

University of California, San Francisco

Theme: Lower urinary tract function in women

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Center Abstract

The proposed renewal of the UCSF SCOR on Lower Urinary Tract Function in Women is an exceptional opportunity to continue the unique and productive translational center. The UCSF SCOR 2002-2007 achieved our overriding goal of innovative translational research by enhancing the productivity of our basic and clinical investigators resulting in 41 published manuscripts and grant support through a U01, four R01's, and a NIH Merit award. Catalyzing "Knowledge Synthesis" on lower urinary tract function in women, our research programs are actively contributing to improved patient care. For our SCOR renewal, we are building on strong leadership and senior scientists from many disciplines with a growing foundation of funded, successful research programs. The greatest strengths of our UCSF SCOR include the close proximity of internationally recognized laboratory and clinical researchers, the productive achievements of our current SCOR projects and effective translational research collaborations. The UCSF SCOR multidisciplinary, multi-institutional program proposes three new projects and continuation and expansion of the Biostatistics and Data Management and Administrative Cores,

The 4 major areas of scientific integration and collaboration include:

1. Advancing novel treatments for stress incontinence:
Characterizing adipose-derived stem cells for treatment;
2. Identifying mechanisms by which obesity, pre-diabetes, and diabetes cause incontinence:
In a realistic type 2 diabetes rat model and prospective population-based ethnically diverse cohorts;
3. Exploring genetic risk factors for incontinence:
Using our population-based DNA bank and gene expression in a unique incontinent rat model;

4. Understanding the effects of hormones and selective estrogen receptor modulators on incontinence:

Including basic mechanism investigations and linkage to pharmacy records and use of phytoestrogens To achieve our overall goal of innovative translational research on the female lower urinary tract, the UCSF SCOR has strong institutional support, collaborations with UCSF senior scientists and other internationally recognized researchers, outstanding leadership and a cadre of senior and junior investigators with a record of excellent productivity. The UCSF SCOR will continue to accelerate the pace at which discoveries in basic science can serve the health of our patients and populations.

Project 1: RRISK Prospective Cohort

Type: Clinical

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Project Abstract

Urinary incontinence (UI) is a common problem in middle-aged and older women that results in tens of billions of dollars in health care expenditures and has been associated with an increased risk of nursing home admissions, falls, and decreased quality of life. The proposed epidemiologic study would follow a well-characterized cohort of 2000 women originally enrolled under the Reproductive Risks of Incontinence Study at Kaiser (RRISK). The RRISK cohort is probably unique in being a population-based prospective cohort with excellent representation of Black, Asian, Hispanic and non-Hispanic White women devoted to the study of voiding dysfunction and incontinence. It is also part of the UCSF Specialized Center of Research which includes a laboratory-based research group investigating underlying mechanisms for voiding dysfunction and incontinence. The proposed study will continue this highly successful collaboration by investigating questions that have arisen from our clinical and basic science investigations under the current SCOR. The overall goal of our proposed study is to advance our understanding of the mechanisms of voiding dysfunction and UI and to facilitate the translational development of novel approaches to treatment and prevention. Specifically, we propose to address the following 6 questions: what is the basis for the two to three fold higher prevalence of stress incontinence in White, compared to Black or Asian women; what is the longitudinal relationship between pre-diabetes and UI; do adipocytokines explain the relationship between obesity and incontinence; do phytoestrogens increase the risk of UI; are estrogen receptor gene polymorphisms risk factors for UI; and what are risk factors for incident UI and progression of existing UI. Lay Language: Urinary incontinence is a common problem for which there are limited treatments. Our study will investigate several promising areas to increase our understanding of the mechanisms underlying incontinence and suggest new approaches to treatment and prevention. We will study

an ethnically and racially diverse group of 2000 women to determine the nature of the recently reported relationship between pre-diabetes and incontinence, and to investigate 3 possible new risk factors for incontinence: adipocytokines (substances secreted by fat cells), phytoestrogens (plant molecules with estrogen-like effects) and genetic variations in estrogen receptors (molecules that allow estrogen to act on cells).

