FY 2003 ORWH-SUPPORTED RESEARCH INITIATIVES

ADOLESCENT HEALTH

TITLE: **Mothers living with HIV and their adolescent children** **NIMH**
P.I.: **Mary Jane Rotheram-Borus, PhD**
INSTITUTION: **The Regents of the University of California, Los Angeles, CA**
GRANT NO.: **1 R01 MH068194-01A1**
KEYWORDS: **women, HIV infections, adolescents, intervention, parenting**
TYPE STUDY: **Clinical**
AMOUNT: **$300,000**

The number of parents living with HIV is significant and rising, as the length and qualify of life of persons living with HIV has increased. When mothers become infected with HIV, they face not only the challenges associated with their infection, but their entire family is affected, with long-term negative outcomes for themselves and their children. This research team completed previous randomized controlled trials with parents with HIV and their children and young people living with HIV, suggesting the benefits of improving coping skills, family relationships, and dealing with illness-related tasks (e.g., disclosure). The proposed trial builds on these results to implement prevention services in treatment settings to improve long-term outcomes for mothers and their adolescent children, gathering evidence to inform dissemination. All mothers living with HIV with adolescent children at three sites in the Los Angeles Pediatric AIDS Consortium (n= 400 MLH) will be randomly assigned within site to one of two conditions: 1) a four module intervention (16 sessions) and access to booster sessions, as needed (n=200 MLH; 320 youth); or 2) a standard care condition (n=200 MLH; 320 youth). The MLH's intervention will address improved health behaviors (Module 1), parenting skills and family relationships (Module 2), reduced transmission acts and problem behaviors (Module 3), and improved mental health (Module 4). For youth who know the MLH's serostatus, the intervention will be delivered in conjunction with three of the MLH's modules and address coping with parental illness (MLH's Module 2), reducing multiple problem behaviors (Module 3), and improving mental health (Module 4). Youth whose MLH die will receive a fourth module to cope with parental bereavement and to set new life goals. The impact will be assessed over two years (recruitment, 3, 6, 12, 18, & 24 months), in a design that is a blend of an efficacy and effectiveness trial. The outcomes will be MLH's health status, and youth and MLH's parent-child relationships, problem behaviors, and mental health symptoms. In addition, youth's developmental outcomes will be monitored. In order to assess the uniqueness of the impact of HIV, the investigators will assess a cohort of parents and adolescents in a neighborhood control group (n= 200 mothers; 320 youth) matched for age, gender, and ethnicity on the same measures.

AGING

TITLE: **Aging of Brain: Effects of Prenatal Nutrition** **NIA**
P.I.: **Jan Blusztajn, PhD**
INSTITUTION: **Boston University, MA**
GRANT NO.: **2 PO1 AG09525-11**
KEYWORDS: **prenatal nutrition, choline, folic acid, nutrition, neuroscience, aging**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

The goal of this study is to determine the mechanisms by which the availability of choline and folic acid during the prenatal period modifies brain structure and function in development, adulthood and old age. The proposed studies will 1) determine the molecular mechanisms involved in the brain reorganization that is governed by choline and folate availability by studying signal transduction pathways and developmental patterns of gene expression in brain; 2) measure synaptic function and plasticity in hippocampus of rats exposed to varying levels of choline or folate in utero; 3) examine age-related changes in conditioned stimulus processing (attention) as a function of the prenatal availability of choline and folate; 4) determine if supplementation with folate in early development leads to lifelong changes in spatial memory, brain anatomy and neurochemistry; 5) investigate whether choline supplementation either prenatally or across the lifespan ameliorates behavioral, anatomical, and biochemical deficits seen in mice lacking the apolipoprotiein E.

TITLE: **A Fall Prevention Program for High Risk Elderly Women** **NINR**
P.I.: **Jean F. Wyman, PhD, RN**
INSTITUTION: **University of Minnesota, Minneapolis, MN**
GRANT NO.: **5 R01 NR005107-03**
KEYWORDS: **injury prevention, nursing intervention, aging**

TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

The long-term objective of this study is to develop cost-effective, community-based strategies for the prevention of falls in high-risk elderly women. Specific aims include: 1) Test the efficacy of a fall prevention program for high risk elderly women on fall rates over one and two years; 2) Determine the effects of the fall prevention program on postural competence, functional performance, and a variety of other outcome measures; and 3) Identify demographic, clinical, personal, functional, and postural competence variables that predict long-term exercise adherence for participants in the fall prevention program. The participants will be 250 community-dwelling women who are aged 70 and over, mentally intact, ambulatory, with postural instability and at least one other fall risk factor, not currently involved in regular exercise, and medically stable with physician approval for independent exercise participation. This study will provide information on the efficacy and cost of simple interventions designed to prevent falls and fall-related injuries, reduce preclinical disability, maintain long-term exercise adherence, and improve quality of life for older women.

TITLE: **Role of estrogen in the pathogenesis of tubulointerstitial disease in aging** **NIA**
P.I.: **Christine Maric, PhD**
INSTITUTION: **Georgetown University, Washington, D.C**
GRANT NO.: **1 R03 AG22233-01**
KEYWORDS: **Menopause, estrogen, renal, rennin-angiotensin system, nitric oxide**
TYPE STUDY: **Basic**
AMOUNT: **$77,600**

Despite the most recent report on the risks of combined estrogen (E2) and progestin therapy on cardiovascular disease, there is still no evidence to suggest that E2 alone is not protective in these disease processes. This stresses the importance of further studies to determine the precise role of E2 in mediating systemic and cellular function that may adversely be regulated in age-related disease. Renal disease is an underlying and/or contributing factor to cardiovascular and other age-related diseases. Age-related renal disease is associated with glomerulosclerosis and tubulointerstitial fibrosis; however the factors mediating these processes have thus far not been examined. Based on preliminary data showing that the renal renin-angiotensin system (RAS) is downregulated with ovariectomy, it is hypothesized that the protective role of E2 is partially mediated by downregulation of the RAS. Previous studies also show that expression of enzymes involved in nitric oxide (NO) synthesis is downregulated with ovariectomy, and it is hypothesized that the protective role of E2 will be mediated by upregulation of NO synthesis. Both Ang II and NO regulate cell proliferation and extracellular matrix (ECM) metabolism, the two major processes that are adversely affected and contribute to the development of glomerulosclerosis and tubulointerstitial fibrosis. The overall hypothesis of this research is that E2 regulates the RAS and nitric oxide pathways and that the increased responsiveness of their specific target cells (proximal tubule and renal interstitial fibroblasts) contribute to the pathogenesis of age-related tubulointerstitial injury. Specific Aim 1 will examine the functional changes in the aging kidney, due to abnormal regulation of the RAS and NO pathways: renal expression of the components of the cell-specific RAS and NOS will be measured by real-time PCR and Western analysis. Specific Aim 2 will examine the structural changes in the aging kidney, due to of the abnormal regulation of the RAS and NO pathways: tissue morphological changes, cell proliferation and ECM metabolism will be examined by immunohistochemistry, light miscrocopy, Western analysis and zymography. Knowledge gathered from these studies will contribute to our overall understanding of processes that are adversely affected with aging and may lead to development of novel therapeutic strategies to prevent age-related disease in women.

TITLE: **Relaxation Therapy for Alzheimer's Caregivers** **NINR**
P.I.: **Sharon Lewis, PhD, RN**
INSTITUTION: **University of Texas Health Science Center, San Antonio, TX**
GRANT NO.: **2 R01 NR04345-06A1**
KEYWORDS: **minority, multidisciplinary, behavioral, aging brain**
TYPE STUDY: **Clinical**
AMOUNT: **$99,999**

Aging baby boomers, longer life spans, and rising levels of Alzheimer's disease and related disorders (ADRD) will result in a major caregiver crisis in the near future. Although family caregivers perform an incredibly valuable service, they do so at a considerable cost to themselves both emotionally and physically. Effective stress management programs for caregivers are vitally

needed to 1) help them decrease their stress, 2) improve their emotional and physical health, and 3) empower them to gain control of their lives. The overall goal of this randomized controlled clinical trial is to determine the effectiveness of a stress-busting program (SBP) for caregivers of patients with ADRD. Specific research aims include: 1) to prospectively determine the effects of a SBP compared to a standard support group (SSG) on quality of life, immune response, and relaxation response using bioinstrumentation to measure muscle tension, electrodermal response, skin temperature, blood volume pulse, and blood pressure and 2) to assess the effectiveness of SBP or SSG for adult children caregivers as compared to spousal caregivers based on quality of life measurements, immune parameters, and relaxation response. Subjects will be tested at baseline, at completion of 4 and 8 weeks of a SBP or SSG, and at 2-and 4-month follow-up sessions to determine the long-term effectiveness of the intervention. The proposed 8-week multimodal SBP will focus on stress management, relaxation therapy, and education related to stress and relaxation, managing challenging behavior, depression, coping strategies, positive thinking, and taking time for oneself. The setting will be an educational support group. A repeated measures design will be used to determine the effectiveness of SBP compared to SSG. Outcomes will be measured using psychosocial instruments as well as state-of-the-art science technology including bioinstrumentation and immune parameters to measure biological responses. The SBP is proposed as a way to decrease the level of stress experienced by caregivers and teach them effective coping strategies. If SBP is found to be more effective than SSG in decreasing stress, improving quality of life, promoting relaxation, and/or enhancing immunocompetence in family caregivers, these findings could have important clinical significance for providing a cost effective health promotion strategy for a group of people who experience tremendous ongoing stress.

TITLE: **Custodial Grandparents and Religion and Spirituality** **NIA**
P.I.: **Martha Crowther, PhD**
INSTITUTION: **University of Alabama, Tuscaloosa, AL**
GRANT NO.: **1 R03 AG 022650-01**
KEYWORDS: **caregiving, stress, minority**
TYPE STUDY: **Clinical**
AMOUNT: **$61,800**

This proposal is to study the reduction of health disparities among older persons and populations by conducting research to disentangle the effects of socio-economic status, social and environmental factors, health behaviors, and race and ethnicity on health. There has been a steady increase in the number of African American custodial grandparents. Many grandparent caregivers experience stress, decreased social and economic well-being and reduced physical health as a result of caregiving. As interest in this area grows, questions as to methods grandparents use to cope with the stress of caregiving increase. There is a paucity of data available on the use of religious and spiritual practices among grandparents who raise their grandchildren. Preliminary results suggest that African American custodial grandparents are very religious and spiritual, and that religiosity and spirituality may serve as coping mechanisms for grandparents who are primary caregivers for their grandchildren. Research in the area of cognition and aging suggests that there may be differences in the cognitive abilities of those actively involved in social activities. Preliminary results suggest that older African Americans that gave support have higher levels of everyday problem solving abilities. The primary aim of this study is to examine the impact of the social activities many custodial grandparents engage in which include religious activities and activities surrounding raising their grandchildren as a protective factor against the stressors associated with caregiving and a method to enhance their cognitive abilities. While designed primarily to assess the relation between the stressors of custodial grandparenting, religion/spirituality and cognition, the proposed study has clinical and policy implications. Clinically, the results of the proposed study could help identify topics to be addressed in grandparent caregiver support groups, such as problem solving skills and coping skills. It will also aid in assessing the types of practical skills needed to provide care for others. In the realm of policy, the results of the current study could identify the areas of concern for grandparent caregivers, such as obtaining access to medical care for their grandchildren.

TITLE: **Health, Illness, and Social Life at Older Ages** **NIA**
National Social Life Health and Aging Project
P.I.: **Linda Waite, PhD**
INSTITUTION: **Department of Sociology, Center on Aging, University of Chicago, IL**

GRANT NO.: **R01 AG021487-01**
KEYWORDS: **sexuality, aging, mental health**
TYPE STUDY: **clinical**
AMOUNT: **$250,000**

It is well established that social support, particularly marriage, bolsters psychological and physical health as people age. Human sexuality constitutes one essential, but poorly understood parameter of both healthy aging and social life at older ages. Physicians and public health policy makers lack a scientific base of information for advising older people or designing programs that might promote sexual health, support prolonged independence, relieve anxiety, prevent dysfunction or disease, or address current issues influencing intimate social and sexual relationships among older Americans. The Interactive Biopsychosocial Model (IBM) developed for this research is an extension of Engel's biopsychosocial model. Health is conceptualized as a function of biophysical and psychocognitive dynamics between individuals over time and incorporates social embeddedness in shaping that process. A nationally-representative probability sample of 3,000 community-residing women and men ages 57-84 will be followed longitudinally in two waves over five years. We will oversample African American and Hispanic adults. Face –to-face interviews and biomarker collection will take place in respondents' homes. Data collection will elicit: 1) demographics; 2) social networks; 3) social and cultural activity; 4) physical and mental health including cognition; 5) well-being; 6) illness; 7) medications and alternative therapies; 8) history of sexual and intimate partnerships; 9) patient-physician communication regarding sexuality; sexual identity, functionality, desire, opportunity, and attitudes about sexuality and intimacy. Biomarker collection will include: height, weight, blood pressure, serum (glucose metabolism, HIV, hepatitis, syphilis), urine (gonorrhea, chlamydia, trichomonas), saliva (endocrine evaluation), and sensory testing (vision, hearing, touch, taste, smell). Three specific aims will be addressed: 1) describe health and health transitions of older community-residing Americans; 2) evaluate the relationship between health and older adult sexuality; and 3) examine sexuality within social networks and their sociocultural context.

ALCOHOL AND OTHER SUBSTANCE ABUSE

TITLE: **Alcohol, HIV Risk Behaviors, and Sexual Victimization** **NIAAA**
P.I.: **Maria Testa, PhD**
INSTITUTION: **Research Institute on Addictions, Buffalo, NY**
GRANT NO.: **5 R01 AA12013-05**
KEYWORDS: **risk behaviors, HIV, sexual victimization, STDs**
TYPE STUDY: **Clinical**
AMOUNT: **$50,000**

This application suggests that childhood sexual abuse and risk-prone personality (high sensation-seeking, high negative affect, low assertiveness) lead women to engage in risky behaviors (heavy alcohol and drug use, high levels of sexual activity and exposure to risky settings such as bars) which in turn increase the likelihood of experiencing both sexual victimization and HIV/STD infections. There will be a three wave cross-legged panel design using a representative sample of 1,000 unmarried women, ages 18-30, recruited from random digit dialing.

TITLE: **Effects of Smoked Heroin Across the Menstrual Cycle on Cessation** **NIDA**
P.I.: **Suzette Evans, PhD**
INSTITUTION: **Research Foundation for Mental Hygiene, New York, NY**
GRANT NO.: **1 R01 DA016762-01**
KEYWORDS: **drug abuse, menstrual cycle, heroin**
TYPE STUDY: **Basic**
AMOUNT: **$298,391**

There is growing evidence that there are sex differences in response to drugs of abuse. However, only a limited number of studies in rodents have assessed whether there are sex differences in the reinforcing effects of opioids and the human data are sparse. Nevertheless, some of the sex differences observed can be attributed to cycling ovarian hormones in females. This proposal will parametrically evaluate the behavioral and reinforcing effects of smoked heroin across the menstrual cycle in normally-cycling, adult female rhesus monkeys. Levels of estradiol (EST), progesterone (PRO) and luteinizing hormone (LH) will be routinely monitored, correlating changes in hormone levels to the behavioral effects of heroin. Exp. 1 will carefully characterize the time course of heroin blood levels across the menstrual cycle. Subsequently, heroin seeking and taking will be measured using a second-order schedule, choice and location preference procedures when the monkeys are not dependent (Exp. 2) and again (Exp. 4) when they are dependent on opioids; and the reinforcing effects of heroin will be measured using a Progressive Ratio procedure

when the monkeys are not dependent (Exp. 3) and again (Exp.5) when they are dependent on opioids. These experiments will provide valuable data about changes in the behavioral and reinforcing effects of heroin across the menstrual cycle when heroin is available under non-dependent and dependent conditions. In addition, this proposal will provide important information on the effects of self-administered opioids on the regulation of the menstrual cycle. The proposed studies will be the first to systematically evaluate these effects in female non-human primates.

TITLE: **Gender Differences in Drug Abuse** **NIDA**
P.I.: **Jill Becker, PhD**
INSTITUTION: **The Regents of the University of Michigan, Ann Arbor, MI**
GRANT NO.: **2 R01 DA012677 -04**
KEYWORDS: **cocaine, steroid hormones, behavioral activation, psychomotor stimulants**
TYPE STUDY: **Basic**
AMOUNT: **$291,889**

The experiments proposed will utilize well characterized animal models to study the neurobiological basis for gender differences in drug abuse. Neuroadaptations associated with sensitization to psychomotor stimulants are thought to play an important role in the process of addiction. Furthermore, gender differences in the behavioral and neurochemical effects of psychomotor stimulants have been repeatedly reported to occur in rodents and more recently in humans as well. In order to begin to understand gender differences in drug abuse, basic research on the role of gender and ovarian hormones in response to acute and repeated exposure to cocaine is an important next step. Research on the acute behavioral research to psychomotor stimulants indicates that treatment of female rats with the ovarian hormone estrogen is sufficient to induce changes comparable to the effects of the estrous cycle. There are two hypotheses to be tested. The first is that there are gender differences in behavior induced by repeated exposure to the psychomotor stimulants and gender differences in self-administration of cocaine. The second is that estrogen potentiates both the acute and sensitized response to cocaine in female rats enhancing these gender differences. In order to begin to understand the underlying neurological bases for gender differences in cocaine addiction there are two important factors that must be teased apart: 1) differences between males and females (independent of gonadal hormones); and 2) whether gonadal hormones in either males or females affect responses to cocaine. In humans these factors are intermingled because chronic cocaine use can disrupt and even cause cessation of a woman's menstrual cycle. In such women estrogen may play a role in acquisition of drug taking behaviors but not in maintenance of these behaviors (since in women with amenorrhea the serum concentrations of estrogen are extremely low). On the other hand more men than women abuse drugs and many boys begin using drugs prior to sexual maturation. The experiments proposed will allow the relative importance of gender vs gonadal hormones to be teased apart in animal studies investigating the effects on cocaine-induced psychomotor behavior and cocaine self-administration.

TITLE: **College Women: The Alcohol and Victimization Link** **NIAAA**
P.I.: **Kathleen A. Parks, PhD**
INSTITUTION: **State University of New York at Buffalo, Amherst, NY**
GRANT NO.: **R01 AA013986-**
KEYWORDS: **violence against women, sexual and physical assault, alcohol abuse**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Victimization of young college women is a problem with potentially devastating consequences. Approximately 2 million women are new freshmen each year. A recent report, estimates that 600,000 (13.3%) college students were assaulted because of drinking by other students over a 1-year period. 6.4% of women reported being raped during their first year in school. Research findings indicate that 50% of sexual assaults in college involve alcohol. Based on these figures, 3.2% or 64,000 freshmen women experience an alcohol-related rape annually. Clearly victimization (nonsexual and sexual) is a significant alcohol-related problem on college campuses. The research proposed focuses on the longitudinal relationship between alcohol consumption and victimization among college women The primary objectives of the proposed investigation are to 1) describe the rates of alcohol consumption and alcohol-related victimization across four years of college attendance, 2) assess the temporal relationship between alcohol consumption and alcohol-related victimization (sexual and nonsexual, verbal and physical), 3) assess risk factors for experiencing victimization during college, and 4) assess primary (e.g.. injury, psychological trauma) and secondary (e.g., academic, psychological) consequences of alcohol-related victimization. Two longitudinal research components will be used to achieve these research objectives.

Component 1 involves a brief telephone survey, administered annually during the fall semester, of the drinking patterns, victimization and other alcohol-related problems that occur in a cohort of women entering college for the first time during the Fall semester of 2003. Component 2 of the research involves an 8-week prospective assessment of drinking patterns and victimization experiences administered annually during the Spring semester, to a sub-sample of women randomly selected during Year 1 from Component 1 participants. Component 2 will use state-of-the-art technology (Interactive Voice Response) to collect daily data on alcohol consumption and any victimization that occurs. Event-based measures will be used to provide detailed data on victimization experiences. This research is innovative in the use of long- and short-term measures, within a longitudinal design, to assess alcohol-related victimization of college women.

TITLE: **Reducing Alcohol and Risks Among Young Females** **NIAAA**
P.I.: **Lydia N. O'Donnell**
INSTITUTION: **Education Development Center, Inc, Newton. MA**
GRANT NO.: **1 R01 AA014515-01**
KEYWORDS: **alcohol, African American, Latina adolescent females, HIV/ AIDS**
TYPE STUDY: **Clinical**
AMOUNT: **$150,000**

An intervention study will be undertaken to characterize and address the combined effect of early alcohol use and risky behavior within a population of urban African American and Latina adolescent females who are at high risk for HIV, AIDS, and other infections. Past research by the investigative team has documented that nearly 10% of females in our target population are at risk in 7th grade and more than half by spring of 10th grade. Although alcohol use is more comparable with national figures, the combination of early alcohol and risky behavior is troubling, yet under-addressed by existing interventions. This randomized experiment will test a theoretically-derived and empirically-grounded "selective" intervention that specifically targets high-risk young adolescent females. The intervention builds upon a promising strategy for influencing adolescents: parent education. Three parenting mechanisms (PM) shown to influence adolescent risk behavior will be targeted: parental monitoring (P-PM), household rule setting (HR-PM), and communication (C-PM).

