive effect on the ability of other candidate microbicides to inhibit HIV-1 infection in the presence of semen. In the final Aim, we will assess the toxicity and inflammatory effects of the most promising candidate molecules, using beneficial Lactobacillus strains and cervical explants. The R33 phase will culminate with an evaluation of the safety and tolerability of the most promising compound in the rabbit vaginal irritation (RVI) model. The overall goal of these studies is to carefully determine whether small molecules that target SEVI have potential utility as a novel class of microbicides.

1-R21-AI-094514-01
Designing optimal microbicide delivery integrating rheology and acceptability
Hayes, John Edward
Pennsylvania State University
$18,750

Globally, HIV is a heterosexual disease, so there is a strong demand for women initiated and controlled prevention options. Microbicides have strong potential to meet this need, but only if formulation scientists can make products that effectively prevent HIV transmission while being acceptable to users - if products are sticky or messy, women will not use them, even if they work in the lab. Here, we incorporate user acceptability early in the optimization process to make formulations that maximize drug delivery and user acceptability at the same time, instead of considering acceptability only as an afterthought in the formulation process. This year perhaps 2.5 million people will be added to the approximately 35 million already infected with HIV/AIDS, 50% of whom are women. Topical microbicides offer these women a means to prevent sexually transmitted infections (STIs), including HIV. However, in addition to concerns about the biological efficacy of current microbicides, user acceptance of and adherence to their use is suboptimal. It has been estimated that a single microbicide with even limited efficacy could prevent millions of new HIV cases annually. The design of vaginal microbicide dosage forms has challenged formulation scientists. Safe and efficacious products are necessary, but not sufficient to assure adherence. User acceptability depends both on the physical properties of the material and behavioral factors. Constraints that drive acceptance must be identified and addressed early in development. The acceptability of the product to women must be evaluated preclinically. We propose the rational preclinical design and development of a dosage form that delivers an immediate efficacious dose of active pharmaceutical ingredient (API) followed by the slow release of API over a period of 1-3 days to maintain efficacy. This dosage form can be thought of as a temporal vaginal ring/diaphragm that releases API(s) as it slowly erodes away. These products will be an adaptation of current softgel capsule technology. However, unlike current gelatin capsules, we will develop a range of non-gelatin capsules varying in shape and firmness (texture). Human perceptual data will be assessed throughout and guide the design process. Carrageenan will be used for the development of heat-stable softgels that, unlike current gelatin capsules, will not melt in tropical environments. The two-phase nature of softgels ('ovules') will permit the inclusion of a second component. Our R21 goals provide for proof-of-concept of this new delivery system, and the R33 goals will optimize both acceptability and biophysical functionality. The R33 will also explore potential higher-order functionality, like mucoadhesion or delivery of probiotics. Here, we propose a new microbicide delivery system, designed to overcome both biological (insufficient HIV neutralization) and behavioral (poor acceptability and adherence) deficiencies of current products. By designing formulations that function for optimal efficacy and optimal use (acceptability / adherence), microbicides produced via these methods are likely to have a greater impact on the HIV/AIDS pandemic than those currently in the development pipeline. Also, by developing a methodology for design of vaginal products where multiple factors (shape, texture, size, and multi-stage delivery) play a central role, we increase the options women have in microbicide use. Critically, our product type is flexible - allowing for multiple textures, sizes, shapes and antiviral strategies - to accommodate a range of user preferences.

1-R21-AI-094515-01
Mucosal Tissue Explants As Surrogates For In Vivo Efficacy Of Microbicides
Herrera, Carolina
St. Georges's, University Of London
$18,750

This project seeks to establish methods to predict in humans the potential of candidate microbicides to prevent sexual HIV infection. Currently microbicides are often tested in non-human primates (NHPs) to determine if they can prevent vagina or rectal infection with SHIV (a monkey equivalent of HIV). However there is no way to determine whether the dose of drugs shown to be protective in NHPs would be the same as that required to protect humans. The main goal of this project is to test whether biopsies taken from animals or humans treated with microbicides are protected from infection when challenged in the laboratory. The series of experiments proposed in this study will test whether use of human biopsies have potential for predicting the dose of drug required to protect individuals using a microbicide from sexual transmission of HIV. The HIV microbicide field is dependent upon testing in non-human primates (NHPs) as the only relevant model to study infection. However, the predictive accuracy of NHP studies of efficacy in humans has not been validated and as such the economic value is unknown. Hence, refinement of this model and development of a novel correlate of efficacy in humans that will reduce the potential use of NHPs is key for the global progress of microbicides and specifically of the Microbicide Innovation Program's mission. This proposal addresses these issues by testing the hypothesis that ex vivo tissue explant cultures can provide a potential surrogate of in vivo efficacy through measurement of intra-tissular drug pharmacology and ex vivo infection/protection. This will be investigated using combined expertise in modeling mucosal tissue infection and measurement of antiretroviral (ARV) drug pharmacokinetics and pharmacodynamics in tissue. The proposal will focus on a reverse transcriptase inhibitor, PMPA (tenofovir), and an entry inhibitor, maraviroc, used alone and in combination as candidate microbicides. In the R21 component of the proposal we will demonstrate the robustness of our ex vivo explant models for analysis of pharmacological parameters and ex vivo infection independently of the origin (human or NHP) and the type of mucosa (cervicovaginal or colorectal). This will be investigated through two Specific Aims: 1) to define ex vivo pharmacological dose-responses (pharmacokinetics and pharmacodynamics) in human and rhesus macaque mucosal tissue explants; 2) to define whether the viral backbone affects pharmacological correlates of activity. The next step of our proposal in the R33 component will involve validation of the model as a surrogate for prediction of in vivo efficacy of ARV drugs as vaginal and colorectal microbicides. Here the two Specific Aims are: 3) to assess whether activity of drugs titrated in vivo can be predicted with ex vivo challenge models: 4) to correlate ex vivo and in vivo protection and drug dosing in NHPs. The iterative design of the overall proposal will allow us to assess correlates between intra-tissular pharmacological dosing and efficacy at all levels: tissue type, origin of tissue, route of dosing and challenge, and nature of experiment (ex vivo, in vivo). These correlates will define "conversion factors" of microbicides efficacy between the NHP model and in humans, which will be key for the rational development of existing and future candidate microbicides.

1-R21-AI-094519-01
Mucus Penetrating Particles for Rectal Microbicides
Hanes, Justin S.
Johns Hopkins University
$18,750

Rectal transmission of HIV significantly increases the AIDS pandemic. The aim of this project is to develop mucus penetrating particles for colorectal drug delivery that will maximize protective efficacy and minimize toxic effects of rectal microbicides for protection against HIV and other STDs. These novel particles can be delivered in enemas and lubricant gels designed to be highly acceptable to potential users since enemas and gels are frequently used for rectal intercourse even though they provide no disease protection. For reliable protection against STD transmission, rectal microbicides must be formulated in a way that will deliver the active agent to all the surfaces that are susceptible to infection. These include the entire rectum as well as a large fraction of the colon (due to peristaltic stirring of colonic contents). Colorectal surfaces are columnar epithelia that are mechanically and osmotically fragile, and are highly susceptible to STD transmission. Although continuous mucus secretion by these susceptible surfaces helps protect against trauma and pathogens, this continuously secreted mucus also poses a significant barrier against effective delivery of microbicides to the epithelial surface. Recently we developed novel mucus penetrating nanoparticles (MPP) that can overcome this barrier and provide sustained, well-distributed delivery of drugs to mucosal surfaces. Our hypothesis is that MPP will significantly increase the protective efficacy of rectal microbicides by achieving more uniform and complete colorectal distribution, sustained drug activity, and thus longer duration and more complete protection compared to drug delivered in gels ("free drug") or drug delivered in conventional nanoparticles, "CP", that adhere to mucus and fail to penetrate mucus barriers. In the R21 phase, we will determine optimal MPP properties for penetration of mouse colorectal mucus, and we will characterize the uniformity of MPP distribution and retention times in the mouse colorectum compared to CP and free drug. We will then prepare drug-loaded biodegradable and biocompatible MPP that provide sustained release of antiviral drugs (valacyclovir for HSV and UC-781 for HIV). We will deliver these MPP in both a rectal enema format and a rectal lubricant gel format since both formats are frequently used for enhancing rectal intercourse. Moreover, an enema may deliver MPP to large regions of the colon unlikely to be reached by a gel. The key milestone for the R21 phase will be development of valacyclovir-MPP and UC-781- MPP that provide more complete and persistent coverage of the rectal epithelial surface, with minimal toxicity, compared to CP formulations or free drug. In the R33 phase, we will extensively test these MPP formulations for safety and protective efficacy in our mouse/HSV rectal model and in the hu-BLT-SCID mouse/HIV model (via a subcontract with Dr. J. Victor Garcia-Martinez at UNC).

1-R21-AI-094555-01
Development Of An HIV-1 Entry Inhibitor Pre-Drug As A Microbicide
Lu, Min
University Of Medicine/Dentistry Of New Jersey-NJ Medical School
$18,750

In the absence of an effective vaccine against HIV-1, there is an urgent public health need to find alternative approaches, such as vaginally applied microbicide gels, to prevent heterosexual HIV-1 transmission. Since blocking HIV-1 entry is the first line of defense against viral infection, the HIV-1 envelope glycoprotein is a favored target for microbicide development. Several HIV-1 fusion and entry inhibitors have been shown to be effective in blocking SHIV transmission in a rhesus macaque model. The results of this project will lead to preclinical proof-of-concept for optimized fusion-inhibitory peptides as a practical microbicide. With no vaccine in sight, there is an urgent public health need to develop an effective topical microbicide that can reduce the number of new HIV-1 infections in women. The potential role of virus-cell fusion inhibitor-based microbicides in preventing mucosal transmission of HIV-1 has been clearly identified. However, none of the reported gp41 fusion inhibitors has made significant progress toward clinical trials. HIV-1 infection requires fusion of the viral and cellular membranes, driven by association of two heptad-repeat regions in the gp41 ectodomain to form a highly stable six-helix bundle structure. Whereas this postfusion motif comprising native N36 and C34 peptides has no inhibitory activity, the isolated peptides inhibit HIV-1 entry by binding to their cognate sites on gp41. Our goal in this MIP VI application is to develop an inexpensive, potent, structured 'pro-drug' form of the N- and C-peptide fusion inhibitors that exhibits significant microbicidal activity upon use in situ. Our development effort will be based on preliminary data obtained with a truncated six-helix bundle that inhibits in vitro infection by primary HIV-1 isolates with low nanomolar IC50 values. We propose a comprehensive, interdisciplinary approach that combines high-resolution structural determination, recombinant protein production and mutagenic analyses, virology, and animal model efficacy studies. In this project we seek to conduct in vitro and in vivo preclinical and animal model-based research intended to facilitate the development of new HIV-1 gp41 peptide fusion inhibitor as a practical microbicide. The Specific Aims are: 1. To optimize and identify HIV-1 peptide fusion inhibitors for development as a vaginal microbicide. (a) To identify and incorporate specific amino-acid residue substitutions that optimize both potency and solubility of fusion inhibitor peptides. (b) To develop and optimize robust procedures for the large-scale bacterial expression and purification of select fusion inhibitor peptides. (c) Investigate the mechanisms of resistance to peptide inhibitors so as to avoid eliciting resistance. 2. To characterize the specificity, potency and toxicity of optimized peptide fusion inhibitors and their in vitro synergistic interactions with the CCR5 inhibitor CMPD167 and the entry inhibitor BMS-378806. (a) Determine the virucidal activity of optimized fusion inhibitor peptides against a diverse set of primary HIV-1 isolates. (b) Evaluate their toxicity, immunogenicity and drug stability in the rabbit model. (c) Study antiviral synergy in vitro in order to make rational predictions for lead inhibitor combinations for in vivo efficacy

testing. 3. To test the effectiveness of the fusion inhibitor peptides to protect against mucosal HIV-1 infection. (a) Characterize the specificity and potency of effective peptide inhibitors in an in vitro model of HIV-1 infection of human cervical and vaginal tissue. (b) Use the NOD/SCID-hu BLT mouse vaginal transmission model to assess the in vivo potency and breadth of activity of highly effective peptide inhibitors alone and in combination with the small-molecule CCR5 inhibitor CMPD167 and the small-molecule entry inhibitor BMS-378806. 1

1-R21-AI-094584-01
Cervical/Vaginal Mucus and Microbicides
Hope, Thomas
Northwestern University
$18,750

To develop a functional microbicide it is critical to know how it will interact within HIV in the context of the female genital tract. This is a critical issue as previous clinical trials have indicated that microbicides do not function as expected in the presence of semen. Likewise, other factors, such as cervical/vaginal mucus, might also modulate microbicide function. To date, little is known about how HIV interacts with these fluids and how the interaction of these fluids changes the local environment. Even less is known about how microbicides interact with HIV within this milieu. For example, the vehicle delivering the microbicide might interact with the biological fluids of sexual transmission to either increase or inhibit HIV acquisition or microbicide potency. The Hope laboratory has recently developed methods that allow the transport of HIV with cervical and cervical/vaginal mucus to be analyzed and quantified. These studies have revealed that mucus can perturb HIV transport and is pH sensitive. At acidic pH, as is found in the lactobacilli influenced environment of the vaginal vault, HIV transport is greatly reduced. At neutral pH, such as when semen is introduced into the system, HIV transport is reduced 10-15 fold relative to what is observed in media (water). Additionally, we have found, but not yet published, that virus-binding antibodies can further reduce transport in neutral pH cervical mucus. These antibodies do not need to be neutralizing as any antibody binding to the virus can decrease virus transport. Semen also contains mucins and other components that have the potential to alter HIV transport as we have observed in cervical mucus. How HIV is transported within semen and how this changes when mixed with mucus or microbicides is not defined. How this process influences HIV transport and interaction with mucosal barriers is not understood. In the first phase (R21) of this proposal we will define how HIV is transported in semen alone and mixed with mucus and/or microbicide vehicles such as carbopol gel and hydroxy ethyl cellulose (HEC). In the second phase (R33) of this proposal we will extend our studies into the environment of the rhesus macaque female genital tract to determine how biological fluids and microbicide vehicles alter the way that virus interacts with the mucosal barriers of this environment and how these changes can increase or decrease SIV acquisition. These studies will lead to a better understanding of how virus interacts with biological fluids and how these interactions might alter microbicide efficacy.

IMMUNITY/AUTOIMMUNITY

5-U19-AI-082719-03
Autoimmunity Center Of Excellence (ACE) At Stanford
Fathman, Charles
Stanford University
$30,000

The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune disease. The major theme of the Stanford Autoimmunity Center of Excellence (the Center) is the study of the regulation of CD4 T cells in pathogenesis and treatment of autoimmune diseases. The Center will support and be supported by other ACE groups across the United States; and will take advantage of Stanford's documented leadership in basic and clinical research, technology development, and education in clinical immunology. Success of the Center will be supported by the interrelationships previously established at Stanford among clinician scientists from multiple departments studying autoimmune diseases in multiple organs and tissues. The Stanford ACE will be composed of outstanding basic and clinical investigators from multiple disciplines at Stanford Medical School 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) 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, we 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. 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.

5-U19-AI-082714-03
Oklahoma Autoimmunity Center Of Excellence
James, Judith
Oklahoma Medical Res Foundation
$30,000

The Oklahoma Medical Research Foundation is home to outstanding clinical and basic science investigators who have research interests in the etiology and pathogenesis of autoimmune diseases and seek to identify novel therapeutics for more effective patient treatments. The scientific expertise, extensive clinical trial experience, access to geographically distinct patient populations, as well as unique patient registries, repositories and core technologies provide a solid foundation for the Oklahoma Autoimmunity Center of Excellence (ACE) application to which we 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. 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, our 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, Sj"gren'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 our 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. Our Clinical Center proposes two potential clinical concepts. Based upon our

basic science investigation regarding pivotal roles for increased interferon activity in pre-clinical SLE, Sj"gren's syndrome and potentially TTP, our 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 our 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.

5-U19-AI-082715-03
A Systems Biology Approach For Pediatric And Adult Autoimmune Diseases - ACE
Pascual, Maria Virginia
Baylor Research Institute
$30,000

We propose to create an Autoimmunity Center of Excellence that will incorporate the efforts of clinicians, human immunologists (both basic and translational), physician-scientists with clinical expertise and research experience in autoimmunity, bioinformaticians, and geriomics/systems biologists. Together, the assembled group has an extensive background in clinical trials and a proven track record for merging basic and clinical science. This team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. Within this collaborative setting, a systems biology approach is proposed to focus on both pediatric and adult autoimmune diseases. The goals of the Center are: 1) To assess the efficacy of novel targeted therapies, 2) To develop simple and robust biomarkers using state-of-the-art genomic approaches, 3) To understand the role of recently identified T cell subsets in disease pathogenesis, and 4) To assess antigen-specific responses in pediatric and adult autoimmune diseases. These projects will provide a better understanding of the pathogenesis of specific autoimmune diseases and allow us to develop a strategy to assess disease activity based on novel transcriptional markers as well as to identify autoantigen-specific immune responses. The Center will deliver: 1) Innovative clinical trials targeting specific cytokines in psoriasis & dermatomyositis. 2) Development of biomarkers for dermatomyositis, psoriasis, lupus and multiple sclerosis. 3) Identification of novel therapeutic targets in dermatomyositis. 4) Development of assays to test autoantigen-specific immune responses. 5) Development of a unique microarray database of human autoimmune diseases. Clinical Component (Cush, J): Baylor Institute for Immunology Research aims to bring together a distinguished team of clinical investigators to conduct cutting-edge clinical trials on specific autoimmune diseases. This unique group of investigators and clinicians has appointments at Baylor University Medical Center, UT Southwestern Medical Center, Texas Scottish Rite Hospital in Dallas and Northwestern University. These talented individuals have been enlisted from diverse programs with subspecialties in dermatology, rheumatology, neurology, pediatrics, and human immunology. They provide a set of inimitable resources for clinical trials and have a proven track record for merging basic and clinical science. Indeed, this team is committed to bringing innovative

treatments from the laboratory bench to their patients' bedside. With such outstanding collaborative players, a systems biology approach is proposed here which investigates both pediatric and adult autoimmune disease. To this end, two Phase II randomized, double-blind, placebo-phase controlled clinical trials are proposed. The first trial investigates whether blocking IL-1 with Anakinra will result in objective disease improvement for patients with Juvenile Dermatomysitis. 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.

5-U19-AI-056363-08
Mechanisms Of Beta Cell Responses In Autoimmune Disease - ACE
St Clair, Eugene William
Duke University
$30,000

This application is a competitive renewal of the Autoimmunity Center of Excellence (ACE) at Duke. Its research focus will continue to be modulation of B cell responses in autoimmune disease. The ACE will be under the leadership of Dr. E. William St. Clair, Professor of Medicine and Immunology. For the past 5 years, Duke has been a productive member of the ACE network, contributing new insights into the developmental pathways of B cells and the mechanisms of B cell directed therapy. The proposed ACE builds on these discoveries and will support 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. We 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 our 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 our understanding of the roles played by B cells in human autoimmune disease. The projects are designed to be highly integrative between the bench and the bedside, with collaborations between basic and clinical scientists. These studies may lead to better treatments. Clinical Component (ST CLAIR, W): The Clinical Research Component of the Autoimmunity Center of Excellence shares with the Basic Research omponent an overall goal of advancing our 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. We are also participating in 3 other ongoing ACE-sponsored clinical trials. Therefore, substantial clinical research activity will carry over to the next funding cycle. Our center is organized to support clinical trials in rheumatology, dermatology, gastroenterology, hematology, and neurology. We 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, we 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.

5-R21-AI-090344-02
Sex Differences in Protective Immunity Against Influenza A Viruses
Klein, Sabra
Johns Hopkins University
$243,540

Sex differences in the incidence and severity of influenza A virus infection as well as in response to vaccination have been documented in humans. Small animal models are critical for establishing the mechanisms mediating why males and females respond differently to influenza virus infection and vaccination. They will evaluate whether higher humoral immune responses following sublethal infection confers greater protection from challenge with pathogenic influenza A viruses in females compared with males and the extent to which these differences are mediated sex steroids, which may provide clues into why responses to pandemic influenza A viruses differ between the sexes and during pregnancy. Sex differences in the incidence and severity of influenza A virus infection have been documented in humans. Although exposure rates are often higher in men, fatality following exposure to pathogenic influenza A viruses is reportedly higher in women. Sex differences also are reported in response to influenza virus vaccines, with women consistently mounting higher antibody responses and developing more frequent and severe side effects following vaccination than men. Small animal models are critical for establishing the mechanisms mediating why males and females respond differently to influenza virus infection and vaccination. Following primary inoculation with the mouse-adapted influenza A viruses A/PR/8/34 (PR8; H1N1) or A/HK/68 (HK68; H3N2), female mice mount higher inflammatory and humoral immune responses than males. Their preliminary data further reveal that elevated immunity in females against influenza A viruses represents a delicate balance between immune responses conferring protection or causing pathology. The goal of this proposal is to develop a small animal model to test the hypothesis that protective immunity to heterosubtypic influenza A virus challenge differs between the sexes and is modulated by sex steroid hormones. In Specific Aim 1, they will establish whether neutralizing antibody responses, virus-specific T cell responses, and protection against lethal influenza A virus challenge is greater among females than males. Whether males and females differentially rely on subsets of adaptive immune cells for protection against lethal influenza A virus infection has not been documented; thus, they also propose to compare heterosubtypic immune responses between male and female mice devoid of specific adaptive immune cell populations. If protective heterosubtypic immunity is elevated in females compared with males, then estrogens and/or progestins may enhance and androgens may suppress adaptive immunity against heterosubtypic influenza A virus challenge. In Specific Aim 2 they will test this hypothesis by manipulating sex steroid concentrations in vivo and establishing the effects on humoral and cell-mediated immunity as well as protection from lethal influenza A virus challenge. These are a series of high risk-high return experiments because there are no data to date assessing the sex-specific induction of heterosubtypic immunity in response to influenza A virus infection. Demonstrating that females mount a broadly protective immune response, however, will have important implications for dealing with annual epidemics of influenza, as this may explain why the attack rates for influenza are higher in men than in woman and influenced by pregnancy.

