

Grant# DK64538

Center Director: Jeanette S. Brown, M.D.

Center Overview

The proposed Specialized Centers of Research (SCOR) on Sex and Gender Factors affecting Women's Health is a unique opportunity to create a premier center in basic and clinical research at UCSF in the area of lower urinary tract function and urinary incontinence. The proposed UCSF SCOR will provide the organizational structure to further develop and support multi-disciplinary, collaborative research projects from both basic and clinical investigators. The focus of the proposed Center will be to expand basic knowledge about female urethral, bladder, and pelvic floor function; improve understanding of the natural history of incontinence; and provide information for the development of novel treatments for female urinary incontinence. The long term goals of this SCOR are to:

- * Foster the growth of innovative translational research on female lower urinary tract structure, function, and dysfunction.
- * Identify pathogenetic mechanisms with implications for clinical practice.
- * Increase understanding of lower urinary tract biology using animal models and in vitro studies.
- * Use basic and clinical research to develop and evaluate novel, innovative treatments for female urinary incontinence.
- * Create a collection of relevant human specimens for analysis.

To achieve our overall goal of innovative translational research on the female lower urinary tract, the UCSF SCOR has strong institutional support, leadership and a cadre of senior and junior investigators with a record of productivity. The SCOR will integrate laboratory and clinical research on lower urinary tract function and incontinence in women with a "bench to bedside" collaborative research paradigm that will facilitate direct translation of scientific results to improved patient care.

Principal Investigator: David H. Thom, M.D., Ph.D.

Project 1: Urinary Incontinence: Reproductive/Hormonal Risk Factors

Urinary incontinence (UI) is a common problem in middle aged and older women that substantially impacts quality of life, increases caregiver burden and risk of institutionalization, and results in billions of dollars in health care expenditures annually. Our studies, and those of other investigators, have identified several established and potential risk factors for incontinence, including childbirth, hormone use, diabetes, obesity and surgery, urinary tract infections, pelvic organ prolapse, and physical activity. Dr. Lue, another UCSF SCOR investigator, have used animal models to investigate several major risk factors identified epidemiologically, including vaginal birth (normal and traumatic), obesity, hysterectomy, menopause, and oral estrogen therapy. In vitro studies of hormone receptors using tissue cultures from the lower urinary tract of laboratory animals and humans by investigators at UCSF and elsewhere have advanced our understanding of the complex interaction between exogenous and endogenous hormones and urogenital physiology. The primary objective for the proposed study is to increase our understanding of risk factors for incontinence by identifying risk factors for incident UI, assessing biologic markers as risk factors for prevalent UI, and integrating our investigations with laboratory investigation in this area. We will accomplish this by prospectively following a population-based, ethnically diverse cohort of 2100 middle-aged and older women over 5 years to: (1) determine the incidence of and risk factors for new urinary incontinence; (2) determine the incidence of and risk factors for major changes in incontinence frequency; and (3) investigate serum 17- β -estradiol and progesterone as risk factors for prevalent incontinence. A major strength of this study is our retrospective cohort of 2100 women for who we have detailed data on lifetime reproductive events from abstraction of up to 50 years of medical records, detailed interviews, and linkage to excellent pharmacy, laboratory, outpatient and hospital databases. Another strength is our established relationships with laboratory investigators in this area. Combining a prospective epidemiologic study of our unique cohort with laboratory studies will help translate findings into new preventive and therapeutic approaches to reduce the individual and social burden of urinary incontinence.

Principal Investigator: Tom F. Lue, M.D.