Project 2: Diabetic Voiding Dysfunction and Stem Cell Therapy for Stress Urinary Incontinence

Type : Basic

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Project Abstract

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 4 years, supported by a SCOR grant (P50 DK64538, PI: Brown, J), we have developed a new 70-mer oligonucleotide glass microarray to examine and identify genes associated with stress urinary incontinence (SUI) in our rat model. We also identified several growth factors that promote nerve growth from the female pelvic ganglion-the origin of cholinergic neurons innervating bladder and urethra. We changed our original proposal from using organ-specific acellular matrix to growing autologous adipose tissue derived stem cells (ADSCs) onto the acellular matrix for the treatment of SUI and obtained very encouraging results. We therefore propose to study the in vivo tissue engineering and molecular mechanisms involved so that we can develop a method to instruct and regulate the differentiation of ADSCs shortly before and after implantation.

To better integrate with the research in project 1 (Dr. Thorn's group) and project 3 (Dr. Brown's group), we also developed a comprehensive urodynamic test to study the voiding function of a type 2 diabetic model-the Zucker Diabetic Fat (ZDF) rat. We have since discovered that these rats developed a whole spectrum of voiding dysfunction from overactive bladder to urinary retention similar to the symptoms of women with "diabetic cystopathy". We propose to continue our research to examine the natural course and reversibility of diabetic voiding dysfunction in the diabetic ZDF rat model and identify the molecular mechanisms involved.

Our long-term goal is to better understand stem cell biology and diabetic voiding dysfunction so that the information can be "translated" to better prevention, diagnosis and treatment of stress urinary incontinence and diabetic voiding dysfunction in women. To achieve this overall goal we have set three specific aims for our proposed study.

Specific Aim 1: To study the in vivo tissue engineering and molecular mechanism of adipose derived stem cell (ADSC) differentiation

Specific Aim 2: To apply ADSCs for the prevention and correction of stress urinary incontinence in our rat model

Specific Aim 3: To study the molecular mechanism of diabetic voiding dysfunction in a type 2 diabetic rat model

Project 3: Diabetes RRISK Prospective Cohort: Urinary Incontinence and Diabetic Voiding Dysfunction

Type: Clinical

PI: Jeanette S. Brown, M.D.

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Project Abstract

Urinary incontinence and voiding dysfunction are common, chronic, and costly health problems in women with type 2 diabetes. Nearly 60% of women with diabetes report weekly incontinence and consider their incontinence bothersome, and about 20% report that it interferes with their daily lives- two times more frequent than incontinent women without diabetes. However, our understanding of the natural history, risk factors of new onset and worsening symptoms, possible mechanisms, and interventions to prevent or reduce severity of incontinence among women with type 2 diabetes is limited.

The proposed prospective study will build upon the well-characterized Diabetes Reproductive Risks of incontinence Study (RRISK). The Diabetes RRISK is a population-based ethnically diverse cohort of 400 women with type 2 diabetes that includes extensive assessment of lower urinary tract function by in-person interview, self-report, chart abstraction, voiding diaries, post-void residual volumes, and in a sample, objective measures of bladder function including uroflow and urodynamics. In addition, the Diabetes RRISK includes a broad range of diabetes measures such as duration, treatment, glycemic control, complications of diabetes, and laboratory data. With links to all laboratory, radiology, inpatient, outpatient, pharmacy, and surgery Kaiser clinical databases, the study provides an unequalled level of detail. The proposed longitudinal Diabetes RRISK will follow the women for 5 years to determine risk factors for and new onset and increases in the severity of incontinence.

The overarching goal of the proposed study is to advance our understanding of the natural history and pathophysiology of incontinence in diabetic women. The linkage of our clinical study and the SCOR Basic Mechanisms Project using a unique type 2 diabetes rat model will help us to understand the broader context of incontinence and diabetic voiding dysfunction as well as

characterize underlying molecular mechanisms. Ultimately, a deeper understanding of the epidemiology and pathophysiology of incontinence and diabetic voiding dysfunction in women with diabetes may be helpful in the development of new prevention and early treatment strategies for these conditions.

