



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

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January 2025

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Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

University of Wisconsin-Madison George M. O'Brien Urology Cooperative Research Center

- **PI William Ricke, PhD** (2014-2019, 2019-2024, NCE 2025)

Cellular and molecular mediators of fibrosis in the development of urinary tract dysfunction

PROJECT SUMMARY - OVERALL. No consequential advances in medical treatment of prostate-related lower urinary tract symptoms (LUTS) have emerged in decades. Existing medical therapies improve LUTS but robustness of these effects are marginal. Not all men respond to existing therapies, some respond with adverse effects requiring discontinuation of therapy, and most experience a progressive worsening of symptoms pursuant to initial relief. Multiple mechanisms drive development and progression of prostate-related LUTS. The overarching goal of the O'Brien Center for Benign Urology Research is to identify mechanisms that result in lower urinary tract dysfunction and prostate-related LUTS. The overarching hypothesis of the center is that fibrosis is a cause of male LUTS. In contrast to benign prostatic enlargement and smooth muscle dysfunction, prostatic fibrosis remains untargeted by existing therapies. In order to advance the scientific understanding and medical management of prostatic fibrosis, it will be necessary to: (1) identify cellular and molecular mediators of fibrosis and therapeutically-susceptible pathways using clinical specimens, (2) develop and validate preclinical mouse models of prostatic fibrosis and strategies for granular assessment of voiding function, (3) test new therapies in these preclinical models with the long term goal of treating fibrosis in men, and (4) develop new non-invasive radiologic imaging strategies with the long-term goal of diagnosing prostatic fibrosis in men. Two additional goals will advance the urologic research community: (1) develop and publicly disseminate resources to increase research efficiency, reproducibility, and rigor, and (2) cultivate an outstanding educational enrichment program to attract and retain young basic- and physician-scientists into the benign urologic research field. The Center will apply state of the art molecular and histological methods to visualize and characterize fibrosis in a range of human and animal prostatic tissues and examine how prostatic fibrosis develops, progresses, and responds to treatment. Interactions and engagement with the O'Brien Centers' Interaction Core, the UW O'Brien Centers Website, and GUDMAP will accelerate the dissemination of data, software, methods, and tissue resources to the greater biomedical community. The leadership and experience within the Center will allow for the promotion of interactions among Center Projects, the Biomedical Research Core, and other Centers (U54, P20, K12) through communication, collaboration, and coordination. The larger vision is that O'Brien Centers will be a nidus for ideas, research, resources, training, and a unified voice across the urologic research community. To realize this vision, the Centers must become more than the sum of their parts. The UW O'Brien Center and its affiliates will contribute to this synergism by leveraging existing Center assets and relationships, conducting rigorous investigation, fostering teaching and learning, and through vigorous pursuit of innovation. With the solid financial support and "buy-in" from UW and its affiliates, Core A will lead this vision for this O'Brien Center.



Public Health Relevance Statement

PROJECT NARRATIVE - OVERALL. There are no FDA approved therapies to treat prostatic collagen accumulation (fibrosis). Fibrosis drives prostatic stiffening and impaired passage of urine, leading to lower urinary tract symptoms and urinary voiding dysfunction. We will identify molecular targets and test potential therapies in preclinical models we developed, using methods we optimized. We will publicly disseminate resources and provide an outstanding training environment for young investigators to advance the benign urologic research field into the future.

Administrative Core

PROJECT SUMMARY - The Administrative Core (Core A), has an overall mission to coordinate and successfully manage the UW- Madison O'Brien Research Center including UM-Boston and UT-Southwestern and lead benign urology research into the future. The overarching goal of the O'Brien Center for Benign Urology Research is to identify mechanisms that result in lower urinary tract dysfunction (LUTD) that result in benign prostatic hyperplasia (BPH) related lower urinary tract symptoms (LUTS). Criteria for successful completion are defined by the RFA 18-029 and include performing and disseminating outstanding benign urologic research, provide highly needed resources for the field, and provide outstanding

educational enrichment while promoting the next generation of benign urology researchers. The Center targets new and exciting mechanisms of LUTD namely prostate fibrosis and translates it to clinically relevant therapeutics and biomarkers for patient stratification. BPH/LUTS can be life-threatening, affect quality of life, and is a costly disease, which NIDDK wants eradicate. Core A will achieve these goals by providing outstanding leadership, vision, and efficiency in the overarching administrative duties. The organization structure and leadership of Core A includes two outstanding investigators with recognized and complementary abilities in leading research groups and training programs. Dr. Ricke continues to serve as Core A director and will assume primary responsibility for day to day management and oversight of Core A. He will also be responsible for obtaining and managing the Opportunity Pool and maintain extensive interactions within the biomedical community. Dr. Vezina will serve as Associate Director for Core A and will direct the Educational Enrichment Program. Core A will interact with members of its external advisory board (EAB) and internal advisory board (IAB) on a semi-annual basis. All members or associated members of the center will be invited to partake in center functions including seminars, retreats, business meetings, and other special events. Drs. Ricke and Vezina meet with the NIDDK Executive Steering committee (ESC) and External Expert Panel (EEP) at NIDDK's annual reverse site visit (see letter of reference Mark Nelson, PhD, ESC Chair). Their leadership and experience will allow us to promote interactions between our Center Projects, Core B, as well as other centers (U54, P20, K12) through: communication, collaboration, and coordination. Further interactions and data dissemination will occur in conjunction with the NIDDK's O'Brien Center Interaction core, NIDDK program officials, American Urological Association Office of Research, scientific societies, and other venues. As directed by NIDDK, the benign urology research community has a viable focal point--The O'Brien Centers--in which to centralize ideas, research, resources, training, provide consensus, and offer a unified voice. The O'Brien Centers are more than the sum of parts, rather they provide leadership, synergize with researchers, and provide to the urology community above and beyond serving one's own Center. Core A will lead this NIDDK shared vision.

Estrogens stimulate prostatic collagen synthesis to drive fibrosis and LUTD (William Ricke, PhD)

PROJECT SUMMARY - PROJECT 1. Healthcare costs for lower urinary tract symptoms (LUTS) ascribed to benign prostatic hyperplasia (BPH) are in the billions of dollars annually. Therapies for BPH/LUTS target smooth muscle contractility with α -blockers or hyperplasia with 5 α -reductase inhibitors. Although these therapies can be medicinal, they are not effective/durable for all; this leaves millions of men in the US needing more effective therapies. The standard of medical care for BPH/LUTS currently over-treats this patient population, in part due to a poor understanding of etiology and progression. There is an apparent need to define what BPH represents in patient populations as well as to identify the true anatomic, cellular, and molecular causes of the disease. This may elucidate the true causes in development and progression of the disease as well as institute effective therapies. The overarching goal of the O'Brien Center for Benign Urology Research is to identify the mechanisms that result in lower urinary tract dysfunction and prostate-related LUTS. Previous studies have demonstrated prostatic collagen deposition coincident with prostate stiffness, LUTS, and failed medical treatment supporting the concept that BPH/LUTS is, in part, a fibrotic disease. However, this brings up a translational challenge because treatment of prostatic fibrosis cannot occur until cellular and molecular pathways have been identified. As such, the goal is to identify the anatomical, cellular, and molecular origins of prostate fibrosis in men with BPH/LUTS. Recently, estrogens, specifically signaling through estrogen receptor (ER) α , was discovered to be necessary for the development of prostatic fibrosis and LUTD in mice. Although, multiple stromal and epithelial cells express ER α , a subpopulation of ER α positive prostatic fibroblasts and/or smooth muscle cells could be responsible for increased collagen deposition. These cells are sensitive to estrogens and produce large amounts of collagen in vitro and in vivo. Aim 1 will address the ER molecular mechanism of action in the transcription of Col1a1 by determining if classical or non-classical ER signaling is necessary. Next, collagen accumulation has been linked with BPH/LUTS, but it is uncertain if collagen/fibrosis acts independently or in collaboration with prostate hyperplasia; Aim 2 will test the hypothesis that gain of collagen function promotes LUTD independent of prostate hyperplasia. Clinical translation of our findings is a goal of the center; Aim 3 will test the hypothesis that clinically relevant antifibrotics are effective in the treatment of prostatic fibrosis. Lastly, stratification of men with fibrotic prostates is imperative to increase treatment efficacy. To address this challenge, advanced and novel collagen MR imaging techniques will be used to assess whether prostatic fibrosis can be identified in preclinical models. By establishing cellular and molecular mechanistic connections between fibrosis and BPH/LUTS as well as preclinical testing and patient stratification our collaborative and synergistic research, Project 1 will lay the groundwork for impactful discoveries that elucidate an important etiology of BPH/LUTS and may ultimately translate into the clinic.