Project 2: Urinary Incontinence: Molecular Mechanism & Matrix-Based Therapy

It is estimated that 100 million men and women are affected by urinary incontinence (UI). The prevalence of UI is generally higher in women than in men, women being between two (older age groups) and four times (younger and middle-aged) more likely to be incontinent than men. In the past 3 years, supported by an NIH grant, we have studied the effect of pregnancy, delivery, birth trauma, ovariectomy and aging on the ultrastructure and function of the continence mechanism. We have learned that the final common pathway of stress urinary incontinence in the rat model is the alteration of nervous, vascular, and muscular components of the continence mechanism. We therefore propose to further study the molecular mechanism involved in the pathogenesis of female stress urinary incontinence. We hypothesize that pregnancy/delivery, birth trauma, and hormonal deficiency (menopause) alter the gene and protein expression of many factors. We propose to use the state-of-the-art technique such as gene microarray, realtime PCR, multiple PCR etc to identify genes that are associated with female stress urinary incontinence and to further study the molecular mechanism. Further more, we have obtained encouraging results from using organ specific acellular matrix as a scaffold for the repair of bladder and ureteral defects in our lab. We propose to study whether the acellular matrix with or without growth factors can be used for the treatment of stress urinary incontinence. The hypotheses will be tested by completing the following specific aims. Specific aim 1: To identify genes that are associated with stress incontinence and to elucidate the molecular mechanism of stress urinary incontinence associated with pregnancy/delivery, birth trauma, and ovariectomy. Specific aim 2: To identify the best growth factor combinations that can enhance angiogenesis, neural growth and urethral smooth/striated muscle proliferation in a novel in vitro assay system. Specific aim 3: To apply acellular matrix with or without growth factors identified from specific aim 2 to animals with stress urinary incontinence.

Principal Investigator: Jeanette S. Brown, M.D.

Project 3: Diabetes: Lower Urinary Tract Dysfunction and Infections

Diabetes, lower urinary tract dysfunction (LUTD) and urinary tract infections (UTI) are common health problems in older women. Although it has been suggested that LUTD and UTI are more common in women with diabetes, little is known of prevalence, incidence, risk factors and pathogenesis of these health problems in women with diabetes. In particular, there has been limited research on specific aspects of diabetes severity (duration, treatment, glycemic control, presence of complications) that may contribute to the development or severity of lower urinary tract dysfunction and infection. We are completing the Reproductive Risk factors for urinary Incontinence Study at Kaiser (RRISK), a 2100 community- dwelling cohort of ethnically racially diverse women ages 40 to 69 on which we have extensive assessment of urinary incontinence and potential risk factors. Project #1 of our SCOR will follow the women for 5 years. We propose to compare 400 women with type 2 diabetes to a group of 400 women without diabetes from the RRISK cohort. To attain a sample of 400 women with type 2 diabetes, we will sample additional women from the Kaiser population using the same methods. Both groups will be followed for 5 years to determine the incidence and increases in severity LUTD and UTI. We will also determine risk factors, especially measures of diabetes severity associated with increase risk. We will compare the accuracy of non-invasive diagnostic measures to an extensive objective exam including postvoid residual volume, uroflow and urodynamics for LUTD. We will also determine the role of biological factors that may increase risk for UTI including secretor status, secretion of IL-6 in urine and adherence of uropathogens to vaginal epithelial cells. The proposed study offers a unique and efficient opportunity to understand the natural history and possible mechanisms for LUTD and UTI in women with type 2 diabetes. Our overarching goal is to facilitate a better understanding risk factors for and pathogenesis for LUTD and UTI with the aim of guiding the development of preventive interventions.

Principal Investigator: Eric Vittinghoff, Ph.D.

Core: Biostatistic

The UCSF Specialized Center of Research (SCOR) Biostatistics and Data Management Core (BDMC) will provide all needed data management and statistical support to the SCOR investigators. The objective of the BDMC is to apply state-of-the-art science in biostatistics and data management to support the design, conduct, quality assurance, analysis, and reporting of the projects which comprise the UCSF SCOR. By providing expert methodologic support, this Core will ensure rigorous and timely initiation and completion of the projects. Specifically, the BDMC will provide:

1. Assistance to SCOR investigators with study design and planning of analyses.
2. Review of forms for clarity, internal consistency, and implications for analysis.
3. Efficient data management and quality control.
4. Study monitoring.
5. State of the art data analysis, including economic analyses.

The BDMC will play a number of important roles in this SCOR. Centralization of data management and analysis has a number of compelling advantages. In particular, because two of the proposed studies will use data from the Reproductive Risk of Incontinence Study at Kaiser 2 (RRISK2) cohort, centralization will provide efficiencies of scale, improved quality control, and cross-fertilization across the two studies. It will also foster communication between SCOR investigators by stimulating discussion of design, analysis, and interpretive issues, and thus contribute to the interaction of basic research and clinical investigation.