FY2005 Vulvodynia Research

Grant Number: 5K24HD043076-03
PI Name: REED, BARBARA D.
PI Email: barbr@med.umich.edu
PI Title: PROFESSOR
Project Title: Midcareer Vulvodynia Research and Mentoring Project
Institute: National Institute of Child Health and Human Development

Abstract: *DESCRIPTION (provided by applicant): Midcareer* ***Vulvodynia*** *Research and Mentoring Project. This application is in response to the K24 Midcareer Investigator Award in Patient-Oriented Research Program Announcement (PA-00-005), which is designed to provide support for clinicians for protected time to increase their expertise and activities in patient-oriented research and to serve as mentors for beginning clinical investigators. Barbara D. Reed, M.D., M.S.P.H. has developed a research career that focuses on gynecologic disorders of women, with an emphasis on neuroimmunological factors associated with vulvar dysesthesia (****vulvodynia****). This award would allow her to become increasingly involved with state-of-the-art immunological/neurological technology, to increase multicenter collaborations among* ***vulvodynia*** *researchers, and to further her investigations on the pathogenesis and epidemiology of* ***vulvodynia****. Mentoring is also a vital aspect of this award. The award will allow Dr. Reed to augment her own mentoring activities with more junior researchers, while simultaneously developing a program to improve the consistency and accountability of the mentoring of each of the junior investigators throughout her department. Dr. Reed is currently conducting a three-year NICHD-funded project on "Neuroimmunology/cytokine alterations in* ***vulvodynia****." This patient-centered case control project assesses specific cytokine/neurokine responses to lymphocyte stimulation and their association with neurohistochemical changes found in vulvar tissue. Further studies on other aspects of the neuroimmune interactions that clarify differences among women with and without* ***vulvodynia*** *are at various stages of development, including assessing the relationship of cytokine production to local and peripheral psychophysical sensory responses of women with* ***vulvodynia*** *and controls, assessment of the immediate and delayed hypersensitivity reactions and cytokine correlates, evaluation of neuroimmunological changes following treatment, and the use of proteomics for immunological assessment of these women. Support from this award would allow further development, pursuit of funding, and implementation of these projects. Dr. Reed's research experience, ongoing investigations, and mentoring experience provide the context for this expanded program of study,* ***vulvodynia*** *research, and personal and departmental mentoring.*

Grant Number: 1R01HD045661-01A2
PI Name: REED, BARBARA D.
PI Email: barbr@med.umich.edu
PI Title: PROFESSOR
Project Title: Characterization of Pain Processing in Vulvodynia
Institute: National Institute of Child Health and Human Development

Abstract: ***Vulvodynia*** *is a chronic pain disorder, consisting of vulvar pain (burning, stabbing, irritation) for three months or longer, and lack of an infectious or dermatologic diagnosis consistent with the pain. The clinical characteristics of* ***vulvodynia****, and response to pharmacological therapy, are consistent with those of neuropathic pain. However, previous data from our group indicate increased sensitivity to pressure not only at the vulva, but also in the periphery (thumb, deltoid, and shin), suggesting that central mechanisms may be playing a role in women with* ***vulvodynia****. Further clarification of central and peripheral pain processing in women with and without* ***vulvodynia*** *has the potential to dramatically increase our understanding of this disorder, and will direct further study of pathophysiologic mechanisms and treatment options in* ***vulvodynia****. The specific aims of this study are: 1) to assess multi-modal sensory profiles at the vulva and in the periphery of 100 women with* ***vulvodynia*** *and 50 women without vulvar pain, and to use principal component and cluster analyses to identify novel subgroupings within the groups of cases, identify potential confounders, such as age, that can significantly affect the variation in the sensitivity data, possibly differentially in women with and without* ***vulvodynia****, and, 2) to further identify underlying mechanisms of vulvar pain in the established subgroupings by identifying, via fMRI, the qualitative and quantitative differences in location and character of supraspinal activity evoked by non-painful and painful sensory provocation at both vulvar and peripheral sites. We expect to find significant differences among the validated groups, and to then be able to use the known functional role of specific activated neural structures in the central nervous system to further refine hypotheses about the mechanisms that initiate and maintain painful vulvar disorders. Information from this research is anticipated to further define* ***vulvodynia*** *and its variants, to define subgroups based on underlying mechanisms, and to further our understanding of the pathophysiology of women with this disorder.*

Grant Number:	5R01HD039699-05
PI Name:	WESSELMANN, URSULA
PI Email:	pain@jhmi.edu
PI Title:	ASSOCIATE PROFESSOR OF NEUROLOGY
Project Title:	Mechanisms of Vulvodynia
Institute:	National Institute of Child Health and Human Development