CANCER

TITLE: **Clinical Trials of Two Human Papillomavirus (HPV)-like Particle Vaccines** **NCI**
P.I.: **Douglas R. Lowy, MD**
INSTITUTION: **NCI, Bethesda, MD**
GRANT NO.: **1 Z01 BC09052**
KEYWORDS: **human papillomavirus, cervical cancer, vaccine development, STDs**
TYPE STUDY: **Clinical**
AMOUNT: **$600,000**

Worldwide, Cervical cancer annually accounts for over 400,000 incident cases, resulting in approximately 200,000 deaths. The impact of this disease is particularly devastating in developing countries where women are medically underserved and access to Pap smear screening is not readily available. To address this major issue in women's health, NCI and the Office for Research on Women's Health, is launching a large, double blinded, randomized clinical trial to evaluate whether vaccination with the bivalent HPV16/18 VLP-based vaccine developed at NCI and manufactured by GlaxoSmithKline will protect against the development of histopathologically confirmed, incident CIN2+ (cervical intraepithelial lesion grades 2/3), adenocarcinoma in situ, and invasive cervical cancer. This pivotal efficacy trial will be conducted in Costa Rica, an area with high rates of cervical cancer. Approximately 20,000 young women will be invited to join the trial, with 12,000-15,000 women expected to participate. Eligible women who agree to participate will be administered 3 doses of either a control vaccine or the HPV 16/18 VLP vaccine over a six month period and will be followed for four years. The trial is expected to extend through 2009. It is hoped that results from this effort will support licensure of a prophylactic HPV16/18 vaccine that protects against the development of HPV16/18 induced cervical cancer and its precursors.

TITLE: **RCT of plant-based diet in breast cancer recurrence** **NCI**
P.I.: **John P. Pierce, PhD**
INSTITUTION: **The Regents of the University of California, San Diego, CA**
GRANT NO.: **1 R01 CA 069375-06**

KEYWORDS: **carotenoid-rich vegetable diet, prevention, dietary intervention, biological mechanisms**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

This proposal is to complete and close out the Women's Healthy Eating and Living (WHEL) Study, an ongoing multi-center (7 clinical sites) randomized controlled trial examining the hypothesis that a plant-based dietary pattern affects additional breast cancer events and mortality. The study has enrolled 3109 women who were within 4 years of a primary diagnosis of Stage I (≥ 1 cm), Stage II and Stage IIIA breast cancer and who had completed standard therapy. The study uses a behavior-change- theory-driven comprehensive and tailored intervention to motivate intervention group participants to substantially increase daily consumption of vegetables fruit and fiber while reducing fat in a dietary pattern that should result in a large increase in circulating carotenoids. The study includes regular measures of self-reported dietary and supplement intake, personal habits, quality of life and health status along with recording of physical measures and the collection and storage of samples of plasma, serum, buffy coat and washed red blood cells. 10 tissue slides are stored from the original tumor. All participants are contacted every six months for a health status assessment and medical records are reviewed for all reported cancer events as well as deaths. All women who recur are encouraged to stay in the study with a flexible schedule for assessments to reduce participant burden. At year 4 of the study,complementary and alternative medicine services are assessed. At baseline, each group reported consuming approximately 3 vegetable servings/day. At one year the reported daily vegetable/vegetable juice servings were 7.1 for the intervention vs. 3.1 for the control and, for those who had been at least 2 years in the study, daily vegetable servings were at 6.4 Intervention vs. 3.1 Control. The maintained change in circulating carotenoids is: a-carotene +89%Intervention —3% comparison; β-carotene levels +57% Intervention 0 in comparison and lutein +23% Intervention and +7% in the comparison group. The study will use an intent-to-treat analysis to assess whether the study intervention effected outcomes both for the overall study sample, as well as those under and over 55 years of age at randomization. For each analysis, four options will be identified: the dietary pattern reduced recurrence and mortality; it reduced recurrence but not mortality; it did not reduce recurrence but reduced mortality and it had no effect on either recurrence or mortality. The study will also investigate relationships between different components of the dietary pattern, circulating carotenoids and study endpoints.

CARDIOVASCULAR DISEASE

TITLE: **Genetics of Early Onset-Stroke** **NINDS**
P.I.: **Steven J. Kittner, MD**
INSTITUTION: **University of Maryland, School of Medicine, Dept. of Neurology, Baltimore, MD**
GRANT NO.: **1 R01 NS045012-01A1**
KEYWORDS: **ischemic stroke, thrombomodulin, potein C, fibrinolysis systems, endothelial protein C receptor, plasminogen activator inhibitor-1, endothelial protein C receptor polymorphisms, African-American, Caucasian**
TYPE STUDY: **Clinical**
AMOUNT: **$300,000**

The long-term objective of this application is to characterize the genetic basis for ischemic stroke susceptibility in order to develop more effective prevention and treatment strategies. Current evidence suggests that the genes encoding the thrombomodulin-protein C and fibrinolysis systems are promising candidate stroke susceptibility genes because of their pivotal importance in thrombosis regulation and response to inflammation. The researchers postulate, that: 1) novel genetic variants in the thrombomodulin, endothelial protein C receptor, and plasminogen activator inhibitor-1 genes predispose to the development of stroke, particularly infection-associated stroke and 2) endothelial protein C receptor polymorphisms are associated with large vessel stroke, while thrombomodulin polymorphisms are associated with lacunar (small vessel) stroke. To obtain a sample size adequate to test these hypotheses, we propose a population-based case-control study of ischemic stroke (1,033 cases and 1,064 controls) among young African-American and Caucasian men and women. To complement an existing sample of female cases and controls, male cases (n=600) will be recruited using a network of 59 hospitals in the Baltimore-Washington area. Age, gender, and race matched controls (n=600)will be recruited by random digit dialing. A neurologist panel will perform stroke phenotyping. Historical risk factor data and blood samples for genetic studies will be obtained at a face-to-face interview. A comprehensive molecular analysis of the coding, promotor, and intronic regions of the three candidate genes will be performed to determine if sequence variation in these loci is associated with stroke. In addition to analyses of individual polymorphisms, intragenic haplotypes will be constructed and common haplotypes tested for association with stroke. Population substructure

analysis will be used to identify and account for population stratification bias in the analyses. The proposed study will complement other associated studies of older stroke patients and will be a continuing resource for understanding the genetic basis of stroke risk.

TITLE: **Altered Glucose and Lipid Metabolism In Obesity and CVD** **NHLBI**
P.I.: **Maureen J. Charron**
INSTITUTION: **Albert Einstein College of Medicine, Bronx, NY**
GRANT NO.: **1 R01 HL073163-01**
KEYWORDS: **metabolic disturbances, cardiovascular disease, insulin-stimulated GLUT4 transporter**
TYPE STUDY: **Basic**
AMOUNT: **$200,000**

This application proposes studies in mice to examine metabolic disturbances and cardiovascular disease in animals that express only one functional copy of the insulin-stimulated GLUT4 transporter (a mouse model of type 2 diabetes), and hypothesizes that metabolic and cardiovascular changes may be mediated by altered expression of adipocyte-specific Acrp30 (adiponectin). The specific objectives of this proposal are 1) to understand the molecular mechanisms underlying the metabolic changes that specifically affect male, but not female GLUT4+/- mice or GLUT4+/- mice that over-express GLUT4 in muscle; 2) to test genetically whether correction of Acrp30 downregulation in male GLUT4+/- will prevent or delay the onset of insulin resistance, visceral obesity and/or cardiovascular disease (CVD). Additionally, they will test whether complete lack of circulating Acrp30 in Acrp30-/-mice will provoke metabolic disturbance in female GLUT4+/- and exacerbate disease in male GLUT4+/- mice; 3) to assess the effects of high fat diet-induced changes in disease progression in GLUT4+/- compared to C57BL/6J mice; and 4) to determine transcripitional and translational changes in white adipose tissue (WAT) associated with visceral obesity and alterations following treatment with thiazolidinedione insulin sensitizers in hope of identifying novel therapeutic targets. Combined, this approach will provide a comprehensive systematic characterization of a mouse model of obesity associated CVD derived from early impairment of insulin mediated glucose flux into WAT, and directly address for the first time whether alterations in Acrp30 influence disease progression.

CRANIOFACIAL

TITLE: **Brief Focused Treatment for TMD: Mechanisms of Action** **NIDCR**
P.I.: **Mark D. Litt**
INSTITUTION: **University of Connecticut, School of Medicine, CT**
GRANT NO.: **1 R01 DE014607-01A1**
KEYWORDS: **temporomandibular disorders (TMD), pain, copying, mood, cortisol, cytokines**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

TMD is a widespread chronic pain condition. Successful psychosocial treatments for TMD have been developed, but the mechanisms by which these treatments achieve their effects are not well known. The goal of this project is to evaluate the possible mechanisms responsible for treatment gains in TMD treatment. Men and women (N--106) with complaints of chronic facial pain for at least 3 months' duration will be recruited from the University Dental Clinics and from the community via advertisements and randomly assigned to either a Standard Conservative Treatment (STD) employing an intraoral splint plus anti-inflammatory agents, or to a Standard Treatment + Cognitive-Behavioral Treatment Program (STD+CBT), that will include standard treatment but also focus on changing self-efficacy and decreasing catastrophization. Both treatments will entail 6 clinic visits. Dispositional and situational variables derived from a comprehensive model of pain coping will be measured before and after treatment. The situational variables, including coping responses, mood states, situational appraisals and self-efficacy, will be measured in an experience sampling paradigm four times daily using a hand-held computer. This will be done to minimize retrospective biases that may have hampered earlier studies of treatment process. Dependent variables will be self-report measures of distress, pain, and interference with activities, as well as blood plasma levels of cortisol and selected cytokines, measured at the end of the 6-week treatment period, and at follow-up points thereafter up to a 12-month follow-up. It is expected that the STD+CBT treatment will result in measurable changes in constructs such as self-efficacy and catastrophization, and that these changes will be related to improved outcomes compared to the STD controls. It is also expected that outcome differences between groups will be associated with changes in inflammatory mediators (cytokine levels). Finally, it is suggested that changes in

situational treatment process variables will be associated with changes in cytokine levels. The results may indicate the true active mechanisms of successful TMD treatment. If these mechanisms can be successfully identified it would have important implications for the development of more effective treatment programs.

TITLE: **Genotype and TMJD Vulnerability Types** **NIDCR**
P.I.: **Christian S. Stohler**
INSTITUTION: **University of Michigan at Ann Arbor, MI**
GRANT NO.: **1 R01 DE 015396-01**
KEYWORDS: **temporomandibular, pathogenesis, candidate gene, estrogen**
TYPE STUDY: **Basic and Clinical**
AMOUNT: **$100,000**

Temporomandibular joint disorders represent a major health problem and persistent TMJD pain is difficult to manage successfully. The majority of cases involve muscle. Laboratory evaluations proposed in this application permit new and critically important insight into the pathogenesis of persistent TMJD pain. The use of approaches from several different scientific disciplines, such as genetics, endocrinology, neurobiology of pain and imaging of peripheral tissue are proposed to probe and understand the system response of human subjects with respect to disease characteristics of TMJD and for which measurement opportunities in animals are limited. Based on supporting data, this research aims to provide new knowledge regarding the significance of a candidate gene that appears to exert a strong effect on critical hallmark features of persistent TMJD muscle pain. Because sensitivity to pain and inhibition of pain are traits of considerable variability, the effect of this gene on subject's response characteristics to experimentally induced jaw muscle pain will be studied. Furthermore, because women in their reproductive age make up the majority of patients treated with TMJD, the proposed research also focuses on whether estrogen significantly alters the system's response in subjects of a particular genotype.

TITLE: **Neuronal Plasticity Related To TMJ and Fibromyalgia** **NIDCR**
P.I.: **Dean A. Dessem**
INSTITUTION: **University of Maryland, Baltimore, MD**
GRANT NO.: **1 R01 DE 015386-01**
KEYWORDS: **temporomandibular, fibromyalgia, neurons, musculoskeletal, gender**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

The long term objective of this project is to elucidate the role of craniofacial primary afferent neurons in musculoskeletal disorders such as temporomandibular disorders and fibromyalgia (FM) using animal models. Two hypotheses are proposed: Hypothesis 1) Masticatory muscle inflammation increases the number of trigeminal ganglion (TG) muscle afferent neurons that express: substance P (SP), calcitonin gene-related peptide (CGRP), neurokinin-1 receptor (NK-lr) and CGRP receptor (CGRPr). This increase involves a phenotypic switch in which muscle primary afferent neurons that do not normally express neuropeptides express SP, CGRP, NK-lr, CGRPr following inflammation. It is proposed that this change contributes to muscle allodynia and hyperalgesia and can be modulated by pharmacologic manipulations thus providing insight into therapeutics for deep tissue pain. This hypothesis will be tested by quantifying the distribution of TG muscle afferent somata and peripheral axons containing SP, CGRP, NK-lr, CGRPr in three groups: i) control, ii) inflamed muscle, iii) inflamed muscle with intervention (anti-nerve growth factor, NK-lr and CGRPr antagonists). This hypothesis will also be tested by determining the levels of CGRP, SP and gene expression for CGRP, SP within the TG using radioimmunoassay and reverse transcriptase polymerase chain reaction. Hypothesis 2) SP and CGRP alter the functional properties of TG muscle afferent neurons in part by evoking spontaneous activity and increasing their excitability. It is predicted that substantially more group II, III and IV TG muscle afferent neurons will be modulated by SP and CGRP following inflammation and that these functional alterations can be modulated pharmacologically. This hypothesis will be tested by characterizing the a) spontaneous and evoked activity and b) active and passive membrane properties of TG muscle afferent neurons prior to muscle inflammation, following muscle inflammation, and following muscle inflammation combined with pharmacological intervention. This will be achieved using intracellular electrophysiological recordings from masseter muscle afferent neurons in a trigeminal ganglion-masseter nerve in vitro preparation. Determination of soma size, axon diameter, and SP, CGRP immunoreactivity for physiologically characterized TG muscle afferent neurons will also test

Hypothesis 1. Because a gender difference is reported for TMD and FM, both hypotheses will be tested in males, estrous females and diestrous females.

TITLE: **Estrogen Regulation of Inflammation Related to TMJ** **NIDCR**
P.I.: **Phillip R. Kramer**
INSTITUTION: **Texas A&M University Health Science Center, TX**
GRANT NO.: **1 R01 DE 015372-01**
KEYWORDS: **gene, macrophage, rheumatoid factor, autoimmune**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

The long-range goal of this research is to identify and characterize genes through which steroidal hormones affect the onset and/or severity of human disease. The objective is to determine a gene in macrophages affected by estrogen withdrawal, as seen post-partum and at menopause, that functions in immune processes. The central hypothesis is that changes in estrogen concentrations directly regulate IgG Fc gamma receptor III-A (CD16a) expression resulting in a modulation of pro-inflammatory cytokine production and/or release from macrophages upon receptor binding. This hypothesis is based on recent findings in vitro that 1) the level of Fc gamma RIIIA transcript increased in macrophage-like THP-1 cells and in primary, peripheral blood macrophages after estrogen removal and 2) that the observed increase was dependent on transcription. The hypothesis also includes data from another lab that binding of Fc gamma RIIIA by anti-Fc gamma RIII monoclonal antibodies stimulates macrophage TNF-alpha and IL-1 alpha release. Fc gamma RIIIA is a receptor that selectively binds IgG molecules, an important rheumatoid factor (RF) in auto-immune disease. Collectively, these data suggest that RF binding of this receptor stimulates cytokine release in rheumatoid arthritis and associated temporomandibular joint disorders (TMJD). To test the central hypothesis, aim one will characterize macrophage cytokine production and release from stimulated macrophages after modulating Fc gamma RIIIA expression. TNF-alpha and IL-1 alpha will be measured after changing Fc gamma RIIIA expression levels using various estrogen and Fc gamma RIIIA antisense treatments. Aim two will focus on the mechanism inducing cytokine production and/or release upon Fc gamma RIIIA crosslinking. Signal transduction pathways and activated transcription factors will be identified as well as regulatory TNF-alpha and IL-1 alpha promoter sequences. Aim three will address the mechanism by which estrogen regulates Fc gamma RIIIA gene transcription in macrophages. The function of estrogen receptors ER alpha and/or ER beta will be directly addressed pharmacologically (e.g., antiestrogen) and through mutation studies of the Fc gamma RIIIA promoter.

TITLE: **International Research Registry Network for Sjogren's Syndrome** **NIDCR**
P.I.: **John Greenspan, Troy Daniels**
INSTITUTION: **University of California, San Francisco, CA**
GRANT NO.: **N01 DE32636**
KEYWORDS: **research registry, Sjogren's syndrome, international**
TYPE STUDY: **Clinical**
AMOUNT: **$200,000**

This contract will support the creation of an International Research Registry Network for Sjögren's syndrome. As part of this registry, key elements will include: 1. to establish a set of standardized diagnostic criteria for the recruitment of Sjögren's syndrome patients; and 2. to collect, process, store, ship and analyze clinical information and biological specimens from patients and families with Sjögren's syndrome; and 3. to disseminate to researchers clinical information and biological specimens from patients with Sjögren's syndrome.

DIABETES

TITLE: **Diabetes Prevention Program Outcomes Study(DPPOS)** **NIDDK**
P.I.: **Sarah Fowler, PhD**
INSTITUTION: **George Washington University**
GRANT NO.: **5 U01 DK048489-09**
KEYWORDS: **diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, prevention**
TYPE STUDY: **Clinical**
AMOUNT: **$300,000**

While the primary goal of the Diabetes Prevention Program (DPP) was to prevent the development of diabetes, an important secondary goal was to decrease the rate of cardiovascular disease and its risk factors. These clinically important outcomes were considered as secondary during the DPP due to a lack of sufficient power in the time allotted to the study to detect potential differences between the treatment groups (ongoing analyses of the DPP data suggest that there are significant differences between the groups with regard to some CVD risk factors). Following the early conclusion of the DPP, the lifestyle and metformin arms were kept on their study interventions. Due to the marked effect of lifestyle in preventing or delaying type 2 diabetes, placebo and metformin participants were also offered the same lifestyle 16 session curriculum provided to the intensive lifestyle group during what was named the 'bridge period.' The DPP cohort being followed in the DPPOS, is the largest study population with pre-diabetes, and the only population with Type 2 diabetes studied from time of onset. The study cohort will provide insights regarding the clinical course of these metabolic disorders and will provide information on the persistence of the prevention or delay of type 2 diabetes. In addition, the DPP is the longest follow-up study of sustained weight loss ever conducted. Of major interest is the outcome of continued lifestyle and long term weight loss, and metformin intervention in the gender specific and minority sub-groups during the DPPOS

GASTROENTEROLOGY

TITLE: **Biofeedback for Fecal Incontinence and Constipation** **NIDDK**
P.I.: **William E. Whitehead, PhD**
INSTITUTION: **University of North Carolina, Chapel Hill, NC**
GRANT NO.: **3 R01 DK57048-03**
KEYWORDS: **biofeedback, fecal incontinence, constipation, pelvic floor dyssynergia, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$75,000**

Among constipation patients, half are reported to have pelvic floor dyssynergia, a condition marked by an inability to relax pelvis floor muscles during evacuation. Biofeedback has been recommended for the treatment of both conditions because uncontrolled studies over the past 10-25 years suggest that these treatments are as effective as medical or surgical management and involve no risk. However, placebo-controlled trials are lacking in this area. The aims of the proposed research are: 1) to compare biofeedback to alternative therapies for which patients have a similar expectation of benefit; 2) to identify which patients are most likely to benefit; and 3) to assess the impact of treatment on quality of life. Two long-term, prospective, single-blind studies will be conducted. Study I will compare biofeedback for the treatment of fecal incontinence to a standard therapy, Kegel exercises. Study II will compare biofeedback for pelvic floor dyssynergia to a skeletal muscle relaxant drug (diazepam) and to placebo medication. These studies will help to establish the efficacy of biofeedback on the treatment of defecatory disorders.

TITLE: **Identification and Characterization of SDK Channels** **NIDDK**
P.I.: **Sang D. Koh, MD, PhD**
INSTITUTION: **University of Nevada, School of Medicine, Reno, NV**
GRANT NO.: **1 R01 DK060687-01A2**
KEYWORDS: **tunica muscularis, gastrointestinal tract, smooth muscle, digestion, myocytes, myogenic response**
TYPE STUDY: **Basic**
AMOUNT: **$175,000**

The tunica muscularis of the gastrointestinal (GI) tract contains continuous sheets of smooth muscle cells. The diameters of GI organs change dramatically during digestion as food and chyme pass through the GI lumen. As a result of the distension and contractions that occur, individual myocytes experience dramatic changes in length, which may affect membrane potential, excitability and responsiveness to agonist stimulation. Although many investigators believe that smooth muscles exhibit stretch-dependent contraction, stretch of colonic muscles does not initiate an obvious contractile response. Therefore, contraction does not appear to be a basic response to stretch in many GI organs. This may be a unique feature of GI smooth muscle that allows for

volume expansion necessary for reservoir function . Thus it is likely that cells of GI smooth muscles include ionic conductances that stabilize membrane potential and limit excitability during distension of the bowel wall. This may be an important aspect of the 'myogenic response" to stretch that facilitates the reservoir function of regions of the GI tract and prevents interference in the coordination of segmental and/or peristaltic movement provided by the enteric nervous system. Such a mechanism likely involves stretch-dependent K+ (SDK) channels expressed by GI smooth muscle cells and interstitial cells of Cajal (ICC). If SDK channels are expressed in smooth muscle and ICC, they would provide a negative-feed back pathway (stabilizing the membrane potential) by generating outward current in response to stretch. The following specific aims will be addressed: Aim 1) What is the distribution, biophysical and pharmacological properties of SD channels in smooth muscle and ICC? Aim 2) What mechanisms modulate SDK channels? Aim 3) What is the physiological role of SDK channels in regulating membrane potential and excitability? Aim 4) What is the molecular species responsible for SDK channels in GI muscles? This study will demonstrate an important new class of channels in GI smooth muscles that may participate in the regulation of membrane potential and excitability and may mediate some of the response of these tissues to neurotransmitters.