5-R21-AG-034523-02
Exploring Factors Influencing Gender Disparities in Access To Transplantation
Segev, Dorry
Johns Hopkins University
$205,000

Although kidney transplantation is safe, effective, and life-extending for many patients, women have significantly less access to transplantation than their male counterparts, and they have shown that this disparity is widest among older women compared with older men. It is unknown whether this happens because of patient-level barriers to seeking transplantation or because of provider-level biases against referral of women compared with men. Since over 50% of dialysis patients are over the age of 65, equal access to transplantation for this subgroup is important; the goal of this project is to explore potential sources of the gender disparity in access to transplantation, and access to healthcare in general, so that interventions to minimize this disparity can be designed. In the modern era, kidney transplantation is a safe and effective treatment for many patients with kidney failure. However, choosing the right patients for kidney transplantation is difficult, especially among older patients. Although older patients who receive transplants survive longer than if they had stayed on dialysis, still very few older patients are placed on the transplant waiting list. This is because no tools exist for determining risk in older patients undergoing transplantation, so clinical decision making has to be based on subjective perceptions of a patient's strength and reserve. Misclassification of these factors by the patient or provider likely results in decreased access to transplantation in a population that stands to greatly benefit from this treatment. Although transplant outcomes and survival benefit are similar in men and women, it has been well established that women have significantly less access to transplantation than men. They recently showed that this disparity is strongest in older patients, with older women having 30-60% less access than their male counterparts. However, it remains unclear whether patient or provider level factors contribute to this disparity. In this study they will explore differences by gender and age in factors influencing a patient's decision and ability to pursue transplantation. They will then use a new technique to explore the potential role of gender and age biases in a provider's choice to refer a patient for transplantation. Understanding the root causes of this gender/age disparity is crucial to developing interventions to improve access to transplantation, and healthcare in general, for women and older adults.

1-R21-NS-076200-01
p38 MAPK As A Female-Specific Drugable Target In CNS Autoimmune Disease
Teuscher, Cory
University Of Vermont & St Agric College
$ (NINDS funded this ANSWHR award)

The objective of this proposal is to explore a new molecular pathway which is likely to be important in the pathogenesis of multiple sclerosis (MS), and understanding of this pathway can yield new therapeutic targets for treatment of this devastating disease. Further, this proposal explores the bases for sexual dimorphisms in efficacy of drug treatment in autoimmune disease. This point is highly salient today given the increasing female incidence of MS. Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS)

characterized by myelin loss, varying degrees of axonal damage, and progressive neurological dysfunction. MS is the most common disabling neurologic disease of young adults and adolescents affecting ~350,000 individuals in the United States and more than 1 million individuals worldwide. Current MS disease-modifying therapies (DMTs) have limited efficacy and untoward toxicities, underscoring the need for new approaches based on targeting underlying disease mechanisms. The p38 mitogen-activated kinase (MAPK) is a central molecule in autoimmune/inflammatory responses in diseases such as rheumatoid arthritis (RA) and Crohn's disease, and inhibition of p38 MAPK is currently being explored clinically as a DMT for these diseases. However, the role of p38 MAPK in the pathophysiology of MS (or MS models) and its potential as a therapeutic target has not been investigated. Using experimental allergic encephalomyelitis (EAE), the principal autoimmune model of MS, we tested whether inhibition of p38 MAPK can influence EAE susceptibility and disease progression. Treatment of female mice with the pharmacological p38 MAPK inhibitor, SB203580, either completely prevented disease or halted disease if administered at the onset of clinical signs. Strikingly, male mice were completely unresponsive to treatment. These findings suggest that sex-specific factors contribute to SB203580 mediated inhibition of p38 MAPK activity and EAE susceptibility. In this application, we propose to: 1) determine the molecular and cellular mechanisms targeted by p38 MAPK inhibition in EAE and 2) determine the basis of the sexual dimorphism in the therapeutic response to SB. Understanding the mechanisms of drug action is likely to provide novel, more specific drug targets for MS therapy. The gender dichotomy with regard to efficacy of SB203580 is particularly important, since many autoimmune diseases, including MS, exhibit a female-specific sexual dimorphism in disease susceptibility. The finding that SB203580 is fully capable of selectively inhibiting disease in females provides for the possibility of a unique DMT that selectively targets the increasing female MS patient population. No study to our knowledge has evaluated the DMT potential of inhibiting p38 MAPK in MS, despite the fact that many compounds targeting this pathway are already approved for phase 2 clinical trials in other autoimmune diseases. Further, relatively few studies focus on the basis of sex differences in therapeutic responses in MS or its models. Inhibition of the p38 MAPK pathway may not only provide a novel DMT which selectively targets the increasing female MS patient population, but also will likely provide mechanistic insight relevant to development of additional DMTs for MS, by uncovering new targets for therapeutic intervention.

MENOPAUSE

5-R21-AG-037832-02
Ovarian Hormone-Independent Sex Chromosome Effects in Menopause
Ji, Hong
Georgetown University
$153,500

This project is designed to make new discoveries into why postmenopausal women are at increased risk for diseases like metabolic syndrome, hypertension and cardiovascular disease compared to premenopausal women. They will make these new discoveries by studying sex

chromosome effects independently of the ovarian hormones using a unique animal model in which they can separate, for the first time, sex chromosome differences between males (XY) and females (XX) from the sex hormone differences (e.g., differences in estrogen and testosterone levels). By discovering new genes and pathways responsible for the increased incidence of these diseases in ovarian deficient females, new therapeutic treatments are likely to ensue for post-menopausal women and women with ovarian hormone deficiency. Postmenopausal women have a higher incidence of diseases such as metabolic syndrome, cardiovascular and renal disease than premenopausal women. To begin to uncover genes and pathways that contribute to these adverse effects of aging in the postmenopausal woman, they propose two distinct strategies for discovering novel genes and pathways that may contribute to the increased risk postmenopausal women face towards these diseases. They will take advantage of the "four core genotypes" mouse model in which sex chromosome effects can be separated from the gonadal sex thus enabling comparisons among XX and XY animals independently of whether they were born with ovaries (e.g., XX- vs. XY-females) or testes (XX- vs. XY-males). While recent microarray studies in mice have demonstrated that thousands of genes are regulated by gonadal hormones, the number of genes regulated by the sex chromosome complement independently of the gonadal hormones is far more limited. Thus, they expect to discover a handful of genes (<10) that are differentially regulated by the sex chromosome complement (SCC) in the ovarian hormone deficient female during over activity of the renin angiotensin system (RAS). Aim 1 will use a tightly focused microarray approach leveraging their ability to differentiate SCC from gonadal sex to identify genes in the kidney that are differentially regulated by the SCC in the Ang II infused E2-deficient female. Aim 2 will use a candidate gene approach to test the hypothesis that the regulation of the tissue-specific renin angiotensin system (RAS) in the kidney by ovariectomy and hypertension is sex chromosome dependent. They hypothesize that the interaction between the XX SCC with the E2-deficient state of ovariectomy tips the vasoconstrictor/vasodilator balance of the renal RAS towards vasoconstriction to a greater extent than in the XY-Female by increasing plasma and renal levels of Ang II, the ratio of the Ang II synthetic enzyme, angiotensin converting enzyme (ACE) to the catabolic enzyme, angiotensin converting enzyme 2 (ACE2) and the ratio of the type 1 angiotensin receptor (AT1R) to the vasodilator type 2 angiotensin receptor (AT2R).

1-R21-AG-040568-01
Metabolic Syndrome as Women Undergo the Menopausal Transition: A Multi-Ethnic Study
Lee, Jennifer Shuwen
University Of California Davis
$195,983

The Metabolic Syndrome (MetS) is the major predictor for both CVD and type 2 diabetes, and can manifest as having one of several constellations of at least 3 of 5 risk components, such as high blood pressure and large waist girth. MetS occurs more often in women undergoing the menopausal transition, a key 5- to 10-year biological stage in a woman's lifespan. This study seeks to enhance significantly our understanding of how women in their 40s and early 50s, over time, develop MetS and hormonal changes and other factors during the menopausal transition that contribute to their increased risk of MetS. With this better understanding, we intend to

ultimately prevent MetS in women who are high risk due to identifiable and modifiable characteristics of their transition to post-menopause. This potentially impacts tens of millions of midlife women and their families who face a nearly 1 in 3 chance of developing MetS in their remaining lifetime. Young women have much lower rates of cardiovascular disease (CVD, including stroke) than men. However, as midlife women transition to post-menopause, they lose this 'cardiovascular protection,' and CVD is most common in post-menopause than any other stage of a woman's lifespan. Metabolic Syndrome (MetS) is a clustering of 5 metabolic abnormalities and is a major predictor of CVD and type 2 diabetes. MetS is clinically diagnosed as having any, and at least, 3 of the 5 components. MetS occurrence increases during the menopausal transition (MT). Reasons for this are unclear; however this may be due to androgen excess, relative to estrogen, during the MT. The proposal's goal is to establish basic aspects of how the constellations of the MetS components evolve during the course of the MT, a key 5- to 10-year biological stage in a woman's lifespan. In turn, this is intended to identify customized ways of preventing MetS early and related CVD and diabetes, with effective intervention strategies during the MT. The proposal incorporates a shift in our thinking of menopause and sex hormones in midlife women, namely, that the increase in MetS occurrence may be due more to androgen gain (and less to estrogen loss), in the MT. Our starting hypothesis is that mapping the constellations of MetS components, and the number of MetS components satisfied, in the midlife will provide a window into bridging the MT, its changing sex hormones, and loss of CV protection in women. If correct, this would shift our clinical focus to individualize hormone strategies against characteristic MetS constellations and related CVD and diabetes in midlife and early post-menopausal women. Aim 1. To characterize the constellations of MetS components satisfied over time in women, of 5 race/ethnicities, who develop MetS as they undergo the MT. Aim 2. To determine the hormonal and inflammatory factors that predict the course of MetS constellations in midlife women as they undergo the MT. We propose an efficient study that analyzes unique, existing longitudinal data from the largest U.S. study of the MT, the Study of Women Across the Nation (SWAN), a multi-ethnic cohort of 3302 women. Our long-term objective is to prevent the dramatic increase in CVD in older women by implementing, in midlife, individualized preventative strategies. Both our aims bear directly on this wider objective. These would impact 60+ million midlife and older U.S. women.

5-U01-AG-012531-18
SWAN: Study of Women's Health Across The Nation
Finkelstein, Joel S
Massachusetts General Hospital
$75,000

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.

5-U01-AG-012553-17
SWAN: Study of Women’s Health Across the Nation III
Tyrrell, Kim Sutton
University of Pittsburgh
$125,000

Study of Women's Health Across the Nation (SWAN) has compiled the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. Of particular public health importance is that the continuation of SWAN will permit the study to increase understanding of the effects of these menopause-related changes on subsequent health and risk factors for age-related diseases.

The SWAN is a 7-center multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition. SWAN has amassed ten years of data about endocrinology of the transition and other factors relevant to midlife health and aging. As SWAN requests its fourth competing renewal, the study itself proposes to transition from a study of the menopause to a study of aging in women. The average age of participants at the beginning of the SWAN IV project will be 59 years (54 to 65) and SWAN IV will follow these women through the age range of 59 to 70. SWAN has the unprecedented capability to link the expansive biological, medical, social, behavioral, and demographic data it has collected during mid-life and the menopausal transition to the development of both positive and adverse health states in early oldage. The primary objectives of SWAN IV are to: 1) Characterize the endocrinology and symptomotology of the post-menopause (2 to 12 years after final menses); 2) Ascertain additional health outcomes (such as measured physical performance) that are relevant to the early old age range and that may be affected by the factors that they have studied in mid-life and 3) Understand the relations between the mid-life and menopausal transition experience of women and subsequent positive and negative health outcomes. To accomplish this, the investigators propose annual phone contact to closely track menopausal status, menopausal symptoms and selected health events. In addition, two in-person clinic visits are proposed to accomplish detailed physical measures of early disease. The major thematic areas of SWAN IV include 1) Physical Functioning; 2) Bone/Osteoporosis; 3) Cognitive Function/ Symptoms/ Mental Health and 4) Cardiovascular. New areas for SWAN include physical performance and osteoarthritis, history of major depression, and carotid wall thickness. SWAN will continue to monitor symptoms, cognition, cardiovascular risk factors, endocrinology, bone density and fractures. SWAN IV will advance their understanding of how modifiable risk factors related to the menopause transition are linked to sub-clinical disease measures and hard outcomes. This may lead to improved strategies for the primary prevention of disease in women.

5-U01-AG-032699-04
Ultra-Low-Dose Estrogen Gel for Vasomotor Symptoms In Women Failing Placebo Or A Behavioral Intervention: A Randomized Trial
Lacroix, Andrea
Fred Hutchinson Cancer Research Center (FHCRC)
$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.

5-R21-NS066147-02
Effects Of Estrogen On Brain Morphology And Neuronal Integrity in Early Menopause
Kantarci, Kejal
Mayo Clinic
$ (NINDS funded this ANSWHR award)

This study will provide evidence on the neuroprotective effects of estrogens with non-invasive imaging markers of structural and functional neuronal integrity in newly menopausal women, during a hormone treatment trial. This evidence would potentially have a significant impact on women making the decision to use hormone treatments for dementia prevention as they transition into menopause. Neuroprotective effects of estrogens offer the possibility of preventing or delaying Alzheimer's disease in menopausal women. Estrogen treatment in older women who were late into menopause in the Women's Health Initiative Memory Study, did not prevent dementia. The question remains as to whether or not estrogen can preserve neurological function and decrease the risk of dementia when administered early in menopause from 6-36 months of the last menses. This project is proposed as an ancillary to the Kronos Early Estrogen Prevention Study (KEEPS), which is a nationwide, multi-center, randomized blinded study designed to provide evidence on the benefits and risks of oral and systemic estrogen treatment in recently menopausal women. Their goal is to test the neuroprotective effects of estrogen treatment in early menopause, during the 48 months of the randomized clinical trial. They will determine the rates of hemispheric atrophy on MRI, and the change in neuronal metabolite N-acetylaspartate (NAA) on proton MR spectroscopy (1H MRS) as a surrogate for the neuroprotective effects of estrogen treatment during the early postmenopausal years. In addition to the longitudinal serial measurements of whole brain, hippocampal and ischemic lesion volumes, they will use exploratory 3-dimensional voxel-based analysis of the serial MRI to determine the differences in the change in whole brain morphology in women who are taking estrogens compared to placebo. Their collaboration with the investigators of the KEEPS Cognitive and Affective Study will give us the ability to relate the change in neuronal metabolic integrity and brain morphology with the concurrent change in cognitive function in newly menopausal women. As an outcome of the proposed investigations, they expect to determine

whether or not oral and transdermal estrogen treatment preserves brain structure and neuronal function during the immediate years after menopause. Several decades of follow-up are necessary to determine if estrogen treatment in newly menopausal women prevents Alzheimer's disease. This project will provide the necessary in vivo evidence on the neuroprotective effects of oral and transdermal estrogens in early menopause in the short term, for future large-scale, long term trials. The original contributions of this study to women's health research will include the demonstration of the effects of estrogens on longitudinal change in brain morphology and neuronal integrity, and the relationship between these biological changes and the concurrent change in cognitive function in recently menopausal women.

1-R13-AG-039961-01A1
STRAW+10: Addressing the Unfinished Agenda of Staging Reproductive Aging
Harlow, Sioban
University of Michigan
$3,500

The purpose of this multi-disciplinary 2-day symposium is to organize and synthesize knowledge accumulated during the past decade in order to update the 2001 Stages of Reproductive Aging Workshop (STRAW) model for staging the end of reproductive life in women. We also propose to extend the STRAW recommendations to be more broadly applicable to the range of women's diverse experience of reproductive aging. We propose a multi-disciplinary symposium "STRAW+10: Addressing the Unfinished Agenda of Staging Reproductive Aging" to update the 2001 Stages of Reproductive Aging Workshop (STRAW) recommendations. The menopausal transition is a period of critical change, including loss of fertility, increased bone resorption, change in lipid profiles and temporal increases in symptoms, sleep disturbances and depression. STRAW proposed nomenclature, a staging system, and menstrual and endocrine criteria to define stages of ovarian aging. It has become the gold standard for characterizing reproductive aging, as the Tanner Stages characterize puberty. In the past decade, understanding of the critical junctures in hypothalamic and ovarian function before and after the final menstrual period and their implications for women's health has advanced considerably. We will convene 30 investigators from key research groups in the United States and worldwide. The specific aims are to refine criteria for the early menopausal transition given new population-based data relating to follicle-stimulating hormone, antral follicle count, anti-mullerian hormone and inhibin-B; to assess how to include women with higher body-mass-index and who smoke in staging algorithms; to provide recommendations regarding staging of women following gynecological surgery, chemotherapy, and hormone therapy and in women with polycystic ovarian syndrome and chronic diseases such as HIV/AIDS; and to assess potential criteria for staging the post-menopause. The Day 1 public scientific sessions will present recent advances and discuss implications of new data for staging. On Day 2, small working groups will propose modifications to the STRAW criteria. Following discussion, final recommendations will be adopted and research priorities defined. The expected outcome will be a set of recommendations for modifying the STRAW criteria that characterize the end stages of reproductive life including their extension to be more broadly applicable to the range of women's experience. Short- and long-term research priorities will be specified including studies needed to replicate and validate proposed criteria as well as to address gaps in knowledge. The meeting, co-sponsored by The

North American Menopause Society (NAMS), The American Society for Reproductive Medicine, The International Menopause Society and The Endocrine Society, will be held September 20-21, 2011 prior to the NAMS Annual Meeting in Washington D.C. STRAW+10 recommendations will be presented at the NAMS meeting. A peer-reviewed executive summary will be published simultaneously in the co-sponsors' journals, Climacteric, Menopause, Fertility and Sterility; with a non-technical version published on their websites. The STRAW+10 staging system will facilitate consistent classification of menopausal status, ensuring comparability of research studies and clinical trials. Once specified, a staging system can be developed into a clinical tool to guide assessment of fertility and contraceptive choices, and healthcare decision-making. Funds will be allocated to support participation of 4 trainees/new investigators.

3-U01-AG-017719-12S1
SWAN Repository III
McConnell, Daniel S
University Of Michigan
$200,000

This competing renewal application is to provide for continued maintenance of and activities associated with the SWAN Repositories of serum, plasma, urine, DNA and transformed cells generated from a 10-year study of a population of 3302 women from 5 ethnic groups who have been evaluated annually prior to, during and following the menopausal transition. These Repositories, an arm of the Study of Women's Health Across the Nation (SWAN), are meant to support, facilitate and extend the Core SWAN; additionally, the Repositories provide a mechanism for opening the resources of SWAN to the greater scientific community. Implementing activities associated with three proposed specific aims of this competing renewal will 1) provide for the continued management of the current 1.7 million Repository specimens and the additional specimens that will accrue as a result of fielding SWAN IV in 2009 to 2014; 2) expand the DNA Repository, the most frequently requested specimen type that is uniquely renewable because of our investment in cell immortalization; 3) promote effective information interchange about the SWAN Study, its data and the Repository resources through development of a 2-level web-based "data warehouse"; 4) provide for continued administration of the application review process for specimen utilization and administrative management of specimen distribution including Material Transfer Agreements; 5) engage in strategies to promote utilization of specimens; and, 6) expand the scope of the genetics studies associated with the SWAN study and its Repository.

MENTAL HEALTH

5-DP1-OD003312-05
Emotions are Emergent Events Constrained by Affective and Conceptual Processes
Barrett, Lisa
Northeastern University
$192,431

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.

1-R01-MH-090071-01A1
Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia
Kelly, Deanna L
University of Maryland, Baltimore
$99,833

At least one in every two women treated with risperidone, the most frequently used dopamine antagonist antipsychotic, will experience hormonal side effects (i.e., menstrual abnormalities, galactorrhea, gynecomastia) and this same percentage will experience sexual dysfunction. These side effects are one of the greatest unmet needs specific to women with schizophrenia and currently no evidence-based treatments for this side effect are available. Our proposed study will test whether adjunctive aripiprazole in women will resolve prolactin related hormonal effects and

will improve bone health, psychiatric symptoms, quality of life, wellness and sexual function. Risperidone is available generically and one of the most widely used antipsychotic medications; but is associated with elevated prolactin. This elevation is particularly pronounced in women and most recent studies show that the vast majority of women have elevated prolactin levels with approximately 50% also having the corresponding side effects of amenorrhea, oligomenorrhea or galactorrhea. Elevated prolactin may be associated with sexual dysfunction, decreased quality of life, medication nonadherence and decreases in bone mineral density over time. Lowering the dose or switching medications due to this side effect in stabilized patients is not a practical option in most cases. There is little evidence to guide treatment in this important area however dopamine agonists such as bromocriptine or amantadine may exacerbate symptoms, have lacking efficacy data and are associated with side effects. We have sizeable pilot data to suggest that a low dose of aripiprazole (10 mg/day), a dopamine partial agonist, added to Risperidone can improve symptomatic prolactin side effects. We will complete a double blind randomized 16-week control trial examining adjunct aripiprazole (10 mg/day with increase to 15 mg/day at 8 weeks if no response) vs. placebo in 70 women with symptomatic hyperprolactinemia and hypothesize it will be effective in the resolution of amenorrhea, oligomenorrhea and galactorrhea. We also hypothesize that aripiprazole will significantly improve quality of life, personal well-being and sexual function. And, we will examine improvements in positive, negative and depressive symptoms, sex hormone levels and measures of bone turnover. The significance and innovation of this application is high as this is a significant complaint and concern of women and very little evidence is available to guide treatment in women who are stabilized and doing well on antipsychotic treatments but develop these significant side effects. If funded, this important treatment research study of adjunct aripiprazole treatment will provide invaluable data and treatment options for thousands of women who suffer from schizophrenia and will help move the field towards better tailoring and personalizing antipsychotic treatment, particularly for women who suffer from these problems.