Abstract: *DESCRIPTION: (provided by applicant) The long range objective of this research is to elucidate the pathophysiological mechanisms of* ***vulvodynia****, a chronic pain syndrome of the vaginal and vulvar area, in order to develop improved treatment strategies for alleviating chronic pain in these women, targeted at the underlying pathophysiological mechanisms.* ***Vulvodynia*** *is a major challenge for women who suffer from this chronic pain syndrome, and has a detrimental impact on their sexual lives. Treatment strategies, including medical and surgical approaches, are empirical only and are often unsuccessful. We propose two approaches to gain a better understanding of the pathophysiological mechanisms of* ***vulvodynia****: (1) We will develop an animal model in the rat, that will allow to study the spinal cord pathways involved in the processing of noxious input from the vagina. The specific goals of this animal research project are (a) to obtain detailed information about the spinal cord pathways that process nociceptive afferent input from the vaginal area, (b) to determine the influence of the estrous cycle on the spinal cord processing of noxious vaginal stimulation, (c) to assess the effects of pharmacological agents on the spinal cord processing of noxious vaginal stimulation, (d) to study the influence of previous vaginal/vulvar trauma on the response to noxious vaginal stimulation. (2) We propose to characterize pain in patients with* ***vulvodynia*** *in detail. Our hypothesis is that patients with* ***vulvodynia*** *can be differentiated into distinct groups based on their pain characteristics, and that treatment of pain in* ***vulvodynia*** *will be more effective, if based on recognition of the underlying neurophysiological mechanisms. The specific goals of this clinical research project are to (a) to assess the response to non-noxious and noxious stimuli in the vulvar and vaginal area in women suffering from* ***vulvodynia*** *in comparison to healthy controls using quantitative sensory testing, (b) to determine the influence of the gonadal hormonal milieu on pain in patients with* ***vulvodynia****. These studies will provide fundamental new insights into the pathophysiological mechanisms of* ***vulvodynia****. The results of these studies may rapidly contribute to the design of new treatment strategies specifically targeted at the underlying neural mechanisms of chronic pain in women with* ***vulvodynia****.*

Grant Number: 5K23HD045769-02
PI Name: KENNEDY, COLLEEN M.
PI Email: colleen-kennedy@uiowa.edu
PI Title: ASSOCIATE PROFESSOR
Project Title: Vulvar Disease and Bladder and Bowel Symptoms
Institute National Institute of Child Health and Human Development

Abstract: *DESCRIPTION (provided by applicant): Patient-oriented research in vulvar and vaginal disorders has primarily been descriptive. In addition to lack of formal training and education of clinical researchers in this field, pelvic disorders are divided among various specialties. Each pelvic organ is compartmentalized and treated without regard to global or systemic effect. Despite identification of various pelvic and vulvar disease entities such as* ***vulvodynia****, little is known about their etiology, treatment, or prevention. Case-series have noted the presence of painful bladder syndrome in women who have* ***vulvodynia*** *and vestibulitis. We propose an epidemiologic study to determine the extent to which painful bladder syndrome and functional bowel disorders overlap with specific vulvar diseases and to determine whether the rate of painful bladder syndrome and functional bowel disorders differ between women with vulvar disease and controls. This will establish whether the association noted in the case-series is significant. In addition to expanding current knowledge regarding the epidemiology of* ***vulvodynia*** *and vestibulitis, this will provide a foundation for global evaluation of pelvic disorders in general. This in turn may encourage a more effective multi-disciplinary approach to the management of pelvic floor disorders including* ***vulvodynia****. Dr. Colleen Kennedy is committed to a career as a productive academic clinical researcher studying vulvar and vaginal diseases. This award would allow Kennedy to pursue a clinical investigation foundation through didactic training, mentoring, and research development. Further training in research methodology and advanced statistical techniques will increase her potential to make significant contributions to the field of vulvar and vaginal diseases. The overarching aim of this research program is to significantly improve the quality of care of women with vulvar and vaginal diseases. Dr. Kennedy's immediate goals during the award period include: 1) further didactic training in patient-oriented research methods, and enhance ongoing mentoring relationships, 2) gain further experience in the area of vulvar and vaginal disease, by working with experts in vulvar disease, by reviewing current literature, and by attending professional meetings, 3) conduct research to further the knowledge of vulvar vaginal disease manifestation, treatment, and outcomes, and 4) further pursue an academic career through clinical research, teaching, and mentoring. Her long-term career objectives include: 1) advance the state of the science in vulvar vaginal diseases, 2) improve quality and outcomes of care for women with these disorders, and 3) serve as a role model, and train new clinical scientists who are interested in vulvar vaginal and pelvic floor disorders.*

Grant Number: 5R01HD040123-04
PI Name: FOSTER, DAVID CHARLES.
PI Email: david_foster@urmc.rochester.edu
PI Title: ASSOCIATE PROFESSOR OF MEDICINE
Project Title: Vulvar vestibulitis trial: Desipramine-Lidocaine
Institute National Institute of Child Health and Human Development