CTGF drives voiding dysfunction through expression of collagen in perurethral SRD5A2+ fibroblasts (Chad Vezina, PhD and Douglas Strand, PhD)

PROJECT SUMMARY- PROJECT 2. Lower urinary tract symptoms cost more than \$4 billion annually. Though current medical therapies reduce prostate volume and relax smooth muscle to address symptoms, existing therapies are not curative. Three things are clear: (1) male lower urinary tract symptoms derive from multiple underlying pathologies, not just prostatic enlargement or muscle dysfunction (2) current therapies do not effectively target pathologies outside of benign enlargement and smooth muscle dysfunction, and (3) there is a need to identify additional mechanisms underlying lower urinary tract symptom etiology to formulate therapies that are more effective. The overarching goal of the O'Brien Center for Benign Urology Research is to identify mechanisms that result in lower urinary tract dysfunction and prostate-related

lower urinary tract symptoms (LUTS). Prostatic collagen accumulation (fibrosis) has been identified as a cause of male lower urinary tract symptoms. Prostatic collagen accumulation has been linked to prostatic stiffness, lower urinary tract symptoms, and failed medical treatment. It will not be possible to treat prostatic fibrosis and associated voiding dysfunction until prostatic collagen-producing cells are identified. The goal of this project is to tackle this challenge by pinpointing the cellular and molecular origins of pathological collagen production in the prostate. A subpopulation of human prostatic fibroblasts residing in close proximity to the urethra and expressing steroid five alpha reductase type II (SRD5A2) has been identified, supporting the central hypothesis that inflammation causes these fibroblasts to proliferate, synthesize connective tissue growth factor (CTGF) and produce collagen. Collagen accumulation in turn leads to urethral stiffening, bladder outlet obstruction, urinary retention, and voiding dysfunction. The proposed studies offers essential insight into the pathogenesis of prostatic fibrosis, a mechanism of lower urinary tract symptom medical therapy failure. Aim 1 will test the hypothesis that inflammation increases human prostatic SRD5A2+ fibroblast frequency and drives CTGF and COL1A2 expression. Aim 2 tests whether inflammation increases frequency of mouse prostatic Srd5a2+ fibroblasts and whether depletion of these fibroblasts resolves inflammation-mediated collagen accumulation and voiding dysfunction. Aim 3 will test whether CTGF overexpression is sufficient to drive mouse prostatic collagen accumulation and voiding dysfunction and whether an investigational new CTGF blocking drug resolves the problems. The proposed studies will pinpoint CTGF expression in SRD5A2+ fibroblasts as a therapeutic target for treating lower urinary tract symptoms. By establishing mechanistic connections between inflammation, CTGF and COL1A2 abundance, and urinary dysfunction, the studies launch an original line of research into a disease process that is yet-to-be leveraged as a target for medical therapies addressing lower urinary tract symptoms.

Persistence of an IL-4/IL-13 autocrine loop promotes fibrosis-mediated urinary voiding dysfunction (Jill Macoska, PhD and Paul Marker, PhD)

PROJECT SUMMARY - PROJECT 3. Lower urinary tract symptoms (LUTS) are a costly and potentially critical medical problem for millions of aging men. This spectrum disorder encompasses symptoms such as weak stream, nocturia, incomplete emptying and intermittent urination, all of which are indicative of lower urinary tract dysfunction (LUTD). Surgical ablation of prostate tissue and medical approaches may improve urinary flow, but such treatments are not effective for all men, can produce adverse effects that result in discontinuation of the therapeutic regimen, and do not abrogate the risk for disease progression. If left untreated or treated ineffectively, LUTD can progress to bladder dysfunction, which can lead to urinary retention, recurrent UTI, bladder calculi, and, eventually, renal impairment. Work accomplished by the Macoska laboratory and this Center have shown that collagen accumulation around the prostatic urethra consistent with tissue fibrosis is an untreated pathobiology contributing to LUTD. The overarching goal of the O'Brien Center for Benign Urology Research is to identify mechanisms that result in lower urinary tract dysfunction and prostate-related lower urinary tract symptoms (LUTS). New evidence (presented in this application) indicates heterogeneity among peri-urethral collagen-producing cells as well as inflammatory cells within the prostatic microenvironment. Inflammatory cells secrete a medley of pro-fibrotic proteins into the prostatic microenvironment. Among these proteins, IL-4 and IL-13 are of particular interest because they share a common signaling axis which, as shown here for the first time, establishes and perpetuates an autocrine loop that activates JAK/STAT signaling to promote the expression and maintenance of IL-4, IL-13, their cognate receptors, regulatory transcription factors, and ECM components, even in the absence of inflammatory cells. Based on preliminary data presented here we hypothesize that some peri-urethral stromal cell populations establish an IL-4/IL-13 axis that self-perpetuates, induces myofibroblast phenoconversion and survival, and upregulates collagen accumulation, thereby promoting consequent urinary voiding dysfunction. To test this hypothesis, Project 3 will: 1) Determine whether signaling through the IL-4 receptor creates a STAT6- and GATA-3-mediated positive feedback loop; 2) Elucidate the mechanisms through which the IL-4/IL-13 axis promotes myofibroblast phenoconversion and concordant collagen expression; 3) Determine whether IL-4 pathologically represses myofibroblast apoptosis and thereby promotes myofibroblast survival, and 4) Test whether the IL-4/IL-13 signaling axis promotes lower urinary tract fibrosis and urinary voiding dysfunction in vivo. The results of these preclinical studies will elucidate previously unknown interleukin-mediated molecular and cellular mechanisms that promote lower urinary tract fibrosis and dysfunction. Using JAK/STAT inhibitors to therapeutically target this potentially self-perpetuating mechanism may 'break the cycle' and successfully treat recalcitrant peri-urethral prostatic fibrosis contributing to LUTD development and progression.