MUSCULOSKELETAL SYSTEMS

1-R21-AR-059931-01A1
Health of Children Born by Mothers with Rheumatoid Arthritis
Olsen, Jorn
University Of California Los Angeles
$193,877

Results from this study will add evidence on adverse birth outcomes and disease patterns in childhood and early adulthood among children born by mothers with rheumatoid arthritis (RA). Furthermore, using this disease as a model makes it possible to study long-term programming effects related to the expected impact the disease has on fetal growth. Our results will contribute to the sparse knowledge about the long-term impact of RA treatment during pregnancy, and knowledge will be generated about the potential differential impact of different RA treatments on the unintended outcomes. The findings can be extrapolated to the U.S. population since both diagnostic practice and treatments are similar. Many women with rheumatoid arthritis (RA) will

have one or more pregnancies while having RA. Little is known about long term pregnancy outcomes for children born by women with RA but studies show more perinatal complications and fetal growth restriction which may activate fetal programming. Fetal programming in this group of children has not been investigated due to lack of large datasets that allow long-term follow up of children born to mothers with RA. Medications used to treat RA may also be harmful to the fetus, since medications are often required to manage disease activity during pre-conception and early stages of pregnancy. Our long-term aim is to investigate health conditions as measured by mortality and hospital discharge diagnoses in children born by mothers who had RA taking into consideration birth weight, gestational age and perinatal complications. Specific aims: To set up a cohort of children born by women who had been hospitalized for RA and a cohort of children born by mothers without this history. To record congenital malformation, gestational age, birth weight and other reproductive failures in these cohorts. To further characterize exposed pregnancies according to treatment for RA in the pregnancies that occurred after 1995. These cohorts can be followed for up to 30 years at present but follow may be continued if needed. Design and Methods: A National cohort study using national registries in Denmark, with complete information on all Danish citizens (5.5 million and about 65,000 births per year) as well as long-term follow up of their children. Prescription data will be obtained from the National Registry of Medicinal Product Statistics and diagnoses will be obtained from the National Patient Registry of Hospital Discharges. Data on social and occupational factors will be available from the other national registers. All data in all registers are personally identifiable by means of the civil registration number (CPR) that has been given to all citizens from 1968 and forward in time. The CPR allows for linkage between registers and for linkage of biological and adopted children to the parents. Outcomes: Miscarriages, birth defects, adverse pregnancy outcomes, disease pattern in childhood and early adulthood. Exposures: RA, medical treatments for RA during pregnancy, RA in mother, mothers with RA who were medically treated during pregnancy. Statistical analyses: Data will be analyzed using Cox models. Several potential confounders will be taken into consideration such as age, parity, cohabitation, social conditions and place of living. All analyses will be performed using Stata/SAS Statistical software packages. Implications: The findings will add evidence on adverse birth outcomes and long term disease patterns in children born by mothers with RA. Knowledge will be generated about the potential differential impact of different RA treatments on the unintended outcomes. The results will indicate if more active monitoring and early intervention are needed to reduce the potentially increased risk for the unborn child. The study may also provide additional information on the potential fetotoxic effects of drugs used in treating RA.

1-R01-AR-059357-01A1
FAK/Pyk2 Signaling Pathway And Bone Formation
Bellido, Teresita M
Indiana University
$200,000

These studies will advance our understanding of the mechanism of action of mechanical forces and GC on bone and have the long-term goal of developing new therapeutic strategies for preservation or restoration of skeletal health in patients treated with GC or exhibiting endogenous elevation of the steroids, such as during aging. Mechanical forces enhance bone

mass and strength, whereas glucocorticoid excess (GC) decreases bone formation and increases bone fragility. Mechanical stimuli increase proliferation of pre-osteoblasts, accelerate osteoblast differentiation, and inhibit osteoblast and osteocyte apoptosis; and directly activates Wnt-dependent transcription and downregulates the Wnt antagonists sclerostin and Dkk1. In contrast, GC inhibit osteoblast differentiation and induce osteoblast and osteocyte apoptosis; and inhibit Wnt-dependent transcription and increase Dkk1 expression. Work leading to this application indicates that these converse effects might stem from opposing actions on the focal adhesion kinases FAK and Pyk2, which regulate interactions between cellular integrins and the extracellular matrix. Thus, mechanical stimuli prevent osteoblast/osteoblast apoptosis by outside-in signaling mediated by integrins resulting in activation of FAK and ERKs; and GC oppose these survival signals by activating Pyk2 and its target JNK, leading to inside-out signaling and cell detachment- induced apoptosis. Remarkably, FAK/ERK activation and anti-apoptosis induced by mechanical stimulation is abolished by Dkk1 or beta-catenin degradation. Conversely, Pyk2-dependent apoptosis by GC is inhibited by Wnts; and Pyk2 activates GSK3beta, the enzyme responsible for degrading beta-catenin. Based on these lines of evidence, it is hypothesized that there is an antagonistic interplay between mechanical forces and GC governed by FAK/Pyk2 signaling, which regulates the Wnt/beta-catenin pathway, bone formation, and osteoblast/osteocyte survival. This hypothesis will be tested by a combination of in vitro studies using established cell lines and primary osteoblasts and osteocytes, and in vivo approaches using transgenic and knockout mice. Aim 1 will determine the role of FAK-mediated outside-in signaling and Wnt activation in mechanotransduction. It will be investigated whether loading-induced anabolism is impaired in mice lacking FAK in osteoblasts and/or osteocytes, and whether this response is rescued by beta-catenin stabilization; and whether there is a cell autonomous requirement of FAK for mechano-responsiveness using osteocytes and osteoblasts in which FAK was knocked-down or knocked-out. Aim 2 will determine the role of Pyk2-mediated inside-out signaling and Wnt inhibition in GC effects. It will be investigated whether inhibition of Pyk2 or downstream targets JNK and RhoA/Rock prevents osteoblast/osteocyte apoptosis, the decrease in bone formation, and the loss of strength induced by GC, by using Pyk2 and FAK null mice and mice treated with Pyk2, JNK, or Rock inhibitors; whether beta-catenin stabilization or enhanced Wnt signaling prevents GC deleterious effects, using mice treated with GSK3beta inhibitors or Sost null mice; and whether activation of Pyk2 is responsible for Wnt inhibition by GC in vitro, using cells in which Pyk2 is knocked-out or knocked-down, or cells treated with Pyk2 inhibitors. Aim 3 will investigate whether mechanical forces and GC antagonize in vivo and the role of FAK in the protective action of loading when applied simultaneously, before, or after initiation of GC treatment.

1-R21-AR-060811-01
A New Hip Fracture Risk Prediction Tool Based on Common Predictors and Hip Geometry
Chen, Zhao
University Of Arizona
$165,622

This study will use innovative approaches, existing cohort resources, and interdisciplinary expertise to address a significant public health challenge: assessing the risk of hip fracture, the

most detrimental type of fragility fractures. The study aims for a better risk assessment tool on the web that can be used by researchers and clinicians to assess an individual's hip fracture risk. This research will test new predictors and use the assumption free modeling approach to capture complex and non-linear relationships of predictors with fracture risk. This research is significant for reducing fracture burdens in the large and growing U.S. older women population. Osteoporosis is a major public health problem. Women are at a particularly high risk for osteoporosis and 50% of women age 50 or older may suffer from a fragility fracture in their remaining lifetime. Hip fractures are the most detrimental type of fractures. Research has been conducted to assess hip fracture risk so prevention methods could be used to reduce this risk in the growing number of older women. However, previous risk assessment approaches are limited to a few variables and linear combinations of these factors. Also, there is an increasing number of available measures, such as bone structures and skeletal muscle mass, that can be extracted, for instance, from dual-energy X-ray absorptiometry (DXA), and no reliable risk prediction model exist based on this wealth of information. The overall goal of this study is to develop a comprehensive and flexible model to assess the risk of hip fracture for a specific woman. This will be achieved by constructing a novel predictor that classifies data that include hip structural geometry, sarcopenia measurements as well as risk factors identified in previous studies. The construction of the predictive model will be partly based on a study conducted among a large (n = 11,432) multi-ethnic bone cohort from the nationwide Women's Health Initiative (WHI). In addition, to enhance the quality of the risk prediction, computational data from finite element simulations will be used. There are three specific aims. The first aim is to generate a risk model, based on clinical data that accounts for the coupling effects of the factors involved in hip fracture. This research introduces a new approach in the field of hip fracture, Support Vector Machines (SVM), which explicitly identifies the configurations of factors that are likely to lead to hip fracture. The second aim is to refine the prediction/decision model from the first aim using both the SVM classifier and finite element modeling. A scheme has been developed to select, in a high dimensional space, data points that would improve the accuracy of the SVM-based risk prediction model. These data points would be evaluated (fracture or not) using a finite element model. The novelty of the proposed finite element model stems from its full parameterization so that the variability of the bone response can be studied with respect to variations (even small) of structural geometry and material parameters. The third aim is to validate and compare the SVM-based risk with and without the use of finite element analysis and develop a hip fracture risk calculator for the web. A cross validation will be performed using data sets from the WHI as well as other cohorts. The flexibility of the SVM classification approach makes it easily deployable on the Internet. This study will be carried out using existing cohorts by an interdisciplinary team with experience in epidemiology of osteoporosis research, DXA measurements including hip structures and sarcopenia, fracture assessments, biostatistics approaches for large datasets, high dimensional analysis and finite element modeling, thus making this study highly feasible. The study results will have an extremely significant public health impact by providing an innovative tool for hip fracture risk assessments.

1-R21-AR-059989-01A1
Fatigue and Lifestyle Physical Activity in Lupus
Ramsey-Goldman, Rosalind
Northwestern University
$100,000

Systemic lupus erythematosus (SLE) affects up to 1.5 million persons in the US. Although excess mortality has decreased in SLE patients since the 1970's, substantial morbidity persists. Fatigue is the most disabling and enduring complaint in patients affected with this chronic incurable inflammatory autoimmune disease. The ramifications of fatigue are significant and include decreased quality of life, an increased risk of work disability and an associated increase in health care costs. The overall goal of this R21 application is to determine the relationship between two constructs, fatigue and physical activity, as a necessary first step in a broader effort to implement a behavior management intervention that combats fatigue by increasing lifestyle physical activity in persons with SLE. Thus, we propose the following specific aims and primary hypothesis to be tested in this R21 application: Aim 1. Evaluate the frequency, intensity, and duration of physical activity as measured by accelerometry to obtain patient-specific average daily activity counts, average daily moderate-to-vigorous minutes of activity (MVPA) (defined as e 2020 activity counts/min), average daily minutes of light physical activity (< 2020 activity counts/min), and average daily minutes of any activity (i.e., minutes of non-zero activity counts) in patients with SLE. Aim 2. Characterize the cross-sectional relationships between objectively measured physical activity and fatigue (primary outcome, Fatigue Severity Score, [FSS]) in patients with SLE. We will do this with and without adjustment for the major factors that influence fatigue including sleep and wake disturbance, depression, anxiety, and pain interference using PROMIS tools, and SLE disease activity and severity. The adverse clinical, social, and economic implications of fatigue support the critical need for an improved understanding of factors contributing to fatigue in SLE, a research priority identified in the NIH/NIAMS monograph entitled, The Future Directions of Lupus Research. Systemic lupus erythematosus (SLE) affects up to 1.5 million persons in the US. Although excess mortality has decreased in SLE patients since the 1970's, substantial morbidity persists. Fatigue is the most disabling and enduring complaint in patients affected with this chronic incurable inflammatory autoimmune disease. The ramifications of fatigue are significant and include decreased quality of life, an increased risk of work disability, and an associated increase in health care costs. The overarching goal of this R21 application is to explore ways to improve the measurement of two constructs, physical activity and fatigue, as a necessary first step in a broader effort to use a behavior management intervention to lower fatigue scores by increasing lifestyle physical activity in persons with SLE. We propose a novel application of a relatively new technology to objectively measure physical activity (triaxial accelerometry, which provides a validated measurement of daily physical activity in the community dwelling setting). In addition, we propose to measure covariates of fatigue using computerized adaptive tests (CATs) patient-reported outcomes (PROs) that have been developed using state-of-the-art cognitive, qualitative, quantitative and health survey methodologies as part of the NIH-funded Patient-Reported

Outcomes Measurement Information System (PROMIS). PROMIS tools were developed to standardize measurement of self-reported health domains affected by many chronic illnesses and these tools offer the advantages of minimizing patient burden and maximizing precision. Using a cross-sectional study design, the following specific aims will be tested in this R21 application: Aim 1. Evaluate the frequency, intensity, and duration of physical activity as measured by accelerometry to obtain patient-specific average daily activity counts, average daily moderate-to-vigorous minutes of activity (MVPA) (defined as e 2020 activity counts/min), average daily minutes of light physical activity (< 2020 activity counts/min), and average daily minutes of any activity (i.e., minutes of non-zero activity counts) in patients with SLE. Aim 2. Characterize the cross-sectional relationships between objectively measured physical activity and fatigue (primary outcome, Fatigue Severity Score, (FSS) in patients with SLE. We will do this with and without adjustment for the major factors that influence fatigue including sleep and wake disturbance, depression, anxiety, and pain interference using PROMIS tools, and SLE disease activity and severity. The adverse clinical, social, and economic implications of fatigue support the critical need for an improved understanding of factors contributing to fatigue in SLE, a research priority identified in the NIH/NIAMS monograph entitled, "The Future Directions of Lupus Research".

5-R01-AR-044422-13
NARAC: The Genetics of Rheumatoid Arthritis
Gregersen, Peter K
Feinstein Institute For Medical Research
$175,363

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 we 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. We now wish to identify the specific causal variants and understand their mode of action. In specific aim 1 we will identify the causal genetic variants within the common genes that confer risk for rheumatoid arthritis. We have already identified several genes and regions of interest, including STAT4 on chromosome 2q. In specific aim 1a we 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 we will carry out fine mapping of candidate regions. This will generally involve haplotypic analysis using custom sets of SNP markers. In specific aim 1c we 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, we 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, we 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. We 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.

5-R01-AR-049772-09
Predictors of Pregnancy Outcome In SLE and APS
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Hospital for Special Surgery, New York, NY
$192,240

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. We 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 our 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, we 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 our hypothesis that complement is a proximal mediator of fetal loss and IUGR. We propose to increase our 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 we 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, we will use the PROMISSE cohort to affirm in humans our 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. We 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.

1-R21-AI-095921-01
Sexual Dimorphism and Dysregulated Immune Responses in SLE: The Role of Leptin
La Cava, Antonio
University Of California Los Angeles
$ (NIAID funded this ANSWHR award)

In this application we will explore new mechanisms that may contribute to the increased susceptibility to develop systemic lupus erythematosus (SLE) in females. We will investigate the role of a hormone that is expressed in much higher concentration in females as a possible major contributor to the pathogenesis of SLE. The role of this hormone, leptin, will be investigated in great detail for its capacity to inhibit the activity of cells that suppress autoimmunity in SLE, as preliminary work seems to suggest. This proposal aims to advance the current understanding of the cellular and molecular immune events that associate with the increased susceptibility to develop systemic lupus erythematosus (SLE) in females. Gender disparities associate with several biological differences that most apparently involve an evident dissimilarity between sexes in the levels of sex hormones and their receptors. However, although very important, the differences in the expression and responsiveness to sex hormones may not be sufficient to fully explain the increased incidence of SLE in females. During the past decade, our group has been interested in investigating the effects of the hormone adipokine leptin on immune responses. We and others have shown that this sexually dimorphic hormone - found at concentrations 5-10 times higher in females than in males with similar body mass index - has proinflammatory activities that greatly favor the development and the progression of several autoimmune diseases including SLE. We have also shown that leptin constraints the ability of regulatory T cells to suppress autoreactive immune responses in vitro and in vivo, and together with others we have shown that regulatory T cells can modulate SLE disease activity. Here we propose to dissect the effects of leptin on regulatory T cells in SLE by testing the hypothesis that elevated levels of leptin in females can modulate key characteristics of the regulatory T cells in SLE. Three integrated aims will study the influence of leptin on the phenotype and function of regulatory T cells in SLE at the cellular, molecular and biochemical levels. By identifying specific events that can be modulated by leptin in SLE, we aim to ultimately identify surrogate markers of therapeutic intervention that could lead to a better management of the disease.

5-R21-AR-056404-02
A Link Between Parity, Trunk Muscle Function, And Degenerative Spondylolisthesis
Cholewicki, Jacek
Michigan State University
$ (NIAMS funded this ANSWHR award for FY11)

The costs associated with the treatment of degenerative low back disease make it one of the top 5 most expensive conditions in the American healthcare economy. Women suffer from DS at a 3-9 times higher rate than men, as yet, without a clear explanation. If the number of childbirths and cesarean sections predisposes women to this condition later in life, proactive planning of effective intervention strategies and educational campaigns would be prudent. This study will examine relationships between pregnancy, cesarean section (CS) and other abdominal surgery, trunk and abdominal muscle deficiency, and degenerative spondylolisthesis (DS) in older females. The key question is whether pregnancy and/or CS mediated trunk muscle deficiency could be a precipitating factor in the development of DS later in life. Three specific aims are to determine whether: (1) parity/CS/other abdominal surgeries are associated with DS, (2) trunk muscle deficiency is associated with DS, and (3) parity/CS/other abdominal surgeries are associated with trunk muscle deficiency. The costs associated with the treatment of degenerative low back disease make it one of the top 5 most expensive conditions in the American healthcare economy. DS is considered one of the major causes of low back pain among the older population. Women suffer from DS at a 3-9 times higher rate than men, as yet, without a clear explanation. Previous studies documented relationships between pregnancy and low back pain, and suggested abdominal muscle deficiency as an underlying cause. Of special concern is the effect of CS. The rates of CS rose three-fold over the last 3 decades and may cause significant public health problems regarding DS in coming years. We propose to conduct a case-control study of 200 DS patients and 200 age-matched (in 5 year age groups) controls, including a more detailed assessment of trunk muscle function in 80 DS and 80 matched control subjects. Group designation will be based on a DS diagnosis from a sagittal view x-ray. The 400 subjects will be administered a detailed questionnaire regarding their parity, CS, previous surgeries, and other potential covariates. A subset of 80 subjects from each group will in addition undergo a physical examination of their abdominal and trunk muscle function and quantitative assessment of motor control. Physical exam will include abdominal muscle and hip extension tests. These tests examine the ability of the abdominal and paraspinal muscles to stabilize pelvis and the lumbar spine during simple hip flexion and extension maneuvers. Motor control tests will quantify muscle reflex latencies in response to sudden trunk perturbations, and postural control while balancing on an unstable seat. Both delayed muscle reflex responses and poor postural control are associated with low back pain and constitute predisposing risk factors to future low back problems. Poor motor control could lead to spine instability, chronic problems and degenerative changes in the spine over time. All measures will be quantified (continuous or categorized) and used in the regression and chi-square analyses to test the hypotheses. Innovative aspects of this proposal comprise of quantifying muscle function objectively and documenting variables related to parity in women with and without DS, which gives a better chance of finding any relationships that might exist.

5-R21-HL-093068-02
Sexual Dimorphism of Skeletal Muscle
Huxley, Virginia H
University of Missouri-Columbia
$ (NHLBI funded this ANSWHR award)

This project is to develop and validate a skeletal muscle model for the study of the primary functions of the smallest blood vessels in age-matched male and female animals of the same species, the mouse. The 2 primary functions of the microcirculation 1) blood flow to metabolizing tissue, and 2) the movement of nutrients from blood to tissue as well as the removal of wastes from tissue to blood, appear to differ between males and females in health and cardiovascular disease including hypertension and secondary to type 2 diabetes. As materials distribute themselves between blood and tissue, so too will fluids move between compartments; thus if exchange regulation differs between males and females it is likely that volume distribution will also differ. Therefore it is imperative to have access to a model to learn the differences and similarities between the sexes as the data from males, disease incidence and severity and subsequent treatment strategies will not apply equally to females. Skeletal muscle (SKM) microvasculature has been studied extensively with respect to respiratory gas and nutrient exchange, volume distribution, and blood flow control, into and within the organ, in health and disease. This R21 is in response to a PFA requesting development of models for the study of function in males and females. This is terribly important as most studies of SKM have been conducted in males (animals and humans) with the presumption that the data apply equally to both sexes. Evidence from multiple studies accumulated over the last decade is making it clear that this assumption in error. One model used widely for in vivo study is the rodent cremaster, a thin muscle derived from the abdominal wall that raises and lowers the testes. Surprisingly, no microvascular skeletal muscle preparation of equivalent metabolic and fiber type substitutes presently for the cremaster that facilitates study of both males and females. This proposal aims to rectify this lack by validating the abdominal wall skeletal muscle preparation in males and female rodents. The hypothesis is that microvascular skeletal muscle functions do not differ between age-matched males and females of the same species. Accordingly, 3 aims will be carried out in in situ and isolated abdominal muscle microvessels from age- and strain-matched female and male mice: Aim 1 will assess whether sexual dimorphism exists with respect to blood flow regulation from measures from microvascular diameter to selected endothelium-dependent and -independent agents. Given recent data they expect to reject their hypothesis as they anticipate that a) arterioles from males will develop greater basal tone and b) the dose-response relationship for the endothelium-dependent dilation will differ between males and females. Aim 2 will assess whether sexual dimorphism exists with respect to exchange regulation from measures from measures of microvessel solute permeability (Ps). Given their data, they expect to reject their hypothesis as they anticipate that a) venules from males will be leakier than those from females, b) basal arteriole and capillary barrier properties will not differ by sex, and c) the vasoactive agents will produce a variety of exchange responses reflecting differences in sex-specific mechanisms regulating solute distribution between the vascular and tissue compartments of males and females. Aim 3 will compare the sex, age, organ and species matched diameter (Aim 1) and exchange data (Aim 2) from microvessels as they lay in the living tissue and following isolation from the tissue. This is an incredibly opportunity to make these comparisons as not all

tissues are amenable to study in situ and it is assumed that the data from the isolated vessels reflect the behavior in the tissue. Data from this project will form the foundation for future genetic, biochemical, and physiologic studies of microvascular function in males and females. It is imperative that they validate a model for study of microvascular function in both sexes to understand intelligently the sex-dependent mechanisms regulating vascular function in health and dysfunction in disease. With the knowledge the foundation, and provide rational means for prevent and treating vascular disease specific to the needs of males and females.