TITLE: **Improving IBS Outcomes** **NINR**
P.I.: **Margaret M. Heitkemper, PhD**
INSTITUTION: **University of Washington, Seattle, WA**
GRANT NO.: **3 R01 NR04142-06S1**
KEYWORDS: **irritable bowel syndrome (IBS), polymorphisms, gender, serotonin**
TYPE STUDY: **Translational**
AMOUNT: **$100,000**

In the United States, it is estimated that 10-20% of the population experience symptoms compatible with a diagnosis of irritable bowel syndrome (IBS). IBS is a functional condition characterized by change in bowel patterns, (e.g. constipation, diarrhea), interfering with functional activities and increasing health care utilization. Current recommended therapies include diet manipulation, self-management, psychotherapy, and motility and pain modulation via pharmacological therapy. The primary aim of this research is to compare the distribution of SERT polymorphisms across predominate bowel pattern subgroups and gender in people with IBS. It is hypothesized that the distribution of SERT polymorphisms (5'-flanking promoter region [5-HTTLPR] and in exon2 [VNTR] will differ across predominate bowel pattern subgroups and the distribution of SERT polymorphisms will differ by gender. Exploratory aims of this study include: 1) Evaluate the relationships of SERT polymorphisms to symptom experiences and psychological profile ; 2) Test whether the degree of improvement in response to the CSM therapy differs by SERT polymorphism; and 3) Evaluate the relationship of platelet rich plasma 5-HT levels to SERT polymorphisms, predominate bowel pattern. This study will provide information on the potential role of serotonin processing in IBS as well as potential gender and bowel symptom predominance. Such results may ultimately be used to tailor therapies for this common health problem.

GENITOURINARY

TITLE: **Regulation of Renal Xenobiotic Transport by Estrogens** **NIDDK**
P.I.: **Carlotta Groves, DVM, PhD**
INSTITUTION: **University of Arizona, Tucson, AZ**
GRANT NO.: **1 R01 DK62097-1A1**
KEYWORDS: **gender differences, estrogens, environmental agents, nephrotoxicity**
TYPE STUDY: **Basic**
AMOUNT: **$186,345**

Secretion of substrates from the blood into the urine by the renal proximal tubule plays an essential role for removal of potentially hazardous xenobiotics from the systemic circulation and out of the body. Many such xenobiotics are organic anion substrates and may, therefore, be cleared via interaction with the basolateral membrane organic anion transport (OAT) pathway. Recently, attention has been given to the study of cellular regulation of the OAT pathways, particularly OAT1- and OAT3-mediated transport. Knowledge of the regulation of OAT1 and OAT3 has much practical significance since factors that either suppress or prevent organic anion transport may increase exposure to dangerous xenobiotics to produce or at least exacerbate toxicity, whereas factors

that stimulate organic anion secretion may be employed to enhance xenobiotic excretion to reduce environmental exposure. Studies have demonstrated that regulation by various hormonal systems modulates the expression and physiological function of various transport processes in the proximal tubule of the kidney. The sex steroid hormones testosterone and estrogen may serve to upregulate or downregulate, respectively, renal organic anion transport and may account for sex-related differences in xenobiotic accumulation, excretion and response to toxicity. The decrease in organic anion transport associated with estrogen was reported in several studies to be related to an increased susceptibility to toxicity. In spite of the manifestation of gender-related differences in xenobiotic transport, little is understood about sex steroid hormone modulation of transport, particularly estrogens. Also, the presence of various endocrine disrupting chemicals, environmental chemicals that possess sex steroid hormone and particularly estrogenic activity (i.e., xenoestrogens)may, through their estrogenic effects, downregulate various transporters involved in renal accumulation and excretion of xenobiotics. To this end the proposal will address the following overall objectives: 1) To characterize the effect of endogenous estrogen, 17b-estradiol and the environmental xenoestrogens such as diethylstilbestrol (DES) and genistein on renal proximal tubule organic anion transport (OAT1 and OAT3) and 2) to determine the mechanisms by which these estrogens mediate their regulatory control of transport.

TITLE: **Patient-Centered Goals for Pelvic Floor Dysfunction** **NICHD**
P.I.: **Kathie L. Hullfish, MD**
INSTITUTION: **University of Virginia, Charlottesville, VA**
GRANT NO.: **1 R03 HD42754-01A1**
KEYWORDS: **pelvic floor dysfunction, urinary incontinence, pelvic organ prolapse, fecal incontinence, treatment interventions, patient goals and outcomes**
TYPE STUDY: **Clinical**
AMOUNT: **$74,000**

Outcomes of pelvic floor dysfunction (PFD) treatments remain poorly measured, precluding scientific conclusions about their effectiveness. Currently available surgical and non-surgical therapies for these common conditions have not been rigorously scrutinized with regard to subsequent impact on individual quality of life or morbidity reduction. Although patient subjective opinions concerning surgical results are important, they are subject to interpretative difficulties. Several PFD-specific quality of life scales have been developed and validated. These measures, however, do not assess the specific treatment goals of individual patients, and therefore are limited when incorporating patient-centered goals into therapy. This prospective cohort study will classify and compare patient subjective goals and outcomes with respect to treatment interventions for disorders of the female pelvic floor. Preliminary investigation indicates an ample patient base for recruiting participants, and feasibility of recruitment and follow-up. 405 patients with PFD will be enrolled and followed (270 in the conservative management arm and 135 in the surgical management arm). The primary outcome will be self-reported achievement of patient-derived goals. Data will be collected from patient interviews, questionnaires, physical examination, and laboratory testing. Patient-derived goals will be defined at baseline and followed over 12 months to determine the degree to which patient-derived goals are reported to have been met. Goal achievement among surgical patients will be compared to that among non-surgically managed patients. The study will provide the first estimates of goals and goal attainment in PFD, and determine whether goal attainment in surgically and non-surgically managed PFD is likely to differ. In addition, objective outcome measures and established quality of life instruments will be compared and contrasted with the perception of goal achievement. While quality of life measures allow consistent assessment of general PFD outcomes, assessing patient-centered goals allows individually tailored care of women with pelvic floor dysfunction. Patient goals, combined with clinical and QOL measures, may be used to provide comprehensive, multidisciplinary, patient-centered approaches to prevention, management, treatment, and rehabilitation.

TITLE: **Weight Reduction for Incontinence Network (WIN)** **NIDDK**
P.I.: **Deborah G. Grady, MD**
INSTITUTION: **University of California, San Francisco, CA**
GRANT NO.: **1 R01 DK064358-01**
KEYWORDS: **urinary incontinence, obesity, behavior, quality of life**

TYPE STUDY: **Clinical**
AMOUNT: **$250,000**

Urinary incontinence is a common problem among women that causes distress, diminished quality of life and dramatic limitations in daily functioning. Overweight women are at significantly increased risk of urinary incontinence and over 65% women with incontinence are overweight. Data from short-term, preliminary studies suggest that weight reduction may significantly reduce incontinence episodes. Thus, weight loss may present a promising new approach to urinary incontinence, one likely to produce a cascade of broader health improvements in addition to reductions in frequency of urinary incontinence. Therefore, we propose to randomize 330 overweight and obese women with urinary incontinence (165 at each of two clinical centers) to a 6-month intensive behavioral weight control program or to usual care to determine the short-term effect of weight loss on frequency of incontinence and quality of life, to identify women most likely to benefit from weight loss and to begin to explore the urodynamic mechanisms underlying incontinence improvement following weight loss.

HIV/ AIDS

TITLE: **Impact of Delivery Models in HIV Health Care** **FIC**
P.I.: **Ximena L. Burbano, MD**
INSTITUTION: **Fundacion Santa, Bogota**
GRANT NO.: **1 R01 TW006218-01A1**
KEYWORDS: **HIV/AIDS, health services research**
TYPE STUDY: **Clinical**
AMOUNT: **$20,000**

Colombia, which ranks fourth in the total number of HIV reported cases in Latin America, has designed different Delivery Health Care Models to provide coverage for HIV infected patients. The proposed health research initiative, by a new foreign investigator, will evaluate for the first time, the utilization and cost implications of different representative delivery health care models in Bogota, Colombia. Assessment of cost-effectiveness is vital not only in the area of treatment but also in regard to the use of diagnostics, provision of care, support services, and prevention strategies and programs. A multi-step evaluation of three main Delivery Health Care Models (Open Pre-Paid, EPS, Social Security) available in Bogota, will be undertaken. First, information will be obtained to determine the type of specific services available for each delivery model. Second, data obtained from 450 HIV-infected individuals (150/model) will be systematically collected and prepared for statistical analysis. In the third phase, models will be compared in terms of health services utilization, costs, cost-effectiveness and which health care model best accomplishes delivery and sustains adherence to HAART. Evaluation of service utilization will consider the impact on disease progression, as indicated by CD4 cell count and viral burden. Outcomes will be aggregated to determine the level of total services required for adequate care for each delivery model. Findings from this project should provide necessary information to help determine the optimal use of HIV delivery services and help develop public health strategies to achieve equity in health services, for HIV infected people in Colombia, and possibly other countries in Latin America.

TITLE: **Interventions to reduce HIV1 incidence after Delivery** **FIC**
P.I.: **James N. Kiarie, MD**
INSTITUTION: **University of Nairobi, Kenya**
GRANT NO.: **1 R01 TW006640-01**
KEYWORDS: **HIV/AIDS, postpartum, counseling**
TYPE STUDY: **Clinical**
AMOUNT: **$20,000**

Women in sub-Saharan Africa face a high risk of HIV-1 acquisition during the first year postpartum which can be reduced by antenatal voluntary counseling and testing (VCT) and using female controlled HIV-1 prevention methods. In preventing heterosexual HIV-1transmission, the success of female controlled methods such as female condoms, the vaginal diaphragm, and vaginal microbicides depends on their use by women at a high risk of HIV-1 infection. In studies of prevention of mother-to-child transmission little attention has been paid to women identified as HIV-1 negative and their risk of becoming infected after delivery. An understanding of the factors that influence HIV-1 incidence among uninfected mothers, and which female controlled prevention methods are most acceptable to them, is crucial for preventing HIV-1 acquisition in these women, and hence, preventing additional mother-to-child transmission of HIV-1 in future

pregnancies. This study proposes to determine the potential effectiveness of female controlled HIV-1 prevention methods, and the impact of participation in perinatal HIV-1 prevention programs on HIV-1 incidence in the first year after delivery (assessed using a detuned ELISA at 9 to 12 months postpartum) in three sites in Kenya. The specific aims of the study are to: 1. Determine the correlates of incident HIV-1 infection among Kenyan women in the first year postpartum; 2. Compare the incidence of HIV-1 infection among women who have participated in perinatal HIV-1 prevention programs to the incidence among those who have not participated in these programs; 3. Determine women's knowledge, attitudes, and willingness to use vaginal microbicides, the female diaphragm, and female condoms; 4. Estimate the effectiveness of the various HIV-1 prevention methods based on theoretical efficacy, the number and HIV-1 infection risk of women willing to utilize these methods. This study will provide important information on how to increase the effectiveness of female controlled HIV-1 prevention methods by targeting women at a high risk of acquiring HIV-1 infection. The study will also identify ways to increase the impact of antenatal VCT in reducing HIV-1 incidence.

TITLE: **Family Therapy Mechanisms in HIV+ Women in Drug Recovery** **NIDA**
P.I.: **Victoria Mitrani, PhD**
INSTITUTION: **University of Miami, Coral Gables, FL**
GRANT NO.: **1 R01 DA016543-01A1**
KEYWORDS: **HIV infection, addiction, treatment adherence, structural ecosystems therapy, family functioning**
TYPE STUDY: **Clinical**
AMOUNT: **$335,609**

This application proposes to investigate the family mechanisms by which Structural Ecosystems Therapy (SET) has its impact on HIV+ women in drug recovery. This proposed study is a companion to NIDA Grant DA15004 (SETA Protocol), which investigates the efficacy of SET in a clinical trial with HIV+ women who are in drug recovery. In the SETA Protocol, 176 women are randomly assigned to either SET or an HIV health group. The interventions last 4 months. SET works to transform the family system to reinforce sobriety, increase adherence with HIV medical care, and decrease sexual transmission risk behaviors in the target woman. The SETA Protocol only assesses the effect of SET on the recovering woman, not her family. Because SET targets changing the whole family as a means of helping the woman, we hypothesize that effects on the family as a whole (family functioning) and on individual family members will help to explain the woman's outcomes. The proposed study will enroll the women in the SETA Protocol and their families. A total of 538 family members are anticipated. Families are assessed at 4-month intervals for a period of 12 months. SET is hypothesized to affect family functioning (measured by self-report and observational methods). Changes in family functioning are hypothesized to affect the woman's drug abuse, HIV medication adherence and HIV risk behaviors as well as the individual functioning of her family members (psychological distress, drug use and parent report of problem behaviors in children). The hypotheses will be tested using Latent Growth Curve Modeling. Understanding these mechanisms will facilitate the development of the next generation of family-based interventions for HIV+ women in drug recovery.

TITLE: **Drugs, Gender, and Healthcare Use Among HIV+ Homeless** **NIDA**
P.I.: **Elise Riley, PhD**
INSTITUTION: **Regents of the University of California, San Francisco, CA**
GRANT NO.: **1 R01 DA015605-01A1**
KEYWORDS: **women, substance abuse, mental health, HIV/ AIDS, health services**
TYPE STUDY: **Clinical**
AMOUNT: **$200,000**

This is a study of the impact of gender on health status and health care utilization among HIV-infected homeless individuals. The specific aims of the study are as follows: 1) to examine health care utilization in the cohort (i.e., primary care, drug treatment, and mental health services) and to determine differences in the patterns of health care utilization between HIV-infected marginally housed women and men at baseline and over a three-year follow-up period: 2) to examine health outcomes in the cohort (physical and mental) and to determine the extent to which HIV-infected homeless women experience differences in health outcomes from men at baseline and over a three-year follow-up period; and 3) to determine predisposing, enabling, and need factors

influencing the differences that women experience in health care utilization and health status. To achieve these specific aims, the following activities will be accomplished: (1) recruit an additional 49 women into the REACH cohort (the parent study), in order to increase statistical power for gender comparisons; (2) add detailed drug use, women's health, victimization, subsistence needs, and health care utilization variables to the existing REACH questionnaire; (3) implement a new SCID diagnostic assessment, in addition to the current REACH assessment, to thoroughly assess mental health; (4) employ the use of electronic health service databases to conduct new validity studies; and (5) conduct analyses specific to these new areas of interest. Achieving the proposed specific aims will only be possible with the addition of these new activities that will ultimately yield a new class of analyses. A detailed study of the impact and interactions of drug use, mental illness, health service use, competing needs like access to food, and health status will lead to a better understanding of ongoing mortality among HIV-infected marginally housed individuals, and create the foundation for more effective health interventions in a variety of settings.

TITLE: **Aids International Training and Research Program (AITRP)** **FIC**
P.I.: **Arthur L. Reingold, MD**
INSTITUTION: **University of California, School of Public Health, Berkeley, CA**
GRANT NO.: **3 D43 TW000003-16S3**
KEYWORDS: **training, virology, HIV/AIDS**
TYPE STUDY: **Clinical**
AMOUNT: **$50, 000**

The University of California, San Francisco-Gladstone Institute of Virology & Immunology Center for AIDS Research (UCSF-G1VI CFAR) will collaborate with the University of California, Berkeley's (UCB) Fogarty International AIDS Training Program (AITRP) providing support for competitive training grants. Training grants will be led by CFAR members in collaboration with in-country collaborations in five resource-limited settings selected for the scale and stability of on-going international HIV research. Training will focus on scientists from countries and projects integral to the UCB/UCSF AITRP. Training will be provided in country or in San Francisco and will take advantage of CFAR member expertise and CFAR Scientific Core capabilities. Training projects will be selected in a competitive mentored process after a publicly announced request for training proposals. Letters of intent responsive to the UCSF-GIVI focus on enhancing cross disciplinary translational research will be invited to submit full but brief proposal linking training needs in country with ongoing research projects. Proposals will be reviewed by an expert peer panel with final funding decisions made by the UCSF-G1VI CFAR Co-Directors. Effectiveness of training will be monitored and assessed by written progress reports and evidence of subsequent research grant funding and publications. To accomplish this goal, the following aims will be addressed: 1.) Evaluate the training needs at each of the five CFAR international sites; 2.) Support investigators from one or more priority sites in training at the UCSF-GIVI CFAR, and /or; 3.) Support UCSF-GIVI investigators to provide training at one or more priority sites(s); 4) Provide access to UCSF-GIVI CFAR' core laboratories and other resources for UCB/UCSF AITRP priority site investigators in pilot research projects; 5.) Monitor and evaluate the success of research training support at priority sites as evidenced by important research grants, publications, and/or findings.

TITLE: **Scale –up of Community –based HIV Prevention and Care** **FIC**
P.I.: **Warren D. Johnson, MD**
INSTITUTION: **Well Medical College of Cornell University, Dept. of Medicine, New York, NY**
GRANT NO.: **3 D43 TW000018-16S5**
KEYWORDS: **infectious diseases, epidemiology, biosocial, HIV/AIDS, treatment and prevention**
TYPE STUDY: **Clinical**
AMOUNT: **$50, 000**

This proposal requests support for the Harvard University Program in Infectious Disease and Social Change/ Partners in Health/ Zanmi Lasante to continue training Haitian scientists in the performance of biomedical, epidemiological and biosocial research in the programmatic implementation of HIV prevention and treatment and the care of individual patients with HIV in rural Haiti. The program is based at Clinique Bon Saveur in Change, Haiti, with responsibility for the provision of healthcare services for the population of the Central Plateau. The principal investigator is Paul Farmer, MD, PhD, who is based at Harvard Medical School in the Program in

Infectious Disease and Social Change. The training team has many years of experience in HIV prevention and treatment in rural Haiti, including the prevention of mother-to-child transmission, diagnosis and treatment of TB and sexually transmitted disease, the prevention of opportunistic infections and the use of highly active antiretroviral therapy. The principal investigator of the AITRP grant, Dr. Warren Johnson, is a long-standing supporter of the work done in Change and the Central Plateau, and this collaborative training program has been highly successful. The program will continue to emphasize long-term training and advanced research training in Haiti. Because HIV does not exist as a separate entity, the approach at PIH/ZL is to integrate the prevention and treatment of HIV with the most vulnerable and high prevalence groups that are seen at Clinique Bon Saveur. HIV-related services include: 1.) HIV prevention and treatment, including expansion of access to voluntary counseling and testing (VCT); 2) the screening and treatment of STIs; 3.) the prevention of mother-to-child transmission; and 4.) TB case detection, treatment and VCT (approximately 50% of HIV patients in the central plateau present with TB). These four activities are referred to by PIH/ZL as the "four pillars" of HIV control. The overall program goal of this grant is to provide training that will increase local capacity to perform research on service integration, diagnosis and treatment of HIV in central Haiti within these four pillars of HIV control. Long-term benefits will include the increases in research capacity for future HIV related research activities in Haiti.

TITLE: **Aids International Training and Research Program (AITRP)** **FIC**
P.I.: **King K. Holmes, MD, PhD**
INSTITUTION: **University of Washington, College of Medicine, Seattle, WA**
GRANT NO.: **2 D43 TW000007-16**
KEYWORDS: **HIV/AIDS, international, prevention, treatment, immunology**
TYPE STUDY: **Clinical**
AMOUNT: **$50,000**

This program proposes to develop a fifth International AIDS Research and Training Program (IARTP) site in New Delhi at the All India Institute of Medical Sciences (AIIMS) to address the growing HIV epidemic in India. Other target countries have been Kenya, Peru, Mozambique and Thailand. The University of Washington (UW) IARTP selected AIIMS as the site for program expansion for several reasons. First, AIIMS is a premier institution for biomedical research and training in India, and successful collaborative research is already being performed between scientists at the UW (Uma Malhotra and Julie McElrath) and AIIMS (Pradeep Seth and Madhu Vajpayee) within the framework of an existing longitudinal cohort of HIV-1 infected subjects at AIIMS. Second, UW International Training and Research in Emerging Infectious Diseases (ITREID) has a site in New Delhi and the two programs will collaborate in their research and training efforts in the region. The IARTP program direction and the core/resource faculty will be identical to that described for the parent program. The overall goal of this proposal is to develop a center for excellence in HIV-1 research in India with independent and sustainable research capacities in the prevention and control of HIV. A number of training needs and research priorities have been identified and include: a) Strengthening of the infrastructure for field research through training and capacity building in the area, b) Development of the site for international research trials to assess prevention and treatment regiments through training in clinical research, c) Strengthening the immunology research program through training of laboratory scientists in state-of-the-art-immunology assays. The site will emphasize training in the Epidemiology Track and the Laboratory Track and will focus on long-term and medium-term training. Recruitment of scientists into the Laboratory Track will occur in the Department of Microbiology. Recruitment efforts for trainees interested in the Epidemiology Track will take place in the Department of Community Medicine in collaboration with the Head of the AIDS Education and Training Program in New Delhi. Collaborative research and training during the first year will emphasize : a) Seroprevalence and correlates of HIV-1 seropositivity in patients attending the Sexually Transmitted Infection Clinic, b) Clinical profile of HIV-1 clade C infection in India, c) Cellular immunity to HIV-1clade C viruses and diversity consideration in vaccine development, and d) HIV-1 shedding and mucosal immunity. The existing longitudinal patient cohort will provide a foundation for new cohorts and continued collaborative research. Through these endeavors in multidisciplinary research and training, it is anticipated that the program will facilitate the establishment of critical expertise in biomedical and prevention research at the AIIMS to combat the growing HIV-1 epidemic in the region.