Other UW-Madison U54 Urology O'Brien Center Leaders:

Chad Vezina, PhD (UW-Madison)

Doug Strand, PhD (UT Southwestern)

Jill Macoska, PhD (UMass Boston)

Paul Marker, PhD (UW-Madison)

Kim Keil Stietz, PhD (UW-Madison)



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

Columbia University George M. O'Brien Urology Cooperative Research Center

- **PIs Cathy Mendelsohn, PhD, Ali Gharavi, MD, Jonathan Barasch, MD, PhD, and Anne-Catrin Uhlemann, MD, PhD (2014-2019, 2020-2025)**

Investigating the genetic, cellular, and metabolic events important for urothelial homeostasis and response to injury

PROJECT SUMMARY - OVERALL. The Columbia University George M. O'Brien Urology Cooperative Research Center is made up of Columbia's leading Urologists, Microbiologists, Geneticists, Developmental and Cell Biologists dedicated to solving the central problems of Benign Urology. Our focus builds on the work conducted in prior cycles and proposes to identify solutions to clinical diseases at the juncture between clinical urology, epithelial biology and microbiology. Our faculty include the leading clinical and scientific minds at Columbia, including Chairs and Professors of Urology, Nephrology, Pathology & Cell Biology, Genetics & Development and Medicine. Together our faculty provide the expertise to identify the root causes of urologic disability in three scientific groups. Dr Gharavi has identified major risk loci for vesiculoureteral reflux and is now correlating developmental phenotypes with both changes in the urinary microbiome and lower urinary tract symptoms. Dr Gharavi's tools include large datasets such as the Lower Urinary Tract Symptoms Research Network (LURN), the UK Biobank and the eMERGE consortium. This effort establishes the field of personalized genomics in benign urology. Dr Mendelsohn evaluates signaling pathways downstream of Pparg, a nuclear receptor that turns out to be a major regulator of cell type specific differentiation in the urothelium, as well as the inflammatory response to injury and infection. The work identifies an off-the-shelf drug that can be a potential treatment for urothelial repair. Dr Barasch focuses on epithelial metabolism identifying a central mechanism of defense against UTI called "nutritional immunity". He discovered NGAL a protein that blocks iron capture by bacteria, and now has identified a highly active pathway of heme metabolism that produce CO gas. His tools include novel methods of RNA isolation from small amounts of cells, novel probes and chelators of CO, of heme and iron and reporter bacteria and mice. Dr Uhlemann focuses on the evolutionary basis of drug-resistant microorganisms deciphering their molecular mechanisms of virulence. The Microbial Genomics Biomedical Core not only directs all microbiological studies in the O'Brien but also serves as a national resource for microbiome and metagenomic analyses and as a biorepository for drug-resistant UTI isolates. The excitement of our group is encapsulated in the interactions of each component of research from gene discovery to therapeutic applications including both human and mouse models. In this new cycle, we will continue to contribute to urological sciences by generating new genomics datasets (to be shared on dbGAP and GEO), gene lists, animal models (deposited at JAX), bacterial gene editing plasmids and reagents that can be shared with the urology community. We will continue to collaborate with urology experts in Wisconsin, Missouri, Maryland. We will fund new Opportunity Pool recipients, building on the roster of 6 new investigators already funded; and continue to train the next generation of investigators, building on the success of the nearly 90 students who have trained and who have published, received national awards and who are now Urologists and medical doctors.



Public Health Relevance Statement

PROJECT NARRATIVE - OVERALL. Lower urinary tract symptoms (LUTS) and urinary tract infections (UTI) are very common disorders in the general population. The multidisciplinary Research Projects of the Columbia University George M. O'Brien Urology Cooperative Research Center build upon the work conducted in the prior cycle to address questions related to the genetic, cellular, and metabolic events that lead to lower urinary tract disorders such as LUTS and UTI, and devise new methods for prevention and treatment, while providing educational enrichment for future scientists and promoting collaborations with investigators within urology and other fields.

Administrative Core

PROJECT SUMMARY - The mission of the Columbia University George M. O'Brien Urology Cooperative Research Center is to advance the understanding of benign genitourinary diseases/disorders. The Center consists of an Administrative (Admin) Core, a Microbial Genomics Biomedical Research Core, and three Research Projects that include preclinical and clinical studies. Our focus includes: (1) the intersection of the host genome and the urinary microbiome; (2) the transcriptional regulation of urothelial differentiation during homeostasis and repair in response to UTI; and (3) how the regulation of urinary chemistry and urothelial iron metabolism ("iron-heme machine") is a component of the urothelial response to UTI. We anticipate that the proposed studies will provide new insight into the pathogenesis of disorders of high relevance to benign urology and also facilitate introduction of genetic testing into the practice of Urology and even suggest new treatments. We will examine the interactions between host and invading bacteria, and the role of nutrient iron in shaping the outcome of UT infections; we will undertake a new GWAS analysis to search for mutations that lead to LUTD, including incontinence, obstruction and pelvic floor prolapse, we will analyze the urinary microbiome of patients with lower urinary tract dysfunction (LUTD), and we propose to identify pathways that program urothelial cell types that may be used to treat benign urothelial abnormalities associated with disease. The most important goal of this center is to utilize the expertise and experience of the urological community to increase the scope of our studies and to help direct the kinds of questions we will address. We have directly integrated members of the P20/U54 community as well as clinicians and scientists in the benign urological community. Co-investigators on our projects include Indira Mysorekar (P20), an expert in UTI and urothelial biology who will work with Dr. Mendelsohn and Dr. Barasch, Chad Vezina (Wisconsin U54) and collaborating scientists and clinicians from the benign urological community, (Lori Birder, Gerry Apodaca, Doug Strand). In addition, we have invited outside experts to join our work, for example, the heme biologist, Iqbal Hamza (University of Maryland). We are also highly focused on education and outreach: Our summer program has trained 73 students since our center has been established, including undergraduates, fourth year medical students and urology residents. we have provided opportunity pool funds to Dr. Putonti (Loyola University) and Dr. Catherine Brownstein, (Harvard University). We held a Symposium in October of 2019 that was extremely successful "The problem of UTI: The microbiome of the Urogenital Tract and its immune Defense" bringing together a dozen experts with >138 members of the Urological community.

Human genetic approaches to lower urinary tract phenotypes (Ali Gharavi, MD)

PROJECT SUMMARY - **PROJECT 1.** Genomic technologies such as exome sequencing and GWAS have not been systematically applied for most benign urological phenotypes prior to our work at the Columbia O'Brien Urology Research Center. We have already successfully applied genome-wide association study (GWAS) and rare copy-number variant analysis to identify novel genes and loci associated with vesicoureteral reflux (VUR). Here we propose to perform exome sequence of VUR patients to identify diagnostic rare single nucleotide variants and perform an exploratory VUR whole exome association study. In collaboration with the Microbial Genomics Biomedical Core we will conduct 16S rRNA sequencing from urine samples of a set of these patients, with both VUR and urinary tract infections (UTI) to generate urinary microbiota profiles. We will then analyze microbiota profile associations with phenotypic variants and outcomes and with rare genetic variants, and perform a microbiota-common variant genome-wide association study (mGWAS). To extend these genomic studies to other important benign urology phenotypes we will perform a GWAS of common lower urinary tract symptoms (LUTS) phenotypes, followed by phenome-wide association study to uncover risk factors and comorbidities with common genetic etiology. Our proposed studies will leverage existing data and biospecimens from four NIDDK-funded national cohorts, the RIVUR (UTI with VUR), CUTIE (UTI without VUR), CKiD (pediatric chronic kidney disease, including reflux VUR) and LURN (LUTS) study cohorts; as well as two large population cohorts that combine electronic medical records and genomics, from the UK Biobank and the NHGRI-funded eMERGE network. The proposed studies will provide new insight into the pathogenesis of disorders of high relevance to benign urology and also facilitate introduction of genetic testing into the practice of Urology.