1-R03-AR-057518-01A1
Delayed Pubertal Development on The Mechanism Of Bone Loss At Maturity
Yingling, Vanessa R
Temple University
$ (NIAMS funded this ANSWHR award)

Fracture risk in the elderly has its origins during growth and development. A delay in the onset of puberty results in both low bone mass and an increased incidence of stress fracture in young women. Therefore, the failure to accrue peak bone mass during the adolescent years represents a missed opportunity to optimize bone mass during one's life. 1. Osteoporosis is "a pediatric disease with geriatric consequences". Simply stated, suboptimal skeletal. 2. Development in childhood and adolescence may result in decreased bone strength and an increase in lifetime 3 fracture incidence. A delay in the onset of puberty (primary amenorrhea) correlates with both low bone mass; 4. and an increased incidence of stress fracture. Suboptimal bone accrual may have long term consequences. 5. Even with current treatment options as studies that treated amenorrheic dancers for 2 years with hormone 6 replacement therapy found no difference in bone mineral density between treated and placebo groups. The 7 most significant factors during development may be nutritional and lifestyle factors. Therefore, our overall goal 8 is to ascertain the affect of delayed pubertal development on the mechanism of bone loss at maturity. 9 Density measures alone, although widely used clinically, cannot identify osteoporotic subjects who will sustain 10 fractures, due to the large overlap in bone mass measures in individuals with fractures and those without 11 fractures. Other factors including bone size, architecture and material properties must be considered. We 12 have recently developed a texture analysis approach using Gabor filters, which is capable of providing insight 13 into bone structure from localized texture information on a pixel level. The texture approach is therefore a 14 potentially powerful tool in analyzing trabecular bone texture where orientation, shape and architecture as well 15 as density are the fundamental components. Our previous work was analyzing 2D images but we propose to 16 transfers this approach to 3D images. This novel approach will indicate not only bone mass changes but 17 changes in orientation which may be very significant later in life. In Aim #1, We will test the hypothesis that 18 the mechanism and magnitude of bone loss in a mature animal is dependent on bone development. 19 Specifically, delayed pubertal onset will alter the architecture of bone that will affect the mechanism of 20 bone loss at maturity. Pubertal delay will be completed by gonadotropin releasing hormone antagonist 21 (GnRH-antagonist) injections. At 50 days of age changes in bone morphology will be evaluated using a novel 22 3D texture analysis. The following biomarkers will be measured to assess the response of pubertal delay on 23 systemic changes in bone metabolism osteocalcin (a marker of bone formation) and N-telopeptide of collagen 24 type I (NTx) (a marker of bone resorption). Serum estradiol and

IGF-1 will also be assayed to confirm the 25 hormonal response to the protocol. Flourescent histomorphometry will assess bone formation rates on 26 trabecular bone. At maturity (150 days of age) the experimental rats will undergo ovariectomy surgery to 27 model post menopausal bone loss. Changes in bone morphology will be evaluated using static and dynamic 28 histomorphometry, micro-CT and texture analysis. By using a systems approach relating environmentally 29 induced delayed puberty to bone growth, we propose to gain a new understanding of the important relationship 30 between growth and its variability and the bone structure we become heir to during the aging process 31.

The Osteoarthritis Initiative (OAI)
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.

N01-AR022258
The Osteoarthritis Initiatives II -- Data Coordinating Center
Nevitt, Michael
University of California San Francisco
$600,000

This Data Coordinating Center oversees data collection, imaging, functional assessments, collection and archive of biospecimens from the four Osteoarthritis Initiative Clinical Centers and provides the data and images to the research community through the OAI web site: http://oai.epi-ucsf.org/datarelease/ . Two of the 4 clinical sites are also co-funded by ORWH.

N01-AR22259
The Osteoarthritis Initiatives II -- Clinical Center
Hochberg, Marc
University of Maryland Baltimore, Baltimore, MD
$25,000

N01-AR22261
The Osteoarthritis Initiatives II -- Clinical Center
Jackson, Rebecca
Ohio State University, Columbus, OH
$25,000

NEUROLOGY/NEUROSCIENCES

1-R21-NS-075608-01
Modifiable Risk Factors In Stroke Incidence And Mortality Among Women
Wang, Sophia
Beckman Research Institute Of The City Of Hope, Duarte, CA
$ (NINDS funded this ANSWHR award)

Successful completion of these aims will permit evaluation of the population impact of a decade of profound transition in obesity, physical activity, and MHT use on women's stroke incidence and mortality, and provide insight into the interplay between these and other relevant exposures. This proposal focuses on the etiology of stroke incidence and causes of stroke mortality and emphasizes common, modifiable, behavioral risk factors in ways that can facilitate future population-wide stroke prevention efforts. The California Teachers Study spans more than a decade of profound transitions in women's health behaviors, including increasing physical inactivity and obesity, and decreasing use of hormone therapy. By examining how exposures to these common, modifiable risk factors over a woman's lifespan influences rates and risk of stroke incidence and mortality, this study will provide critical new knowledge that can serve as the basis for behavioral public health interventions that benefit women on a population-wide scale. Stroke is the third leading cause of death in the United States (U.S.) and women account for 60% of all deaths from stroke. Major shifts in modifiable exposures over the past decade - increasing obesity and physical inactivity and decreasing menopausal hormone therapy (MHT) use - are changing the profile of women's health, but their effect on stroke among women is unclear. The California Teachers Study (CTS), a prospective cohort study that has actively followed 133,479 female California public school professionals for a broad range of health outcomes since 1995, is poised to evaluate how these societal transitions in modifiable exposures affect incidence of and mortality from stroke. The unique repository of life course exposure data on modifiable risk factors in the CTS cohort provides a near-singular resource for prospective assessment of women's health risks associated with long-term history of physical activity, longitudinal anthropometry data on body fat distribution, and detailed MHT use. Our specific aims address the impact of these shifting exposures both individually and together on stroke incidence and mortality, both overall and among the two major stroke subtypes (ischemic and hemorrhagic). In Aim 1, we will determine the impact of obesity and physical inactivity on the rates, risk, and population attributable fraction of incident and fatal stroke. Our detailed questionnaires permit us to evaluate the effect of lifelong and changing patterns of obesity phenotypes (defined as a combination of temporal changes in overall adiposity with adult body fat distribution) and physical activity, including by age and recency. In Aim 2, we will determine whether the effects

on rates, risk and population attributable fraction observed from obesity and physical inactivity (Aim 1) become more pronounced in the years following widespread cessation of MHT use (after 2002). To accomplish these aims, we will calculate age-adjusted and age-specific annual incidence and mortality rates, standardized to the U.S. population in 2000. To calculate risk associations, we will use time-dependent exposure data on these key exposures from teenage years to old age and analyze associations with stroke risk and mortality using statistical approaches that account for missing data and secular changes in exposures. We will calculate the population attributable fraction for each etiologic risk factor, and by time period when MHT was widely used versus the recent sharp decline in use.

5-R21-NS-071210-02
Sex differences in the CNS during disease
Voskuhl, Rhonda R
University of California Los Angeles
$ (NINDS funded this ANSWHR award)

This is an exploratory (R21) grant to determine the effect of sex chromosomes and sex hormones on the central nervous system's response to an immune attack using the multiple sclerosis model, experimental autoimmune encephalomyelitis. This proposal will establish a model system to determine the effect of sex chromosomes and sex hormones on a variety of neurological diseases characterized by a sex difference. Numerous neurological diseases are characterized by a sex difference. The neuropathology often includes infiltration of immune cells, with this immune infiltration potentially contributing to disease pathogenesis. Since it is known that sex differences exist in the immune system, this confounds investigations into sex differences in the CNS. Thus, they will use bone marrow chimeras to investigate sex differences in the CNS. By varying sex chromosomes or sex hormones in hosts reconstituted with a common immune system, one can ascertain the role of sex chromosomes and sex hormones on the brain response to injury. They will use one of the most inflammatory of all CNS disease models, the multiple sclerosis model, experimental autoimmune encephalomyelitis (EAE), to show applicability of this approach to a variety of neurological diseases. They will employ mice which differ in the complement of sex chromosomes (XX vs. XY), while having the same gonadal type, to determine the effect of sex chromosomes in the absence of confounding effects of exposure to different types of sex hormones. Specifically, in aim #1 they will determine whether the greater severity of EAE in XX, as compared to XY-, mice is due to sex chromosome effects in the CNS. In aim #2, they will determine if the sex chromosome effect in the CNS during EAE is due to the dose of X or Y genes. Finally in aim #3, they will use mice which differ in gonadal type, female vs. male, while having the same sex chromosome complement (XX vs. XX Sry) to determine whether the greater severity of EAE in female, as compared to male, mice is due to sex hormone effects in the CNS.

1-R01-AG-042189-01
Epigenetics of the Aging Astrocyte: Implications for Stroke
Sohrabji, Farida
Texas A&M University Health Science Center
$100,000

The risk and disability associated with stroke increases with age. In order to develop more effective therapies for this disease, this application will focus on age-related changes in a specific brain cell called the astrocyte. Our studies using an animal model show that middle-aged females sustain more brain damage after stroke than younger females and this is associated with functional changes in the neuroprotective ability of astrocytes. We will seek to understand global age-related changes in this cell type so as to develop markers for disease severity as well as new therapeutic targets. Stroke is the leading cause of disability in the US and with heart disease, the leading cause of death. The risk for stroke with consequent functional disability is increased with age, and in women this risk is elevated after the menopause. Paradoxically, hormone therapy at menopause increases the risk for stroke. Animal models of stroke confirm that stroke severity is worse in aged animals as compared to younger animals. In middle age, our recent data shows that female rats sustain a greater degree of tissue damage in the cortex and striatum as compared to younger females. Middle aged males, on the other hand, do not differ significantly from younger males in the extent of cortical infarction. This age difference in cortical cell loss is also paralleled by functional changes in astrocytes, a specific brain support cell. Astrocytes play a key role in normal and pathological conditions. Following stroke, astrocytes are rapidly mobilized to the peri-infarct area, detoxify the injured brain via glutamate uptake and fluid efflux and secrete growth factors known to promote angiogenesis and neuronal survival and neurogenesis. Astrocytes culled from the ischemic cortex of middle aged female rats show profound loss of protective functions including a reduced ability to sequester glutamate, decreased growth factor release, increased release of chemokines and increased ability to recruit leukocytes. These changes are consistent with increased infarct volume observed in older females. Hence in this proposal we will determine age and sex-specific epigenomic changes in astrocytes obtained from the ischemic cortex, to determine critical translational and transcriptional modulators. In Specific Aim 1 we will determine age-related changes in the expression of small non-coding RNA. MicroRNA, a key translation regulatory element, regulates large gene networks, and have been shown to play a central role in cell senescence and injury (stroke). In Specific Aim 2 we will determine age-related changes in DNA and histone methlyation patterns. Methylation patterns of specific leucines associated with activation (H3K4me3 and H3K9ac) or repression (H3K9me3 and H3K27me3) of gene transcription will be targeted. These complementary approaches will allow us to develop a molecular fingerprint of the aging astrocyte. Finally, in Specific Aim 3, select molecular targets will be manipulated using (1) miRNA mimetics or antagomirs and (2) demethylases to reverse age-specific patterns in astrocytes. Data gathered from these studies is expected to aid in the eventual identification of epigenomic changes that predict disease severity and facilitate discovery of therapeutic targets.

OBESITY/OVERWEIGHT

1-R21-DK-092718-01
Ovarian Hormone Suppression And Regulation Of Adipogenesis In Women
Kohrt, Wendy M
University of Colorado Denver
$229,500

Women are largely protected against abdominal adiposity prior to the menopause. The loss of estrogen at the time of the menopause triggers an increase in abdominal fat accumulation, which likely contributes to increased risk for the metabolic syndrome, type 2 diabetes mellitus, coronary artery disease, and hypertension. The proposed studies will test the novel hypothesis that estrogen deficiency results in abdominal fat gain by triggering an increase in the number of fat cells. Estradiol (E2) deficiency triggers weight gain, and specifically abdominal fat gain, in women. The shift toward central adiposity after menopause likely contributes to increased risk for the metabolic syndrome and associated chronic diseases (i.e., type 2 diabetes, coronary artery disease, hypertension). The long-term aim is to understand the mechanisms by which E2 deficiency mediates increases in abdominal adiposity. The primary aim (PA1) of the R21 is to determine whether ovarian hormone suppression in premenopausal women, which is known to cause fat gain, triggers an increase in adipogenesis (i.e., increase in cell number) in abdominal adipose tissue. This will be assessed by measuring the changes in cell size distribution and the incorporation of deuterium (2H) into DNA of cells in the non-stromal (i.e., mature adipocyte) fraction. Secondary aims are to determine: SA2) effects of ovarian hormone suppression on mRNA expression of factors involved in adipogenesis (C/EBP1, PPAR3) and markers of macrophage infiltration (CD68, Emr-1) and inflammation (IL-6, TNF-1); and SA3) whether new adipocytes arise from non-resident bone marrow progenitor (BMP) cells using cell surface markers (Notch 4, Platelet-derived Growth Factor Receptor (PDGFR) 2, Integrin 15, CD36) that enable detection by flow cytometry. To achieve these aims, 24 premenopausal women will be studied before and after 30 and 60 days of ovarian hormone suppression via gonadotropin releasing hormone agonist therapy with add-back of placebo (GnRHAG+PL) or estradiol (GnRHAG+E2). Hypotheses are: H1a) GnRHAG+PL for 60 days will result in a larger increase in small adipocytes (<40 5m) when compared with GnRHAG+E2. Because fat mass increases during GnRHAG+PL, an increase in the number of small adipocytes will be interpreted as an increase in adipogenesis and not as evidence of adipocyte atrophy; H1b) The incorporation of 2H in the non-stromal cell fraction DNA will be increased in response to GnRHAG+PL, as compared with GnRHAG+E2. Because the non-stromal fraction contains mature adipocytes, an increase in 2H- enriched DNA should reflect adipogenesis; H2) Ovarian hormone suppression will increase mRNA expression of factors associated with adipogenesis, macrophage infiltration, and inflammation (C/EBP1, PPAR3, CD68, Emr-1, IL-6, TNF-1) when compared with baseline (before vs after GnRHAG+PL) and when compared with E2 add-back (GnRHAG+PL vs GnRHAG+E2); and H3) Ovarian hormone suppression will increase BMP-derived adipocytes when compared with baseline (before vs after GnRHAG+PL) and when compared with E2 add-

back (GnRHAG+PL vs GnRHAG+E2). To the best of our knowledge, this will be the first in vivo study of the role of E2 as a regulator of adipogenesis in humans. Because it is believed that adipocytes are programmed to achieve a certain volume of fat, an increase in adipocyte number would lead to a gain in fat mass that would be very difficult to reverse. Thus, identifying strategies that effectively prevent an increase in adipogenesis during ovarian hormone withdrawal would be of high clinical importance.

1-R01-DK-092608-01
Intestinal Satiation In Roux-en-Y Gastric Bypass Rats: Brain Mechanisms And Sex Differences
Asarian, Loredana
University of Zurich
$200,000

Bariatric surgery, in particular Roux-en-Y gastric bypass (RYGB) surgery, is currently the only effective therapy for morbid obesity, which is a grave and growing national health problem. The mechanisms through which RYGB increases satiation and reduces eating and body adiposity are poorly understood. It is thought that increased intestinal satiation caused by the entry of ingesta more distally into the small intestine, leading to increased release of the gut hormones GLP-1 and PYY, is the major cause of early satiation at meals and reduced overall intake. This proposal builds on classical rat models to test RYGB's effects on intestinal satiation, at the levels both of gut-brain signaling and of brain neural processing. In addition, as > 80% of RYGB patients are women, the application includes experiments to assess whether sex differences in the physiology of intestinal satiation affect RYGB outcome. This work should lead to new insights that may help improve how bariatric surgery is done and may suggest targets for pharmaceutical alternatives to bariatric surgery in patients for whom is it not desired or appropriate. Bariatric surgery, in particular Roux-en-Y gastric bypass (RYGB) surgery, is currently the only effective therapy for morbid obesity, which is a grave and growing national health problem. The mechanisms through which RYGB increases satiation and reduces eating and body adiposity are poorly understood. It is thought that the major cause of early satiation at meals and reduced overall intake is increased intestinal satiation caused by the entry of ingesta more distally into the small intestine, i.e., into the jejunum, thus leading to increased release of the gut hormones glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY). This proposal adapts classical rat models to test RYGB's effects on intestinal satiation, at the levels of both of gut-brain signaling and of brain neural processing. RYGB will be done by one of the co-PIs who performs the technique both experimentally and clinically, assuring a close match between the experimental model and the clinical standard. The experiments include tests of nutrient-specific controls of ingestion that are hypothesized to be affected by RYGB. In addition, both the release patterns and the satiating potency of endogenous GLP-1 and PYY are tested. The brain work builds on progress in the past decade concerning the neural processing of intestinal negative-feedback controls of eating in the caudal brainstem and in the hypothalamus. Finally, because about twice as many women than men suffer from morbid obesity in the USA and because about 85% of patients electing RYGB are women, all the proposed experiments include tests of physiological sex differences, both male-female difference and estrogen-regulated effects in females, the latter especially relevant to understanding and treating the increase in adiposity

associated with menopause. Three Specific Aims are proposed: (1) Determine whether the satiating actions of intra-jejunal infusions of Ensure, Intralipid and glucose are increased by RYGB surgery, including the impacts of adipose-tissue loss and of sex differences, i.e., male vs. female and estradiol-treated vs. untreated ovariectomized rats; (2) Determine the effects of RYGB surgery on brain c-Fos expression in response to intra-jejunal infusions of Ensure, glucose and Intralipid, and determine the neurochemical phenotypes of neurons expressing c-Fos, including the impact of sex differences, i.e., male vs. female and estradiol-treated vs. untreated ovariectomized rats and (3) Determine the effects of RYGB on neural signaling mechanisms underlying the satiating actions of intra-jejunal infusions of Ensure, Intralipid and glucose in male vs. female and in estradiol-treated vs. untreated ovariectomized rats. State-of-the-art behavioral, physiological and molecular techniques are used. Thus, the work (1) should help inform behavioral and nutritional counseling for RYGB patients, (2) may suggest strategies for improvement in the RYGB technique, and (3) should provide rational bases for the development pharmaceutical tools to augment or replace RYGB, which is especially desirable for patients who do not desire bariatric surgery or for whom it is not recommended.

1-U01-DK-094416-01
Weight Management in Obese Pregnant Underserved African American Women
Klein, Samuel
Washington University
$100,000

This project will test a novel lifestyle intervention to help obese socioeconomically disadvantaged African American women achieve healthy weight control during and after pregnancy and improve the health of their offspring. The treatment will be given through an existing national home visiting program, Parents As Teachers, which will facilitate sustainability and nationwide dissemination, if effective. Maternal obesity and inappropriate gestational weight gain (GWG) increase both maternal and neonatal morbidity and mortality. In addition, offspring of obese women are at increased risk for neurodevelopment delay, becoming obese, and developing metabolic diseases. Women who are socio-economically disadvantaged (SED), especially from African American (AA) populations, are particularly susceptible to adverse pregnancy-related outcomes because of their high prevalence rates of obesity. Therefore, successful weight management during pregnancy in SED, AA women has considerable public health implications. We have experience in testing lifestyle interventions among SED non-pregnant women that have been implemented and sustained within community organizations such as Parents As Teachers (PAT), a national home visiting program that provides parent-child education and services free-of-charge to high needs women, prenatally and post-partum, through up to 25 home visits per year until kindergarten. We propose to conduct a 24-month (6-month prenatal and 18-month post-partum) randomized, controlled trial in obese SED AA women to evaluate the ability of an innovative lifestyle intervention program (PAT-i-), delivered by PAT parent educators during prenatal and post-partum home visits, to improve maternal and neonatal/infant weight, metabolic and health outcomes. An extensive programmatic evaluation will determine the applicability of the PAT+ intervention in real world settings by measuring programmatic reach, implementation, acceptability, and sustainability. If effective, PAT+ can be

disseminated through this national organization, which currently reaches over 249,000 mothers and 319,000 children participating in 2,173 PAT programs across all 50 states.

1-U01-DK-094463-01
Lifestyle Interventions in Overweight and Obese Pregnant Women
Pi-Sunyer, Xavier
St. Luke's-Roosevelt Institute For Health Sciences, New York, NY
$100,000

The prevalence of overweight and obesity in reproductive age US women is extremely high. These women when pregnant tend to gain higher than the recommended GWG, produce disproportionally fat babies, and retain much of the GWG post-partum. It is unknown whether maintaining GWG within the new lOM guidelines will produce leaner babies who have less risk of becoming obese adults, and will lead to less retention of GWG in women. A trial demonstrating these outcomes could lead to public health recommendations. A randomized controlled trial is proposed to study the effect, in a cohort of racially and ethnically diverse group of overweight and obese pregnant women, of an Intensive Lifestyle Intervention (ILI) compared to Usual Care (UC) on gestational weight gain (GWG), infant fatness, and mothers' post-delivery weight retention. Women in the ILI arm will receive intensive counseling during pregnancy and group counseling after delivery regarding behavior, nutrition, and physical activity change. Visits to counselors will be weekly and additional telephone and internet contacts will occur. The mothers' will be assessed at 14 and 36 weeks of pregnancy and at 12 weeks and 52 weeks post-delivery. The measurements will be anthropometry, whole body MRI, EchoMRI, and whole body plethysmography (BodPod). The infants' measurements will be anthropometry, whole body MRI, EchoMRI, and whole body plethysmography (PeaPod) for fatness 12 weeks and 52 weeks. Mothers and children will have cardio-metabolic risk factors measured in plasma. Data will be collected regarding mothers' dietary intake and physical activity (questionnaires and accelerometry) to assist in counseling. Other data to be collected include questionnaires on quality of life, socio-economic status. Careful record will be kept of expenses in providing the ILI, so that cost analysis of the intervention can be calculated. The study is powered on the primary outcome, fatness of the infants at birth. We require 180 participants to attain appropriate power. We will enroll 210 so as to allow for some dropouts along the way. Each mother will be followed during pregnancy and for a year post delivery. Each infant will be followed for a year after birth. We have the ability o continue to follow these participants if further funding is forthcoming, as they are all local to or hospital's catchment area and our own physicians. If aims are achieved, namely that both children and mothers profit from the intervention, there should be a paradigm shift in how overweight pregnant women are treated. At present, there is a dearth of behavioral advice and intervention relating to GWG and physical activity provided to these women. Positive results from our study would provide evidence for ILI preventative intervention.