TITLE: **HIV-1 Shedding from Female Genital Tract** **NICHD**
P.I.: **Robert W. Coombs, MD, PhD**
INSTITUTION: **University of Washington, Seattle, WA**
GRANT NO.: **5 P01 HD040540-03**
KEYWORDS: **Bacterial Vaginosis, HIV infection, Africa, microbicides**
TYPE STUDY: **Clinical**
AMOUNT: **$253,187**

Bacterial Vaginosis (BV), the most common bacterial vaginal infection in women of reproductive ages, has been linked to the prevalence and incidence of HIV infection in women in cross-sectional and prospective studies. Women in sub-Saharan Africa have the highest prevalence of BV, approximately 40-50% in Uganda and Kenya. Prior research has demonstrated that while women can have their BV treated, recurrence rates are high due to poor male genital hygiene. The proposed research will test the hypothesis that poor genital hygiene in men represents an important risk factor for BV, and that improved male genital hygiene through application of an ethanol-based microbicides, especially in uncircumcised men will reduce the frequency of BV recurrence in women.

IMMUNITY/AUTOIMMUNITY

TITLE: **Sex-based Differences in Anti-viral Immunity and SLE** **NIAID**
P.I.: **Sally R. Sarawar, PhD**
INSTITUTION: **LaJolla Institute**
GRANT NO.: **1 R21 AI51862-01**
KEYWORDS: **Lupus, autoimmunity, EBV, animal research**
TYPE STUDY: **Basic**
AMOUNT: **$50,000**

SLE is a prevalent autoimmune disease with a significantly higher ISLE is a prevalent autoimmune disease with a significantly higher incidence in females than in males. Studies on the etiology of SLE indicate that both genetic and environmental factors influence disease penetrance. A strong correlation between SLE and previous infection with Epstein Barr virus (EBV), but not with other viruses has been reported. However, some studies have failed to find evidence of a viral etiology for SLE. This may be due to the high prevalence of EBV infection, unknown host/virus parameters, and the fact that multiple genetic loci control susceptibility to SLE. New Zealand mice are susceptible to SLE, and genetic loci that control disease susceptibility in these mice has been identified. C57/BL6 congenic mouse strains carrying one or more of three of the susceptibility loci designated SLE 1, 2, and 3 have been generated. It has been shown that the presence of at least two loci is necessary for high disease penetrance. We propose that a mouse viral homologue of EBV could substitute for the presence of a second locus, and could trigger disease in mice congenic for a single locus. We also suggest that this effect may differ in males and females, due, in part, to the more vigorous response to infection in the latter. We have a mouse model of gammaherpesvirus infection, which closely resembles EBV infection in humans and, like EBV, is able to induce non-specific B cell activation and autoantibody production, but does not induce overt autoimmune disease in C57BL/6 mice. In the present study, we will determine whether there are sex-based differences in the immune response to MHV-68 infection. We will determine whether infection of susceptible mice, bearing one or more SLE susceptibility locus, with MHV-68 can induce or exacerbate autoimmune disease and whether this effect differs in male and female mice. We will also determine whether there are genes whose expression is similarly modified by the presence of disease loci and the viral infection and whether their expression correlates with the induction of autoimmune disease.

TITLE: **Predictors of Pregnancy Outcome in SLE and APS** **NIAMS**
P.I.: **Jane E. Salmon, MD**
INSTITUTION: **Hospital for Special Surgery, New York, NY**
GRANT NO.: **1 R01 AR049772-01A1**
KEYWORDS: **thrombosis, pregnancy loss, systemic lupus erythematosus, antiphospholipid antibodies, genetic polymorphisms, recurrent fetal loss, poor fetal outcome, placentas**
TYPE STUDY: **Clinical**

AMOUNT: **$900,000**

Thrombosis and pregnancy loss are common features of systemic lupus erythematosus (SLE), particularly in the presence of antiphospholipid (aPL) antibodies. The in vivo mechanisms by which aPL antibodies lead to vascular events and, specifically, to recurrent fetal loss are largely unknown. Our studies in a murine model of antiphospholipid antibody syndrome (APS) indicate that in vivo complement activation is necessary for fetal loss caused by aPL antibodies. This proposal represents a first time effort to translate novel research observations on the potential role of complement activation in the pathogenesis of aPL antibody-mediated pregnancy loss to a clinically relevant human study. No study has investigated whether complement is activated in patients with aPL-associated poor pregnancy outcomes (with or without SLE), and whether particular patterns of complement activation characterize and thus can distinguish these patients from SLE patients without aPL antibodies or fetal loss, and from patients with normal pregnancy. Preliminary data in murine APS, the availability of more accurate tests of complement activation, and the recent development of effective and specific complement inhibitors argue persuasively that the role of complement in aPL associated pregnancy complications should now be examined. Accordingly, the specific aim of the study is: To determine whether elevations of split products generated by activation of the alternative or classical complement pathways predict poor fetal outcome in patients with antiphospholipid antibodies and/or SLE. The investigators propose a prospective observational study of over 400 pregnant patients, enrolled at 6 major clinical centers, and grouped and analyzed according to the presence or absence of aPL and preexisting SLE. A core group of investigators with recognized expertise in SLE and aPL pregnancy, high-risk obstetrics, the basic biology of complement, and statistical methods in SLE studies have been assembled. Detailed medical and obstetrical information during the course of pregnancy and serial blood specimens for complement and cytokine assays will be obtained, and analyzed to identify predictors of poor fetal outcome. Placentas will be studied to characterize tissue pathology and mediators of injury. RNA, DNA, serum, and urine will be stored for studies to elucidate temporal changes in gene expression during the course of complicated and uncomplicated pregnancies and to investigate genetic polymorphisms. The investigators hypothesize that this study will provide insights into the mechanisms of complement-mediated inflammatory disorders and suggest means to prevent, arrest, or modify these conditions. Characterization of clinically applicable surrogate markers that predict poor pregnancy outcome will enable the investigators to initiate an interventional trial of complement inhibition in patients at risk for aPL antibody-associated fetal loss. The identification of such surrogate markers in aPL and SLE patients may also prove generally applicable to anticipate complications during pregnancy in disease-free women.

TITLE: **Mechanism Regulating Neutrophil Activation in Pregnancy** **NIAID**
P.I.: **Howard R. Petty, PhD**
INSTITUTION: **Wayne State University**
GRANT NO.: **1 R01 AI51789**
KEYWORDS: **autoimmunity, rheumatoid arthritis, pregnancy**
TYPE STUDY: **Translational**
AMOUNT: **$50,000**

This grant will identify and characterize differences in the innate and adaptive immune response between genders, with a specific call for interdisciplinary clinical and basic research studies that may be important in the understanding and treatment of autoimmune diseases. Neutrophils are key cells in the development of homeostatic as well as pathologic inflammatory responses. These cells play a central role in the generation of tissue damage in autoimmune diseases (i.e., rheumatoid arthritis) as well as in infectious diseases, including sepsis. The studies outlined in this application are designed to study the differences in neutrophil function in non-pregnant women, pregnant women, and men. The study offers a unique opportunity for the identification of endogenous mechanisms affecting women's health. Studying neutrophil biology during pregnancy will result in a mechanistic understanding of factors responsible for clinical improvement in certain autoimmune diseases during pregnancy and will also lead to the development of novel therapeutic approaches to control inflammation and autoimmunity.

TITLE: **Sex-based Differences in the Immune Response** **NIAID**
P.I.: **Betty Diamond, MD**

INSTITUTION: **Albert Einstein College of Medicine**
GRANT NO.: **1 R01 AI51767-01**
KEYWORDS: **autoimmunity, hormones, animal models**
TYPE STUDY: **Basic**
AMOUNT: **$50,000**

The grant will undertake studies to investigate the effects of estradiol on the negative selection of naive autoreactive B cells in BALB/c and C57B1/6 mice. The goal of the study is to understand what genes and pathways are involved in estrogen-mediated B cell survival and B cell activation, and to understand what underlies an estrogen mediated breakdown in humoral self-tolerance. The 3 Specific Aims are: Aim 1, investigates the estradiol-induced alterations in marginal zone (MZ) B cell phenotype, function, and gene expression, and finally addresses B cell repertoire selection. Aim 2, addresses the role of estradiol in the generation of MZ B cells and the role of intracellular tyrosine kinase, Pyk-2, in the phenotype formation of these cells, and focuses on how estradiol rescues MZ B cells, and some potentially autoreactive B cells, in Pyk-2 deficient mice. Aim 3 will characterize estradiol-induced signaling pathways that may alter B cell repertoire selection in BALB/c versus C 57B1/6 mice, and will identify the cell type responsible for differential responsiveness to estradiol. The work should provide informative data about the survival of cells that may initiate an autoimmune response, and the role of sexual dimorphism in this phenomenon.

TITLE: **Brain Connections** **NIAMS**
P.I.: **Michelle A. Petri, MD**
INSTITUTION: **John Hopkins University, MD**
GRANT NO.: **1 R01 AR49125**
KEYWORDS: **Systemic Lupus Erythematosus, cognitive dysfunction**
TYPE STUDY: **Clinical**
AMOUNT: **$40,000**

Neuropsychiatric manifestations of Systemic Lupus Erythematosus (NPSLE) are both common and an important source of morbidity. Of the case definitions for NPSLE syndromes that have recently been developed, cognitive dysfunction appears to be the most prevalent. Little is known about the influence of co-morbidities or ethnicity/race on disease outcomes or the underlying biological basis for this important NPSLE syndrome. Perhaps most importantly, no rational therapeutic approach for the treatment of SLE-related cognitive dysfunction currently exists and is unlikely to be developed without a better understanding of disease mechanisms. One hundred newly diagnosed patients with SLE from 10 sites will be studied for the development of cognitive dysfunction, determined using both repeatable computerized and traditional neuropsychological tests. We will evaluate the relationship of structural and functional brain imaging (using anatomic magnetic resonance imaging and resting FDG-PET), several relevant biomarkers (antiphospholipid antibodies, cytokines and adhesion molecules) and co-morbidities (race/ethnicity, depression, fibromyalgia and corticosteroid use) to cognitive dysfunction, and the impact of cognitive dysfunction on quality of life. Factors distinguishing transient or reversible versus irreversible cognitive dysfunction will be determined using a repeated measures analysis approach. The ability to study the relationship between changes in cognitive functioning and these other variables in a group of newly diagnosed SLE patients is crucial to the successful discovery of early pathologic changes that could be potentially amenable to disease-reversing therapies.

TITLE: **Identifying Genes for Neuropsychiatric Lupus** **NIAMS**
P.I.: **Nilamadhab Mishra, MD**
INSTITUTION: **Wake Forest University, NC**
GRANT NO.: **1 R21 AR49153**
KEYWORDS: **systemic lupus erythematosus, gene expression, cerebellum, hippocampus, immunopathology, autoantibody, autoimmune disorder, cytokine, histopathology, messenger RNA**
TYPE STUDY: **Basic**
AMOUNT: **$20,000**

In brief, this project will examine the genes responsible for neurologic disturbances in murine models of SLE by microarray analysis. Systemic lupus erythematosus (SLE) is a chronic, idiopathic autoimmune disease characterized by episodic flares and progression of disease, substantial morbidity and mortality. It is a multisystern rheumatic disease with a wide variety of associated

clinical neurological and psychiatric syndromes including cognitive, behavioral, affective, and/or motor manifestations that may effect up to 75 percent of SLE patients. Both morbidity and mortality remain high because of lack of understanding of the underlying mechanisms related to abnormal central nervous system (CNS) function. Although the gene responsible for neurological disturbances in SLE is not finely dissected out, preliminary studies in mouse models of lupus suggests aberrant cytokine gene expression in hippocampus and cerebellum are responsible for the neurological deficit.

TITLE: **Antibodies to NR2 in SLE** **NIAMS**
P.I.: **Betty Diamond, MD**
INSTITUTION: **Yeshiva University, NY**
GRANT NO.: **1 R01 AR49126**
KEYWORDS: **NMDA receptor, antibody, cognition disorder, systemic lupus erythematosus, glutamate receptor, inhibitor/antagonist, human tissue**
TYPE STUDY: **Clinical**
AMOUNT: **$40,000**

Cognitive impairment occurs in a large percent of lupus patients. We have recently demonstrated that a subset of anti-DNA antibodies in patients with Systemic Lupus Erythematosus (SLE) binds to a defined linear epitope on the NR2 NMDA receptor. These antibodies can be found in the cerebrospinal fluid (CSF) as well as in serum. This project will explore further the antigenicity of the NR2 receptor in SLE and the functional consequences of anti-receptor antibodies. The serum from lupus patients will be studied to determine whether there are antibodies to other epitopes that function as a receptor agonists or antagonists and whether there is T cell recognition of NR2 epitopes. Also rodent models will be studied to determine whether serum antibody can penetrate an intact blood-brain-barrier, what concentrations of antibody that must be present in the CSF to cause disease, and whether there are selectively vulnerable populations of neurons. The overall goal of this collaborative interactive program is to develop the scientific foundation for prevention therapies for cognitive decline in SLE.

TITLE: **Brain Cell Death in MRL Mice: Targets and Mechanisms** **NIAMS**
P.I.: **Boris Sakic, PhD**
INSTITUTION: **McMaster University, Ontario Canada**
GRANT NO.: **1 R21 AR49163**
KEYWORDS: **Systemic Lupus Erythematosus, brain cell death**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

This research will elucidate pathogenic mechanisms of neuropsychiatric systemic lupus erythematosus by studying neuroimmunologic disease in autoimmune MIRL-lpr mice. Lymphoid cell infiltration into the choroid plexus, neuronal atrophy, CSF neurotoxicity and an anxiety/depressive behavioral state in MRL-lpr mice suggest that cytotoxic cells and metabolites in the CSF accelerate apoptosis in limbic regions, thus accounting for altered performance in tasks reflective of emotional reactivity and motivation. The project aims to examine: 1. Whether DNA fragmentation involves neurons, glial and/or endothelial cells (will be achieved by combining immunofluorescence with TUNEL staining). 2. Whether population of periventricular brain stem cells is susceptible to neurotoxic effects of CSIF (will be achieved by culturing neurospheres and assessing the effects of incubation with CSF from MRL-lpr mice). 3. Whether brain cell death involves apoptotic pathways (will be achieved by examining nuclear morphology with electron microscopy, by detecting DNA laddering with chemilumnescent method and caspase activation with immunohistochemistry). 4.whether immunosuppression prevents neurodegeneration and CSF neurotoxocity.

TITLE: **Virginia Mason/UCHSC Autoimmune Center** **NIAID**
P.I.: **George S. Eisenbarth, MD**
INSTITUTION: **University of Colorado, Denver, CO**
GRANT NO.: **1 U19 AI50864-03**
KEYWORDS: **autoimmunity, diabetes, Rheumatoid Arthritis**
TYPE STUDY: **Translational**
AMOUNT: **$200,000**

This grant consists of 3 research projects. The overall objective of this application is to derive markers of autoimmune disease in its preclinical phases that would allow identification of individuals at high risk and the design of a rational prevention strategy. The projects deal in genetic, immunologic and environmental determinants that lead to disease. Project 1 will use tetramers to analyze the peripheral antigen-specific T cell profile in IDDM. Project 2 will identify three cohorts of individuals at increased risk for RA and attempt to define immunologic markers for this risk and subsequently derive prevention strategies based on this information. The third project will identify three population-based cohorts at high risk for celiac disease and study these for environmental and genetic factors leading to disease.

TITLE: **T-Cell Reconstitution After Stem Cell Autograft** **NIAID**
P.I.: **Jan Storek, MD, PhD**
INSTITUTION: **Fred Hutchinson Cancer Research Center, Seattle, WA**
GRANT NO.: **5 R01 AI46108-04**
KEYWORDS: **autoimmunity, T-cell, stem cell, lymphocytopenia, chemotherapy**
TYPE STUDY: **Clinical**
AMOUNT: **$60,000**

The goal is to evaluate how the T cell repertoire is reestablished in patients with autoimmune diseases who have undergone lymphocytopenia from high dose chemotherapy/radiation plus anti-thymocyte globulin followed by reconstitution with autologous transplantation of hemopoietic (CD34+) precursors. The hypothesis is that in young individuals, a substantial number of regenerating T cells originate from hemopoietic progenitors whereas in older individuals, the vast majority of T cells originate from the expansion of preexisting T cells. The techniques used will be spectra typing, sequencing of the T cell receptor genes within a single spectra typing band and quantifying T cells that contain T cell receptor-rearrangement circles.

TITLE: **How Does Blockage of CD40/CD40L Prevent Autoimmunity?** **NIAID**
P.I.: **Matthias Von Herrath, MD**
INSTITUTION: **Scripps Research Institute, La Jolla, CA**
GRANT NO.: **1 U19 AI51973-02**
KEYWORDS: **autoimmunity, diabetes**
TYPE STUDY: **Basic - Animal Models**
AMOUNT: **$100,000**

This grant consists of two Pilot Projects, three Projects, and two Cores. Investigators will use three different models of autoimmune diseases to analyze effector functions of dendritic cells, lymphocytes, and regulatory antigen presenting cells. The Program focuses on the blockade of a single pathway and it's study in several different autoimmune scenarios. The program utilizes some novel techniques and is studying the detailed mechanism by which CD40L blockade effectively prevents the development of autoimmunity.

TITLE: **Fine Specificity of Scleroderma Autoantibodies** **NIAMS**
P.I.: **Judith James, MD**
INSTITUTION: **Oklahoma Medical Research Foundation, Oklahoma, OK**
GRANT NO.: **1 R01 AR48045-02**
KEYWORDS: **Scleroderma, immune response, autoimmunity**
TYPE STUDY: **Translational**
AMOUNT: **$200,000**

This application addresses the important problem of the significance of autoantibodies in Scleroderma patients. The project proposes to identify the initial epitope on nRNP and topoisomerase I which is identified by sera from patients with Scleroderma. This will lead to the search for a pathogen in the environment, which could lead to an immune response to the cross-reacting antigen. The possibility of tissue damage due to autoantibodies will also be investigated.

TITLE: **Studies of Collagen Gene Regulation in Two Murine Models** **NIAMS**
P.I.: **Stephen H. Clark, PhD**
INSTITUTION: **University of Connecticut, Farmington, CT**
GRANT NO.: **1 R01 AR48082-02**
KEYWORDS: **Scleroderma, fibroblasts, microarrays, autoimmunity**

TYPE STUDY: **Basic - Animal Models**
AMOUNT: **$200,000**

This research project will utilize two mouse mutations that are models for Scleroderma, tight skin (Tsk) and tight skin2(Tsk2). Both mutations display excessive accumulation of collagen and other extracellular matrix components in the skin, a hallmark of the human disease. The long-range objective of this research is to utilize the two mutations, combined with several lines of transgenic mice as experimental tools, to dissect molecular mechanisms of disease pathogenesis.

TITLE: **EBNA-1 in Lupus** **NIAID**
P.I.: **John B. Harley, MD**
INSTITUTION: **Oklahoma Medical Research Foundation**
GRANT NO.: **2 R01 AI31584-09**
KEYWORDS: **Systemic Lupus Erythematosus, Epstein-Barr virus**
TYPE STUDY: **Basic**
AMOUNT: **$200,000**

The environmental factors associated with systemic lupus erythematosus (SLE) include Epstein-Barr virus (EBV). Once infected, EBV is well known to persist in all human hosts for life. Novel approaches to the detection of this pathogen and to the assessment of the host response to this pathogen are warranted. Among the most interesting viral products is Epstein-Barr virus Nuclear Antigen-1(EBNA-1), which contains a peptide sequence that inhibits antigen presentation and class 1 HLA-dependent cytotoxic T cell responses. Preliminary data show that EBNA-1 also contains sequences that appear to be differentially bound by SLE as opposed to normal sera. SLE will be studied from the perspectives of the anti-EBNA-1 humoral immune response, of EBNA-1 expression in B cells and of EBNA-1 sequence variants.