Transcriptional regulation of urothelial differentiation and cell type specification during homeostasis and regeneration (Cathy Mendelsohn, PhD)

PROJECT SUMMARY - **PROJECT 2.** The mission of the Columbia University George M. O'Brien Urology Cooperative Research Center is to advance the understanding of benign genitourinary diseases/disorders. The Center consists of an Administrative (Admin) Core, a Microbial Genomics Biomedical Research Core, and three Research Projects that include preclinical and clinical studies. Our focus includes: (1) the intersection of the host genome and the urinary microbiome; (2) the transcriptional regulation of urothelial differentiation during homeostasis and repair in response to UTI; and (3) how the regulation of urinary chemistry and urothelial iron metabolism ("iron-heme machine") is a component of the urothelial response to UTI. We anticipate that the proposed studies will provide new insight into the pathogenesis of disorders of high relevance to benign urology and also facilitate introduction of genetic testing into the practice of Urology and even suggest new treatments. We will examine the interactions between host and invading bacteria, and the role of nutrient iron in shaping the outcome of UT infections; we will undertake a new GWAS analysis to search for mutations that lead to LUTD, including incontinence, obstruction and pelvic floor prolapse, we will analyze the urinary microbiome of patients with lower urinary tract dysfunction (LUTD), and we propose to identify pathways that program urothelial cell types that may be used to treat

benign urothelial abnormalities associated with disease. The most important goal of this center is to utilize the expertise and experience of the urological community to increase the scope of our studies and to help direct the kinds of questions we will address. We have directly integrated members of the P20/U54 community as well as clinicians and scientists in the benign urological community. Co-investigators on our projects include Indira Mysorekar (P20), an expert in UTI and urothelial biology who will work with Dr. Mendelsohn and Dr. Barasch, Chad Vezina (Wisconsin U54) and collaborating scientists and clinicians from the benign urological community, (Lori Birder, Gerry Apodaca, Doug Strand). In addition, we have invited outside experts to join our work, for example, the heme biologist, Iqbal Hamza (University of Maryland). We are also highly focused on education and outreach: Our summer program has trained 73 students since our center has been established, including undergraduates, fourth year medical students and urology residents. We have provided opportunity pool funds to Dr. Putonti (Loyola University) and Dr. Catherine Brownstein, (Harvard University). We held a Symposium in October of 2019 that was extremely successful "The problem of UTI: The microbiome of the Urogenital Tract and its immune Defense" bringing together a dozen experts with >138 members of the Urological community.

A novel metabolic pathway regulates urinary tract infections in the bladder (Jonathan Barasch, MD, PhD)

PROJECT SUMMARY - PROJECT 3. Urinary tract infections are the most common urogenital abnormality worldwide affecting multiple organs of the urinary tract including the urethra, bladder, prostate, ureter, and kidney. To establish a urinary tract infection, bacteria must obtain nutrients in order to undergo continuous replication. These nutrients derive from the urine and the epithelia of the urinary tract. Iron is a "precious metal" for bacteria because metabolic processes including energy production and cell division require ~100,000 atoms of iron per bacterium. Yet it is the most difficult nutrient to obtain because the common form, called ferric iron, is insoluble in water ($K_{sp}=10^{-12}M$). Gram-negative organisms have devised methods to obtain iron even with these vanishing low concentrations. They do this by the production of a series of small molecules known as siderophores, each with astronomical affinity for iron. One type of siderophore, called Enterochelin is the most prevalent. Yet, the epithelial cells of the urogenital tract recognize this threat and rapidly produce a protein called NGAL (Lcn2) in great abundance. NGAL captures Ent:Fe and prevents its iron from reaching bacteria. We discovered that the urothelium and the tracts up into the kidney expresses NGAL. While most of our studies have focused on NGAL:Ent:Fe, there must be alternative nutrient pathways and alternative mammalian defenses. We propose that bacterial heme transporters also steal our iron and that epithelia in turn capture and metabolize heme. By adapting a novel method to analyze "snapshots" of nascent RNA, we found that bladder urothelia and collecting ducts express heme capture, heme metabolism, and iron sequestration and transport proteins, which compete with bacteria for heme. Most intriguing is our finding that upon infection, the urothelial "heme machine" is activated and releases a byproduct of heme metabolism, called Carbon Monoxide, a bacteriostatic agent. Moreover, the heme machine is the core complex of the Circadian Clock, which is regulated by CO. Here we test the basic tenets of our hypothesis. We carefully document heme and iron transport and metabolism in the urothelium to test the notion of that the urothelium and bacteria compete for heme. We suggest that these mechanisms are re-purposed for "nutritional immune defense" from the daily defense against the lysis of RBC that traverse the bladder each day. To investigate these mechanisms, we have invented novel methods of RNA isolation, imaging tools to detect bacterial responses, a method to detect and capture CO in vivo, novel mouse ko's, and bacteria isolated from our patients with UTI's carrying mutations in siderophore and heme pathways. We are working with a leading microbiologist (Uhlemann), animal geneticist (Mendelsohn), UTI specialist (Mysorekar) and the leading scientist in heme biology (Hamza). Taken together, our studies demonstrate that rather than a passive barrier, the urothelium is a metabolically active cell layer, that uses iron biology to detoxify hematuria and defend itself from UTI.

Microbial genomics biomedical core (Anne-Catrin Uhlemann, MD, PhD)

PROJECT SUMMARY - MICROBIAL GENOMICS BIOMEDICAL CORE. The mission of the Columbia University O'Brien Urology Research Center is to identify genetic factors and congenital malformations, such as vesicoureteral reflux, that predispose individuals to urinary tract infections (UTI) and to explore host-bacterial metabolic processes, such as heme pathways, that enable or prevent infection. UTI represent one of the most common infections, affecting 150 million people per year worldwide. In support of the goals of the Columbia O'Brien Urology Research Center the Microbial Genomics and Biomedical Core (MGBC) will provide high quality services for biobanking, extended bacterial culture, microbial genomics (microbiome analyses, comparative genomics), microbial genetics, consultation for study design and outreach for novel investigations into the pathogenesis of urinary tract infections. The MGBC will enable Columbia O'Brien Center investigators to have access to specialized genomic technologies and coordinated expert consultations for improved rigor and reproducibility in genomics and precision medicine. In recognition of the increasing impact of antimicrobial resistance in urinary tract infections the MGBC has established a biorepository of multi-drug resistant UTI isolates. The services and biorepository are specifically designed to meet the needs of two of the Research Projects of the Columbia O'Brien Center and Opportunity Pool Awardees and will be available to the wider urology research community. The MGBC will accomplish these goals through the following aims: 1) Expand a biorepository of multi-drug resistant UTI isolate to multiple sites across New York City, establish a urine biorepository from clinically well-defined patients with different UTI symptoms and perform extended urine culture for organism identification; 2) Provide Microbiome and metagenome analyses and Hi-C/MetaPore-C sequencing; 3) Facilitate whole genome sequencing of dominant UTI pathogenic clones to elucidate bacterial

determinants of UTI symptomatology; 4) Generate bacterial mutants in multi-drug resistant clinical UTI isolates leveraging a highly efficient CRISPR-Cas system; and 6) Provide consultations and support of study design for the Research Projects. Importantly, the MGBC will serve as a national resource for members of other George M. O'Brien Cooperative Research Centers and other NIDDK Urologic Research Programs. In close collaboration with the Administrative Core the MGBC will ensure adherence to all fiscal, administrative, and resource sharing policies. The MGBC will also contribute to the goals of the Educational Enrichment and Opportunity Pool Programs through lectures, student mentorship, and guidance on experimental design related to microbial genomics for Opportunity Pool awardees. Taken together, the Columbia O'Brien U54 MGBC will enable state-of-the-art characterization of microbes in UTIs, with a focus on evolving multi-drug resistance, by providing a complementary set of tools harnessing molecular biology, genetics, and 'omics technologies.