PAIN

1-R13-DE-022238-01
Co-morbid Chronic Pain Conditions - Mechanisms, Diagnosis and Treatments
Cowley, Allen W
The TMJ Association
$28,740

Up to 50 million Americans experience one or more of the following six conditions, also seen in many TMD patients - they are chronic fatigue syndrome, endometriosis, fibromyalgia, interstitial cystitis, temporomandibular disorders, and vulvodynia. The estimated cost of the six pain conditions alone is $80 billion, which, because of the lack of understanding their cause and the availability of effective treatments, is essentially wasted. This meeting will accelerate the scientific research which will contribute to the reduction of the suffering and financial burden these conditions place upon the patients, their loved ones and our nation as a whole. The Sixth Scientific Meeting of The TMJ Association, "Comorbid Chronic Pain Conditions - Mechanisms, Diagnosis and Treatments", is scheduled to be held on June 5-7, 2010 at the Federation of American Societies for Experimental Biology Conference Center in Bethesda, Maryland. The need for this meeting and that of previous meetings has been based on two important factors. First, the number of people affected in the U.S. by temporomandibular disorders (TMD) is estimated to be approximately 36 million. The majority are women in their childbearing years. The physical, psychological and financial burden on these patients is compelling. Second, there continues to be a dearth of scientific understanding of the etiology of these conditions upon which to base diagnostics and develop safe and effective treatments. To stimulate research in this field, The TMJ Association has organized five scientific meetings beginning in the year 2000. These meetings have convened scientists in the temporomandibular disorders field and other disciplines to characterize and address the multiple symptoms and frequently found comorbid conditions in TMD patients. The theme of the sixth scientific meeting builds upon evidence from the five previous meetings demonstrating that TMD are a complex family of conditions influenced by genetics, gender, environmental and behavioral triggers mediating the vulnerability of patients to TMD and typically manifesting as more than jaw and muscle pain and jaw dysfunction. The sixth meeting will focus on the pathophysiological processes underlying the chronic pain conditions which co-exist with TMD and constitute comorbid chronic pain conditions (CCPC). They include: chronic fatigue syndrome, chronic headache, endometriosis, fibromyalgia, irritable bowel syndrome, interstitial cystitis, and vulvodynia. The meeting will engage key leaders and representatives from funding and patient advocacy organizations who will develop recommendations to advance research in this field. The specific aims of the meeting are to determine: 1. What is currently known about underlying mechanisms of CCPC; 2. What we need to know about CCPC (e.g., case definition, diagnostics); 3. What research areas are most promising to pursue (best approaches, resources); 4. How best to foster the development of treatment modalities for CCPC; 5. What approaches are necessary to encourage, train, and

sustain a CCPC research community; and 6. What high-risk research areas have the potential to substantially advance our understanding of CCPC.

OD-11-317
Centers of Excellence in Pain Education
NIDA, for the NIH Pain Consortium
$50,000

The NIH Pain Consortium is establishing "Centers of Excellence for Pain Education" at Medical, Dental and Nursing schools across the nation, in an effort to give health care professionals a better understanding of pain as part of their basic education, with the aim of improving pain treatment while reducing the risk of prescription opioid abuse. These Centers will establish curriculum on pain which will be used in courses at these Centers, and the adoption of these curricula at other academic institutions will be encouraged by various forms of outreach. All materials will be accessible on the NIH Pain Consortium's website.

5-R03-AR-057489-02
Epidemiology of Patellofemoral Pain Syndrome: Identifying Gender Specific Risk Factors
Boling, Michelle C
University of North Florida
$ (NIAMS funded this ANSWHR award in FY11)

Patellofemoral pain syndrome (PFP) is one of the most common chronic knee conditions affecting young adults, with an increased occurrence in females. Individuals suffering from this condition may experience symptoms lasting multiple decades, limiting their participation in physical activity, and predisposing them to chronic diseases associated with inactivity such as obesity, arthritis, coronary artery disease, diabetes, and cancer. The results from this investigation may be used to identify those at greatest risk to PFP and develop appropriate prevention programs to decrease the occurrence of this condition, particularly in females. Patellofemoral pain syndrome (PFP) is one of the most common causes of knee pain, affecting approximately 25% of the physically active population, with females being 2-3 times more likely to develop PFP compared to their male counterparts. The overall objective of this proposal is to determine the mechanical (structural and biomechanical) and non-mechanical (demographic and psychosocial) risk factors that are associated with PFP and identify the risk factors specific to females and males. The approach will be to use a prospective cohort design to identify risk factors that are associated with incident PFP. The central hypothesis is that individuals who develop PFP will have altered movement patterns, abnormal lower extremity anatomical alignments, decreased lower extremity strength, previous history of knee injury, previous participation in a low number of athletic activities, decreased levels of hardiness, and increased number of healthcare visits. A secondary hypothesis is that females and males will have different risk factor profiles. They will utilize baseline risk factor data that has been collected on 5690 freshman (males=3482, females= 2208) during the summers of 2005- 2008 at the following military academies: United States Naval Academy, United States Military Academy, United States Air Force Academy. Baseline risk factor data was collected through a current NIH funded project (R01-AR054061001), entitled JUMP-ACL. Each participant will contribute follow up

time for incident PFP until they graduate from their respective academy. Medical record reviews will be performed to identify those participants who developed PFP during their respective follow-up time. Based on the two years for the proposed investigation, follow up time will be 4 years for all participants enrolled in the JUMP-ACL investigation from 2005-2008. Poisson regression analyses will be performed to determine the risk factors for PFP. Additionally, males and females will be analyzed separately to determine gender specific risk factor profiles. The proposed project is making an efficient use of already collected risk factor data by adding analysis of a new outcome (PFP) that would not otherwise be investigated by the JUMP-ACL project. Additionally, the proposed investigation is cost effective due to no funds being required for baseline data collection. Their rationale for the proposed investigation is that there is a crucial need for prospective studies that identify the risk factors for PFP so that more focused prevention strategies can be developed that are appropriately gender specific.

1-R01-HD-065740-01A1
A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response
Brown, Candace S
University Of Tennessee
$200,000

The proposed research is relevant to public health because we will determine the efficacy of gabapentin in women with provoked vestibulodynia, a highly prevalent and distressful condition that causes severe pain in the outer vagina, and which consumes large amounts of health care resources and has few treatment options. We will also identify predictors of treatment response that will have clinical applicability to other chronic pain syndromes, and is relevant to NIH's mission to investigate coexisting pain conditions in order to identify common etiological pathways for developing therapeutic targets. Approximately 14 million U.S. women have provoked vestibulodynia (PVD), a type of localized vulvar pain which causes major disruption in the everyday lives of up to 60% of affected women and negatively impacts sexual function in 45%. The financial burden imposed on the health care system is also significant, as these women visit multiple clinicians and specialists, and try numerous, unproven treatments. To date, few randomized controlled trials (RCTs) have been conducted to establish evidence based protocols for PVD management. The first immediate goal is to conduct a multicenter RCT of gabapentin treatment for PVD. Gabapentin was selected because of its efficacy in treating other neuropathic pain conditions and the promising, preliminary data on its use in PVD. This is a significant research project because PVD is a highly prevalent, chronic pain condition that is costly to the health care system and that currently has limited management options available to affected women. The second immediate goal is to define psychophysiologic measures of gabapentin response and to define mechanistically-based PVD subtypes, which may be related to abnormalities in central sensitization, muscle hypertonicity, and autonomic dysregulation. Identifying predictors of treatment response in PVD would have clinical applicability to other chronic pain syndromes, and is consistent with NIH's mission to investigate coexisting pain conditions in order to identify common etiological pathways and develop therapeutic targets. The specific aims are (1): to test the prediction that pain from tampon insertion (primary outcome measure) is lower in PVD patients when treated with gabapentin compared to when treated with placebo. Additional outcome measures include reported intercourse pain and 24-hour pain, and

(2) to test the prediction that gabapentin treatment will reduce mechanical allodynia, reduce area and duration of hypersensitivity induced by intradermal capsaicin, reduce vaginal muscle pain to palpation, decrease the number and intensity of somatic tender points, and increase cardiac beat-to-beat variability. This 16-week, randomized, double-blind, placebo-controlled, crossover study will enroll 120 women between 18-50 years of age who report tenderness localized to the vulvar vestibule, pain with tampon insertion, and, when sexually active, insertional dyspareunia. Electronically entered daily diaries will be used to determine if pain is lower in PVD subjects when treated with gabapentin (up to 3600 mg/d) compared to when treated with placebo. The approach is innovative because it focuses on an understudied condition, in a multicenter setting, using a novel outcome measure (the tampon test), and a newly developed web-based recruitment and patient-reporting tool. Data management will include a mechanism-based analysis of drug effectiveness. These study outcomes will ultimately lead to our long-range goal of identifying underlying pathophysiologic mechanisms of PVD in order to create evidence-based differential diagnoses of subtypes of PVD for more effective and cost-effective management options.

PHYSICAL ACTIVITY

National Health and Nutrition Examination Survey (NHANES)
Survey of Physical Activity Measures
$170,000, in partnership with the National Cancer Institute

The NHANES measures of physical activity, sleep, and muscle strength will provide important data relevant to women across the life span from a nationally representative sample. The proposed measures will be collected from youth, adults, and older adults, as NHANES has no upper age limit.

Objective measurement of physical activity and sleep. (ages 6+)

Accelerometer data from NHANES 2003-2006 highlighted the dramatic decline in physical activity as children move into adolescence. This decline was particularly striking for girls, whose prevalence of adherence to the recommended 60 min/d of moderate or greater intensity physical activity dropped from 35% for ages 6-11y to 3% for ages, 12-15 y. This contrasts with adherence prevalence for boys of 49% for ages 6-11 y and 12% for ages 12-15 y. The adolescent boys' prevalence dropped to a quarter of that for the younger ages, while the girls' prevalence dropped to less than 10%. For both sexes, the amount of physical activity was fairly constant through adulthood and then declined further at ages 50-60 years. On the other end of the age spectrum from the adolescent decline in activity, poor sleep quality is an issue for women as they age. The accelerometer protocol will allow objective assessment of sleep duration and efficiency in a nationally representative sample, with oversampling of those ages 60 y and older.

Measurement of upper body strength by hand-grip dynamometer. (ages 12+)

Objective measures of muscle strength have not been collected across a wide age range in a national sample for several decades. This measure will provide a measure that is well associated with total body strength for adolescents through older adults. The recent focus on childhood obesity should be balanced with concerns about health-related fitness. Muscle strength is an important aspect of fitness for youth that is related to ability and propensity to engage in physical

activity. Muscle strength has also been shown to be an important predictor of independent living as well as mortality among older adults. The NHANES strength data will allow evaluation of sex differences in prevalence of low muscle strength across the full age spectrum.

PREVENTION

1-R13-NR-013623-01
Advancing Transdisciplinary Translation for Prevention of High-Risk Behaviors
Fishbein, Diana Hanna
Research Triangle Institute, Research Triangle Park, NC
$50,000

Both the social and basic sciences have recently made notable advances in identifying factors that influence development of high-risk behaviors, with potentially significant implications for their prevention. Translation of this information from the basic to the prevention sciences and back again is, however, lacking. We propose to hold two round-table meetings for 60 experts to "connect the dots" across the translational spectrum by identifying pressing scientific questions in prevention research, as well as the collaborations and capabilities needed to address them with a goal to apply this knowledge toward developing more effective preventive interventions and policies, thus having extraordinary potential significance for mental and public health policy. Several cross-cutting, forward-thinking investigators on the leading edge of both the social (geospatial mapping, contextual behavioral science, developmental psychology, education, social media) and basic sciences (genetic epidemiology, epigenetics, neuroscience, chemistry) have recently made notable advances in identifying factors that influence emergence of high-risk behaviors. This information has potentially significant implications for the prevention of high-risk behaviors, given that etiological social and neurobiological risk factors may also operate as moderators and/or mediators of intervention outcomes. Transfer and application of this knowledge from the basic to the prevention sciences and back again is, however, lacking. This transfer is particularly needed to understand differences in individual response to interventions to prevent high-risk behaviors and develop new interventions tailored for an individual's risk factors. We propose to use the R13 mechanism to hold two round-table meetings that convene a core of 60 relevant experts and advisors to "connect the dots" across the translational spectrum by identifying pressing scientific questions in risk behavior prevention research, as well as the collaborations and capabilities needed to address them. These meetings are designed to facilitate the relevance, operational feasibility, and utility of a transdisciplinary translational program of research to gain a better understanding of the mechanisms underlying individual differences in intervention responsivity. Meetings will promote a cross-disciplinary integration of theoretical perspectives and empirical methods to: a) identify high priority scientific questions yet to be addressed in the prevention sciences that may be informed by a new generation of research suggesting that neurogenetic mechanisms correlate and interact with environmental conditions to promote or interfere with behavioral change in response to interventions; b) conceive of novel psychosocial and technological preventive intervention approaches and policy developments that incorporate transdisciplinary scientific findings, c) discuss an educational agenda for early career

researchers to move into translational prevention; d) identify potentialities for new collaborations that will facilitate the advancement of a Translational Network for prevention research, e) conduct a survey of participants for their perceptions before and after the conferences regarding team science, needs for translational competencies, and market analysis; f) address ethical issues arising from inclusion of genetic and neurobiological markers of risk for behavioral problems, g) publish an open-access monograph of the proceedings; h) publish two special journal editions authored by a subset of attendees who will reanalyze their clinical trials datasets using state-of-the-art statistical techniques to elucidate mechanistic effects of their interventions, and report progress and preliminary findings from new collaborations forged during the meetings.

REPRODUCTIVE HEALTH/DEVELOPMENTAL BIOLOGY

Y2-OD-1200-01
Adrenal hyperplasia among adolescent patients polycystic ovarian syndrome (Bench to Bedside)
Stratakis, C.
NICHD; SUNY Downstate
$135,000

Polycystic ovarian syndrome (PCOS) is a heterogeneous group of disorders presenting with hyperandrogenism in adolescents and young women. The etiology of this condition remains unknown, despite its many identified links to insulin resistance, hypertension and metabolic syndrome, as well as its potential connection to adrenogenital disorders, such as the various forms of congenital adrenal hyperplasia (CAH). We propose that there is a subgroup of patients with PCOS who actually have non-CAH primary forms of bilateral adrenocortical hyperplasia (BAH). To investigate this possibility, we propose to study the hypothalamic-pituitary-adrenal axis (HPAA) over the next 2 years in 100 young girls and women (ages 16 to 25 years) that we will compare to 30 age- and race-matched normal females. Patients will be recruited primarily (although not exclusively) from a busy New York City clinic run by the Pediatric Endocrine Division at the Infants and Children's Hospital of Brooklyn at Maimonides and SUNY Downstate. All patients will undergo standard testing of the HPAA including oral low- and high-dose dexamethasone (DEX)-suppression testing (Liddle's test). "Paradoxical" rise of cortisol and/or other steroid metabolites in response to DEX is considered a sensitive test for the diagnosis of BAH. Patients with such responses will be molecularly investigated for the known causes of BAH (GNAS, PRKAR1A, PDE11A, and PDE8B mutations). The transcriptome will be studied in patients who had paradoxical responses to DEX but are mutation-negative (to these genes). The goal of this study is to identify any possible contributions of the BAH phenotypes and genotypes to the pathophysiology of PCOS, a yet unknown factor in the etiology of this multifaceted disorder. This proposal addresses the possibility that PCOS may be linked to a form of primary adrenal hyperplasia. The clinical protocol resulting from this project will provide new knowledge about the diagnosis, natural history, and potential treatment of PCOS. Our laboratory has committed resources to the investigation of adrenal disorders and cAMP signaling. From the available evidence, we certainly expect that this pathway is involved in

steroidogenesis. Our findings will lead to improved guidelines for treatment, and ultimately, new, therapies for PCOS. This work represents a new initiative; it is not covered by existing protocols; it represents an intramural/extramural collaboration and was stimulated by the availability of this special funding mechanism, as existing laboratory and clinical budgets of the participating investigators could not possibly cover this endeavor.

5-R01-HD-064398-02
Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women
Aissani, Brahim
University Of Alabama
$83,333

Currently, the only effective and non-invasive therapy to treat uterine fibroids is a hormone (gonadotropin releasing hormone) - based therapy with serious side effects. The knowledge to be gained from this study could, at some point in the near future, lead to the development of the first genetic counseling protocol for fibroids and ultimately to a more appropriate therapy. Uterine leiomyomas (ULs) are the most common pelvic tumors in women of reproductive age, accounting for over 600,000 hysterectomies annually in the United States. Several lines of evidence support a genetic liability in the pathogenesis of ULs, yet no susceptibility gene is known. Advances in research on the genetics of ULs (fibroids) have so far been limited by the paucity of genetic epidemiologic studies and infrastructure to conduct them. The goal of this epidemiologic study is to evaluate the contribution of a region of Chr.1q43 that predisposes to uterine fibroids but remains inadequately investigated. Genetic predisposition to ULs has been studied primarily in the context of two rare inherited autosomal-dominant conditions, the hereditary leiomyomatosis and renal cell cancer (HLRCC) and the multiple cutaneous and uterine leiomyomatosis (MCUL1) syndromes, where germline mutations were found in the gene on Chr. 1q43 encoding the tricaboxylic acid cycle (Krebs cycle) fumarate hydratase (FH) enzyme. However, a direct role of this important metabolic housekeeping gene in tumorigenesis remains to be proven. Inactivating FH mutations have rarely (< 1-2% of the tumors analyzed) been observed in nonsyndromic (common) ULs; however, loss of FH appears to be a significant event in the pathogenesis of a subset of these tumors. Furthermore, several observations support the existence of an alternative or additional candidate gene on Chr.1q43 acting alone or interacting with FH to increase the risk of ULs in susceptible individuals: 1) the absence of FH genotype-phenotype correlations, 2) the marked genetic heterogeneity in ULs, and 3) the failure to observe ULs or multiple leiomyomatosis in siblings or parents of cases with fumarase deficiency, a severe recessive disorder. Taken together, these observations underscore the importance of exploring an extended FH region in a population-based study of ULs. To this end, they will generate a high-density single nucleotide polymorphism genotyping data across a 2-Mb region spanning FH in subsets of African American (n=582) and Caucasian (n=455) women enrolled in the NIEHS-Uterine Fibroids Study. This is a well designed cross-sectional study of ULs that includes data on most potential confounders. Their study is not intended to shift any paradigm about the origins of ULs; rather it will extensively investigate the role of FH in nonsyndromic ULs, dissect the intricate genetic correlates of Chr.1q43 markers in the expression of the disease phenotype and evaluate their effects in two populations with a marked difference in disease risk. Recent updates in the genome databases have revealed new potential candidate

genes for tumor growth and important structural variations including a large (~ 308 Kb) copy number variation in the vicinity of FH; these new findings further justify a study with the proposed depth and extent of genetic coverage. This study will likely open new avenues for research and may ultimately redirect current preventive and therapeutic approaches or enhance their efficacy.

5-R01-HD-064402-02
Xenograft Study on Growth-Control of Human Uterine Leiomyomata
Kurita, Takeshi
Northwestern University
$83,333

A better understanding of how uterine leiomyomata grow is essential to developing novel therapies for this tumor. While the dependency of uterine leiomyoma on ovarian steroids is well established, the relative importance and function of 172-estradiol versus progesterone are yet to be clarified. Recently, they developed a method of growing human uterine leiomyoma tumors in immunodeficient mice. The xenografts of human uterine leiomyoma faithfully preserved the phenotype and hormone responsiveness of original human tumors in situ, and their growth was totally dependent on progesterone and 172-estradiol. Using this novel xenograft model in combination with viral gene transduction, they will elucidate the cellular and molecular mechanisms of human uterine leiomyoma growth. The ultimate goal of this study is to elucidate the molecular mechanisms of uterine leiomyoma (UL) formation and growth, and identify potential targets for novel therapeutic and preventive treatments of this disease. UL is a benign tumor of the myometrium that affects millions of reproductive-age women. Surgical removal of the entire uterus (hysterectomy) is the primary treatment option, and management of UL puts an enormous burden on the healthcare system. Therefore, finding a new therapeutic treatment replacing surgery is of great interest to the public. Due to the absence of a proper research model system reflecting characteristics of the original tumors, the biological nature and the causes of UL are poorly understood. Although growth dependency of UL on ovarian steroids (172-estradiol and progesterone) is well established, the relative importance and function of 172-estradiol and progesterone are yet to be clarified. In spite of accumulating evidence for the essential role of progesterone in UL growth, no research model has clearly demonstrated a growth-promoting effect of progesterone on UL. To elucidate the function of ovarian steroids in UL, they have established a novel xenograft model in which tissue fragments of human leiomyoma were grafted beneath the renal capsule of immunodeficient mice. The size of the leiomyoma xenografts increased in response to 172- estradiol and progesterone as demonstrated by cell proliferation and accumulation of extra-cellular matrix. In contrast, xenograft growth induced by 172-estradiol and progesterone was blocked by the anti-progestin RU486, indicating the essential role of progesterone and progesterone receptor (PR) in leiomyoma tumor growth. Previously, 172-estradiol has been thought to be the primary stimulus for UL growth. Surprisingly, 172-estradiol by itself neither increased nor maintained tumor size. Likewise, progesterone alone did not affect UL growth in this model. Although not mitogenic, 172-estradiol was required for expression of PR, and was essential for progesterone to act on UL xenografts. Their study clearly demonstrates the pivotal role of progesterone in growth and maintenance of UL. The results of their xenograft model agree with clinical observations, yet

radically change the paradigm of steroid hormone-regulated human UL growth by emphasizing the importance of progesterone instead of 172- estradiol. Using the novel xenograft model, they will elucidate the cellular and molecular mechanisms of human UL tumor growth controlled by 172-estradiol and progesterone.