TITLE: **Registry and Repository of African Americans with Rheumatoid Arthritis** **NIAMS**
P.I.: **Larry Moreland, MD**
INSTITUTION: **University of Alabama at Birmingham, Birmingham, AL**
GRANT NO.: **1 N01 AR002247-000**
KEYWORDS: **African American, Rheumatoid Arthritis, autoimmunity**
TYPE STUDY: **Clinical**
AMOUNT: **$200,000**

This 5 year project will establish a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis and establish a registry which serves to identify genetic and non-genetic prognostic factors of disease outcome using radiographic presence of bony erosions as the primary outcome measure (at 3 years disease duration). The registry will serve as the basis for prospective analyses of factors predictive of the clinical phenotype and outcomes. Four major academic medical centers in the southeast U.S. will gather data, which will provide a resource for investigators interested in the genetics of RA in AA. The CLEAR registry will be utilized to examine the hypothesis that HLA-DR alleles and cytokine polymorphism in the tumor necrosis factor- alpha [TNF-alpha]/lymphotoxin (LT)- alpha, interleukin-1 (IL-1), and IL-6 loci, predict the presence or absence of erosion on hand and feet radiographs at 3 years disease duration in AA.

TITLE: **Inflammation and Cardiovascular Disease in Rheumatoid Arthritis** **NIAMS**
P.I.: **Joan Bathon, MD**
INSTITUTION: **Johns Hopkins University, Baltimore, MD**
GRANT NO.: **1 R01 AR050026-01**
KEYWORDS: **autoimmunity, arthritis, atherosclerosis, biomarkers, disease risks**
TYPE STUDY: **Clinical**
AMOUNT: **$99,999**

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in rheumatoid arthritis (RA). CV-related deaths, congestive heart failure, and acute CV events are increased 2-4-fold in RA patients compared to matched controls, but the prevalence of conventional risk factors for CVD is not increased. This suggests that the disease itself, presumably via chronic inflammation, is an important risk factor for accelerated CVD. Our hypothesis is that RA constitutes an independent risk factor for accelerated CVD. The investigators hypothesize that inflammation due to RA

promotes and exacerbates CVD, independent of conventional CV risk factors. This proposal is an ancillary proposal to the Multi-Ethnic Study of Atherosclerosis (MESA), a unique prospective multi-center study to identify risk factors for incident and progressive subclinical and clinical CVD in the general population. 200 RA patients followed in the Johns Hopkins Arthritis Center will be recruited and will be compared to the prevalence and progression of subclinical CVD in this population to the 1066 MESA participants, who are not RA patients, from the Hopkins Field Center. The degree to which inflammation contributes to increased CVD in RA patients will be examined, after adjusting for conventional CVD risk factors. Specific aims are as follows: 1. In a cross-sectional analysis, the distributions of a measure of atherosclerosis (coronary calcium by computed tomography) and measures of left ventricular (LV) structure and function (by magnetic resonance imaging) between RA patients and controls will be assessed and compared; whether differences between the groups in coronary calcium and LV dysfunction are explained by markers of inflammation in RA. 2. In a prospective analysis, the changes in coronary calcium over three years between RA patients and controls will be compared. The degree to which elevated markers of inflammation contribute to differences in progression of coronary calcium will be determined. 3. The associations of various markers of inflammation and disease activity/severity, as well as conventional CVD risk factors, with coronary calcium and LV dysfunction at baseline and over three years, among RA patients will be assessed. Particularly, the potential dose-response relationships of various markers of inflammation and disease activity/severity to coronary calcium and LV dysfunction will be examined. RA is a chronic inflammatory disease that can be considered to be a model of accelerated CV disease. Lessons learned from the study of CVD in RA may promote the fundamental understanding of inflammatory mechanisms of CVD.

TITLE: **UCSF Autoimmunity Center of Excellence** **NIAID**
P.I.: **David Wofsy, MD**
INSTITUTION: **University of California, San Francisco, CA**
GRANT NO.: **1 U19 Ai056388-01**
KEYWORDS: **immunology, molecular biology, autoimmune diseases, clinical trials, immunotherapies, murine lupus, lupus nephritis**
TYPE STUDY: **Clinical**
AMOUNT: **$60,000**

The broad aim of this application is to translate advances in immunology and molecular biology into practical, safe, and effective therapies for people with autoimmune diseases. Toward this end, the investigators will participate in collaborative clinical trials of novel immunotherapies, and we will conduct basic research into the mechanisms that lead to autoimmunity as well as the mechanisms that can be harnessed to prevent autoimmunity. This proposal to become an Autoimmunity Center of Excellence consists of a Clinical Center, two basic research projects, and an Immune Function Monitoring Core as described below: Clinical Center. Investigators involved in this application have extensive experience in the conduct of clinical trials in diverse autoimmune diseases. This application focuses primarily on systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type I diabetes mellitus (IDDM). Two clinical protocols are proposed, both based on basic research conducted at UCSF by participants in this proposal. Protocol 1 is based on the observation that blockade of T cell costimulation by CTLA4Ig, in combination with conventional therapy with cyclophosphamide, produces long-lasting benefit in murine lupus. It tests the hypothesis that this approach to therapy will be effective in people with lupus nephritis. Protocol 2 is based on the observation that HMG-CoA inhibitors ('statins') retard murine models for MS. It tests the hypothesis that atorvastatin will prevent progression to MS in patients at high risk.

TITLE: **Treatment of Autoimmune Disease by Cost Costimulatory Signal** **NIAID**
P.I.: **Samia J. Khoury, MD**
INSTITUTION: **Brigham and Women's Hospital**
GRANT NO.: **2 U19 AI046130-05**
KEYWORDS: **autoimmune disease, prevention**
TYPE STUDY: **Clinical**
AMOUNT: **$60,000**

There have been tremendous advances in the field of autoimmunity in the last 20 years, and our understanding of the mechanisms underlying autoimmune disease has grown exponentially. True

tolerance is likely to arise not from improved immunosuppression, but from improved understanding of the normal mechanisms that generate and maintain self-tolerance, and the ability to manipulate these mechanisms for the prevention and treatment of autoimmune diseases. The mechanisms of autoimmunity that underlie many diseases are similar, and an integrated multi-specialty approach for evaluating new and emerging therapies would provide the opportunity to integrate knowledge from the various specialties.

TITLE: **Suppression and Exacerbation of B and T cell Responses** **NIAID**
P.I.: **Ignacio Sanz, MD**
INSTITUTION: **University of Rochester**
GRANT NO.: **1 U19 AI056390-01**
KEYWORDS: **Diabetes Mellitus, Multiple Sclerosis, Systemic Lupus Erythematosus, autoimmune diseases, pathogenesis, disease-specific autoantibodies**
TYPE STUDY: **Clinical**
AMOUNT: **$60,000**

The overarching goal of this proposal is to establish an Autoimmunity Center of Excellence at the University of Rochester. This goal is based upon our belief that the understanding of human autoimmunity requires the concerted effort of basic and clinical scientists working together in an intellectual framework that provides constant feedback between bench studies and therapeutic interventions. Our Center will concentrate on studies relevant to the pathogenesis and treatment of Type 1 Diabetes Mellitus (T1DM), Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE). Both types of studies are based on the unifying idea that abnormalities of B- and T-cell function are at the core of these autoimmune diseases. Basic Project 1 will investigate the role of regulatory T-cells (Treg) in the pathogenesis of T1DM and will generate new reagents that will allow investigators to more specifically identify human Treg cells. Basic Project 2 will elucidate the role of IL- 12p40 monokines in MS and determine whether defects in Treg function exist in patients with this disease. Basic Project 3 will study B-cell homeostasis and the cellular origin of disease-specific autoantibodies in SLE. In addition, this project will investigate whether abnormal Treg function contributes to the activation of autoimmune B-cells and T-cells in SLE. These pathogenic mechanisms will serve as the theoretical basis for our clinical trials. Clinical Project 1 will study the clinical and immunological consequences of B-cell depletion in SLE using the anti-CD20 monoclonal antibody Rituximab. Clinical Project 2 will test the clinical and immunological effects of anti-IL-12 in patients with MS. We expect that the studies proposed will result in information that will not only improve our understanding of the disease in question but will also suggest new avenues of research for the other autoimmune diseases targeted by our Center.

TITLE: **Modulation of B Cell Responses in Autoimmunity** **NIAID**
P.I.: **Eugene W. St Clair, MD**
INSTITUTION: **Duke University**
GRANT NO.: **1 U19 AI056363-01**
KEYWORDS: **B cell responses, immunotherapy, autoimmune diseases**
TYPE STUDY: **Clinical**
AMOUNT: **$60,000**

The proposed Center will focus on the modulation of B cell responses in autoimmunity. In autoimmunity, B cells not only serve as the source of pathogenic autoantibodies, but they also may function as antigen presenting cells (APCs) and stimulate pathologic inflammation through a variety of mechanisms. B cell function is regulated via the B cell receptor complex as well as other B cell-specific cell surface ZAI1 CL-I (M2) 3 1 U19 AI056363-01 ST CLAIR, E antigens, including CD20 and CD22. Growing evidence, including our results, indicates CD20 and CD22 are attractive targets for immunotherapy of autoimmune diseases. In addition, the investigators have shown inflammatory stimuli, such as tumor necrosis factor a (TNFa), can promote the emigration of B cells from the bone marrow, transferring large numbers of developing B lymphocytes to the periphery. We hypothesize aberrantly activated B cells are pivotal to the clinical expression of autoimmunity, and the resulting inflammatory state affords an environment for abnormal development of autoreactive B cells and further dysregulation of the immunological response. Two interrelated basic research projects are proposed to investigate this hypothesis. Dr. Thomas Tedder, Professor and Chair of Immunology, will direct a project examining the roles of CD20 and CD22 in the regulation of B cell function in mouse, taking advantage of a unique panel of CD20 and CD22-

directed monoclonal antibodies developed in his laboratory. The other project will be headed by Dr. Garnett Kelsoe, Professor of Immunology, and will investigate to what extent inflammatory stimuli, such as TNFa influence the trafficking of immature B cells and selection of the autoreactive B cell repertoire. A clinical component led by Dr. St. Clair and other experienced physician-scientists will complement the basic research projects. This group has expertise in rheumatoid arthritis (RA), systemic lupus erythematosus, pemphigus vulgaris (PV), and other autoimmune diseases as well as access to many different patient populations for clinical studies. One of the proposed trials will evaluate the safety and clinical efficacy of anti-CD22 monoclonal antibody therapy for RA, while the other will investigate infliximab (anti-TNFa) therapy for PV. Each of the trials includes mechanistic studies that are integrated with the goals of the basic research projects, providing synergy within the Center. An Administrative Core will oversee the management of these projects. Overall, the Proposed Center will efficiently bridge basic and clinical investigations and should produce new insights into the immunotherapy of autoimmune disease.

TITLE: **UAB Autoimmunity Center for Excellence** **NIAID**
P.I.: **Robert H. Carter, MD**
INSTITUTION: **University of Alabama at Birmingham**
GRANT NO.: **1 U19 AI056542-01**
KEYWORDS: **translational therapies, immunology, autoimmune diseases**
TYPE STUDY: **Clinical**
AMOUNT: **$60,000**

The University of Alabama at Birmingham (UAB) has an outstanding record in basic immunology and in testing of novel, translational therapies for autoimmune diseases. The UAB Autoimmunity Center of Excellence (ACE) is a multidisciplinary, collaborative program to unite these strengths to accelerate the development and testing of translational therapies for autoimmune disease. To accomplish this, the UAB ACE will promote basic and translational research and sponsor clinical trials of novel immunomodulatory agents. As part of this mission, the UAB ACE will foster communication between basic and clinical investigators and between those focused on different immune-mediated diseases at UAB and nationally.

TITLE: **Autoimmunity Centers of Excellence** **NIAID**
P.I.: **Betty Diamond, MD**
INSTITUTION: **Albert Einstein College of Medicine, Bronx, NY**
GRANT NO.: **1 U19 A1056362-01**
KEYWORDS: **autoimmunity, lupus**
TYPE STUDY: **Clinical**
AMOUNT: **$278,506**

The Autoimmunity Center of Excellence at the Albert Einstein College of Medicine will encompass research projects, an infrastructure for clinical trials and an administrative core. This Center reflects an interdisciplinary approach to autoimmune disease. It involves a collaboration of clinicians and basic scientists that is focused on translational studies to develop new therapeutic strategies. The research component includes three research projects. Each project has the goal of developing new targets for therapy in autoimmune disease. The first project is a study of the effects of statins alone or in conjunction with CTLA-4Ig in the NZB/W mouse model of lupus. This project will include a study of the effect of statins on peripheral blood mononuclear cells of lupus patients. The second project is a study of the effect of CD22 overexpression on B cell development and on autoantibody production in murine models of SLE and includes a study of a CD22 polymorphism reported to associate with lupus. Overall it will explore whether inhibition of CD22 represents a useful therapeutic strategy. The third project is a biophysical study of the polymorphism of murine 2 microglobulin that is required for the expression of diabetes in NOD mice. This study will provide a comprehensive biophysical characterization of the features of TCR/MHC-peptide complexes that are directly relevant to eliciting diabetes. These studies promise to provide the atomic and molecular mechanisms responsible for disease development and thus may lead to novel strategies for the design of therapeutics that will limit disease-associated T cell reactivity. The clinical infrastructure is capable of performing clinical trials in autoimmune rheumatic diseases, type 1 diabetes, autoimmune hematologic diseases, and inflammatory bowel disease. In addition, there are proposals for a clinical trial of DNase I in serologically active, clinically inactive lupus and for a

trial of statin therapy as a steroid sparing agent in rheumatoid arthritis. Finally, the Center will include an administrative core for coordination and implementation of Center activities.

TITLE: **An Animal Model for Graves' Disease/Ophthalmology** **NEI**
P.I.: **Juan C Jaume, MD**
INSTITUTION: **UCSF/ VAMC, Dept. of Medicine, San Francisco, CA**
GRANT NO.: **1 R03 EY014962-01**
KEYWORDS: **graves' disease, hyperthyroidism, autoantibodies, ophthalmopathy, animal model**
TYPE STUDY: **Basic**
AMOUNT: **$126,000**

The ophthalmopathy of Graves' disease is a disfiguring, sight threatening condition of unclear pathogenesis and no specific of definitive therapy. Graves' disease primarily manifests with hyperthyroidism that results from the stimulation of the TSHR by specific autoantibodies that mimic the effect of TSH. Often the ophthalmopathy accompanies the hyperthyroidism. Rather than being considered two separate entities, hyperthyroidism and ophthalmopathy are different manifestations of the same underlying autoimmune process. No spontaneous animal model of Graves' disease exists. Recently, an animal model has been developed in which a proportion of individuals manifest immunological and endocrinological features of Graves' disease.

INFECTIOUS DISEASES

TITLE: **Sex in Viral Myocarditis** **NIAID**
P.I.: **Sally A. Huber, PhD**
INSTITUTION: **University of Vermont**
GRANT NO.: **1 R21 AI51850**
KEYWORDS: **autoimmunity, myocarditis, hormones, host defense responses**
TYPE STUDY: **Translational**
AMOUNT: **$50,000**

Myocarditis is an inflammatory disease of the myocardium. Approximately 65% of cases follow recent enterovirus infections and occur in males. As in humans, CVB3 infections cause severe myocarditis in male, but not virgin female mice. Androgens (progesterone and testosterone) increase virus receptor expression on cardiac myocytes while 17-beta-estradiol treatment does not. Since lymphocytes also express CVB3 receptors, we hypothesize that hormones might modulate lymphocyte expression of these molecules as well. Cytokine release differs between male and female lymphocytes with male cells producing interferon (IFN)gamma and female cells producing interleukin (IL)-10. We hypothesize that viruses, which have repetitive symmetry of the virus capsid, cross-link important cell surface molecules on lymphocytes and cause rapid non-antigen-specific lymphocyte activation. These studies may provide new insights as to how viruses affect developing host defense responses and how hormones can modulate this initial response.

TITLE: **Seroprevalience/incidence of genital herpes** **FIC**
P.I.: **Edith Nakku-Joloba**
INSTITUTION: **New Mulago Hospital, Uganda**
GRANT NO.: **1 R01 TW006672-01**
KEYWORDS: **herpes, epidemiology**
TYPE STUDY: **Public health, clinical**
AMOUNT: **$20,000**

Prevalence of herpes simplex type 1 and 2 virus (HSV-1 and 2) infection is high worldwide and is highest in developing countries like Uganda. International and local health organizations have called for studies to characterize genital herpes epidemiology in sub-Saharan Africa. Population estimates are needed for policy, for planning interventions, for valid measures of the effect of interventions and for research on new therapies and potential vaccines. The overall goal of this study is to determine the burden of infection and assess the modifiable risk factors associated with Herpes simplex types 1 and 2 infection in Kampala, Uganda with an aim of prevention of spread and relief of those who suffer with genital herpes. The proposed study will aim i) To estimate the age and sex specific prevalence of Herpes simplex type 1 and 2. ii). To estimate the incidence of Herpes simplex type 1 and 2 in an inception cohort of HSV-2 negative persons in an urban population in Uganda and iii) to identify modifiable risk factors associated with Herpes simplex

types 1 and 2 prevalence and incidence in this population. The proposed study will be a two-stage stratified random population sample survey of female and male participants 15 to 65 years old in Kawempe division of Kampala District. To estimate prevalence of HSV-1 and 2, a cross-sectional serological survey at baseline will be done using type specific ELISA tests for herpes simplex type 1 and 2. Incidence will be assessed in an inception cohort of HSV-2 negative persons by 6 monthly testing for HSV-2. Risk factors for genital herpes will be assessed using a standardized questionnaire to collect information on age, sociodemographic characteristics, sexual behavior, sexual partner characteristics such as age differentials, and HIV infection status. Incidence densities and relative risks will be calculated from new HSV-2 infection and risk factors that predispose to HSV-2 incidence such as age, sex, (gender), sexual behavior, and HIV infection analyzed in a Cox proportional hazards model. By conducting a population study in an urban area in a country where rural studies show high prevalence we will describe the epidemiology genital herpes, gaining new knowledge about genital herpes in urban Uganda and highlighting the modifiable risk factors which can be targeted for effective interventions.

MENOPAUSE

TITLE: **Study of Women's Health Across Nation II: (SWAN II)** **NIA**
P.I.: **Karen Mathews, Ph.D., Coordinating Center (University of Pittsburgh), and Multiple sites (UCLA, University of Michigan, University of California, Davis, Mass General, Rush -Presbyterian-St. Luke's Medical Center, UMDNJ and University of Pittsburgh)**
INSTITUTIONS: **New England Research Institute, Watertown, MA**
GRANT NO.: **5 U01 AG12546-10**
KEYWORDS: **Menopause, aging, hormones, minorities, risk factors, disease**
TYPE STUDY: **Clinical**
AMOUNT: **$250,000**

SWAN consists of both cross-sectional and longitudinal studies on the natural history of menopause and a characterization of endocrinology/physiology of premenopause. Five ethnic groups are included - Caucasian, African American, Hispanic, Chinese, and Japanese. There are 7 sites across the country - Boston, Pittsburgh, Chicago, Michigan, UCLA, UC Davis and New Jersey. For the cross-sectional study, there are approximately 16,000 women enrolled ranging in age from 40-55 years to determine the age of menopause. The longitudinal study has approximately 3150 women (450 at each site) between the ages of 42-52 to determine menopause-specific physiological changes and their predictors and the impact of menopause on subsequent disease. Measurements are being made of the major reproductive axis hormones (LH, FSH, estradiol, progesterone, and testosterone), adrenal markers of aging (DHEAs), other endocrine markers (TSH, sex hormone binding globulin [SHBG]) and new ovarian markers which have the potential to define the menopausal transition and the postmenopause.

TITLE: **The Study of Women's Health Across the Nation (SWAN II) sub/pilot projects** **NIA**
P.I.: **Gail Greendale, MD, and Kim Sutton-Tyrrell, PhD**
INSTITUTION: **The University of California, Los Angeles, CA, and The University of Pittsburgh, PA**
GRANT NO.: **3U01AG012539-10S2**
KEYWORDS: **multi-ethnic, community based, menopausal transition, menopausal hormone therapy**
TYPE STUDY: **Clinical**
AMOUNT: **$202,756**

The proposed research is comprised of 3 analyses, which would use data collected under the aims and protocols of the most recent SWAN renewal application. These data will form the basis of a pilot study with analyses to determine the characteristics of those subsets of women selecting hormone therapy, discontinuing therapy and their experience regarding the emergence (or re-emergence) of symptoms and accelerated bone loss. These themes have been chosen because in the wake of the WHI findings, the NIH and physicians worldwide have been besieged by calls and correspondence from women who were distressed about having to relinquish MHT, experiencing symptoms and left in the dark about how these problems might resolve. Since SWAN

is a natural history study in a multiethnic population, it will be very valuable in generating preliminary data to begin addressing some of these issues (e.g., why women selected MHT, the impact of the WHI findings on their short and long-term choices and behavior and/or indicating where more research is needed). Preliminary findings from these analyses can serve as the basis for hypothesis-driven investigator-initiated studies in this area.

TITLE: **Menopausal Depression: Chronobiologic Basis** **NIMH**
P.I.: **Barbara L. Parry, MD**
INSTITUTION: **University of California, San Diego, La Jolla, CA**
GRANT NO.: **5 R01 MH059919-03**
KEYWORDS: **depression, menopause, hormone therapy, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

The specific focus of this project will be to examine the effects of estradiol and progesterone administration on circadian rhythms in humans. The subjects will be healthy postmenopausal women. The investigators will test the hypothesis that estrogen advances the phase and enhances the amplitude and synchrony (the stability of timing relationships) of biological rhythms as measured by melatonin, sleep and activity, whereas progesterone antagonizes these effects. This proposal represents an extension of the investigators' previous work that examined the effects of endogenous changes in estradiol and progesterone during the menstrual cycle on measures of mood and circadian rhythmicity. This work led to the development of new hypotheses and treatment strategies. The current proposal will allow investigation of these hypotheses further but in a more controlled design. The investigators anticipate gaining important information on possible mechanisms mediating the effects of reproductive hormones on mood and behavior and deriving relevant clinical treatment guidelines for menopausal women.