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

Stanford University George M. O'Brien Urology Cooperative Research Center

- PI James Brooks, MD (2021-2026)

Stanford O'Brien Urology Research Center

PROJECT SUMMARY - OVERALL. Benign prostatic hyperplasia (BPH) is the most common cause of urinary symptoms in older men, yet we understand little about its origins, drivers of growth, and how it causes lower urinary tract symptoms. Since BPH-caused Lower Urinary Tracts Symptoms (LUTS) appears unique to man, we propose a highly integrated project to create an atlas encompassing the molecular, cellular, microenvironmental, histological and macroscopic dimensions of human BPH. Definition of the features responsible for growth and progression of BPH could ultimately lead to new therapeutic approaches to treat or prevent BPH. Our overall goal is to expand research in benign urology to improve our understanding and treatment of urological diseases. The components of the Stanford O'Brien Urology Research Center include: The Administrative Core is based in the Department of Urology and directed by Dr. James Brooks, an experienced clinician and translational scientist in prostate disease who will administer the Center to ensure the scientific and training goals are realized and interface with the NIDDK and Urology Research Consortia. He will be advised by an Internal and External Advisory Board, to ensure progress is made and to provide scientific advice to ensure success. He will meet with the Investigator Committee to formulate plans, integrate findings between projects and allocate Project and Core resources to ensure projects succeed. The Biospecimen/Bioimaging Core, directed by Dr. Robert West provides critical support to projects of the Center by providing human BPH tissues with deidentified data, generates histological images and manages these and the MRI images and provides Multiplexed Ion Beam Imaging (MIBI) and data analysis for Projects 1, 2 & 3. The Core also provides this service to the O'Brien Urology Centers and Urology Disease Centers. Project 1 seeks to define the role of fibroblast subtypes in the development and progression of BPH. Project 2 characterizes the immune microenvironment and investigates how it is shaped by the stromal cells and how it influences the stromal and epithelial compartments of BPH. Project 3 uses MR Images with associated International Prostate Symptom Scores (IPSS) and Bothersome Indices (BI) to construct 3D models of BPH overlaid with histology. These models serve as an atlas for integrating stromal and immune microenvironment data and gene expression subtypes and will provide a means to test how molecular, cellular, microenvironment, histological and radiologic features and their heterogeneity relate BPH to LUTS. These projects serve as the nucleus for training of undergraduate, graduate, and post graduate students to become the next generation of leaders in urological science.



Public Health Relevance Statement

PROJECT NARRATIVE – OVERALL. Benign Prostatic Hyperplasia (BPH) is the most common cause of Lower Urinary Tract Symptoms (LUTS) in men, yet we understand little about how it arises and progresses to cause LUTS. We propose an integrated O'Brien Center in which we will develop a molecular and cellular characterization of BPH, akin to the human tumor atlas, and will lead us closer to identify BPH specific treatments by uncovering its pathophysiology.

Administrative Core

PROJECT SUMMARY. The Administrative Core will be an essential resource in the success of the Stanford O'Brien Center. The goals of the Administrative Core will encompass external engagement, including integration with the O'Brien Center Collaborative Network, interfacing with other programs in urological research, coordinating training activities between research centers, and coordinating activities with NIDDK leadership. The Administrative Core also directs the Research Center's Educational Enrichment and Opportunity Pool Programs. The overarching goal of the Administrative Core is to provide the operational support necessary to successfully achieve the goals we have laid out for each project and program as a whole. The Administrative Core will be responsible for managing, coordinating, and monitoring overall progress, and supervising the entire range of the program's activities. Moreover, the Administrative Core will distribute results to scientific audiences and the general public. We will maximize efficiency, cost-effectiveness, and productivity by centralizing resources used by each of the projects and core. The Administrative Core has the following specific aims: (1) provide operational oversight and integration of projects and cores, (2) promotion of effective collaboration, communication,

and interactions within and outside the Center, (3) provide an effective, centralized unit to manage finances and resources, (4) broadly disseminate results and report Center activity, and (5) develop and execute the Center's Educational Enrichment and Opportunity Pool Programs. The organization of the Administrative Core will have clear lines of authority and will leverage both an Investigator Committee and Internal and External Advisory Committees to ensure effective use of resources, scientific guidance and evaluation, and clear decision-making processes. Overall the Administrative Core will provide fully integrated administrative services for the management, communications, coordination, and financial administration of the Stanford O'Brien Center.

Fibroblast subsets in BPH pathogenesis (Jonathan Pollack, MD, PhD)

ABSTRACT - PROJECT 1. Benign Prostatic Hyperplasia (BPH) is the benign enlargement of the prostate gland that occurs in older men, obstructing bladder outflow. The resultant lower urinary tract symptoms, such as urgency, frequency and incomplete emptying, have considerable morbidity, and carry annual healthcare costs in the Billions. Current BPH treatments are not very effective because the drugs target normal prostate physiology but not BPH pathophysiology, which is still poorly understood. New disease-targeted therapies will require a more detailed knowledge of BPH pathogenesis. In genomic studies of BPH clinical samples, we discovered a stromal gene signature that correlated with BPH symptoms, and an enrichment of fibroblasts overexpressing signaling proteins BMP5 and CXCL13. Fibroblast BMP5 enhanced prostate epithelial proliferation and drove gene expression profiles to mimic BPH tissue. From these data, we hypothesize that BPH is driven (at least in part) by pathogenic fibroblast cell subset(s), where defining those subsets will provide important new opportunities for disease targeted therapies. Towards that goal, the proposed studies aim to Define the fibroblast subsets in BPH versus normal prostate; Determine the key interactions between BPH fibroblast subsets and prostate epithelium that drive prostate enlargement; and Distinguish between BPH origins in embryonic re-awakening versus injury response. Study findings will provide new understanding of the contribution of prostate stroma to BPH pathogenesis, and identify new strategies for targeted treatment.