5-R01-HD-060530-02
Genetic Studies of Uterine Leiomyomata
Morton, Cynthia Casson
Brigham And Women's Hospital
$83,334

The importance of this research is to further their understanding of the biology of uterine leiomyomata. Uterine leiomyomata, or fibroids, are the most common pelvic tumors in females and occur in a minimum of 20-25% of women of reproductive age. Uterine leiomyomata may serve as an important model system to study the genetic events that distinguish benign and malignant neoplasms. A more complete understanding of the genes involved in the pathogenesis and pathobiology of uterine leiomyomata will provide a foundation for future diagnosis, management and treatment of uterine fibroids. Uterine leiomyomata, or fibroids, are the most common pelvic tumors in females and occur in a minimum of 20- 25% of women of reproductive age. Although benign neoplasms, they constitute a major public health problem as 25-50% of affected women experience debilitating symptoms including excessive menstrual bleeding and pelvic discomfort as well as reproductive failure. Fibroids are the major indication for hysterectomy accounting for over 200,000 procedures annually in the United States. It is highly likely that there is a genetic liability to develop fibroids; they are at least three times more frequent in African American than Caucasian women (representing a serious health disparity) and twin-pair correlations for hysterectomy in monozygotic twins are about twice that observed in dizygous twins. Despite these findings and enhanced research in this area in recent years, much remains to be known about this racial predisposition and specific genes involved in the pathogenesis of fibroids. Also of particular interest and of unknown molecular mechanism, fibroids rarely proceed to their malignant counterpart, uterine leiomyosarcoma. Thus, it follows that uterine leiomyomata may serve as an important model system to study the genetic events that distinguish benign and malignant neoplasms. Consistent chromosome aberrations have been observed in fibroids indicating the location of genes involved in these tumors. A number of cytogenetic subgroups have been identified and they have been successful in using positional candidate gene approaches in determining that two high mobility protein genes, HMGA2 and HMGA1, located on chromosomes 12 and 6, respectively, participate in the pathobiology of uterine leiomyomata, in addition to MYST4, located on chromosome 10. The major goal of this proposed application is to further their understanding of the biology of uterine leiomyomata. Experiments are focused on continuing to develop and use a uterine leiomyomata tissue bank and database for gene discovery, gene expression studies, and genotype-phenotype correlations. A variety of molecular and cytogenetic approaches will be used in the identification, isolation and characterization of genes involved in the pathogenesis and pathobiology of uterine leiomyomata. Chromosomal rearrangements in tumor cells will provide biological landmarks for positional cloning experiments. Transcriptional profiling offers a powerful approach to discriminate genes that differentiate fibroids of different cytogenetic subgroups as well as fibroids of variant

histologies from their normal smooth muscle counterpart, the myometrium, or their malignant counterpart, uterine leiomyosarcoma. Lastly, the potential role of sequence variants in HMGA2 will be explored by a variety of mechanistic experiments to assess their role in uterine leiomyomata.

5-R01-HD-061821-03
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.

5-R01-HD-061811-03
Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team
Moalli, Pamela A.
Magee-Womens Research Institute
$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.

5-R01-HD-061787-03
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.
University of Utah
$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.

1-R21-HD-065138-01A1
Molecular Basis of Treating Endometriosis by Prostaglandin E2 Receptor Inhibitors
Arosh, Joe A
Texas A&M University
$200,000

The objective of the proposed research is to determine molecular and cellular mechanisms through which selective inhibition of prostaglandin E2 (PGE2) receptors EP2 and EP4 inhibits survival of endometriosis in order to identify PGE2 as potential nonestrogen or nonsteroidal target for the treatment of endometriosis in women. The expected outcomes of this project are that selective inhibition of EP2 and EP4-mediated PGE2 signaling will: (i) inhibit survival of endometriosis through suppressed cell survival and activated intrinsic apoptotic pathways; (ii) increase phagocytic ability of infiltrated peritoneal macrophages around endometriosis per se; (iii) inhibit local estrogen production in endometriosis; and (iv) provide exciting new knowledge that fill the gap in understanding of the pathogenesis of endometriosis. The novel findings of this project are expected to establish potential translational opportunities for treatment of endometriosis by blocking EP2 and EP4 receptors and could emerge as potential nonestrogen or nonsteroidal therapy for endometriosis in child- bearing age women. Endometriosis is an estrogen dependent disease. Current medical therapies to inhibit estrogen biosynthesis and actions fail to prevent reoccurrence of the disease and compromise success of pregnancy in child-bearing age women. This suggests a crucial need to identify potential cell signaling pathways for nonestrogen therapeutic targets for endometriosis. Prostaglandin E2 (PGE2) promotes survival of endometriosis, however; the underlined molecular mechanisms are largely unknown. Our long-term goal is to understand molecular and cellular aspects of PGE2 biosynthesis and signaling cross-talk in the pathogenesis of endometriosis in order to identify new targeted therapies. The objective of this application is to understand PGE2 signaling pathways in survival and growth of endometriosis. Our central hypothesis is that loss-of-function of PGE2 receptors EP2 and EP4 inhibits survival and growth of endometriosis. Specific Aim-1 will determine the mechanisms through which loss-of-function of EP2 and EP4 induces apoptosis of endometriosis. Specific Aim- 2 will determine the mechanisms through which EP2 and EP4-mediated PGE2 signaling immunomodulate and enhance the phagocytic ability of macrophages in endometriosis. Specific Aim-3 will determine the mechanisms through which loss-of-function of EP2 and EP4 decrease estrogen production in endometriosis. Our experimental approaches include: (i) genomic and pharmacological inhibition of EP2 and EP4; (ii) stable fluorescence-labeled human endometriotic epithelial cells, stromal cells, macrophages, and eutopic and ectopic endometria from endometriosis patients, (iii) nude and Rag2g(c) mice xenograft models, (v) molecular, cellular, biochemical, and microscopy-based assays; and (vi) whole animal bioimaging method. The rationale is that successful completion of the proposed research will contribute a missing and fundamental element to our base of knowledge without which the mechanism through which selective inhibition of EP2 and EP4 induces apoptosis of

human endometriotic cells cannot be understood. In addition, the expected results will advance the current knowledge of the pathogenesis of endometriosis and increase the understanding of PGE2 signaling in survival of endometriosis. The acquisition of such knowledge is critical and could be translated to treat women suffering from endometriosis. It is our expectation that selective inhibition of EP2 and EP4 will induce apoptosis of endometriotic cells, increase phagocytic ability of infiltrated macrophages in endometriosis per se, and decrease estrogen production by the endometriotic cells through multiple mechanisms. Our findings would have clinical impact because it would allow for the first time to develop new and much needed therapeutic strategies to inhibit EP2 and EP4 signaling as novel nonestrogen targets for the treatment of endometriosis in child-bearing age women. This is a R21 application addresses the mission of NIH/NICHD on women's reproductive health.

1-R21-HD-069165-01A1
Novel Approaches For Disrupting Gene Expression In Mammalian Oocytes
Evans, Janice P
Johns Hopkins University
$200,000

Investigations of the biology of the mammalian oocyte are of significant value, both for increasing our basic biological knowledge and for applications to human reproductive health. This project will accelerate the pace of research in this important area of reproductive health by developing new research methods for use in studying oocyte biology and female fertility and infertility, and for development of new female contraceptive methods. This R21 project seeks to develop new approaches for the genetic manipulation of mammalian oocytes, which we envision will accelerate advancing our knowledge of oocyte function and reproductive health. Genetic manipulation of mammalian oocytes has primarily used two methods: RNA interference and knockout mice. While RNAi has been a highly successful method of RNA ablation and subsequent protein knockdown in oocytes, RNAi approaches are not without limitations, as knockdown can be inefficient. Furthermore, double-stranded RNA and siRNAs have to be introduced into oocytes by microinjection, which is labor- and time-intensive and makes it impractical do use a large-scale RNAi approach (e.g., siRNA library-based screens). Knockout mice certainly have provided significant insights into mammalian oocyte biology as well, but knockout approaches also are not without pitfalls, including the time and expense involved in obtaining a knockout. This project seeks to develop alternatives to these methods, utilizing different established nucleic acid-based methods in novel combinations and with specialized modifications for the applications proposed here. In Aim 1, we will augment the use of siRNAs for post-transcriptional gene silencing with another reagent, a short single-stranded nucleic acid called a triplex-forming oligonucleotide (TFO) for pre-transcriptional silencing. TFOs bind to homopurine tracts in double-stranded DNA, and have been used to regulate gene expression in cultured cells and in vivo. The hypothesis for Aim 1 is that TFOs will inhibit transcription of a targeted gene, while siRNAs will mediate degradation of any residual mRNAs that were transcribed. This will be tested in vitro with isolated oocytes as well as with follicle-enclosed oocytes for longer-term culture. In Aim 2, we will develop methods for delivery of agents into oocytes. We will identify a novel agent for oocyte- specific delivery, using a screen of an aptamer library (with 1.2 X 1018 oligo-2'-deoxyribonucleotide sequence isomers) to isolate an

aptamer that will interact with the oocyte's zona pellucida (ZP). Aptamers are nucleic acid-based molecules that bind with high affinity to target molecules. Aptamers can be used for delivery of agents such as siRNAs into cells; this delivery works in vivo, and aptamers currently are being developed as therapeutics to target drugs and other agents to specific cell types for treatment of a variety of diseases (13 aptamers are in clinical trials). Additionally, as an alternative tool, we will also test a cell-penetrating peptide for intra-oocyte delivery. We will couple siRNAs or TFOs to ZP-binding aptamers and/or a cell-penetrating peptide, and test these for their actions in oocytes. The future direction of this work will be to test the ZP-targeting aptamer for systemic delivery of siRNAs and TFOs, as a means of in vivo oocyte-specific knockdown as an alternative to knockout/transgenic methodologies, as well as potentially the foundation of a novel female contraceptive.

1-R03-HD-067413-01
Phospholipid-reactive T cells in Pregnancy Loss
Halder, Ramesh C.
University Of California Los Angeles
$77,000

Pregnancy loss is a major unsolved complication of many autoimmune diseases. The proposed studies will investigate a new mechanism of pathogenesis of autoimmune-mediated pregnancy loss and improve our understanding of the role of certain T cells in the development of autoimmune pregnancy loss. Recurrent pregnancy loss is associated with the presence of autoantibodies against phospholipid (PL) antigens in some patients. Mechanisms underlying the development of such autoimmune pregnancy loss are not well understood. Recent reports have suggested existence of T cells that recognize PL antigens bound to an antigen presenting molecule, CD1d. My hypothesis is that such CD1d-restricted PL-reactive T cells induce the production of anti-PL autoantibodies and pregnancy loss associated with these antibodies. In support of this hypothesis, we have found that CD1d-knockout autoimmune-prone (NZB X NZW) F1 mice have significantly reduced serum levels of anti-PL antibodies as compared to their wild-type littermates, suggesting a possible role of CD1d in the development of anti-PL antibodies. Building on my expertise in the biology of CD1d-restricted glycolipid-reactive T cells and based on the above observations, I will test this hypothesis in three Specific Aims. In Aim 1, I'll test the hypotheses that mice with spontaneous or induced anti-PL antibodies have increased numbers and/or activation of PL-reactive T cells in lymphoid organs; such T cells will infiltrate the pregnant uterine mucosa, called decidua, in increased numbers. Then, I'll determine the effect of CD1d-restricted PL-reactive T cells on the production of anti-PL antibodies by B cells in vitro in Aim 2. In Aim 3, I'll determine the effect of CD1d-restricted PL-reactive T cells on pregnancy outcome. We will further investigate whether PL-reactive T cells directly induce pregnancy loss or whether pregnancy loss is mediated via anti-PL antibodies induced by PL-reactive T cells. It is hoped that this study will elucidate a novel pathogenetic mechanism of recurrent pregnancy loss in autoimmune diseases. The data obtained will also form the basis for my first R01 or another extramural proposal.

1-R01-HD-065939-01A1
Molecular Mechanism Of LPA3-Mediated Uterine Receptivity

Ye, Xiaoqin
University Of Georgia
$200,000

The proposed research is relevant to public health because defective uterine receptivity is a key factor for two important public health problems, infertility and early pregnancy loss. This proposal aims to decipher how a local factor LPA3 interplays with progesterone receptor in uterine luminal epithelium to control uterine receptivity. The understanding of the molecular mechanism in establishment of uterine receptivity will provide the foundation for drug discoveries to treat infertility and early pregnancy loss associated with defective uterine receptivity. Defective uterine receptivity, including delayed uterine receptivity and non-receptive endometrium, is the key maternal factor for infertility and early pregnancy loss. The molecular mechanism of how a uterus transforms into a receptive state for embryo implantation is not well understood. It is well recognized that progesterone receptor (PR)-mediated hormonal signaling is essential for the establishment of uterine receptivity in all mammals studied. PR has dynamic spatiotemporal expression patterns in the peri-implantation uterus. The disappearance of PR from uterine luminal (LE) and glandular epithelium is associated with the establishment of uterine receptivity. Failure of such down regulation of PR in uterine epithelium during the expected "implantation window" is associated with defective uterine receptivity. LPA3 (LPAR3/EDG7) is the third receptor for lysophosphatidic acid. Down regulation of uterine LPA3 is implicated in defective uterine receptivity in endometriosis patients and deletion of Lpar3 in mice leads to delayed uterine receptivity. Sustained PR expression in LE is detected in the non-receptive day 4.5 Lpar3(-/-) mouse uterus (normal implantation: ~day 4.0 in mouse). How the sustained PR expression in LE during the expected "implantation window" blocks uterine receptivity and how PR-mediated hormonal signaling interacts with local targets to control uterine receptivity remain as significant knowledge gaps. The long-term goal is to understand the molecular mechanism of uterine receptivity thus help overcome infertility and early pregnancy loss associated with defective uterine receptivity. The overall objective of this application is to fill the mentioned knowledge gaps, specifically the significance of sustained PR expression in LE and the interplay between PR and LPA3 in LE. The central hypothesis, formulated based on supportive preliminary data, is that PR interplays with LPA3 to coordinately regulate uterine receptivity. The rationale is that understanding the significance of PR in LE and its interplay with LPA3 will provide more insight into the molecular mechanism of uterine receptivity. To achieve the goal of this application, three specific aims will be pursed. Aim 1. Determine molecular pathways dysregulated in LE with sustained PR expression, based on the working hypothesis that sustained PR expression in LE dysregulates genes/molecular pathways leading to a non-receptive uterus. Aim 2. Determine interplay between PR and LPA3 in LE, based on the working hypothesis that PR and LPA3 mutually regulate each other in LE for the establishment of uterine receptivity. Aim 3. Determine role of LPA3 in regulating molecular pathways in preimplantation day 3. 5 endometrium, based on the working hypothesis that LPA3 regulates its uterine target genes to influence uterine receptivity directly and/or via PR in LE. Laser microdissection, gene profiling, immunoblotting, ChIP assay, and immonoprecipitation are among the approaches that will be employed. The proposed work is significant because understanding the molecular mechanism of uterine receptivity is critical for developing diagnostic and therapeutic approaches

to detect and treat infertility and early pregnancy loss associated with defective uterine receptivity.

5-P01-HD-057877-03
Uterine Leiomyoma Research Center Program
Bulun, Serdar E.
Northwestern University
$250,000

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. 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.

1-S06-GM-092238-01
Oklahoma Native American Research Centers for Health (NARCH VI)
Grim, Gloria Ann
Cherokee Nation

$100,000

The purposes of this project are: to encourage competitive research linked to reducing health disparities; to increase the capacity of the Tribes and University of Oklahoma to work in partnership to reduce distrust by the Native American communities and peoples toward research; and to develop a cadre of Native American scientists and health professionals engaged in biomedical, clinical and behavioral research that is competitive for NIH funding. The sixth Oklahoma Native American Research Center for Health (0NARCH6) continues the productive research and training partnership with the University of Oklahoma Health Sciences Center (OUHSC) by the Tribes, especially the Chickasaw, Creek, Choctaw and Cherokee Nations. Population served consists of 42,749 Chickasaws and 121,680 Cherokees, 49,714 Choctaws and 30,181 Creeks for a total of 244,324 in North East and South Central Oklahoma. The research will include 1) the impact of infections on maternal and child health in Native Americans, 2) research to develop better diagnostic and prognostic tests for rheumatic disease in Oklahoma tribal members, and to examine the potential roles of environmental triggers for autoimmunity focusing on vitamin D levels, tobacco smoke exposure (through serum cotinine levels) and abnormal immune responses to common viruses, 3) research to prevent excessive gestational weight gain in otherwise healthy but overweight Native American women and consequently decrease the proportion of women who gain in excess of the guidelines has the potential to decrease the risk and costs of obstetric complications associated with excessive weight gain, and 4) to develop methods to understand attitudes, beliefs, and perceived barriers or motivators to organ/tissue donation among American Indians living off-reservation.

5-S06-GM087165-02
Research to Improve Preconception Health of Adolescent Women (NARCH VI)
Jumping Eagle, Sara
Oglala Lakota Oyate
$128,436
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.

Z01-HD008737-11
ORWH-NICHD Leiomyoma Tissue Bank
Segars, James
NICHD Intramural program
$50,000

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-R21-HD-066248-01A1
Prostaglandin E2 Signaling in Growth and Pains of Endometriosis
Arosh, Joe A
Texas A&M University
$ (NICHD funded this ANSWHR award)

The objectives of the proposed research are to determine molecular and cellular mechanisms through which selective inhibition of prostaglandin E2 (PGE2) receptors EP2 and EP4 inhibits growth of endometriosis and endometriosis-induced pain and to develop EP2 and EP4 inhibitors as new non-steroidal targets for the treatment of endometriosis in women. The expected outcomes of this project are that selective inhibition of EP2 and EP4-mediated PGE2 signaling will decrease growth and pain of endometriosis and fill the substantial gap in the current knowledge of the pathogenesis of endometriosis and perception of endometriosis pain. This highly significant advancement in our understanding of endometriosis will provide the knowledge needed to translate selective inhibition of EP2 and EP4 into clinical application as a potential novel non-steroidal therapy for endometriosis in women. Endometriosis is an inflammatory disease characterized by the presence of functional endometrium outside the uterine cavity. The major two symptoms are intolerable pelvic pain and infertility. Prostaglandin E2 (PGE2) plays important roles in the pathogenesis of endometriosis. PGE2 is the principal mediator in inflammation and pain hypersensitivity. Inhibition of PGE2 biosynthesis using NSAIDs and COX-2 inhibitors has emerged as the main class analgesics. However, clinical use of NSAIDs produces unwanted side effects such as gastric erosion, ulceration, and hemorrhage, and prolonged use of COX-2-selective inhibitors confers a risk for myocardial infarction and stroke. PGE2 produced at the site of inflammation acts on the nociceptors of peripheral terminals through EP1, EP2, EP3, and EP4 receptors by integrating multiple cell signaling pathways. Selective inhibition of PGE2 signaling as therapeutic targets down-stream of COX-2 may provide an opportunity to inhibit pro-nociceptive actions of PGE2 in the pathogenesis of endometriosis. Our long-term goal is to understand molecular and cellular aspects of PGE2 in the pathogenesis and pain of endometriosis with the aim of identifying PGE2receptors as non-steroidal targets for the treatment of endometriosis. The objective of this application is to understand PGE2 signaling in growth and pain of endometriosis. The central hypothesis is that selective inhibition of prostaglandin E2 signaling decreases pain of endometriosis through inhibition of growth of endometriotic cells and development of nociceptive mechanisms. Specific Aim 1 will determine the effects of systemic blockade of EP2 and EP4 receptors on growth, innervations, and pain of endometriosis. Specific Aim-2 will determine molecular mechanisms of through which cell specific knock-down of EP2 and EP4 in endometriotic epithelial and stromal cells inhibits development of innervations and nociceptive mechanisms of endometriosis. Effects of selective inhibition of EP2 and EP4 on growth, innervations, and pain

of endometriosis will be determined using genomic, pharmacological, molecular, cellular, biochemical, microscopy, and bioimaging approaches, and xenograft Rag23(c) mice and pain behavior animal models. The proposed work is innovative: (i) because it capitalizes on a new means of identifying PGE2 signaling in the pathogenesis of endometriosis and induction of endometriosis pain, and (ii) expected to decrease pain of endometriosis through inhibition of growth of endometriotic cells, innervations of endometriosis, and development of peripheral and central nociceptive mechanisms. This highly significant advancement in our understanding of endometriosis will provide the knowledge needed to translate selective inhibition of EP2 and EP4 into clinical application as a potential novel non-steroidal therapy for endometriosis in women. In addition, the expected results will fill the substantial gap in the current knowledge of the pathogenesis of endometriosis and perception of endometriosis pain. This is a R21 application addresses the mission of NIH/NICHD on women's reproduction health.

1-R21-AI-095987-01
Vitamin D And The Prevalence, Incidence, And Persistence Of Bacterial Vaginosis
Norris Turner, Abigail
The Ohio State University
$ (NIAID funded this ANSWHR award)

Bacterial vaginosis is the most common vaginal infection in women of reproductive age worldwide. We hypothesize that low vitamin D levels contribute to increased risk of bacterial vaginosis. This study will test stored, prospectively-collected biological samples and use existing demographic, behavioral and clinical information from almost 600 Zimbabwean women to assess the influence of vitamin D on the prevalence, incidence and persistence of bacterial vaginosis. Bacterial vaginosis (BV) is a vaginal condition that develops when the concentration of healthy Lactobacillus species in the vagina declines and is replaced by other (largely anaerobic) bacterial species. BV is the most common vaginal infection worldwide in women of reproductive age. Pregnant women with BV have increased risks of spontaneous abortion, preterm labor, preterm birth, chorioamnionitis and other detrimental obstetric and gynecologic outcomes. According to a recent meta-analysis of more than 30,000 women, prevalent BV was associated with a 60% increased risk of acquisition of human immunodeficiency virus (HIV). However, the etiology of this complex condition is not clear. We hypothesize that low vitamin D levels contribute to BV pathogenesis. Vitamin D is essential to immune function, serving both to stimulate mechanisms associated with pathogen elimination and to regulate immune response. In the United States (US), the strongest risk factor for BV is non-white race, and non-white women are also much more likely to have insufficient or deficient vitamin D levels. Indeed, two recent cross-sectional analyses report that vitamin D insufficiency is associated with prevalent BV in pregnant African-American women; a third publication found the same association between vitamin D and BV in a nationally-representative population of pregnant women including all racial/ethnic categorizations. These data suggest that the consistent association between race and BV (despite adjustment for other BV risk factors) may be mediated by vitamin D. Little data exist on vitamin D levels in resource-limited settings, including sub-Saharan Africa where BV prevalence is high and BV- associated morbidities are substantial. Using stored serum samples from nearly 600 Zimbabwean women who previously participated in the prospective, observational "Hormonal Contraception and Risk of HIV Acquisition" (HC-HIV) study, we

propose to measure the association between serum vitamin D levels and a) BV prevalence; b) BV incidence; and c) BV persistence. In an exploratory analysis using stored cervical and serum samples from a subgroup of 50 BV-positive and 50 BV-negative women, we will also evaluate correlations between BV-associated cervical immunoinflammatory mediators and vitamin D-associated serum immunoinflammatory mediators to elucidate the possible immunological mechanisms through which vitamin D may affect BV. Vitamin D is safe, inexpensive and has many health benefits. If vitamin D is also associated with BV, supplementation with this essential vitamin may have substantial impact on women's reproductive health worldwide.