TITLE: **Centers for Dietary Supplements Research: Botanicals** **NCCAM**
P.I.: **Norman Farnsworth, PhD**
INSTITUTION: **University of Illinois at Chicago, IL**
GRANT NO.: **5 P50 AT00155-04**
KEYWORDS: **botanicals, menopause, black cohosh, red clover, CAM**
TYPE STUDY: **Clinical and basic**
AMOUNT: **$100,000**

This multi-disciplinary team of investigators will focus on the study of the safety and efficacy of botanicals used to treat women for menopause. Studies will address mechanisms of action, identification of active compounds, and characterization of metabolism, bioavailability and pharmacokinetics of active species in these botanicals. The research component will consist of the following: 1) A pharmacognosy project to carry out standardization of botanical dietary supplements and structure elucidation of active compounds; 2) Isolate active compounds for structure elucidation, and then to determine the mechanism(s) of action of botanicals; 3) Study the metabolism, absorption and toxicity of active compounds in botanicals including immunotoxicity; and 4) Carry out phase I and II clinical trials of black cohosh (*Cimicifugai racemosa)* and red clover (*Trifolium pratense*).

TITLE: **Phytoestrogens and Progression of Atherosclerosis** **NCCAM**
P.I.: **Howard N. Hodis, MD**
INSTITUTION: **University of Southern California, Dept. of Medicine, Los Angeles, CA**
GRANT NO.: **5 U01 AT001653-02**
KEYWORDS: **hormone therapy, soy protein, isoflavine-rich soy protein, postmenopausal women, atherosclerosis, common carotid artery**
TYPE STUDY: **Clinical**
AMOUNT: **$200,000**

The fear and discontent with traditional hormone replacement therapy (HRT) coupled with the interest in natural products has resulted in an increased use of soy protein as a postmenopausal therapeutic alternative by both women and their physicians alike. Evidence from epidemiological and non-humane primate studies indicate that isoflavone-rich soy protein has antiatherogenic activity, evidence supported by a large body of data that indicate mechanistic and biologic plausibility. No studies to knowledge have been published or proposed to determine the long-term

effects of soy protein on the progression of atherosclerosis in postmenopausal women. The investigators propose to conduct a 2.5 year, randomized, double-blind, placebo-controlled trial of isoflavone-rich soy protein in 300 healthy postmenopausal women without clinical evidence of cardiovascular disease. They hypothesize that relative to placebo, isoflavone-rich soy protein (supplying genistein, daidzein and glycitein) will reduce the progression of subclinical atherosclerosis in healthy postmenopausal women. The primary end point will be the progression of subclinical atherosclerosis measured as the rate of change in common carotid artery intima-media thickness in computer image processed B-mode ultrasonograms, a well-established noninvasive arterial imaging end point for antiatherosclerosis trials, Isoflavone-rich soy protein may provide a safe and effective alternative approach for extending premenopausal ardioprotection afforded by endogenous estrogen into menopause without the increased risk of thromboembolic events and certain cancers associated with traditional HRT. Since many postmenopausal women are using spy products to maintain their health, it is important to understand whether soy protein has an antiatherogenic effect so that women can make a truly informed decision concerning their expectations of this form of postmenopausal therapy. The question as to whether soy protein is effective in reducing progression of atherosclerosis in postmenopausal women is not only timely, but also of immense medical and financial importance since atherosclerosis remains the number 1 killer of postmenopausal women.

TITLE: **Baseline Measurements for Effects of Soy on Bone, Cancer, and Cognition Health** **NCCAM**
P.I.: **Howard N. Hodis, MD**
INSTITUTION: **University of Southern California, Dept. of Medicine, Los Angeles, CA**
GRANT NO.: **3 U01 AT001653-02**
KEYWORDS: **hormone therapy, soy protein, isoflavine-rich soy protein, postmenopausal women, atherosclerosis, common carotid artery**
TYPE STUDY: **Clinical**
AMOUNT: **$48,000**

The parent application, entitled Phytoestrogens and the Progression of Atherosclerosis, is a five-year study (2.5-year, randomized, double-blind, placebo-controlled clinical trial) to test the hypothesis that diet supplementation with isoflavone-rich soy protein is antiatherogenic due to the estrogen agonist effects of soy isoflavones. The study seeks to resolve the question as to whether soy phytoestrogens are effective in reducing the progression of atherosclerosis in postmenopausal women. Since the effects of soy phytoestrogens presumably extends beyond the benefits to cardiovascular diseases to bone health, cancer prevention, and cognition and vasomotor improvement, additional tests to test the effects of soy on bone, cancer, and cognition would yield tremendous information with little additional investment. The baseline measurements that will be obtained at the initial examination will include DEXA for bone density, mammogram, and cognition tests.

MENTAL HEALTH

TITLE: **Health Survey of Two-Spirited Native Americans** **NIMH**
P.I.: **Karina L. Walters, PhD**
INSTITUTION: **University of Washington, Seattle, WA**
GRANT NO.: **1 R01 MH65871-01**
KEYWORDS: **mental health, cultural and spiritual coping, HIV risk behaviors, Native American, alcoholism/alcohol abuse, clinical research, human subjects**
TYPE STUDY: **Clinical**
AMOUNT: **$175,000**

American Indian and Alaskan Native lesbian, gay, bisexual, transgendered, and two-spirited individuals (two spirits) are a drastically understudied and underserved group, at risk for multiple health and mental health problems. There are no national, quantitative, representative studies of this population on any topic. Building upon solid preliminary data, we will conduct structured survey interviews with 400 two spirits drawn from six sites across the U.S. With these interview data, we will test a theoretical model of stress and coping specific to this population. Sub-aims are to (a) establish preliminary prevalence rates of trauma and health outcomes (i.e., HIV sexual risk behaviors, alcohol and other drug use, and mental health indicators); (b) test the direct

associations between trauma and health outcomes; (c) determine how cultural and spiritual coping factors moderate the effect of trauma on health outcomes; and (d) examine the mediating role of substance use on the trauma-HIV sexual risk behavior and trauma-mental health relationships. The results will contribute toward the refinement of a sample strategy useful in studying other hidden and stigmatized populations. Through the course of this project, we aim to develop the research infrastructure at the six community agencies comprising our participant recruitment sites in order to facilitate future goals of designing and evaluating interventions to address the urgent needs of two spirits.

TITLE: **Stress Response Differences in Females: Estradiol's Role** **NIMH**
P.I.: **Martha M. Faraday, PhD**
INSTITUTION: **The Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, MD**
GRANT NO.: **1 R03 MH065945-01**
KEYWORDS: **stress, depression, estradiol, women's health**
TYPE STUDY: **Basic**
AMOUNT: **$74,350**

In response to stress, pre-menopausal women are more likely to become depressed than are men, suggesting that being female and exposure to cycling female sex hormones may constitute part of depression vulnerability. Only some women develop depressive illness, however, indicating that women differ in stress sensitivity and depression vulnerability. Rodent models of depression that examine responses of stress-vulnerable vs. stress-resistant females would be valuable to understand the biologic basis of differential stress and depression vulnerability in women but models of depression generally have used male rats as subjects. Preliminary data indicate that Sprague-Dawley female rats are markedly more sensitive to stress than are Long-Evans female rats across several behaviors and biologic indices, including a behavioral model of depression and hypothalamo-pituitary-adrenocortical (HPA) axis responses. These differences in response to stress could be the result of many factors, including actions of estradiol on brains that are different and line differences in how stress affects estradiol levels or estrus cycling. Estradiol is the major sex hormone with behavioral and biologic actions in females. Estradiol interacts with stress-sensitive brain systems (i.e., serotonergic, dopaminergic) that control the behaviors under study. Estradiol also interacts with the HPA axis. Therefore, examining estradiol's role in stress responding of stress-sensitive female rats (Sprague-Dawley) and stress-resistant female rats (Long-Evan) is a critical step toward understanding why some females are more vulnerable to stress and depression than others. Behavioral and corticosterone responses of Sprague-Dawley and Long-Evans females that are intact, ovariectomized or ovariectomized with estradiol replacement will be evaluated in response to daily restraint stress. Responses also will be compared with intact male rats. To determine whether female line differences in response to stress are the result of changes in estrus cycling or line differences in estradiol levels, estrus cycle and estradiol levels of intact females also will be assessed.

TITLE: **CARE Intervention for Depressed Mothers & Their infants** **NINR**
P.I.: **June A. Horowitz, PhD, RN**
INSTITUTION: **Boston College, Chesnut Hill, MA**
GRANT NO.: **1 R01 NR08033-01A1**
KEYWORDS: **maternal-infant relational effectiveness, postpartum depression**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Postpartum depression (PPD), a commonly experienced childbirth complication, jeopardizes mothers' ability to interact responsively with their infants. Onset during the critical period of the first few months of infants' lives threatens the maternal-infant relationship and adversely affects infant development. Despite the clinical significance of the problem, there is limited information on the treatment of maternal-infant relational disturbances associated with PPD. The overall goal of this randomized clinical trial is to mitigate negative effects of PPD on infants' development by promoting responsive interaction between depressed mothers and their infants. The specific aim is to test the efficacy of the relationship-focused-CARE intervention (Communicating And Relating Effectively) in increasing maternal-infant relational effectiveness, increasing infant clarity of cues and responsiveness to parent, and reducing parenting stress for the treatment group at 3-months,

6-months, and 9-months after delivery. This proposed study builds on preliminary studies that: (a) demonstrated the feasibility of screening women for postpartum depression, and (b) tested the efficacy of a behavioral coaching intervention delivered by nurses to promote maternal-infant responsiveness between depressed mothers and their infants. In this study, the intervention coaching is adapted to problematic maternal interactive behaviors that are associated specifically with PPD. Nurses will screen approximately 1,500 postpartum women for PPD, randomly assign a minimum of 116 eligible participants to either the treatment or control group, and confirm depression status with a diagnostic interview. Using a repeated measures design, data will be collected at 1, 3, 6, and 9 months postpartum. Standardized instruments will evaluate depression symptoms and parenting stress; blind coding of videotaped maternal-infant interaction will measure maternal-infant relational effectiveness and infant behavioral responses. The CARE intervention will be conducted during home visits at 1, 2, 3, 4, 6 months postpartum by teaching mothers to interpret their infants' behavioral cues and to respond effectively. R-MANOVA will be used to test the study hypothesis and to answer the research questions. Outcomes are expected to contribute to knowledge of evidence-based nursing practice models for the treatment of maternal-infant relational problems associated with PPD.

MUSCULOSKELETAL SYSTEMS

TITLE: **Osteo-Arthritis Initiative** **NIAMS**
TYPE STUDY: **Clinical**
TITLE: **$800,000**

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (OAI) will collect information and define disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical companies: GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, and Pfizer. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. The OAI will support six clinical research centers that will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification.

TITLE: **Glucocorticoids Alter the Birth and Death of Osteoblasts** **NIAMS**
P.I.: **Robert Weinstein, PhD**
INSTITUTION: **University of Arkansas for Medical Sciences, Little Rock, AR**
GRANT NO.: **5 R01 AR46191-04**
KEYWORDS: **glucocorticoids, osteoblasts, parathyroid hormone, osteoporosis**
TYPE STUDY: **Clinical and basic**
AMOUNT: **$100,000**

This study will characterize the effects of chronic glucocorticoid excess on several aspects of bone physiology. Patients with glucocorticoid-induced bone loss will be included. The effect of alendronate (Fosamax) and parathyroid hormone will be tested in mice for efficacy in ameliorating the effect of glucocorticoids.

TITLE: **Low-Dose Doxycline Effects on Osteopenic Bone Loss** **NIDCR**
P.I.: **Jeffrey B. Payne, DDS**
INSTITUTION: **University of Nebraska, Lincoln, NE**
GRANT NO.: **1 R01 DE12872-02**
KEYWORDS: **clinical trials, periodontitis, osteoporosis**
TYPE STUDY: **Translational, Clinical**
AMOUNT: **$324,398**

This study seeks to demonstrate the clinical efficacy of low dose doxycycline (LDD) therapy in reducing bone loss due to periodontitis and estrogen deficiency in a postmenopausal estrogen

deficient osteopenic population. Success in reducing or arresting bone loss related to periodontitis in an estrogen deficient osteopenic group would represent important progress in understanding and managing the pathophysiologic mechanisms that are involved in bone loss with this process.

TITLE: **Factors Affecting the Bone Response and Non-Response** **NIAMS**
P.I.: **Laura A. Milliken, PhD**
INSTITUTION: **University of Massachusetts, Boston, MA**
GRANT NO.: **1 R03 AR047932-01 A1**
KEYWORDS: **postmenopausal women's health, musculoskeletal system health, exercise and diet, modeling**
TYPE STUDY: **Clinical**
AMOUNT: **$99,999**

The effects of exercise and hormone replacement therapy (HRT) on bone mineral density (BMD) have been investigated by many researchers in a wide variety of subject populations. However, there are relatively few studies on postmenopausal women involving substantial sample sizes that have examined the BMD response to longer-term exercise therapies (≥ one year). It has been suggested that any therapy that functions to decrease bone remodeling will initially increase BMD solely as a consequence of the bone remodeling transient. This transient is simply the completion of remodeling packets (formation and mineralization) that were activated prior to the administration of the treatment. Therefore, the true effectiveness of the therapy should be evaluated after this transient has passed. This underscores the need for longer-term studies of exercise, HRT, or any therapy thought to prevent bone loss. Additionally, despite the general notion that exercise and/or HRT can prevent bone loss, there remains a large number of postmenopausal women who do not respond to the prescribed treatment. Conversely, some women respond much more than would have been predicted based on our current body of knowledge. The aims of this study are to 1) develop statistical models to predict one year through four year changes in regional and total body BMD from nutritional, hormonal, biochemical, body composition, physical activity, and psycho-social variables in post-menopausal women, 2) compare the nutritional, hormonal, biochemical, body composition, physical activity, and psycho-social variables in one year BMD responders to one-year BMD non-responders. To accomplish these aims, data from the "Bone, Estrogen, Strength Training" (BEST) study, a large NIH funded project, will be used. The original aim of the BEST study was to determine the effects of a one year exercise training program and HRT on BMD in postmenopausal women. However, many subjects continued on the exercise program after the 1 year study. Sample sizes for 1-, 2-, 3-, and 4-year data are 266, 213, 185, and 171 (projected), respectively. This database presents a unique opportunity to examine long-term BMD changes in a comprehensive database which includes the volume of exercise performed, leisure-time physical activity, nutritional data, body composition, physical fitness, hormonal data, markers of bone formation and resorption, and psycho-social variables such as self-esteem, depression, quality of life, social support, and barriers to exercise. The present study will use the existing BEST data as well as the follow-up data for two, three, and four year effects. The information gained from these analyses will enable the prediction of BMD changes well after the effects of the bone remodeling transient. The study will assist in a better understanding of the pattern of the BMD response over longer periods of time and will be able to identify factors that may relate to the likelihood of responding to a given treatment.

TITLE: **Ethnic Differences in the Management of Osteoarthritis** **NIAMS**
P.I.: **C. Kent Kwoh, MD**
INSTITUTION: **University of Pittsburgh, Pittsburgh, PA**
GRANT NO.: **1 R01 AR50265-01**
KEYWORDS: **health disparities, osteoarthritis, total joint replacement, gender disparities**
TYPE STUDY: **Clinical**
AMOUNT: **$300,000**

The proposed study seeks to examine factors that may provide the basis for health disparities in the utilization of elective total joint replacement, and builds on two federally-funded studies. The first examines ethnic differences in the management of osteoarthritis (OA) among male veterans. The second, the Study of Healthy Aging: Body Composition (Health ABC) study, is a NIA-funded longitudinal evaluation focusing on two population-based cohorts of individuals between the ages of 70 to 79 recruited from the Pittsburgh, PA and Memphis, TN metropolitan areas. The overall goal

of this research is to better understand the reasons behind ethnic variations in the utilization of lower extremity total knee arthroplasty (TKA) or total hip arthroplasty (THA). The proposed study will examine the health beliefs, practices, preferences and perceptions of African American women and men, as well as white women and men with knee or hip OA and how these factors may influence consideration of TKA/THA. A cross-sectional study design will be utilized to examine the following Specific Aims: 1) To examine ethnic/gender differences in individuals' self-report of symptoms and functional status among individuals with OA of similar radiologic severity; 2) To examine ethnic/cultural differences in perceptions of the efficacy of specific treatment options for arthritis and willingness to have TKA/THA; 3) To examine gender differences in perceptions of specific treatment options for arthritis and willingness to have TKA/THA; and 4) To examine ethnic/gender differences in provider-level factors related to access to TKA/THA. The 518 individuals from the Health ABC study with symptomatic and radiographic knee OA and 271 with symptomatic and radiographic hip OA will be surveyed. Regarding Specific Aims 1 and 2, major variables that may confound the relationship between ethnicity or gender and willingness to have joint replacement include understanding the risks and benefits of joint replacement; pain coping strategies; perceptions of the efficacy of a specific treatment option such as prayer, and perceptions of health care. The proposed study is unique in that it will examine ethnic and gender differences in the management of OA across patients with varying disease severity, focusing on specific factors that may explain health disparities.

TITLE: **Longitudinal Changes in Hip Geometry and Skeletal Muscle** **NIAMS**
P.I.: **Zhao Chen, PhD**
INSTITUTION: **Arizona Board of Regents, University of Arizona, Tucson, AZ**
GRANT NO.: **1 R01 AR049411-01 A1**
KEYWORDS: **postmenopausal women's health, musculoskeletal system health, bone fracture risk, hormone therapy, calcium and vitamin D**
TYPE STUDY: **Clinical**
AMOUNT: **$222,980**

This study will be conducted among a large multiethnic cohort (N = 11,432) from the nationwide Women's Health Initiative (WHI), which includes an observational study and four clinical trials. The age range of this cohort is between 50-79 years at the baseline, and it has multiple minority groups: 1583 black, 739 Hispanic, and 149 Native American women. By 2005, the maximal follow-up time of this cohort will be 9 years. Dual-energy x-ray absorptiometry (DXA) is used to measure bone mineral density (BMD) and body composition The randomized clinical trials and longitudinal nature of the WHI study provide a unique opportunity to investigate: 1) treatment effects of menopausal hormone therapy (MHT) and calcium plus vitamin D supplementation on hip structural geometry; 2) longitudinal changes in skeletal muscle mass as a factor in hip fragility; and 3) ethnic differences of mean and rates of changes in hip geometry and muscle mass. Special computer software will be used for analyzing hip scans by dual-energy x-ray absorptiometry (DXA). Cross-sectional area, subperiosteal width, estimated endocortical diameter, estimated mean cortical thickness, buckling ratio and section modulus at the femoral neck, at the intertrochanteric and the femoral shaft regions will be assessed. Magnetic Resonance Imaging (MRI) scans will be used as references to calibrate total and leg skeletal muscle measurements from DXA subregion analyses. Prevalence rates of sarcopenia (low muscle mass) among each age and ethnic group will be studied. Mixed Effects Models will be used to analyze the longitudinal data. Recourses that the WHI program will provide include DXA scans, fall and fracture data, and information on covariates. Since the majority of data collection work has been or will be done by the WHI, the investigators will be able to cost-effectively test multiple important scientific hypotheses in this study. The novel approaches in this ancillary study will enhance scientific contributions of the WHI program. The significance of the proposed study is that it may demonstrate the utility of bone structural analysis in addition to bone mass measurements for understanding ethnic differences in fracture risk and/or for assessing the effect of pharmacologic therapy (i.e. CaD) on bone health. Furthermore, if the muscle variables are found to be related to bone structure in the proximal femur and the risk of fall, then it may be important to further test whether interventions that increase muscle mass in this region will prevent hip fracture.

TITLE: **Bone-Sparing by Ca Salts with and without Extra Phosphorus** **NIAMS**
P.I.: **Robert P. Heaney, PhD**

INSTITUTION: **Creighton University Dept. of Medicine, Osteoporosis, Omaha, NE**
GRANT NO.: **1 R01 AR048846-01A1**
KEYWORDS: **osteoporosis, supplementation, menopause**
TYPE STUDY: **Clinical**
AMOUNT: **$75,000**

Bone mineral is basically calcium phosphate, and both elements (Ca and P) are required for bone acquisition. Typical Ca intakes in the U.S. are lower than current recommendations, and typical P intakes, higher. To test the possible importance and value of supplementing both of the components of bone mineral in support of anabolic therapy of osteoporosis, we propose a 1-year randomized trial, comparing, in two groups of teriparatide-treated postmenopausal osteoporotic women, calcium supplements with and without extra phosphorus (i.e. Ca phosphate vs. Ca carbonate). The principal outcome measure will be change in bone mineral content over the one year of the trial. A secondary outcome is measurement of bone resorption biomarkers so as to assess whether the phosphate salt elevates remodeling relative to the carbonate salt. A finding of superiority of the phosphate-containing Ca supplement would provide evidence leading to a cost-neutral change in Ca sources and a corresponding improvement in osteoporosis co-therapy (and possibly osteoporosis prophylaxis as well).