Immune microenvironment in BPH pathogenesis (Robert West, MD, PhD)

ABSTRACT - PROJECT 2. Benign prostatic hyperplasia affects the majority of men in later life and leads to considerable dysfunction. Current treatments do not address the pathophysiology of the disease but rather target the overall prostate physiology. The goal of our proposal is to identify BPH (Benign Prostatic Hyperplasia) specific treatments by uncovering its pathophysiology. BPH is marked by proliferation of both epithelial and stromal cells in the transition zone of the prostate. This expansion of tissue surrounding the prostatic urethra presumably gives rise to many of the lower urinary tract symptoms (LUTS) associated with BPH. A number of biologic pathways have been proposed to drive BPH including epithelial or stromal senescence, inflammation possibly related to infection, and aberrant activation of developmental pathways. We have recently performed gene expression profiling of BPH and identified at least two subtypes of BPH with possible therapeutic implications. One of the two most significantly differentially expressed genes in our study is CXCL13 which modulates the immune response. The CXCL13 finding represents an important lead in understanding how the immune response is established in BPH. We hypothesize that immune-related pathways play a significant role in BPH pathophysiology and that pathways associated with CXCL13 are drivers. The Aims of this proposal undertake to identify differences in immune response between BPH and normal prostate and to uncover important pathophysiology relationships that arise from these differences. In Aim 1, we will profile immune cell types in BPH and normal prostate using MIBI-TOF (Multiplexed Ion Beam Imaging by Time-Of-Flight) to measure 14 different immune cells and understand their spatial relationships with the epithelium and stroma. In Aim 2, we will identify spatial relationships and interactions between immune and other cell types. We will do this by combining RNA profiling of the stromal and epithelial compartments with multiplex IHC and computational modeling. In Aim 3, we will determine whether CXCL13 expression and accompanying immune cells is part of an immune response or a senescence response. We will examine whether senescent cell accumulation correlates with CXCL13 expression and BPH subtypes. We will also look for the presence of B and/or T cell clonality.

Other Stanford University U54 Urology O'Brien Center Leaders:

Jon Pollack, MD, PhD (Stanford University)

Robert West, MD, PhD (Stanford University)



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

Mayo Clinic Rochester FORWARD P20 Urology Center

- **PIs Kevin Koo, MD, MPH and Jonathan Lieske, MD (2022-2025)**

Renal macrophages in the pathogenesis of human urinary stones and Randall's plaque formation in mice

PROJECT SUMMARY - OVERALL. Urinary stone disease (USD) is the 3rd most common urological disease in men and women. Prevention of USD and its associated costs and morbidity requires an understanding of early and late USD pathogenesis. Emerging evidence suggests pathophysiological interactions between intrarenal crystal nucleation, growth, and phagocytic cellular responses may play a key but unrecognized role in USD. Studies in vitro demonstrate that calcium phosphate (CaP) and calcium oxalate (CaOx) crystals induce renal tubular and phagocytic cellular secretion of cytokines, chemokines, and extracellular vesicles (EVs; exosomes and microvesicles). These biomarkers can attract blood or residential monocytes and convert monocytes into pro (M1) or anti (M2)- inflammatory macrophages (Mφ 's). Observations in experimental animal models and human tissues suggest that renal tissue monocytes and Mφ 's can phagocytose and metabolize intrarenal crystals, and urinary stone formers appear to have increased medullary M1 and decreased M2 Mφ populations. In a hyperoxaluric mouse model, suppression of monocyte to M2 Mφ conversion significantly increased intrarenal CaOx deposition. Our studies also demonstrated that urinary excretion of EVs bearing inflammatory markers derived from specific segments of renal tubules were significantly lower in idiopathic calcium stone formers (ICSFs) compared to controls. Thus, multiple lines of evidence suggest that tubular and monocyte derived Mφ populations can phagocytose and degrade crystals as a crystal clearance mechanism, and defects in these clearance mechanisms could promote interstitial Randall's plaque (RP) and/or collecting duct plug (CDP) formation. The proposed research project is designed to evaluate the role of Mφ 's in RP and CDP formation using a novel hypercalciuric claudin-2 global knockout mouse model (over 3-24 months age) that resembles the phenotype of patients with idiopathic hypercalciuria and USD (Aim 1), and to define the frequency and spatial distribution of monocyte/ Mφ populations in carefully phenotyped ICSFs (20-70 years) with hydroxyapatite, brushite, and calcium oxalate stones plus varying amounts of RP (Aim 2). The proposed innovative study will elucidate the role of renal medullary pro-and anti-inflammatory phagocytic cells in the development of RP, CDP, and USD and whether urinary cytokines, chemokines or EVs carrying biomarkers of pro-/anti-inflammatory phagocytic cells can be used to non-invasively monitor intrarenal crystal deposition. Completion of this study will also facilitate the formation of a skilled multidisciplinary team including a promising early-stage surgeon-scientist (Dr Kevin Koo) under the mentorship of an experienced and skilled USD clinical and researcher (Dr. Lieske). The resulting preliminary data will provide evidence of the effectiveness of our team. This work will also enable submission of future detailed grant or center proposals that will extend these mechanistic studies, and has great potential to elucidate underlying pathogenic steps in USD genesis and identify novel therapeutic targets.



Public Health Relevance Statement

PROJECT NARRATIVE. Although some risk factors for urinary stone disease are known, including urinary supersaturation, other pathogenic events remain elusive. Our preliminary data suggests that altered populations of renal inflammatory cells may contribute to urinary stone risk. We propose formation of a multidisciplinary team that includes early-stage investigators to rigorously investigate renal inflammatory cells in a novel animal model and human stone patients. This P20 center will provide important preliminary data for future grant applications.

Other Mayo Clinic P20 Urology Center Leaders:

Muthuvel Jayachandran, PhD (Mayo Clinic)



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

Duke University FORWARD P20 Urology Center

- **Pls Pei Zhong, PhD and Christine Payne, PhD** [(2022-2025); also a prior P20 Urology Center 2019-2021 (PI Zhong)]

Enhancing laser lithotripsy via nanoparticle fine-tuned NIR absorption

PROJECT SUMMARY - OVERALL. Ureteroscopy (URS) via laser lithotripsy (LL) is the treatment of choice for urinary stone disease (USD), which is the second most costly urologic condition in the US with an annual healthcare expenditure over \$2 billion. The recent clinical introduction of high power/high frequency Holmium (Ho): YAG lasers and Thulium Fiber Laser (TFL) have fundamentally altered the mode of LL operation. Instead of the conventional fragmenting mode with basket extraction of sizable fragments, contemporary LL is often performed using dusting and pop-dusting modes that pulverize stone to dust in situ without the need for fragment extraction. The challenges in dusting and pop-dusting at present, however, are three-fold: 1) the mechanism of action is not fully understood, 2) the optimal treatment condition varies significantly with stone compositions, and 3) rapid temperature rise is produced during high power pop-dusting. Consequently, there is an unmet need to develop new and clinically deployable technologies capable of improving the treatment efficiency regardless of stone compositions, shortening the procedure time, while concomitantly lessening the risk of renal tissue injury. The overarching goal of this Duke University FORWARD Urology Center (P20) application is to foster and support the career development of **Dr. Po-Chun Hsu, PhD** who is a promising early-stage investigator with expertise in nanotechnology, yet new to the field of USD and benign urology. The Center's Research Project has three Specific Aims focusing on (1) Developing biologically safe nanoparticles with absorption peak optimized for Ho:YAG laser ($\lambda=2.1\ \mu\text{m}$) and TFL ($\lambda=1.94\ \mu\text{m}$); (2) Investigating the effects of nanoparticle-enhanced pop-dusting in a hydrogel-based kidney model, and (3) Exploring the effects of nanoparticle-enhanced pop-dusting in a porcine model. The Center's Administrative Core has two Specific Aims: (1) Facilitating productive collaborations among the Research Project Team and with the broader CAIRIBU research community, and (2) Fostering and supporting the career development plan for Dr. Hsu. Furthermore, we will leverage the knowledge, resources, and experience accumulated from a recently completed P20 exploratory center on LL at Duke (PI: Zhong, PhD), together with the support of the NIDDK CAIRIBU Interactions Core (PI: Penniston, PhD) and the Columbia U54 Center (co-PI: Barasch, PhD/MD) on assessment of renal injury in a porcine model. Synergies, preliminary data, and knowledge created by this P20 FORWARD program will support future R01 applications on nanotechnology-enhanced LL and the broad range of USD research through the NIDDK CAIRIBU program.