1-R21-HD-068873-01A1
A Longitudinal Study Of Loss Of Imprinting In First Trimester CVS Samples Compared To Placental Samples At Birth
Lee, Men-Jean
Indiana University
$273,068

We have novel preliminary data to suggest that genomic imprinting in the human placenta takes place across gestation and is not permanently fixed in early pregnancy. We seek to confirm this finding in a longitudinal study of loss of imprinting by monitoring placenta samples from chorionic villus sampling in the first trimester and the same respective placentas at birth. We will also explore how differences in loss of imprinting patterns in first trimester placenta samples may be predictive of pregnancy complications which can ultimately be developed into a bioassay for adverse pregnancy outcomes. For most human genes, maternal and paternal alleles are bi-allelically expressed. However, a specific subset of genes are imprinted and mono-allelically expressed. The current dogma is that this embryonic imprint is stable across the lifespan of the organism. Loss of imprinting (LOI) leads to bi-allelic expression of the imprinted gene, potentially causing a doubling of gene dosage or gene dysregulation, resulting in disease. Because the methylation marks of imprinted genes are considered permanent after fertilization, any acquired changes in the intrauterine environment may lead to stable transgenerational effects. The regulatory complexity of these imprinted gene domains may render them particularly sensitive to environmental changes such as diet and nutrition. Emerging evidence implicates aberrant imprinting in the pathophysiology of many common human diseases, including complications of pregnancy such as intrauterine growth restriction (IUGR) and preeclampsia (PE); and even postnatal disorders such as obesity, cardiovascular disease, and type 2 diabetes. We have developed a highly sensitive and quantitative allele-specific PCR analysis to measure LOI in a panel of imprinted genes in the human genome. Using this methodology, we have already determined that pregnancies complicated by PE and IUGR are associated with dysregulation of a set of imprinted genes in the placenta. Both of these obstetrical disorders have their origins in an early intrauterine environment associated with aberrant placentation and trophoblast invasion. We also have novel evidence to suggest that genomic imprinting patterns are not permanently fixed in placental development. Contrary to the prevailing theory, we hypothesize that patterns of LOI are not static in the human placenta and are subject to developmental and environmental influences over the course of pregnancy that predispose to adverse pregnancy outcome. We now propose a longitudinal trial as a secondary study to the NuMOM2B Trial to monitor LOI in placenta samples from first trimester CVS to birth and

determine which LOI patterns in the first trimester lead to normal pregnancy outcomes and which patterns are predictive of pregnancy complications.

1-U10-HD-069010-01
Pelvic Floor Disorders Network Clinical Sites
Arya, Lily A
University Of Pennsylvania
$25,000

The University of Pennsylvania has the expertise, infrastructure and experience to be a significant contributor to the Pelvic Floor Disorders Network. The proposed study, to investigate the efficacy of a new treatment for urge urinary incontinance, will improve quality of life of women with urge incontinence and result in considerable savings of health care resources. The goal of this application is to competitively identify clinical sites to conduct clinical trials for female pelvic floor disorders. This application from the University of Pennsylvania with Lily Arya MD, MS (Epidemiology) as Principal Investigator demonstrates our research plan for a new treatment for urge urinary incontinence, myofascial physical therapy. This potentially effective and safe method will greatly enhance treatment choice and improve the quality of life of women with urge urinary incontinence. This application outlines our extensive experience with similar large multi-center clinical trials. We highlight our ability to recruit and maintain subjects in female pelvic floor disorder clinical trials, noting we have been one of the leading recruitment centers in the nation for similar trials. We have often been able to recruit a greater number of subjects than our original estimates. The facilities at the University of Pennsylvania are supportive and outstanding. Our existing research unit and personnel has continuously demonstrated highly successful management of large clinical trials with outstanding organization, attention to detail and compliance with Good Clinical Practice, federal regulations and local Institutional Review Boards. Dr. Arya is an active researcher in the field of health measurement for pelvic floor disorders and she has successfully conducted a number of clinical trials in women's health. Specifically, she and her team of co- investigators and staff have been actively involved in surgical and non-surgical trials for urinary incontinence. She will bring significant expertise regarding study design and health measurement research to the Pelvic Floor Disorders Network. She leads a team of co-investigators who have a track record of collaborative clinical and translational research. We feel that the combination of a high quality personnel, experience in the research area, ability to recruit, and outstanding management and organization will contribute to a high likelihood of successful completion of this and future trials of treatment methods of pelvic floor disorders.

2-U10-HD-054215-06
Cleveland Clinic Clinical Site
Barber, Matthew
Cleveland Clinic Lerner Col/Med-CWRU

$25,000

Nearly one quarter of all women report symptoms of at least one PFD, including prolapse. POP is the most common indication for hysterectomy in postmenopausal women and it is unknown whether the addition of hysterectomy to POP surgery is integral to successful surgical outcome. The results of our concept proposal could justify or eliminate the need for as many as 70,000 hysterectomies in the US each year. The goal of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with pelvic floor disorders (PFD) using the highest quality research methods available. The Cleveland Clinic offers a stable academic and research-oriented environment for the conduct of PFDN studies including experienced investigators with complementary clinical and research backgrounds that have a particular interest and a successful history of conducting clinical trials evaluating both surgical and nonsurgical therapies for women with PFD. The specific aims of this application are: 1) to demonstrate that the Cleveland Clinic (CC) Clinical Site has contributed substantially to the academic, administrative, and clinical aspects of the PFDN since joining in its 2nd 5-year cycle; that it possesses the personnel, patient, clinical and administrative resources needed for successful participation; and that continued participation would be advantageous to the successful attainment of the Network's scientific goals and 2) to present a concept proposal for potential conduct by the PFDN. We propose evaluating the comparative effectiveness of sacrospinous hysteropexy (SSH), the most well-studied uterine-sparing pelvic organ prolapse (POP) surgery, relative to total vaginal hysterectomy with sacrospinous ligament fixation (TVH/SSLF), a commonly used hysterectomy-based vaginal uterovaginal prolapse procedure. The specific aims of the concept proposal are: 1) compare the anatomic, functional, sexual and health-related quality of life outcomes of SSH to TVH/SSLF in women undergoing surgery for Stage 2-4 POP uterovaginal prolapse 2 years after surgery; 2) compare surgical recovery and short- and long-term morbidity of SSH and TVH/SSLF in these same women and 3) determine the incremental cost-effectiveness of SSH compared to TVH/SSLF for the treatment of Stage 2-4 POP. Enrolled subjects will be randomized in the operating room on the day of surgery to receive either SSH or TVH/SSLF (1:1) using a random permutated block design. Randomization will be stratified by surgeon to account for the varying experience and expertise. Subjects and study coordinators will be blinded to treatment assignment until completion of the study.

1-U10-HD-069013-01
Brown/WIH Pelvic Floor Disorders Network Site
Myers, Deborah Lee
Women And Infants Hospital-Rhode Island
$25,000

Female pelvic floor disorders including urinary incontinence, pelvic organ prolapse and fecal incontinence are common, disabling conditions and are a significant public health issue. Although a variety of treatment options exist, high quality evidence to guide clinical management and to improve treatment specificity is still needed. Through the PFDN, WIH/Brown is committed to advancing high quality scientific evidence to help improve the care of women and reduce the burden of these disorders. The mission of the PFDN is to identify optimal diagnosis and management strategies for women with pelvic floor disorders (PFDs) and

this is directly in line with Women and Infants Hospital (WIH)/Brown's mission and commitment. WIH is a women's hospital, focused solely on advancing women's health and research and our extremely high volume, stable patient base, expertise of our multi-disciplinary collaborative and established research infrastructure provide the ideal environment to conduct large-scale, clinical research at the highest level. The aim of this application is for WIH/Brown to become the first PFDN site in New England by demonstrating: 1)our academic productivity and experience in multi-site, collaborative surgical, pharmaceutical and non-surgical clinical trials; 2)highly committed investigators with expertise in research methods and a specialized research team qualified to conduct multiple protocols, manage high quality data, and maintain high recruitment and retention; 3)a long-standing, formal relationship with multi-disciplinary collaborators committed to advancing the care of women with PFDs led by Urogynecology (including Urology, Colorectal surgery, Women's Gastroenterology, Women's Physical Therapy, and Women's Radiology); and 4)our high clinical volume (In 2009, the Division of Urogynecology evaluated 1211 new patients and performed 583 PFD surgical procedures; vaginal, abdominal, laparoscopic and robotic approaches are all represented). We present a concept proposal describing a 3-stage, randomized trial of a combined non-surgical and surgical approach to treatment of mixed urinary incontinence (MUl) in women who have failed conservative therapy and/or elect surgical treatment. Women suffering from MUl are at high risk for failure of segregated treatments and are often excluded from clinical trials focused on either stress or urge urinary incontinence alone. Clinical management of MUl remains a challenge and trials targeting this population are urgently needed. WIH has a long-standing history of supporting network collaboratives and our goal is to participate and become a leader in the PFDN in terms of protocol development and completion, data interpretation and quality, recruitment and retention and high quality dissemination of findings.

2-U10-HD-054214-06
Pelvic Floor Disorders Network
Nager, Charles William
University Of California San Diego
$25,000

Our site's participation in the next cycle of the PFDN should allow successful network recruitment for surgical trials. Uterine prolapse is a very common pelvic floor disorder and we should determine the best vaginal surgical treatment for this condition. This proposed research study will answer whether uterine - sparing procedures are reasonable alternatives to hysterectomy for this condition. The objectives and aims of this application are for the San Diego site to continue its work In the Pelvic Floor Disorders Network (PFDN). The unique strength of our application is our proven two site model, which combines the strengths of 7 academic investigators at both a tertiary medical center and a large volume HMO. We would like to provide leadership, continuity, innovation, academic expertise, a captured diverse patient population, and a proven research infrastructure to the network. We have a track-record of being the top 2 recruitment in surgical trials for pelvic floor disorders and we want to continue that into the third cycle of the PFDN. As noted in the RFA," In many cases, clinicians caring for women with pelvic floor disorders have adopted principles of care and surgical techniques before rigorous, objective, controlled evaluation has taken place. New devices and techniques have had

a dramatic influence on surgical practice...".Our study addresses this concern. Vaginal mesh is probably the most controversial topic in pelvic floor disorders and a strong argument can be made that the PFDN is the best group to study it. A growing-trend of women is seeking uterine sparing surgery for prolapse and a growing trend of gynecologists and urologists are managing uterine prolapse with vaginal mesh kit procedures. Our proposed randomized trial of uterine sparing, grafted vaginal apical suspension vs. traditional hysterectomy with native tissue suspension addresses the very important question of whether it is necessary to remove the uterus to treat uterine prolapse. This proposed study recognizes the role of new devices and techniques that are changing our care of women with pelvic floor disorders. Our comprehensive outcome measures should allow us to answer whether these new uterine-sparing, apical vaginal procedures are reasonable alternatives to conventional vaginal hysterectomy and native tissue suspension.

2-U10-HD-041261-11
Perioperative Pelvic Floor Rehab: A Randomized Trial
Richter, Holly E
University Of Alabama At Birmingham
$25,000

In order to improve on the care and individualized treatment for women with pelvic floor disorders, it is important that a credible research program exists that helps guide provider care. The Pelvic Floor Disorders Network (NICHD) performs such research and we are competing to continue to participate in this important initiative. As a part of this application, we propose a concept describing a randomized trial of sacral neuromodulation for the treatment of women with fecal incontinence refractory to current standard of care treatments. This exciting new treatment modality may help a cohort of women with diminished quality of life. The University of Alabama at Birmingham (UAB) is seeking to successfully compete in the third cycle of the NICHD sponsored Pelvic Floor Disorders Network. As a part of this important research infrastructure we have demonstrated our credible, productive, multidisciplinary clinical approach to the evaluation and treatment of women with pelvic floor disorders including urinary and fecal incontinence as well as pelvic organ prolapse. We have substantially contributed to the Network activities by participating at all levels of clinical trial design, implementation, recruitment, intervention implementation, retention and scientific reporting. We have reported outcomes and implication for care of these research initiatives at national and international scientific meetings and we are committed to continuing these activities. Through this application with its concept proposal, we wish to highlight our ability and commitment to continue these meaningful research activities. Current common treatment options for fecal incontinence (Fl) include behavioral therapy consisting of pelvic muscle exercises, diet and defecatory strategies and surgical approaches including anal sphincter repair, artificial bowel sphincter and as a last resort, colostomy. A significant proportion of women with Fl, however, do not gain benefit from behavioral therapy or sphincter repair yet do not wish to undergo colostomy. As the population of post-reproductive women continues to increase, it is imperative to study other treatment options that improve quality of life for this condition. An existing modality called sacral neuromodulation (SNM, Interstim(R)) has been FDA approved and utilized for the treatment of refractory urge incontinence. Two small randomized trials and several cohort studies have shown

efficacy of sacral neuromodulation for the treatment of refractory Fl (although it is not yet FDA approved for this indication). We propose a randomized trial to credibly characterize the effect of SNM on Fl episodes, symptom specific quality of life, effect on other pelvic floor symptoms, sexual function, predictors of response, adverse events, cost effectiveness and the role of biomarkers in optimal and suboptimal responses to this treatment. This information will allow us to more effectively individualize treatment for women with this condition.

1-U10-HD-069025-01
RCT of Hypnotherapy vs Tpolterodine for OAB: Voiding and Brain Activation Changes
Rogers, Rebecca
University Of New Mexico Health Science Center
$25,000

Pelvic floor disorders are common and costly. Performance of rigorously designed, target randomized clinical trials that inform evidence-base health care practices for women with pelvic floor disorders is best done through collaboration with other clinical sites. The University of New Mexico is a highly productive clinical and research site and proposes to join the Pelvic Floor Disorders Network in order to meet the Network's goal of investigating innovative solutions to these common problems. The University of New Mexico (UNM) proposes to join the Pelvic Floor Disorders Network (PFDN) to achieve the Network's primary goal of conducting rigorous, multi-center clinical trials to investigate the clinical and health aspects of pelvic floor disorders in women. Our site, in collaboration with other Network sites, aims to reduce the burden of pelvic floor disorders on women and their families. Through the design of innovative trials and participation in ongoing studies, the UNM PFDN site will make significant contributions to the Network. Dr. Rogers, Principal Investigator, and Dr. Komesu, Alternate Principal Investigator, have extensive experience in the design and conduct of multi-center randomized trials and proven leadership and productivity. The UNM PFDN site brings to the Network a busy clinical service with large numbers of under- represented Hispanic and Native American populations, as well as broad institutional support from the Department of Obstetrics and Gynecology and a recently funded Clinical and Translational Research Center. The concept proposal, based on preliminary data generated by our site and the work of others, is an innovative investigation comparing hypnotherapy to long-acting anticholinergic medicine for the treatment of overactive bladder (OAB). In addition to the hypnotherapy comparative-effectiveness trial, the concept proposal focuses investigation into the underlying mechanisms of OAB on the brain, using functional magnetic resonance imaging (fMRI). This translational, comparative effectiveness clinical trial is an excellent example of cutting edge research that the UNM PFDN site will bring to the Network. Skilled investigators, a busy clinical practice, unique patient populations and broad institutional support make UNM a worthy new clinical site for the PFDN.

2-U10-HD-041267-12
Pelvic Floor Disorders Network - Duke University Clinical Site
Visco, Anthony G
Duke University
$25,000

Female pelvic floor disorders represent a major public health burden given their high prevalence, impairment of quality of life, and substantial economic costs. As part of the Pelvic Floor Disorders Network, Duke University Medical Center is committed to actively participating in innovative clinical trials aimed at improving the evaluation and treatment of pelvic floor disorders through high-quality, high-impact clinical research. Pelvic floor disorders research at Duke University Medical Center (DUMC) is sophisticated and comprehensive with committed investigators addressing issues of great importance to women. DUMC 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 field. DUMC offers detailed evaluation and treatment in a high-volume, multidisciplinary setting that serves as a tertiary referral center for women across the southeast US. Each of the five Duke urogynecology investigators is fellowship-trained with expertise in both surgical and non-surgical management of urinary incontinence (Ul), pelvic organ prolapse (POP), fecal incontinence, and defecatory dysfunction. Last year, our Division cared for more than 1550 new patients and performed more than 400 surgical procedures for Ul and 270 for POP. Our patient population is 80% Caucasian, 15% African American, 2% Asian and 2% Hispanic, from both suburban and rural communities with stable care and follow-up patterns. DUMC is the hub of a multidisciplinary team of outstanding collaborative investigators in urogynecology, urology, colorectal surgery, gastroenterology, maternal-fetal medicine, physical therapy and epidemiology. DUMC offers a wide range of diagnostic resources: multi-channel urodynamic testing, video urodynamics, cystoscopy, defecography, pelvic MRI, endoanal ultrasound, and needle electromyography. During the current PFDN cycle, DUMC-initiated three active RCTs: 1. Anticholinergic vs Botox RCT (ABC, Dr. Visco, currently enrolling), Interstim vs Botox RCT (ROSETTA, Dr. Amundsen, full protocol), and a RCT evaluating transvaginal mesh for prolapse repair (Dr. Weidner, mini-protocol planned for fall of 2010. DUMC has consistently been a high recruitment site across a wide range of non-surgical and surgical studies with unparalleled retention rates. We have proven our ability to support and successfully complete large-scale, multi-centered investigations through our robust clinical practice and exceptional research infrastructure. Accordingly, Duke University Medical Center is well equipped and uniquely qualified to continue as a valuable and productive member of the Pelvic Floor Disorders Network.

1-U10-HD-069006-01
Pittsburgh Pelvic Floor Research Program
Zyczynski, Halina M
Magee-Womens Res Inst And Foundation
$25,000

Though prosthetic mesh enhances durability of prolapse and incontinence repairs, escalating complications have prompted public health warnings. Understanding the pathophysiology of mesh related morbidity and identifying modifiable risk factors through comparative and translational studies will inform on complications, support guidelines on mesh selection and route of delivery, and direct innovations in mesh technologies. The purpose of this proposal is to demonstrate the capabilities of the University of Pittsburgh to participate as a clinical site in the NICHD-sponsored Pelvic Floor Disorders Network (PFDN). Our site has a longstanding track record of successful contribution to multicenter studies of urinary and fecal incontinence, and

pelvic organ prolapse. We are particularly well suited to be a clinical site in the PFDN because of our volume, research infrastructure and track record, basic and translational experience and expertise. Access to large numbers of nulliparous women enables us to contribute uniquely to studies of the role of pregnancy and parturition in the etiology and prevention of pelvic floor disorders (PFDs). Magee-Womens Hospital (MWH) is the central resource for gynecologic specialty care for the 19 hospital University of Pittsburgh Health System serving a very large aging population. Our site brings expertise in urogynecology, physical therapy, geriatrics, urology, gastroenterology and mental health. We offer unique technical expertise in genomics, proteomics, tissue regenerative techniques, biochemical and biomechanical impact of meshes on the vagina and central neuronal control of bladder function. We propose to establish a comprehensive, scientifically rigorous clinical and translational research program within the PFDN for prospective comparative studies of mesh materials used in prolapse and incontinence procedures. The program will generate data of immediate clinical relevance as it will present scientifically sound, vendor independent evidence to guide surgeons' selection of specific graft materials and evidence-based practice guidelines for management of mesh complications. The 3 major components of the proposal are: 1) mesh specific infrastructure for implementation in PFDN clinical trials employing mesh inclusive of the development of a Mesh Morbidity Index and establishment of a Biospecimen Repository 2) the first RCT of meshes selected through rigorous analyses of biomechanical and biochemical properties and 3) translational studies on the cellular response to mesh materials and pathophysiology of mesh complications. The RCT will serve to pilot the database, compare clinical outcomes of meshes whilst providing specimens for translational studies.

RESPIRATORY DISEASES/CONDITIONS

1-U19-AI-095219-01
Pathophysiologic And Therapeutic Mechanisms Of Aspirin Exacerbated Respiratory Disease
Boyce, Joshua
Brigham And Women's Hospital
$12,500

This Proposal for support of an Asthma and Allergic Disease Cooperative Research Center (AADCRC) grant is focused on the mechanistic basis of aspirin-exacerbated respiratory disease (AERD), a distinctive clinical syndrome that accounts for a disproportionate percentage of individuals with severe asthma and recurrent nasal polyps. AERD is associated with both characteristic clinical reactions to ingestion of nonselective inhibitors of cyclooxygenase (COX), persistently elevated generation of the cysteinyl leukotrienes (cys-LTs), especially during reactions to aspirin, and selective airway hyperresponsivness to leukotriene E4 (LTE4), the most stable and abundant of the cys-LTs. We have discovered a molecular pathway through which LTE4 induces pulmonary inflammation (requiring P2Y12 receptors and platelets) and vascular leak (requiring a putative novel LTE4 receptor, GPR99). We have also discovered that leukocytes from individuals with AERD display a defect in expression of COX-2 and COX-2-

dependent generation of prostaglandin E2 (essential to maintain homeostasis in AERD), and that this reverses with desensitization to aspirin. We have also found that platelets and leukocytes from individuals with AERD lack the EP2 receptor for PGE2. A team of highly accomplished investigators with complementary skills will apply cellular, molecular, and whole animal strategies, combined with a proof-of-concept clinical trial to determine the cellular and molecular basis for these findings, their relevance to disease pathophysiology, and their amenability to therapy. Project 1 (J. Boyce, PI) focuses on the physiologic and functional consequences of EP2 receptor deficiency, and determines its epigenetic basis. Project 2 (Y. Kanaoka, PI) will verify the identity and function of GPR99 and determine its susceptibility to desensitization and its requirement for downstream effectors (platelets, P2Y12, and thromboxane) to elicit physiologic responses. Project 3 (E. Israel, PI) will determine the efficacy of P2Y12 antagonism on the severity of clinical reactions to aspirin, and the mechanism by which aspirin treatment restores COX-2-dependent PGE2 generation. The coordination of the AADCRC is enhanced by an administrative Core.