TITLE: **Calcium Absorption in Caco-2 Cells: Molecular Mechanism** **NIDDK**
P.I.: **James C. Fleet, PhD**
INSTITUTION: **Purdue University**
GRANT NO.: **2 R01 DK054111-06A2**
KEYWORDS: **calcium, calcium absorption, menopause, low bone density, homeostasis**
TYPE STUDY: **Basic**
AMOUNT: **$200,000**

The research will clarify the mechanisms used by 1,25 (OH)2D to promote calcium absorption and to determine how dysfunction in the regulatory control of intestinal calcium absorption during aging or due to menopause leads to reduced absorption efficiency and, ultimately , low bone density. Recent research demonstrates that 1,25 (OH)2D rapidly activates scr kinase, protein kinase C (PKC), and MAP kinases and that inhibition of these kinases blunts 1,25 (OH)2D-mediated activation of the CYP24 gene. The goal of the proposed research is to determine how the adaptive increase in intestinal calcium absorption due to 1,25 (OH)2D-dependent; vitamin D receptor (nVDR)-mediated gene activation is influenced by the basal or induced activity if these kinases.

TITLE: **Bone-Sparing Effects of Soy Phytoestrogens in Menopause** **NIAMS**
P.I.: **Silvina Levis, MD**
INSTITUTION: **University of Miami School of Medicine, Dept. of Medicine, Miami, FL**
GRANT NO.: **1 R01 AR048932-01A1**
KEYWORDS: **osteoporosis, menopause, hormone replacement therapy (HRT)**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Women will live a third of their lives after menopause. The complications of prolonged estrogen deficiency during the menopausal years is well established. Although hormone replacement therapy (HRT) can spare women some of these complications, the Women's Health Initiative findings indicate significant potential health risks, risks that prompt more and more women to turn from prescribed HRT to over-the –counter products in the hope that soy phytoestrogens and other "estrogens" from natural sources can replace prescription estrogens in terms of benefits while sparing critical side effects. In spite of the fairly widespread and now rapidly growing use of phytoestrogens, major gaps remain in our knowledge of their long-term efficacy and safety. It is proposed to conduct a "Soy Phytoestrogens As Replacement Estrogen (SPARE)" study in young menopausal women to evaluate the effectiveness of a 2-year treatment with purified soy isoflavones in preventing bone loss. The study will also explore the effectiveness of oral isoflavones in preventing menopausal symptoms and other changes associated with estrogen deficiency. The study will characterize the actions of a defined preparation of soy isoflavones in humans and will correlate these actions with the circulating serum levels of the principal isoflavone metabolites, providing new insights on their long term biological actions. This 5-year study will provide a foundation of knowledge from which menopausal women can begin to make more informed

decisions regarding HRT and menopausal signs and symptoms.

NEUROLOGY

TITLE: **Sex Differences in Dopamine Systems** **NINDS**
P.I.: **Arthur P. Arnold, PhD**
INSTITUTION: **The Regents of the University of California, Los Angeles, CA**
GRANT NO.: **1 R01 NS045966-01**
KEYWORDS: **sexual differentiation, brain function**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

The proposal has the long term goal of determining the factors that cause sex differences in structure, function, and susceptibility to disease in mesencephalic dopamine systems. The studies will investigate the cellular and molecular mechanisms by which sex chromosome genes induce sex differences in the phenotype of dopaminergic neurons in vivo and in vitro. Studies will determine whether the sex chromosome effect is due to genes on the X or Y chromosomes; whether steroid hormones of the Sry gene participate in the induction of sex differences; when during development the sex chromosome effect occurs, whether the sex chromosome effect is direct or indirect on dopamine neurons; the cellular mechanisms of the sex chromosome effect; and whether the sex chromosomes contribute to sex differences in the development and adult structure of the nigrostriatal dopamine system in vivo. The proposed studies will contribute to an understanding of the principles of sexual differentiation of the brain. At issue are the molecular mechanisms by which male and female brains differ, which is relevant to the biological basis of abnormalities of sexual differentiation, and to the explanation of sex differences in neurological and psychiatric disease, not only of those that affect dopamine systems (e.g., Parkinson's Disease, Tardive Dyskinesia, Tourette's Syndrome, schizophrenia), but other sexually dimorphic diseases as well. (e.g., Multiple Sclerosis). Understanding sex differences in brain function will help develop sex-specific strategies for treatment of brain diseases.

NUTRITION

TITLE: **Altered Calcium and Vitamin D Metabolism in PMDD** **NIDDK**
P.I.: **Susan Thys-Jacobs, MD**
INSTITUTION: **St. Luke's-Roosevelt Hospital Center, New York, NY**
GRANT NO.: **1 R01 DK57869-03**
KEYWORDS: **PMDD, nutrition**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Premenstrual Dysphoric Disorder (PMDD) is widely recognized as a recurrent disorder related to hormone variations of the menstrual cycle. Whereas alterations in calcium homeostasis have long been associated with many affective disturbances, recent evidence has suggested that luteal phase symptomatology may be associated with a perturbation in calcium homeostasis. The purpose of this investigation is to understand more completely the extent to which calcium regulation is disturbed in PMDD by utilizing new tools to access calcium and bone turnover. The long-term objective is to elucidate the pathophysiology of PMDD as it relates to the calciotropic hormones and bone markers. The experimental design involves enrolling 70 with PMDD and 35 controls. Following two months of baseline symptom documentation, women with PMDD and controls with be enrolled in a nine-month observational period with frequent hormonal samplings, urinary collections and daily ratings. Understanding the pathophysiology associated with PMDD may lead to effective therapeutic strategies to prevent the neuropsychiatric disturbances and abnormal calcium regulation that are characteristic of this disorder.

OBESITY/OVERWEIGHT

TITLE: **Look AHEAD (Action For Health in Diabetes)** **NIDDK**
INSTITUTION: **Wake Forest University (coordinating center), Winston Salem, NC**
Johns Hopkins University, Baylor College of Medicine, University of Colorado Health, University of Washington, University of Tennessee, St. Lukes-

Roosevelt Institute, University of Alabama at Birmingham, The Miriam Hospital, Pennington Biomedical Research, University of Texas Health Science, University of Minnesota, University of Pittsburgh, Massachusetts General Hospital, University of California Los Angeles, University of Pennsylvania, Southwest American Indian Center (12 clinical centers)

GRANT NO.: **5 U01 DK57136**

KEYWORDS: **Type 2 diabetes, obesity, cardiovascular, cerebrovascular, neurosciences research, behavior**

TYPE STUDY: **Clinical**

AMOUNT: **$100,000**

Look Ahead is a multicenter randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. The Look AHEAD trial will enroll 5,000 obese patients with type 2 diabetes over a 2.5 year period. Participants will be randomly assigned to one of two interventions, the Lifestyle Intervention or Diabetes Support and Education, and will be followed for a total period of up to 11.5 years. The primary aim of Look AHEAD is to study the effects of the two interventions on major cardiovascular events: heart attack, stroke and cardiovascular death. Look AHEAD also will investigate the impact of the interventions on other cardiovascular disease-related outcomes, cardiovascular risk factors, and all-cause mortality. Additional outcomes include: diabetes control and complications, fitness, general health, health-related quality of life and psychological outcomes. The cost and cost effectiveness of the Lifestyle Intervention relative to Diabetes Support and Education will be assessed.

TITLE: **Dysregulated Muscle Lipid Metabolism in African Americans** **NIDDK**

P.I.: **Ronald N. Cortright, PhD**

INSTITUTION: **East Carolina University, Greenville, NC**

GRANT NO.: **1 R21 DK65183-01**

KEYWORDS: **diabetes, obesity, lipid metabolism, insulin resistance**

TYPE STUDY: **Clinical**

AMOUNT: **$139,500**

The prevalence of obesity and diabetes is greater among African-American (AAW) than Caucasian women (CW) in the United States. Although environmental factors may be influential, obese AAW have been shown to possess inherent metabolic defects that suppress lipid oxidation by skeletal muscle. More startling however, is the emerging evidence that these defects may pre-exist in non-obese AAW, predisposing this racial group toward a more rapid onset of fat gain vs. CW. This is fundamentally important because the resultant increase in intramuscular lipid content is strongly linked with insulin resistance and diabetes. Despite the significance of these findings, the cellular mechanisms to explain this racial/ethnic specific metabolic dysfunction remain undefined. Our primary hypothesis is that pre-obese/diabetic AAW possess skeletal muscle with an inherent impairment in the capacity to oxidize long-chain fatty acids (LCFA), leading to a cytotoxic accumulation of bioactive lipids, and precipitation of insulin resistance and diabetes. However, in lean CW, endurance exercise training (EET) stimulates mitochondrial biogenesis, elevating the muscles capacity to oxidize LCFA. The secondary hypothesis is that AAW will respond to EET by increasing the capacity of skeletal muscle to oxidize lipids, thus reducing the propensity toward developing obesity and diabetes. The aims of the investigation are 1) to identify the pre-existing cellular site(s) of dysfunction in skeletal muscle LCFA oxidation in lean AAW and 2) to determine whether AAW are responsive to EET. To accomplish the aims, the investigators will study 12 sedentary, lean AAW and CW matched for age, BMI (< 25 kg/m^2), and menstrual status. Obese subjects from both races will be assessed for comparisons. Skeletal muscle LCFA oxidative capacity will be measured by trapping labeled $^{14}CO_2$ derived from oxidation by intact muscle strips and homogenates (rectus abdominus) in order to identify the specific cellular defects in lipid metabolism as being due to 1) pre-mitochondrial events 2) mitochondrial activation of LCFA to acyl-CoA 3) the transport of LCFA across the mitochondrial membrane and/or 4) the post-transport mitochondrial oxidative system. Measures of whole body insulin sensitivity will be made to determine the strength of association between the status of skeletal muscle lipid metabolism and insulin action. A subset of subjects from aim 1 and new recruits will undergo 7 days and 8 weeks of EET (cycling) to determine the impact of chronic muscle activity (vastus lateralis) on mitochondrial

biogenesis, oxidation of LCFA, and insulin action in AAW. The findings will be used for subsequent research to achieve the long-term objective of understanding the mechanism(s) that underlie the greater morbidity and mortality associated with obesity and diabetes in AAW.

OPTHALMIC DISEASES

TITLE: **Incidence of Late Macular Degeneration in Older Women** **NEI**
P.I.: **Anne L. Coleman, MD**
INSTITUTION: **UCLA**
GRANT NO.: **1 U10 EY13626-01A1**
KEYWORDS: **blindness, quality of life, aging, Caucasian women**
TYPE STUDY: **Epidemiologic (case-control)**
AMOUNT: **$230,000**

Age-related macular degeneration is the number one cause of irreversible blindness in the United States and is more prevalent in older, Caucasian women. Although there have been several studies on the incidence of ARM, none of these studies has been able to provide accurate estimates on the incidence of late ARM and/or the progression of ARM in the oldest old, those individuals over 80 years of age, because of the limited sample sizes in these studies in this age group. The population in the Study of Osteoporotic Fractures (SOF) is an appropriate cohort in which to evaluate the incidence of late ARM and the progression of ARM, because the mean age of the women at the re-examination will be 84.4 years of age and the sample is mainly Caucasian. The proposed research study aims to determine the incidence of late ARM, the rate of progression of ARM, and the association of specific risk factors such as diabetes mellitus and prior cataract surgery with late ARM and the progression of ARM in elderly women. In addition, it aims to determine the trajectory of visual decline in older women over a 14- year period. Secondarily, it aims to determine the impact of late ARM on vision-targeted health-related quality of life and to determine whether or not an association exists between the progression of ARM and the risk of falling and hip/non-spine fractures. In 1997 to 1998 (Visit 6), 5482 women had an eye examination that consisted of a medical and ocular history, nine questions from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and measurements of visual acuity, contrast sensitivity, peripheral vision with automated perimetry, intraocular pressure, and uncorrected refractive error. These women also had a refraction and imaging of their lenses and fundi of both eyes through dilated pupils. Approximately 4.5% of these women have photographically validated late ARM, 41.5% have early ARM, and 54% have no ARM or hard drusen only. In the proposed re-examination, we will update their medical and ocular history and ask them the nine questions from the NEIVFQ. In addition, visual acuity and contrast sensitivity will be re-measured. Fundus photographs of both eyes through dilated pupils will be obtained. These photographs and the relevant photographs from 1997 to 1998 will be graded for ARM with the Wisconsin Age-Related Maculopathy Grading System (WARMGS) in a masked fashion so that the readers do not know which film is from which visit. The University of Wisconsin will also grade the fundus photographs on 30% of the eyes with ARM and 10% of the total sample. This will allow the identification of women in SOF who have had progression of their ARM and developed late ARM since 1997 and 1998.

TITLE: **Visual Dysfunction and Quality of Life in Multiple Sclerosis** **NEI**
P.I.: **Laura J. Balcer, MD**
INSTITUTION: **University of Pennsylvania, Philadelphia, PA**
GRANT NO.: **1 R01 EY13273-02**
KEYWORDS: **visual impairment, quality of life, Multiple Sclerosis, autoimmunity, behavior**
TYPE STUDY: **Clinical Cohort Study**
AMOUNT: **$125,000**

Visual impairment is a leading cause of symptoms in patients with multiple sclerosis (MS). The extent to which vision has been affected by new therapies for MS is not known, and has been difficult to assess using traditional measures of neurologic impairment. The visual profile of MS has not been examined, and the relation of visual function to overall neurologic impairment in patients with MS has not been determined in a large, heterogeneous cohort. This proposal will accomplish the following specific aims: 1. Define the visual profile of MS in a large cohort (400 patients), and determine which measures best identify visual dysfunction in patients with MS; and 2. Determine the relation of visual function to vision- and disease-specific HRQOL in patients with MS.

TITLE: **Effect of Estrogen on Radiation-included Cataractogenesis** **NEI**
P.I.: **Joseph Dynlacht, PhD**
INSTITUTION: **Indiana University, Indianapolis, IN**
GRANT NO.: **1 R03 EY014627-01**
KEYWORDS: **Ophthalamic diseases, aging**
TYPE STUDY: **Basic**
AMOUNT: **$147,367**

The induction of cataracts is often an unfortunate and unavoidable consequence of conventional radiation therapy for head and neck or ocular tumors, whole-brain irradiation, and total-body irradiation prior to autologous bone marrow transplantation. Though not life-threatening, radiation-induced cataractogenesis represents a potentially serious sequelae of radiotherapy which can require surgical intervention. While the cellular and molecular mechanism(s) of radiation-induced cataractogenesis have not been clearly elucidated, damage to the genome at the time of exposure and subsequent proliferation of the radiosensitive cells in the germinative zone of the lens epithelium likely play a role in the process. Using a rat model, preliminary data has been accumulated, which indicate that estrogen reduces the latent period and may increase the incidence and severity of radiation-induced cataracts. High estrogen levels are artificially induced in non-pregnant women using oral contraceptives, or in post-menopausal women on estrogen replacement therapy, and these groups may be at an increased risk for developing cataracts which are more severe or occur with a more rapid onset. Estrogens regulate several proteins involved in cell cycle control and apoptosis, and it's metabolism results in the production of free radicals which may be genotoxic and mutagenic to mammalian cells. Thus, a novel hypothesis to be tested in the proposed studies is that estrogen alters cell cycle regulation, DNA double strand break induction or repair, and proliferation in irradiated lens cells. The dose-time interactions of radiation and estradiol will be investigated to better understand the mechanism of estrogen action, and determine whether estrogen-modulation of radiation cataractogenesis is estrogen receptor (ER)-mediated using knockout mice that are deficient in either ERa or ERb. The lens has frequently been used as a model for predicting delayed (late) effects in other irradiated tissues. Data obtained from the proposed study may demonstrate that the lens is a useful model for predicting late effects in other estrogen-responsive target tissues. Finally, the efficacy of utilizing a novel technique for small animal irradiations shall also be tested; in this study, using the Leksell Gamma Knife, only one eye shall be irradiated in each of the animals, with the contralateral eye serving as a control.

TITLE: **Estrogen Receptors and Maintenance of Lens Transparency** **NEI**
P.I.: **Vicki L. Davis, PhD**
INSTITUTION: **Cedars-Sinai Medical Center, Los Angeles CA**
GRANT NO.: **1 R01 EY014600-01**
KEYWORDS: **ophthalmic diseases, aging**
TYPE STUDY: **Basic**
AMOUNT: **$130,093**

This is a study of the function of the estrogen receptor with regard to lens transparency using transgenic mice models. The project does not employ any novel concepts, approaches, or methods. However, it is of high impact because it will provide information critical for establishing a rational estrogen-signaling modulation therapy for maintaining lens transparency.

PAIN

TITLE: **Low Back Pain - A Multi-Center Randomized Trial** **NIAMS**
P.I.: **James Weinstein, DO**
INSTITUTION: **Dartmouth Medical School, Hanover, NH**
GRANT NO.: **5 U01 AR045444-04**
KEYWORDS: **neurosciences research, back pain**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Low back pain is considered one of the most widely experienced health problems. Rates of spinal surgery have increased sharply over time and 15-fold geographic variation in rates of these

surgeries has been documented. There is little evidence proving the effectiveness/efficacy of these surgical therapies over non-operative management. This study will use the resource of the National Spine Network to conduct multi-centered, randomized, controlled trials for three common diagnostic groups - lumbar intervertebral disc herniation (IDH), spinal stenosis (SpS) and spinal stenosis secondary to degenerative spondylolithesis (DS). The trials will compare the most commonly used standard surgical treatments to the most commonly used standard non-operative treatments. The primary endpoints will be changes in general health-related quality of life as measured by the SF-36 health status questionnaire and spine-related disability as measured by the Oswestry Low Back Pain questionnaire. Secondary endpoints will include patient satisfaction with treatment, resource utilization of estimation of cost, and utility for current health for estimation of quality adjusted life years.

TITLE: **Pain Management in Temporomandibular Joint Disorders** **NIDCR**
P.I.: **Jennifer Haythornthwaite, PhD**
INSTITUTION: **Johns Hopkins University, Baltimore, MD**
GRANT NO.: **1 R01 DE13906-02**
KEYWORDS: **TMD, pain control, behavioral interventions, neurosciences research**
TYPE STUDY: **Clinical Behavioral**
AMOUNT: **$312,313**

The primary goal of the proposed project is to test the efficacy of psychological interventions, a pharmacological intervention, and the combination of these interventions in reducing pain and improving function in persons with temporomandibular disorders (TMD). Since psychological interventions are costly and require expertise that is frequently unavailable in primary care settings, the proposed project will also examine the efficacy of a minimal contact/self help psychological intervention based on cognitive-behavioral therapy for pain management. In addition to examining the separate and combined effects of psychological and pharmacological interventions for TMD pain, the proposed study will examine whether the minimal contact cognitive-behavioral intervention can accomplish comparable reductions in pain and improvements in function relative to the therapist-administered treatment.

TITLE: **Research Registries and Repository for the Evaluation of Temporomandibular Joint Implants (TMJ Device Registry)** **NIDCR**
P.I.: **James R. Fricton, DDS, MS**
INSTITUTION: **University of Minnesota**
GRANT NO.: **N01 DE22635**
KEYWORDS: **TMJ, medical devices**
TYPE STUDY: **Registry**
AMOUNT: **$100,000**

The development of the National Institute of Dental and Craniofacial Research's TMJ Implant Registry and Repository (NIDCR's TIRR) at the University of Minnesota will allow collection of clinical information and biological specimens on patients with TMJ implants throughout the United States. This will stimulate both basic and clinical studies and improve our understanding of the pathobiology of TMJ diseases and disorders. In addition, the availability of retrieved implant materials will help in the design and development of a new generation of implantable materials and advance our understanding and success of treatment of patients with TMJ implants.

TITLE: **Sex Differences in Opioid Analgesia** **NIDA**
P.I.: **Anne Z. Murphy, PhD**
INSTITUTION: **University of Maryland School of Medicine, Baltimore, MD**
GRANT NO.: **1 R01 DA016272-01**
KEYWORDS: **opioids, gender, pain, analgesia**
TYPE STUDY: **Basic**
AMOUNT: **$50,000**

Chronic pain afflicts millions of people each year. Opioid-based narcotics are the most prevalent therapeutic treatment for chronic pain management, with morphine being the most commonly prescribed. There are now well-established sex differences in the ability of morphine to alleviate pain; in animal models of acute pain, the effective dose of morphine is approximately 5-10x greater for females in comparison to males. Similar results have been reported in humans. To date, the underlying mechanisms mediating sex differences in opiate sensitivity are not known. The midbrain periaqueductal (PAG) and its descending projections to the nucleus raphe magnus

(NRM) are an essential endogenous neural circuit for opioid-based analgesia. The major hypothesis is that the opiate-sensitive intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and is the major determinant of sex-based differences in opioid analgesia. Previous studies examining the dimorphic effect of opioid administration utilized acute assays of nociception. Studies proposed in Aim 1 will characterize the sexually dimorphic effect of central morphine administration using a model of chronic inflammatory pain. Preliminary data indicate that the PAG-NRM pathway is sexually dimorphic. Studies proposed in Aim 2 will use neural tract tracing techniques to delineate the anatomical organization of the PAG-NRM spinal cord circuit in males and females. Aim 3 will examine the functional organization of this circuit in a model of prolonged inflammatory pain. The PAG is enriched in opioid receptors. Studies proposed in Aim 4 will characterize both the distribution and expression pattern of the opioid receptors. The influence of chronic inflammatory pain and gonadal steroid manipulations will also be examined. These studies will establish that the intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and provide the neural substrate for sex based differences in opioid analgesia.