Public Health Relevance Statement

PROJECT NARRATIVE. Urinary stone disease (USD) is a benign but severely painful genitourinary disease that is the second most costly urologic condition in the US with a healthcare expenditure over \$2 billion per year. The surgical treatment of USD in patients is carried out primarily by laser lithotripsy (LL) via ureteroscopy, including pop-dusting to reduce renal calculi with a size up to 1.5 cm to dust in situ in the kidney without the need for fragment extraction. The research project proposed in this Duke University FORWARD Urology Center (P20) application aims to explore a unique and novel strategy of using nanoparticles fine-tuned to improve Holmium:YAG or Thulium fiber laser absorption in the near infrared range to improve the treatment efficiency, while concomitantly reducing the risk of renal tissue injury and procedure time during clinical LL.

Administrative Core

PROJECT SUMMARY. Urinary stone disease (USD) is the second most costly urologic condition in the US, with an annual healthcare expenditure of more than \$2 billion. Ureteroscopy (URS) via laser lithotripsy (LL) is the treatment of choice for USD. Recently, the introduction of high power/high frequency Holmium (Ho): YAG lasers and Thulium Fiber Laser (TFL) has fundamentally altered the clinical mode of operation in LL. Contemporary LL is often performed using dusting and pop-dusting modes that pulverize stone to dust in situ without the need for fragment extraction. However, there is an unmet need

to develop approaches that can address some of the challenges of dusting and pop-dusting in order to significantly improve the clinical treatment outcome regardless of stone composition, shorten the procedure time, and lessen the risk of tissue injury. The proposed Duke FORWARD P20 Urology Center (Duke FORWARD Center) will tackle some of the most pressing problems in treating USD with LL. The Center's Research Project (RP) will focus on modifying the fluid medium to enhance the inherent cavitation or photothermal ablation mechanism for stone ablation during another critical clinical procedure, called pop-dusting, so that the treatment efficiency can be improved, while the procedure time and potentially collateral tissue damage will be reduced. The RP will be led by Po-Chun Hsu, a promising junior investigator new to USD research with expertise in nanotechnology for heat and thermal management that will be central to the RP's strategy. The primary goal of Duke FORWARD's Administrative Core (AC) is to guide and support the efforts of the Center's RP Team to successfully conduct their project and help prepare them to apply for future R01s. The Specific Aims of the AC are to: (1) Facilitate productive collaborations among the RP Team and with the broader CAIRIBU research community; and (2) implement a career development plan for RP PI Po-Chun Hsu for him to gain experience and mastery in USD research knowledge and technical capabilities. If the aims of the AC are achieved, the RP Team will have successfully accomplished the aims of their RP and will be in a position to submit one or more follow-on R01s by Year 3 of the proposed Center. In supporting the Center, the AC will facilitate innovative research with the potential to benefit millions of USD patients worldwide and will have introduced this talented new USD research team to the NIDDK-sponsored CAIRIBU benign urology research community.

Research Project (Po-Chun HSU, PhD)

PROJECT SUMMARY. Urinary stone disease (USD) is a benign but severely painful genitourinary disease that affects nearly 1 in 11 Americans, with an annual health expenditure of over \$2 billion in the US. The introduction of high power/high frequency Holmium (Ho): YAG lasers and Thulium Fiber Laser (TFL) have fundamentally altered the mode of laser lithotripsy (LL), which is the treatment of choice for USD. Pop-dusting is a technique widely used in the final stage of LL, whereby the laser fired in a renal calyx causes the sizable fragments to move rapidly to grind them down to dust, which potentially leads to significant temperature increase in the kidney. Benchtop in vitro, porcine in vivo, and FDA adverse event reports all raise concerns for dangerous thermal dose accumulation and potentially permanent thermal injury. Our recently published findings lead us to hypothesize that cavitation bubble collapse with resultant microjet impact on the stone surface or streaming-induced shear may contribute to this process. In other words, the absorption of laser power of the fluid plays a critical role in the pop-dusting behavior. Therefore, by enhancing the Ho:YAG laser or TFL absorption, we can lower the power requirement for generating equivalent or stronger bubble activities to improve pop-dusting efficiency, while concurrently lowering the risk of thermal damage to the kidney tissue. The overarching objective of the Research Project (RP) of the Duke FORWARD P20 Urology Center is to extend the research efforts of the Center for Urological Research and Engineering (CURE) at Duke University by incorporating previously unexplored nanotechnology approaches. We plan to utilize nanophotonic science to develop a specialized nanofluid with high and selective absorption of the laser and investigate its benefits on LL efficiency, toxicity, and clinical safety from a benchtop model to in vitro and in vivo studies. The center's Research Project has three Specific Aims focusing on (1) Develop biologically safe nanoparticles with absorption peak optimized for Ho:YAG laser ($\lambda = 2.1 \mu\text{m}$) and TFL ($\lambda = 1.94 \mu\text{m}$) and assess cavitation dynamics and cell injury in an optical cuvette model. (2) Investigate the effects of nanoparticle-enhanced pop-dusting in a hydrogel-based kidney model and examine treatment efficiency and thermal damage risk in vitro. (3) Explore the effects of nanoparticle-enhanced pop-dusting in a porcine model and evaluate toxicity, safety, and pop-dusting efficiency in vivo. By achieving these aims, we envision successful progress and critical preliminary data collection, both in vitro and in vivo, for supporting future R01 applications on nanotechnology-enhanced LL. We further anticipate that the synergy and new knowledge created by this FORWARD P20 program will greatly enhance and promote our existing and future collaborations within the broader NIDDK CAIRIBU program, including the U54 Center at Columbia and the KURE K12 program at Duke, as well as through other USD research activities.



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

Endeavor Health System FORWARD P20 Urology Center

- **PI Simon Hayward, PhD** [(2024-2027); also a prior P20 Urology Center 2018-2020 (PI Hayward)]



Validating mouse models of prostatic hyperplasia

PROJECT SUMMARY - OVERALL. This P20 FORWARD Center will support a Project conceived and executed by three Early Stage Investigators (ESIs) to address a problem that is important to the field of benign prostate research and to other fields more broadly: the relevance of specific genetically engineered mouse models to human disease. The need for animal models in biomedical research and the utility of mice, specifically, is well recognized and accepted. A number of mouse models that purport to represent this disease have been generated. It is well recognized in the field that none of these is a good overall representation of the human condition. As such, criticism of models is a common issue in grant and paper review. This is a problem for all investigators in the field and can be particularly damaging to ESIs who do not have resources to generate data from multiple lines. The Center will bring together two biologists ([Drs. Petra Popovics](#) and [Renee Vickman](#)) with complementary skill sets and an interest in BPH, contributing expertise in mouse models and inflammation, with a bioinformatician ([Dr. Natalia Lanman](#)) to develop new approaches to correlate transcriptomic data from mice with existing human BPH datasets to establish a reference database encompassing similarities and differences between individual mouse models and salient aspects of human diseases. Successful development of these methods will allow broad application of the approach across a range of diseases where such problems exist. The project will establish standards and benchmarks for comparing mouse models to human BPH and identifying commonalities and disparities between the two. This will facilitate the selection of the best models and will encourage similar characterization and comparison of other models in the field. The data will be made available to the scientific community, as a collection in the CellxGene portal and as an RShiny application. Consistent with the stated goals of the RFA the Administrative Core and its Director (the PI, Dr. Hayward) will support the Project and specifically will provide access to resources and expertise to assist the three ESIs in the development of new funding proposals derivative from the data generated here. The Administrative Core will also oversee the fiscal and regulatory aspects of the Center and will provide mechanisms for regular contacts between the Project investigators and the broader research community, in particular with past and present CAIRIBU members, fostering opportunities to present data and furthering career opportunities. The Administrative Core will also coordinate with experts in the field to support the development and submission of new grant proposals from the ESIs. The immediate goal of this Center is to support the development of data that will contribute to the career development and funding success of three early stage investigators in the field of benign urologic research, bring new ideas and retain expertise in the field. The long-term goal is for the ESIs to achieve significant independent careers.