Abstract: *DESCRIPTION (provided by applicant): Studies are proposed for the subtype of* ***vulvodynia*** *known as vulvar vestibulitis. The first major aim of this application is to conduct a randomized, placebo-controlled, double-blinded clinical trial to study the clinical efficacy of four medical regimens: topical lidocaine, oral desipramine, topical lidocaine combined with oral desipramine and placebo. The efficacy of standard treatments for vulvar vestibulitis proven by randomized, placebo-controlled, blinded clinical trials has not been assessed. The tricyclic class of antidepressants, represented by desipramine, have gained empiric acceptance for the treatment of vulvar vestibulitis, although favorable therapeutic results have been reported by only a few retrospective studies or uncontrolled clinical trials. Although the precise mechanism of action remains undefined for tricyclic antidepressants, a "central" action through the dorsal horn and brain stem has been suggested. In contrast to oral desipramine, the long-term, topical application of lidocaine may act through a "local" mechanism. This randomized, placebo-controlled, double-blinded clinical trial is designed to determine whether "local" or "centrally-acting" treatments alone, or in combination are efficacious in treating vulvar vestibulitis. Outcome measures of success will include reduced overall pain, reduced pain to touch, reduced pain to standardized mechanical stimuli, increased pain-free intercourse, improved sexual function, improved quality-of-life as measured by psychometric tests, and adherence to active drug regimens. The second major aim of this application is to study the relationship among genetic polymorphisms of the IL-1 Receptor Antagonist locus, tissue levels of pro-inflammatory cytokines, and response to treatment of vulvar vestibulitis. Pro-inflammatory cytokines, such as interleukin-I beta (IL-1 beta) and tumor necrosis factor alpha (TNF-alpha), are secreted from a local cellular source and accumulate above normal levels in the region of the hymeneal ring. Recent genetic analysis finds a 53% homozygosity for allele 2 IL-1 Receptor Antagonist (IL-1 RA*2) in cases of vulvar vestibulitis, in contrast to 8.5% homozygosity in asymptomatic women. Furthermore, the IL-1 RA*2 allele has been linked to increased production of IL-1 beta in vitro. In our second aim, we will determine whether these in vitro results can be extrapolated to clinical cases of vulvar vestibulitis. Using samples from our clinical trial, we will assess the relationship between homozygosity for IL-1 RA*2, tissue levels of IL-1 beta, and TNF-alpha, and response to treatment. In summary, this project will allow us to answer several important questions about vulvar vestibulitis. Is medical treatment effective? Is centrally-acting or locally-acting treatment equally effective or is one superior to the other? Is there any benefit from combined local*

and systemic treatments? And finally, do genetic characteristics and tissue cytokine concentrations influence treatment response?

Thesaurus Terms:
desipramine, female reproductive system disorder, human therapy evaluation, lidocaine, local anesthetic, reproductive system disorder chemotherapy, tricyclic antidepressant
clinical trial, combination chemotherapy, cytokine, genetic polymorphism, interleukin 1, longitudinal human study, oral administration, pain, pharmacogenetics, quality of life, reproductive system pharmacology, topical drug application, tumor necrosis factor alpha, women's health adult human (21+), clinical research, female, human subject, patient oriented research, psychometrics

Grant Number:	5R01DK061666-03
PI Name:	RICHARDS, NIGEL GORDON JOHN.
PI Email:	richards@qtp.ufl.edu
PI Title:	PROFESSOR
Project Title:	Biochemical Studies of Oxalate Decarboxylase
Institute	National Institute of Diabetes and Digestive and Kidney Diseases

Abstract: *DESCRIPTION (provided by applicant): Oxalic acid, a compound that is toxic to almost all organisms, is produced in large quantities by cellular metabolism. A number of pathological conditions can arise if oxalate accumulates in Man, including hyperoxaluria, the formation of calcium oxalate stones in the kidney (urolithiasis), renal failure, cardiomyopathy and cardiac conductance disorders. In addition, high levels of oxalate appear correlated with* ***vulvodynia****, a painful disease in women for which no treatment is currently available. Evidence has emerged to support the clinical application of oxalate-metabolizing enzymes in new, and intriguing, therapeutic strategies for lowering oxalate levels in biological fluids. The Yvrk gene found in Bacillus subtilis encodes oxalate decarboxylase (OxDC), an enzyme that converts oxalate to formate and CO2 in a Mn-dependent reaction for which the catalytic mechanism is not known. As part of our long-term aim to facilitate the use of OxDC in the treatment of oxalate-related illness, this project seeks to characterize Bacillus subtilis OxDC using the techniques of bioinorganic chemistry, molecular spectroscopy, enzyme kinetics and protein engineering. These studies are also likely to impact general understanding of radical mediated enzyme catalysis and to give new insights into (i) the role of protein environment in modulating metal reactivity and (ii) metalloenzyme evolution. Specific aims of this project are: 1) To investigate the catalytic mechanism of bacterial oxalate decarboxylase using steady-state kinetics, site-directed mutagenesis and isotope effects, 2) To determine the metal-*

dependence of OxDC, 3) To evaluate the effect of protein environment in controlling the chemical properties of the metal center(s) in OxDC, and 4) To identify steady-state radicals formed during steady-state turnover of oxalate decarboxylase.