TITLE: **Trigeminal Pain Mechanisms and Control** **NIDCR**
P.I.: **Jon D. Levine, PhD**
INSTITUTION: **University of California at San Francisco, San Francisco, CA**
GRANT NO.: **5 P01 DE08973-12**
KEYWORDS: **pain control mechanism, orofacial neuropathies, neurosciences research**
TYPE STUDY: **Basic**
AMOUNT: **$159,422**

The chemotherapeutic agent paclitaxel(Taxol) is widely used for the treatment of many different types of carcinomas. At present, the dose of paclitaxel that can be tolerated by patients is limited primarily by the development of a painful peripheral neuropathy characterized by parenthesis, myalgia and arthralgia. Similar dose-limiting painful neuropathies are produced by other microtubule-disrupting chemotherapeutic drugs, including vincristine. Therefore, amelioration of the neuropathic pain might not only reduce the suffering of patients who receive paclitaxel or vincristine therapy, but also increase the effectiveness of their treatment by permitting the use of higher doses of the drugs. We propose a series of experiments to elucidate the cellular mechanisms of paclitaxel-induced painful peripheral neuropathy in the rat. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies.

PHYSICAL ACTIVITY

TITLE: **Angiogenesis and Mechanisms of Exercise Training in PAD** **NHLBI**
P.I.: **Brian H. Annex**
INSTITUTION: **Medical Center, Durham, NC**
GRANT NO.: **1 R01 HL075752-01**
KEYWORDS: **artery, atherosclerosis, exercise**
TYPE STUDY: **Clinical**
AMOUNT: **$250,000**

Peripheral arterial disease (PAD) impairs arterial blood flow to the legs and is a major indicator of systemic atherosclerosis. PAD affects 5% of the US population over 50. Approximately 1/3 of patients with PAD have typical claudication, defined as pain in one or both legs on walking that is relieved by rest. Patients with claudication have a marked impairment in exercise performance similar to patients with NYHA class III heart failure. Goals of treatment for PAD patients include risk-factor modification and antiplatelet drug therapy to address increased cardiovascular mortality risk. Supervised exercise training is the most efficacious treatment to improve walking capacity, demonstrated in many (small) randomized trials. Neither the pathophysiology of claudication nor the mechanism(s) by which exercise training improves walking times in persons with IC are completely understood. It is unknown how long term exercise training effects skeletal muscle or to what extent skeletal muscle abnormalities in PAD are reversible. Women have been largely underrepresented in mechanistic studies of IC and exercise training. There is an urgent need for clinical research directed towards defining the basis of the exercise training changes induced in PAD patients in order to: 1) provide insights into the general pathophysiology of the exercise impairment in PAD; 2) permit scientifically plausible and testable modifications to currently

prescribed exercise regiments to better employ this critical therapeutic modality, and 3) identify novel targets from pharmacotherapy that are capable of inducing the repertoire of molecular responses induced by exercise training.

TITLE: **Increasing Physical Activity Levels in Low-Income Women** **NIDDK**
P.I.: **Barbara J. Speck, PhD, RN**
INSTITUTION: **University of Louisville, KY**
GRANT NO.: **1 R01 DK63523-01**
KEYWORDS: **underrepresented minorities, physical activity, intervention**
TYPE STUDY: **Clinical**
AMOUNT: **$178,750**

This project is aimed at reducing community environmental barriers to physical activity in medically underserved women. The setting for the study is a church-sponsored community center with a nurse-managed clinic that is located in a low-income neighborhood. Pretest data will include psychosocial questionnaire, physiologic (cholesterol, blood pressure), and anthropometric measures. The 6-month intervention will be two-fold: 1) provide culturally appropriate educational activities to increase women's comfort level at the community center, and 2) provide multiple culturally appropriate physical activity opportunities utilizing the gymnasium and exercise equipment. The long-term goal to establish physical activity opportunities for women at this community center that could be adapted at other community center.

REPRODUCTIVE HEALTH/DEVELOPMENTAL BIOLOGY

TITLE: **Fragile X Mental Retardation Gene Premutation** **NICHD**
P.I.: **Pamela L. Mellon, PhD**
INSTITUTION: **University of California San Diego, La Jolla, CA**
GRANT NO.: **5 U54 HD12303-23**
KEYWORDS: **premature ovarian failure, genetics, women's health**
TYPE STUDY: **Translational**
AMOUNT: **$113,000**

Fragile X syndrome (FRX) is one of the most frequent forms of congenital mental retardation in humans, usually resulting from lack of expression of the Fragile X Mental Retardation Gene (FMR1). Interestingly, unaffected carriers or so-called FRX premutation carriers show an increased prevalence of Premature Ovarian Failure (POF) which is generally defined as cessation of reproductive function by age 40. While it is estimated that 1% of women worldwide experience POF, the prevalence of POF in FRX premutation carriers has been reported to be 16%. On a more basic science level, the FMR1 gene is expressed in many tissues, but its function is unknown. In both male and female gonads, the gene is expressed in the germ cells. For the ovary, expression of the FMR1 gene in oogonia and oocytes could have profound implications for the regulation of oocyte number and ovarian follicular reserve, which clearly can impact the cessation of reproductive function. Three aims are proposed to: 1) characterize the cell-specific FMR1 gene expression changes in normal human and mouse ovaries through their respective reproductive cycles; 2) define the physiology of hypothalamic-pituitary-ovarian function in human female FRX premutation carriers; and 3) create a repository of genetic material and extensive phenotypic information about women with POF that could eventually be used to test other candidate genes for POF.

TITLE: **Development and Differentiation in Reproductive Axis Cooperative Reproductive Sciences Research at Minority I institutions** **NICHD**
P.I.: **Director–David R. Mann, PhD, Morehouse School of Medicine, Atlanta, GA**
Co-director/Partner–Tony M. Plant, PhD, University of Pittsburgh, Specialized Cooperative Centers Programs in Reproductive Research, Pittsburgh, PA
GRANT NO.: **5 U54 HD41749-02**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation**
TYPE STUDY: **Basic science, translational, clinical**
AMOUNT: **$250,000**

The purpose of this initiative is to form a cooperative program that will augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions by supporting the development of new, and/or the enhancement of ongoing, basic

science, translational, and clinical research that focuses on topics deemed to be of high priority and significance because of their critical importance to reproductive health. The Morehouse Reproductive Science Research Center consists of four research projects and an administrative core. Grant No. 1U54HD41749-01 (Development and Differentiation in Reproductive Axis), David R. Mann, is the parent grant. Grant No. 1–1U54HD41749-010001 (Hypothalamic GnRH Pulse Generator), David R. Mann. Grant No. 2--1U54HD41749-010002 (Role of Prohibitin in Follicular Development), Winston E. Thompson. Grant No. 3--1U54HD41749-010003 (Role of GnRH In Luteolysis), Rajagopala Sridaran. Grant No. 4--1U54HD41749-010004(SP Regulation of Gene Expression in Spermatogenesis), Kelwyn H. Thomas.

TITLE: **Intermediate Outcomes of Hysterectomy and Alternatives** **AHRQ**
P.I.: **Miriam Kuppermann, PhD**
INSTITUTION: **University of California San Francisco**
GRANT NO.: **1 R01 HS11657-02**
KEYWORDS: **hysterectomy, quality of life, pelvic pain**
TYPE STUDY: **Outcome Research**
AMOUNT: **$250,000**

The project expands on our existing prospective longitudinal study of 811 women with non-cancerous uterine conditions for which hysterectomy is a reasonable treatment option: abnormal bleeding, symptomatic uterine leiomyomata, and pelvic pain/endometriosis. The principal aims of the proposed study are to 1) determine whether and how intermediate-term (4-8) year clinical and quality-of-life outcomes differ by treatment group (hysterectomy, uterus-preserving surgery, or non-surgical treatments) for their uterine conditions; and 2) develop predictive models of treatment choice and satisfaction from a broad array of domains.

TITLE: **The Biologic Effects of Androgens in Men and Women** **NICHD**
RFA: **Cooperative Reproductive Sciences Research at Minority Institutions (RFA HD-02-012)**
P.I.: **Shalender Bhasin, MD**
INSTITUTION: **Charles R. Drew University of Medicine and Science**
GRANT NO.: **U54 HD041748**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation**
TYPE STUDY: **Basic science, translational, clinical**
AMOUNT: **$200,000**

The Drew Center would serve to strengthen an existing, established, investigative effort between Charles R. Drew University and UCLA. The role of testosterone in normal female physiology is poorly understood and this center would serve to increase our knowledge of the characterization of this hormone in sexual function, body composition and strength, and cognitive ability in women. One project uses the model of hormone deficient women. Randomized treatment with varying doses of testosterone is proposed to address these important biological questions. Another project will test the hypothesis that female patients with panhypopituitarism would benefit from physiological testosterone replacement. A third project will use an animal model to examine the genetic factors, beyond hormonal effects, that regulate sex differentiation between male and female brains. The fourth project focuses on androgen-dependent stem cell differentiation. Strengths of the Center include the expertise and experience of the investigative team, its clinical approach to examine whether testosterone replacement in physiological range can produce meaningful improvements in quality of life, and its unique approach to investigating the molecular basis of sex differentiation.

TITLE: **MMC/PSU Cooperative Center for Research in Reproduction** **NICHD**
RFA: **Cooperative Reproductive Sciences Research at Minority Institutions (RFA HD-02-012)**
P.I.: **Ponjola Coney, MD**
INSTITUTION: **Meharry Medical College**
GRANT NO.: **U54 HD044315**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation**
TYPE STUDY: **Basic science, translational, clinical**
AMOUNT: **$200,000**

The Meharry Center would serve to facilitate the development of a reproductive science research center at Meharry Medical College through a strong collaborative partnership with Pennsylvania State University. Studies outlined in these projects will generate knowledge and assess outcomes

across the lifespan of women of different ages and racial/ethnic groups: (1) the role of sex steroid hormones as determinants of bone mineral density in African American females, (2) the influence of oral contraceptives on the growth of uterine fibroids, and (3) the efficacy and safety of metformin and lifestyle factors in the amelioration of polycystic ovary syndrome (PCOS) and its symptomatology in both adolescent and adult females. The overall objective is to determine whether ovarian production of estrogens and progesterone differ among women of diverse racial/ethnic groups and whether these determinants are responsible for racial differences in several positive and negative health outcomes. Strengths of the Center include the innovative aspects of the proposed projects, their experimental designs, and the comparisons of lifestyle interventions and therapeutic regimens.

TITLE: **Control of menstrual bleeding disturbances in women** **NICHD**
P.I.: **Ian Stewart Fraser, MD**
INSTITUTION: **Sydney Centre for Reproductive Health Research, Ashfield, AUSTRALIA**
GRANT NO.: **1 R01 HD043192-01**
KEYWORDS: **endometrial bleeding, contraception, progestogens**
TYPE STUDY: **Basic**
AMOUNT: **$35,000**

This project will evaluate two promising approaches to the treatment of prolonged and frequent episodes of breakthrough bleeding which sometimes accompany the use of the implantable, progestogen-only implant Implanon. These erratic episodes of bleeding can be a major reason for discontinuation of use. There is increasing evidence that continuous exposure to progestogens results in a tendency for the endometrium to release active enzymes called matrix metalloproteinases [MMPs], which can promote premature breakdown of the tissue. Inhibition of the action of these enzymes may stabilize the endometrium and improve the bleeding pattern. A commonly used tetracycline compound, Doxycycline, has strong anti-MMP action and preliminary evidence in a mouse model of menstruation suggests that it may indeed stabilize the endometrium. There is preliminary evidence that a short course of an antiprogesterone (Mifepristone) may also stabilize the endometrium, and it is postulated that a combination of antiprogesterone with estrogen may be even more effective. Preliminary evidence in mice indicates that estrogen exposure of the endometrium in the absence of progesterone strongly inhibits the formation of new blood vessels and simultaneous anti-progesterone exposure will mimic this situation.

TITLE: **Female Reproductive Organs and Their Innervation** **NINDS**
P.I.: **Raymond E. Papka, PhD**
INSTITUTION: **Northeastern Ohio Universities, Roostown, OH**
GRANT NO.: **1 R01 NS022526-14A1**
KEYWORDS: **cervix, uterus, sensory innervation, neurotransmitters, neurogenic inflammation**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

Two important problems in obstetrics are control of uterine body contractions and cervical dilatation. The long-term goal of this research is to understand neural mechanisms for integration of uterine cervical information and how these play a role in cervical ripening and parturition (act of giving birth) - particularly as this relates to pre-term or protracted labor, spinal cord-injured females and autonomic dysreflexia. Rationale for these studies is that birthing problems are critical obstetric problems; pre-term labor occurs in 5-10 percent of pregnancies in North America. Within this context, the aims of this proposal are to elucidate the sensory neural substrate of the uterine cervix and how this substrate relates to physical changes in the cervix during cervical ripening and parturition. We propose that this substrate involves sensory nerves, neurotransmitters, receptors, the hormone estrogen, and controlled neurogenic inflammation and leads to the hypothesis: sensory neurons and transmitters innervating the uterine cervix are estrogen responsive, plastic, and are critical components participating in tissue rearrangements occurring at cervical ripening and parturition. Specific aims will determine: 1) if there is enhanced synthesis and release of neurotransmitters by sensory neurons innervating the uterine cervix, specifically at cervical ripening & parturition; 2) if there are specific neurochemically identifiable sensory neurons of lumbosacral spinal ganglia activated expressly at cervical ripening and parturition; 3) if estrogen, working through estrogen receptors, influences levels of neurotransmitters in sensory ganglionic neurons innervating the cervix during pregnancy, parturition, and early postpartum; 4) if cervical ripening and parturition entail a controlled neurogenic inflammatory process; and 5) if specific subclasses of

small C-type (peptidergic and non-peptidergic) neurons have identifiable roles in cervical ripening and parturition. These studies will utilize in situ hybridization, RT-PCR, Western blots, immunohistochemistry, nerve transections and neurotoxins. Health benefits from understanding involvement of neural mechanisms in the uterine cervix include an increased basic understanding of neuroendocrine coordination of gestational events including pregnancy, cervical ripening and parturition and the possibility of remediating problems such as pre-term labor, protracted labor, and autonomic dysreflexia. Finally, knowledge of estrogen responsive sensory neurons has important implications for understanding neuropathic pain syndromes influenced by estrogen levels.

TITLE: **Protein Tyrosine Kinases in Leiomyomata Uteri** **NICHD**
RFA: **Leiomyomata Uteri: Basic Science and Translational Research (RFA HD03-005)**
P.I.: **Jean Wang, PhD**
INSTITUTION: **University of California, San Diego, CA**
GRANT NO.: **1 R01 HD046225-01**
KEYWORDS: **women's health, quality of life, uterus, leiomyoma**
TYPE STUDY: **Basic**
AMOUNT: **$300,000**

In this application, the investigators propose that female sex hormones stimulate the expression and/or activation of protein tyrosine kinases to promote uterine cell proliferation and tumor growth, and predict that inhibition of protein tyrosine kinases involved in the proliferation of uterine cells would halt the growth of uterine leiomyomata. This study will survey the expression and activity of protein tyrosine kinases in normal uterine myometrium and leiomyoma specimens procured from women in different ages and racial/ethnic groups. The investigator plans to create a microarray that is suitable for profiling the expression of all 90 human protein tyrosine kinase genes. A strength of the application is the creation of the microarray, which is important and promises to have wide-scale application beyond the study of uterine leiomyomata. Results from this study may identify protein tyrosine kinases that are important for proliferation of uterine leiomyomata.

TITLE: **Estrogen Dependency of Uterine Leiomyoma** **NICHD**
RFA: **Leiomyomata Uteri: Basic Science and Translational Research (RFA HD03-005)**
P.I.: **Ayman Al-Hendy, MD, PhD**
INSTITUTION: **University of Texas Medical Branch, Galveston, TX**
GRANT NO.: **1 R01 HD046228-01**
KEYWORDS: **women's health, quality of life, uterus, leiomyoma**
TYPE STUDY: **Basic**
AMOUNT: **$300,000**

The hormone dependent phenotype of uterine leiomyomata suggests that interventions targeting the estrogen receptor-signaling pathway may have therapeutic efficacy. This application plans to investigate the immune response and safety of single versus repeated recombinant adenovirus treatment alone or in combination with a selective estrogen receptor modulator (SERM) in mice, rat, and human leiomyoma cells. The strength and overall conceptual framework of this work is to test the validity and regulatory mechanisms of gene therapy as an alternative to non-surgical treatment for uterine leiomyomata as well as to further elucidate the molecular mechanisms of estrogen dependency of uterine leiomyomata. This highly innovative research will add to our understanding of the molecular mechanisms of estrogen-dependence in this common uterine tumor and may open a new area of investigation and treatment of uterine leiomyomata.

TITLE: **Collaborative Research Initiative** **NICHD**
P.I.: **Linda C. Giudice, MD, PhD**
INSTITUTION: **Stanford University, Palo Alto, CA**
GRANT NO.: **U54 HD 31398**
KEYWORDS: **endometriosis, genetics, infertility**
TYPE STUDY: **translational**
AMOUNT: **$150,000**

Endometriosis is a benign, estrogen-dependent, gynecologic disorder that is clinically associated with pelvic pain and infertility and is diagnosed by direct visualization during surgery. Pelvic endometriosis, and thus, eutopic endometrium (i.e. endometrium within the uterus) is presumed

abnormal in women with the disease. The abnormality extends to uterine receptivity, supported by high implantation failure and poor pregnancy rates in IVF cycles in women with disease. Recently, using a global gene profiling approach, we identified candidate genes for uterine receptivity in normally cycling women without endometriosis and in women with mild/moderate endometriosis, through a collaborative, multi-center study. The current collaborative research initiative will lay the foundation for clinical translation of the data collected to date, with the following goals: diagnosis of a receptive endometrium for fertility: diagnosis of a non-receptive endometrium in women with endometriosis and infertility; diagnosis of endometriosis; and diagnosis of the stage (severity) of endometriosis in the pelvis.

TITLE: **Prevalence and Etiological Predictors of Vulvodynia** **NICHD**
P.I.: **Bernard L. Harlow, PhD**
INSTITUTION: **Brigham & Women's Hospital, Boston, MA**
GRANT NO.: **5 R01 HD38428-05**
KEYWORDS: **vulvodynia, survey, controls, cases, cytokines, pain**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Vulvodynia is a syndrome of unexplained vulvar itching, burning, and/or pain that causes major physical and psychological distress. It is diagnosis of exclusion when vulvar discomfort becomes chronic over many months and the presence of any other remediable cause, such as infection or dermatitis, is ruled out. The two major subtypes of vulvodynia- generalized vulvar dysesthesia and vestibulodynia- are often misclassified. Few descriptive or etiologic epidemiological studies have been performed. Thus, the prevalence and incidence in the general population is unknown and no preventable exposures have been identified. A recent NIH sponsored consensus conference stressed the need to determine the prevalence of vulvodynia and conduct population-based observational studies to identify modifiable risk factors. The applicant has conducted a population-based prevalence survey in more than 400 women that achieved a 70% response rate and found that 18% of women reported a lifetime history of chronic vulvar symptoms that lasted three months or longer. Approximately 8% of all women surveyed were currently experiencing these symptoms. In addition, the applicant conducted a pilot case-control study of 31 women diagnosed with either dysesthetic vulvodynia or vestibulodynia, or a combination of the two within the last five years and compared them to 31 similarly aged health women identified from the general population. Cases were, on average, three times more likely to report medical treatments or surgical procedures for conditions that may have influenced perineal pain, or a greater frequency of condom use and use of talcum powder in the genital area that may have lead to mucosal abrasion and inflammation. A survey is being conducted on 16,000 women 20-59 years of age fro the general population to estimate the age-specific prevalence of vulvodynia. From this sample, the applicant will identify 400 cases of vulvodynia, verified through a two-step screening process, and a sample of 400 frequency matched age and county of residence controls. Structured interviews will assess a wide spectrum of exposures related to trauma. A subsample of 80 cases and 80 controls will receive a clinical examination to confirm the presence or absence of vulvodynia, and also will provide a vaginal lavage and vulvar swab specimen for the assessment of cytokines and the culturing of microbiological organisms. It is hypothesized that various types of vulvar trauma may precede the spontaneous and evoked vulvar pain experienced by women with vulvodynia and that vulvodynia may be a variant of a specific type of Complex Regional Pain Syndrome that is consistent with sensory disturbances such as mechanical allodynia.

TITLE: **Vulvodynia Prevalence and Efficacy of 4 Interventions** **NICHD**
P.I.: **Gloria A. Bachmann, MD**
INSTITUTION: **UMDNJ-RWJ Medical School, New Brunswick, NJ**
GRANT NO.: **5 R01 HD40119-05**
KEYWORDS: **vulvodynia, chronic pain syndrome, clinical, epidemiology, outcomes**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Vulvodynia is a complex, multi-factorial chronic pain syndrome that is associated with significant distress and interpersonal. Vulvar vestibulitis and dyspareunia are two common, although not well-understood clinical components or sub-types of vulvodynia. Chronic vulvar pain is experienced by, according to recent surveys, about 10-15% of the female population between 18 and 80. This

project is examining the efficacy, outcomes and cost-effectiveness and associated with four non-surgical interventions for vulvodynia.