CORES

Biostatistics and Data Management Core

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Core Abstract

The University of California, San Francisco, Specialized Center of Research (UCSF SCOR) Biostatistics and Data Management Core (BDMC) provides all needed data management and statistical support to the SCOR investigators. It includes a team of experts in biostatistics, epidemiology, computer programming and data management. The majority of data management activities occur at the Kaiser Division of Research (KDOR) using sophisticated data entry systems. Statistical support comes from the highly productive and experienced research team at the UCSF's Women's Health Clinical Research Center (WHCRC). Together, the BDMC is able to provide state-of-the-art science in biostatistics and data management to support the design, conduct, quality assurance, analysis and reporting of the multiple projects that comprise the UCSF SCOR. This includes assisting UCSF SCOR investigators with study design and planning of analyses, developing and reviewing forms for clarity, internal consistency and implications for analysis, analyses regarding the healthcare and economic burden of incontinence, and sharing data with junior faculty at UCSF as well as faculty from other collaborating institutions. The BDMC ensures that all UCSF SCOR projects have adequate support in statistical analysis and manuscript development. In addition, the BDMC will develop and maintain an informational UCSF SCOR website (<http://www.ucsf.edu/scor>) that will centralize and monitor these tasks.

The centralization of the data management and statistical components of the UCSF SCOR in the BDMC provides efficiencies of scale, improved quality control, and cross-fertilization among multiple studies. It fosters communication between SCOR investigators by stimulating discussion of design, analysis and interpretive issues, and thus contributes to the interaction of basic mechanisms research and clinical investigation. For the last four years, the BDMC's rigorous and timely initiation and completion of projects has contributed to the UCSF SCOR's remarkable productivity, including 41 publications and 30 conference presentations. This is a testament to the continued importance a Biostatistics and Data Management Core for the UCSF SCOR and how it expedites the translation of research into changes in medical practice.

Administrative Core:

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Administrative Core Abstract

Urinary Tract Function in Women (UCSF SCOR) Administrative Core (AC) will provide the foundation for the UCSF SCOR. The UCSF SCOR AC is responsible for the overall administration of the UCSF SCOR and serves as the single administrative structure that joins the many departments, research centers and institutions within the UCSF SCOR. The AC, established in 2001, is running efficiently and effectively to facilitate communication to actively expedite development and application of new knowledge of specific importance to lower urinary tract function and urinary incontinence in women. The team for the AC, including Director, Co-Director, Advisory Council and SCOR Investigators, provides outstanding interdisciplinary credentials to advance our scientific and administrative goals. All activities of the UCSF SCOR are coordinated through the AC and the office of the Director, Dr. Jeanette S. Brown. Included in this Core are the nine members of the Advisory Council who are recognized leaders in basic, clinical and translational research.

Specifically, the Administrative Core will facilitate collaborations among SCOR investigators with:

- 1) Bi-monthly Scientific Meetings for both the Basic Mechanism and Clinical Research groups
- 2) Monthly Translational Research Meetings for all SCOR investigators
- 3) Annual Research Retreats of UCSF SCOR investigators and collaborating investigators
- 4) An annual scientific meeting of SCOR investigators and the Advisory Council, and
- 5) The SCOR website.

The AC also supports the UCSF SCOR mission to,encourage pilot projects related to lower urinary tract function, junior investigator mentorship and training and translation of UCSF SCOR research findings to the broader community through education and training. Working as a single administrative unit, the SCOR provides an efficient mechanism to develop and complete collaborative, multi-institutional, multi-disciplinary research, enhancing the productivity of our group of investigators. The SCOR infrastructure facilitates a mutually supportive interaction between basic and clinical investigators and collaboration both within UCSF and with outside investigators. The Administrative Core leadership and Advisory Council have outstanding administrative and interdisciplinary scientific skills to advance the UCSF SCOR research agenda.