1-U19-AI-095227-01
Host and Viral Determinants of Infant and Childhood Allergy and Asthma
Peebles, R Stokes
Vanderbilt University Medical Center
$12,500

The long term objective of this application is to define the relationship between infant respiratory syncytial virus (RSV) infection and the host response that enables asthma inception. There is abundant evidence that children who experience severe RSV bronchiolitis during infancy are at greater risk for developing asthma later in childhood; however the host and viral determinants of severity of illness are not fully defined. Also unknown is whether mild RSV-induced illness in infancy may protect against the subsequent development of childhood asthma. In Project 1, we utilize the ReSPIRA (Respiratory Study for Protection of Infants from RSV to Asthma) cohort of 2000 infants to focus on host immune responses to RSV infection and the subsequent risk of recurrent wheezing and childhood asthma. Specifically, in Project 1 we will a) establish the relationship between the host phenotypic response to RSV infection in the first 6 months of life and the risk of recurrent wheeze and asthma, and b) identify the host genetic and immune response determinants of the RSV infection phenotype that affect the development of early childhood wheezing and asthma following RSV infection. In Project 2, we will focus on the contribution of specific RSV strains to early childhood wheezing and asthma development. RSV strains isolated from the ReSPIRA cohort will be genotyped and clinical parameters such as bronchiolitis severity score, as well as mediators of the host immune response measured in respiratory secretions will be studied to determine how RSV genotypes impact the host response. In Project 3, we will utilize a mouse model of RSV infection to examine the role of the prostaglandin 12 (PGI2) on airway dysfunction of an RSV strain (01/2-20) that has been associated with severe infant bronchiolitis and which induces airway pathology in the mouse. We previously reported that PG12 and signaling through its receptor (IP) is a critical determinant of severity of illness in RSV strain A2 infection. This project will determine the role of host PGI2 in RSV airway pathogenesis and also determine if a PGI2 analog currently used in the treatment of human disease is a target for RSV bronchiolitis. Further, in Project 3, we will use RSV strains

isolated from ReSPIRA in Project 2 to determine the generalizability of PGI2 as a therapeutic target.

1-U19-AI-095230-01
Airway inflammation and HLA-G in asthma
White, Steven R
University Of Chicago
$12,500

Our program seeks to clarify cellular and molecular mechanisms that lead to chronic asthma in order to identify novel, more effective therapies. We concentrate on immune mechanisms that underlie chronic airway inflammation with a clear focus on one immune tolerance molecule, the class I major histocompatibility complex protein human leukocyte antigen (HLA)-G, that we believe has an important role in modulating airway inflammation that is critical to chronic asthma. The key premise of our AADCRC proposal is that understanding the role of HLA-G will lead to new and better therapies to alleviate the suffering caused by asthma. To this end we propose three highly integrated and related projects: in Project 1, we will examine the presence and regulation of expression of HLA-G in asthmatic airways and in the airway epithelium, and relate presence to asthma severity and to the expression of regulating microRNA. We will examine the regulation of HLA-G expression by key Th2 cytokines such as IL-13 that are important to chronic asthma and relate expression back to airway cytokine concentrations in chronic asthma. In Project 2, we will exploit naturally occurring genetic variations in HLA-G and its LILRB receptors to understand how signaling through HLA-G and its receptors regulate the transition of CD4+ lymphocytes to the Th2 phenotype in mild/moderate asthma and to the Th17 phenotype in severe asthma. This project also will examine how genetic variation in the LILRB receptors modulate the effects of HLA-G on both T cell phenotype and on the SHP1 and SHP2 signaling pathways that modulate airway smooth muscle hypertrophy in chronic asthma. In Project 3, we will elucidate mechanisms that account for the higher risk of asthma among children of asthmatic mothers compared to children of non-asthmatic mothers. Using HLA-G as a model of the interactions of genotype and asthma status in mother and child, we will identify differentially expressed genes and the mechanisms for their differential expression in airway epithelium, CD4+ T cells and airway smooth muscle in subjects with chronic asthma. To complete these projects, each will interact with a robust Patient Recruitment and Data Analysis Core that will recruit 100 carefully phenotyped and genotyped asthmatic subjects and additional control subjects, and collect blood and airway biological specimens to be used in each project through a Lung Biological Specimens Core that will provide analytical and long-term storage. We believe that our current levels of productivity and collaboration combined with new, exciting and cutting-edge questions in this proposal will allow us to be successful in achieving our overall goal - identifying novel therapeutic targets for chronic asthma.

1-U19-AI-095261-01
T Cell Effector And Regulatory Mechanisms In Asthma And Food Allergy
Luster, Andrew D
Massachusetts General Hospital
$12,500

The Massachusetts General Hospital/Harvard Medical School AADCRC entitled "T cell effector and regulatory mechanisms in asthma and food allergy" seeks to gain a better understanding of the role of allergen-specific effector and regulatory T cells in determining the physiological response to an allergen at mucosal surfaces. It is becoming increasingly clear that the net outcome of an inflammatory response is the balance of allergen-specific effector T cell activity and opposing regulatory T cell activity. Antigen-specific effector and regulatory T cell numbers and activity are in large measure determined by the outcome of allergen-loaded dendritic cell (DC) interactions with antigen-specific T cells. The MGH/Harvard AADCRC will explore the balance of effector and regulatory activity in asthma and food allergy and the ability of tolerogenic DCs to affect this balance. The Center will focus on two allergic conditions relevant to the mission of the NIAID, namely allergic asthma and food allergy, and utilize two clinical models [endobronchial segmental allergen challenge (SAC) and oral immunotherapy (OIT)] as a foundation for its studies. Project 1 focuses on the role of antigen-specific effector and regulatory T cells in determining airways inflammation and airways hyper-reactivity by correlating the numbers, phenotype and function of these cells in allergic asthmatics (AA) and allergic nonasthmatics (ANA) using innovative imaging techniques; Project 2 focuses on correlating the numbers, phenotype and function of these same T cell subsets with clinical outcomes of milk allergic patients undergoing milk OIT; and Project 3 focuses on the ability of tolerogenic DC therapy to manipulate the balance between these two opposing T cell populations in favor of regulatory T cells and tolerance in both asthma and food allergy. The three interrelated projects will be supported by Cores that will recruit, enroll and characterize allergic subjects for SAC and OIT, provide MHC class II tetramers to specifically identify and study allergen-specific T cells, and perform sophisticated transcriptome phenotypic analysis on T cell and DC subsets. The goal of this Center is to understand the balance of effector and regulatory allergen-specific T cell activity that determines clinical disease in asthma and food allergy and to establish the utility of using tolerogenic DCs to manipulate this balance to induce allergen-specific tolerance. This would pave the way for new therapeutic approaches to treat these and other allergic diseases.

2-U19-AI-070235-06
Epithelial Genes in Allergic Inflammation
Khurana Hershey, Gurjit K
Cincinnati Children's Hosp Medical Center
$12,500

Allergic disorders are a major global health concern affecting 150 million people worldwide. Recently, epithelial cells have emerged as central participants in the pathogenesis of allergic inflammation: (1) they interface with the environment and initiate the response to environmental triggers; (2) the mucosal epithelium in the lung, skin, and gut functions as a physical barrier against pathogens and environmental exposures including allergens; and (3) epithelial cells have been directly implicated in Th2 responses, serving as a critical interface between innate immune responses and Th2 immunity. The overall objective of these studies is to elucidate the mechanisms by which epithelial cells contribute to the pathogenesis of allergic disorders. The overarching hypothesis of this Center proposal is that epithelial cell genes play a central role in the pathogenesis of allergic disorders. This hypothesis will be tested by three integrated projects

that use the Center for coordination and synergistic extension of the projects beyond the scopes and capabilities of the individual projects. This Center will provide important insights into the genes and pathways that may be Important in epithelial driven allergic inflammation and provide a basis for the design of novel therapeutic strategies aimed at the epithelial surface, i.e. lung (asthma), skin (atopic dermatitis), or gut (food allergy or eosinophilic esophagitis). Furthermore, integration of data across projects will provide novel insights into a key question in allergy - What are the mechanisms underlying tissue specific disease manifestations of allergic inflammation? Each project in the Center is focused on distinct epithelial cell genes and their roles in allergic disorders. Project 1 will examine the association of epithelial genes with allergic diseases that target distinct mucosal surfaces. Project 2 will dissect the role of epithelial desmoglein-1 in the pathogenesis of the allergic disorder eosinophilic esophagitis. Project 3 will focus on delineating the mechanisms by which epithelial-derived IL-33 is regulated by trefoil factor 2 (TFF2) during the early innate immune events that initiate allergy and asthma; and better define the role of the TFF2/IL-33 pathway in the pathogenesis of allergic disorders.

2-U19-AI-070412-06
Role Of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin In Asthma
Baseman, Joel B
University Of Texas Hlth Science Center
$12,500

The San Antonio Asthma and Allergic Diseases Cooperative Research Center (SA-AADCRC) represents a tightly focused, integrative and innovative effort to understand the role of Mycoplasma pneumoniae and its unique ADP-ribosylating and vacuolating toxin, designated Community Acquired Respiratory Distress Syndrome ToXin (CARDS TX) as important mediators of acute and chronic airway diseases, including new onset asthma and exacerbations, as well as persistent pulmonary dysfunction in children and adults. The basic science and clinical investigators who comprise the SA-AADCRC team share broad expertise and are highly collaborative. The SA-AADCRC's broad strategy of attack interlinks basic science and clinical research projects and cores. Project 1 uses the murine model and human materials to address fundamental questions on how CARDS TX induces asthma-like disease and exacerbates allergic pulmonary inflammation. Project 2 focuses on identifying CARDS TX ADP-ribosylating airway protein targets, delineating functionally important CARDS TX domains and essential amino acids that mediate CARDS TX binding to human surfactant protein A (SP-A) and airway cells, and generating antibody reagents that block/neutralize CARDS TX. Project 3 applies state-of-the-art biophysical techniques to uncover the structure and action of CARDS TX by using single crystal X-ray diffraction to determine CARDS TX three dimensional structure in the presence and absence of its cofactor NAD; neutralizing monoclonal antibody Fab fragments; and surfactant protein-A (SP-A). Clinical Core will collect human material from subjects with well controlled asthma, poorly controlled asthma and healthy controls and help in evaluation and follow-up of patient-related studies. Diagnostic Core will process clinical and experimental samples for diagnostic analysis by providing highly sensitive and specific diagnostic assays for rapid detection of M. pneumoniae CARDS TX. Pathology Core will provide necessary biopsy and necropsy procedures, lung pathology interpretation, histochemical and immunocytochemical evaluations, and qualitative and semiquantitative histopathologicai analyses. Administrative Core

will oversee all SA-AADCRC-related activities and coordinate interactions and collaborations between projects and cores. Therefore, the SA-AADCRC represents a network of collaborators/colleagues who continuously ask fundamental and translational questions about asthma, airway-related pathologies, immunopathogenesis, and M. pneumoniae/CARDS TX biology and virulence mechanisms.

2-U19-AI-070489-06
Epithelial Barrier Programs in Asthma and Allergic Disease
Holtzman, Michael J
Washington University
$12,500

The overall goal of this AADCRC proposal is to define the role of the epithelial cell barrier in the pathogenesis of asthma and allergic disease and to use that information to prevent this type of disease. We combine expertise in airway as well as gut and skin epithelial cell biology, and we use cell and mouse models with high fidelity to directly translate our findings to humans. The AADRC therefore consists of three interrelated Projects that ask, first, how airway epithelial cells mediate effective antiviral defense under one condition but asthma under another (Project 1), second, how airway epithelial cells remodel towards an overabundance of mucous cells in post-viral and allergic asthma (Project 2), and third, how epithelial injury in the skin triggers the march from atopic dermatitis to asthma (Project 3). Each project addresses the respective question with a novel but overlapping molecular approach to mechanism and takes advantage of a breakthrough discovery to set a new scientific paradigm for the system under study. Thus, Project 1 unravels a new IFN signaling pathway that offers improved protection against viral infection and post-viral asthma and is specific to the airway epithelial cell barrier; Project 2 dissects a new pathway for autophagy proteins to support proper mucous cell function and prevent mucous cell metaplasia in the airway in a manner reminiscent of the intestinal epithelial barrier; and Project 3 defines a new TSLP production and secretion pathway that drives airway inflammation based on its expression in the skin epithelial barrier. Each Project is constructed so that the first aim will establish a basic pathogenic mechanism using cell and mouse models that are shared among projects and supported by the Cores for tissue and cell processing (Core C) and mouse models (Core D). In turn, each Project will conduct a second aim to validate and translate its findings using samples from children and adults with asthma and/or atopic dermatitis supplied by the Core for human subjects and data analysis (Core B). Sharing samples and overlapping scientific goals among projects create a synergistic program that can be coordinated by a common Administrative Core (Core A). Project and Core interactions are based on the overall principle that each Project begins with molecular hypothesis building in cell and mouse models and translates findings from these models to studies of humans with asthma and/or allergy. In each project, we aim to validate a clinically useful biomarker of the disease process and lay the groundwork for the future development of biological and/or small molecular weight compounds that might influence the process as a therapeutic strategy.

2-U19-AI-070535-06
Airway Inflammation And Airway Remodeling
Broide, David H

University Of California, San Diego
$12,500

Airway remodeling is the term applied to the structural changes observed in the airway in asthma. Although current NIH guidelines recommend maintaining a goal of normal lung function in asthma, current therapeutic strategies do not specifically target airway remodeling as the cellular and molecular mechanisms that result in remodeling are not well defined and thus therapeutic targets are not well understood. Thus, there is an important need to identify mechanisms by which airway remodeling is mediated so that potential novel therapies could be directed at these pathways. In addition, characterization of these pathways could lead to the development of non-invasive blood or sputum biomarkers to identify, monitor, and perhaps subset, patients with asthma and remodeled airways. This UCSD AADCRC proposal will be directed by David Broide (Professor of Medicine) and include three projects (Broide, Croft, Zuraw) that will investigate mechanisms of airway remodeling in asthmatics exposed to allergen and rhinovirus common triggers of asthma. Thus, the overall hypothesis that will be explored in all three projects is that exposure to allergen triggers expression of inflammatory and remodeling pathways in allergic asthmatics that are exacerbated by exposure to respiratory viruses such as rhinovirus. The specific hypothesis that will be explored in each project and that will be driven by samples from asthmatics, is that the innate immune response (airway epithelium, macrophages, natural helper cells) play an important role in initiating and perpetuating the inflammatory and airway remodeling response to environmental triggers in allergic asthmatics. The three interrelated projects will focus on "Innate inflammation and airway remodeling" (Broide, Project 1), "TNF-R family members, inflammation and remodeling" (Croft, Project 2), and "Epithelial GILZ inflammation and remodeling" (Zuraw, Project 3) and be supported by Administrative Core A, and "Asthma Clinical Core B" which will be a source of sputum, BAL, endobronchial biopsy, and blood samples from asthma and control subjects provided by investigators in Core B (Ramsdell, Harrell, and Thistlethwaite, UCSD; Proud and Leigh, University of Calgary; and Hamid, McGill University). An lOFM Core is also proposed as requested by the RFA.

1-R21-HL-109935-01
Uterine-Specific Genetic Modification And Lymphangioleiomyomatosis
Teixeira, Jose M
Massachusetts General Hospital
$50,000

One of the major unknowns in lymphangioleiomyomatosis (LAM) research is the cell or tissue of origin for the smooth muscle cells that infiltrate the lung to form the fibrotic lesions. We have generated mice with defective wound healing in uteri, which results in hemorrhaging, hypertrophic scarring and fibroids. Our preliminary results investigating the lungs suggest that circulating post-traumatic uterine cells might be the cells that cause LAM. The proposed studies will investigate whether the uterine cells are the source of fibrotic cells found in LAM, whether the LAM lung lesions are hormonally responsive, and whether these mutant mice will be a needed model system for investing the mechanisms and pathways involved in the infiltration of the lungs with fibrotic cells and for preclinical studies of possible therapeutic intervention.

Lymphangioleiomyomatosis (LAM) is a rare disease primarily found in females and is characterized by a diffuse interstitial infiltrate of atypical smooth muscle cell lesions in the lung parenchyma resulting in airway restriction. The etiology of the disease is unknown but is thought to involve hormonal regulation because it usually presents between menarche and menopause. Additionally, LAM is often found in patients with mutations in tuberous sclerosis complex (TSC), suggesting that inactivation of TSC can contribute to its development. We are studying uterine development and associated pathologies by conditionally deleting and/or activating candidate genes in pathways critical for normal differentiation and function. We have created mice with uterine-specific leiomyomas (fibroids) by either constitutively activating ¿-catenin or by expressing a truncated allele of adenomatous polyposis coli (APC) and we have shown preliminary evidence that the leiomyomas develop as a result of vascular hemorrhaging and subsequent hypertrophic scarring. The Mullerian duct-derived internal female reproductive tract organs (uterus, oviduct, cervix, and cranial portion of the vagina) are the only structures from the bipotential mammalian embryo not found in males, suggesting that the hormonally responsive mesenchymal stromal cells of the uterus might be the source of the cells for pulmonary fibrosis and account for the female-specificity of LAM. We hypothesized that pulmonary LAM might be caused by uterine vascular pathologies that allow intravasation of uterine stromal cells that can subsequently lodge and proliferate in the lungs. Histological analysis of the lungs from our mouse models with uterine hemorrhaging and leiomyomas showed fibrotic lung plaques similar to that observed in human LAM that were also HMB45-, aSMA- and desmin-positive, markers for human LAM. We propose to investigate this hypothesis further with the following Specific Aims: (1) confirm that cells in the lung lesions are derived from the uterus, (2) determine whether uterine mesenchymal cells can be detected in peripheral blood, (3) test the hormone responsiveness of the smooth muscle cells in the lung lesions, and (4) assess the marker profile of lung lesions for comparison with human LAM. The results from these studies will lay the foundation for continued investigation of the triggers and signaling pathways involved in the development of the LAM lesions as well as provide an in vivo model system for preclinical studies of therapeutics targeting those pathways.

OD-11-289
Workshop On The Health Impacts Of Indoor Air Pollution In Developing Countries
Martin, William
NICHD
$7,854

An international workshop was convened May 9-11, 2011 in Arlington, VA to discuss current evidence on adverse health effects of indoor air pollution and to exchange views on improving human health. Every day, millions of women in developing countries spend several hours crouched over small fires cooking. Often their homes have no chimneys and poor ventilation. This daily proximity destroys lungs and small children staying close to their mothers are equally vulnerable. Exposure to smoke from traditional stoves and open fires – the primary means of cooking and heating for 3 billion people in developing countries – causes almost 2 million deaths annually, with women and young children affected most. The World Health Organization states that indoor air pollution in developing countries is the fourth leading cause of morbidity and mortality, and the second leading environmental contributor to ill health affecting primarily

women and children. New designs in cooking stoves are not always comfortable for the women cooking on them, and require changes in cooking methods, some of which made the food taste different. In the kind of patriarchal societies that keep women tied to stoves and kitchen responsibilities, women don't have a lot of autonomy for decision-making, especially not about major household issues like a new stove. At this workshop, more than 150 scientists and policy makers from multiple countries focused on research gaps, exposure assessment, and the burgeoning global initiative that aims to deliver clean, affordable cook stoves to the developing world. The workshop presented a first-ever opportunity to hear the state-of-the-science on the health impacts of indoor air pollution and to identify critical research needs. The need for such a meeting is considerable since the poorer half of the world's population uses biomass — wood, crop residue, or dung — or coal as fuel to cook and heat, contributing to a variety of health conditions including pneumonia, lung cancer, cardiovascular disease, low birth weight, and cognitive impairment. Speakers described the importance of biomarkers and the development of inexpensive, portable electronic monitors as a means to gather exposure assessment data.

RESEARCH DISSEMINATION

NLM-ORWH Women's Health Web Portal and Research Dissemination
A Partnership between NLM and ORWH
$550,000

The funding for research dissemination projects for the NLM-ORWH Women's Health Resources Web Portal http://www.womenshealthresources.nlm.nih.gov is being distributed throughout the United States to fund meritorious and innovative outreach programs that use Women's Health Resources as an information dissemination tool to consumer and professional audiences. Projects will target consumers, professionals, both groups, or women overseeing and coordinating health of their families. Types of projects include development of campaigns, trainings, toolkits or other activities that can be replicated. These projects will enhance the dissemination of the key elements identified in the ORWH strategic plan, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research* that was released in September 2010. Projects will provide an outcomes summary and evaluation that will be posted to the NLM-ORWH Web Portal. There are two levels of funding for the outreach award; a maximum of $20,000 for each health professional outreach project, or $15,000 for each consumer outreach project. Majority of the awards will be selected from EnHIP member universities and colleges and the National Network of Libraries of Medicine members. Descriptions of each group follows.

The National Library of Medicine's Environmental Health Information Partnership (EnHIP) is a collaboration between the Library and twenty-one Historically Black Colleges and Universities (HBCUs), Hispanic-Serving Institutions (HSIs), Tribal Colleges and Universities, and Alaska Native-Serving Institutions to address health disparities. EnHIP evolved from the Toxicology Information Outreach Program (TIOP) that was established in 1991 in response to the pressing issue of toxic waste and the exposure to toxic chemicals in minority communities.

The mission of EnHIP is to enhance the capacity of minority serving academic institutions to reduce health disparities through the access, use and delivery of environmental health information on their campuses and in their communities. More information, a list of current and former member schools and reports of past efforts can be found at: http://sis.nlm.nih.gov/outreach/enhip.html .

The National Network of Libraries of Medicine (NN/LM) has been serving the biomedical information needs of the nation for over forty years by providing health professionals and the general public with health information resources and services. The mission of NN/LM is to advance the progress of medicine and improve the public health by providing all U.S. health professionals with equal access to biomedical information and improving the public's access to information to enable them to make informed decisions about their health. The Program is coordinated by the National Library of Medicine and carried out through a nationwide network of health science libraries and information centers. The NN/LM equips and encourages Network members to extend their services and expertise to groups, agencies, and institutions beyond their traditional reach into communities also targeting consumers and those that serve consumers. More information about the NN/LM can be found at: http://nnlm.gov/ .