Public Health Relevance Statement

PROJECT NARRATIVE. Benign prostatic hyperplasia is one of the most common symptomatic conditions in aging men, resulting in millions of medical consultations, high healthcare expenditure and loss of productivity. This Center assembles a team of three Early Stage Investigators with expertise in benign urology, inflammation and bioinformatics to pursue a Project to identify the similarities and differences between mouse models of BPH and the human disease, establishing the most appropriate platforms on which to develop and test new medical strategies. The progress of the research, the career development of the team, grant applications derived from the project and data dissemination to the broader research community will be supported by the Administrative Core.

Administrative Core

PROJECT SUMMARY. This Administrative Core provides support and oversight for the P20 FORWARD Center. The Core will have two major tasks: 1) to facilitate the administration and higher-level management of the Center, providing access to expertise and resources as needed by the ESIs to achieve their immediate research goals, and 2) to support the career development of the ESIs through the successful completion of the project and the development of emergent new research proposals. The Core will also facilitate interactions with the NIDDK CAIRIBU and the broader research community as well

as compliance with appropriate local and federal regulations and data availability requirements. The Core Director provides advice, encouragement, and resources, but the overall research project was developed, and will be executed, primarily by the three co-investigator ESIs. The Core will provide a central communications hub between the ESIs who are working in three different locations, providing easy access to videoconferencing for both group discussions and communication with outside experts and with the broader benign urology research community. All three ESI, as well as the PI, have previously been, and continue to be, involved with CAIRIBU and are familiar with the organization and its various in-person and online meetings. The Core Director will ensure that the ESIs attend scheduled CAIRIBU meetings, will arrange for scientific updates by Center investigators at the CAIRIBU Annual Meeting, and facilitate ongoing communication with the CAIRIBU Interactions Core providing an interface with NIDDK. The Research Project will provide a molecular and cellular description of mouse models of prostate inflammation and hyperplasia, their individual transcriptomic, histologic, and functional characteristics, and the parallels to, and differences from, specific aspects of human BPH. The project addresses a major knowledge gap and will generate data that will support the development of new funding proposals to support funding proposals. The Core Director will provide access to resources including human patient transcriptomic databases and annotated human clinical samples that will be used to compare mouse models to human BPH. The Administrative Core will ensure that studies are completed and submitted for publication in a timely manner. The Core will be responsible for ensuring that data are deposited in a publicly available and easily understood form in a timely manner and will publicize the development of a database that can be interrogated through an RShiny application to be developed in the project. The major long-term goal of this Center is to help the ESIs to move to independent research careers. The project will develop data that can be used to support funding proposals. Such proposals require rigorous development to allow them to succeed in the review process. As such, the Administrative Core will oversee the establishment and regular meetings of committees of appropriately skilled and experienced individuals to provide relevant advice and insights on proposals as they are developed and through the submission process.

Research Project (Renee Vickman, PhD)

PROJECT SUMMARY. Benign prostatic hyperplasia (BPH) is common, resulting in significant morbidity, billions of dollars in annual medical expenses, and even greater costs to the economy in lost productivity. BPH is characterized by stromal and glandular hyperplasia, occurring focally in the transition zone of the prostate restricting urinary flow. The underlying causes of this focal growth are still unclear. Chronic inflammation is clearly associated with BPH and some have hypothesized a causal link, but data supporting this are limited. No comprehensive description of the immune environment in the mouse prostate currently exists, likely due to the scarcity of prostatic inflammation in background strains. Inadequate characterization of BPH models leaves them subject to scrutiny during the review process, so a direct comparison of mouse models with prostatic inflammation and hyperplasia both to one another and to human tissue is necessary to identify models appropriate to a specific research direction. This project aims to bridge this knowledge gap by utilizing single-cell RNA-seq (scRNA-seq) to identify the similarities between murine models and human BPH with the hypothesis that specific cell states, with expression profiles that mirror those in human tissues, will be found in individual mouse models indicating those aspects of human disease reflected in the model. The primary objective is to provide a basis to select project-appropriate BPH models through a comprehensive analysis of cellular composition and transcriptomic profiles, supplemented with measures of voiding function and histopathology. Furthermore, these studies will provide an accessible database of cellular, pathological, and voiding function information for each model that can be used as a benchmark and expanded by the benign urologic community. The searchable database will be an invaluable resource for the BPH research community, providing guidance on murine model selection and facilitating molecular and functional queries. Two Specific Aims will be pursued by a multidisciplinary team of three early-stage investigators (ESIs). First, we will complete a comparative cellular and functional characterization of mouse models of prostate hyperplasia. This aim will apply scRNA-seq to individual prostate lobes of six different models of prostatic inflammation and hyperplasia, as well as immune cell profiling for T and B cell receptor sequencing in mouse models and human BPH tissues. Histopathological and voiding function evaluations will also be included. In the second aim, we will develop a reference database and calculate the BPH-indicated functional distance between mouse and reference cellular populations. This aim will provide a bioinformatic comparison of all cells between each model as well as overlay cell types from each model to existing human scRNA-seq data to look for common cell states. Resources to make these data available to the scientific community, as a collection in the CellxGene portal and as an RShiny application, will also be developed in this aim. We anticipate this work will lead to an improved use of current models for BPH research, provide a basis for future R01 applications by each ESI, and lead to future novel pre-clinical studies.



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

Children's Hospital of Philadelphia FORWARD P20 Urology Center

- **PI Gregory Tasian, MD, MSc, MSCE** [(2024-2027)]; also a prior P20 Urology Center 2020-2022 (PI Tasian)]



Personalizing outcomes of nephrolithiasis in youth (PONY)

PROJECT SUMMARY – OVERALL. Kidney stone disease (nephrolithiasis) is characterized by painful, recurrent symptomatic events and is rising disproportionately in youth. Structural and scientific barriers have impeded strengthening the evidence base for management of pediatric kidney stone disease. The overarching objective of the Personalizing Outcomes of Nephrolithiasis in Youth (PONY) P20 Center is to generate knowledge that improves outcomes for youth with nephrolithiasis through an intentional and focused initiative to accelerate the research careers of early-stage investigators and thereby enhance the benign urology research community. To achieve this mission, this proposal strengthens partnerships among Dr. Gregory Tasian (PI at Children's Hospital of Philadelphia, [Dr. Jonathan Ellison](#) (early-stage investigator at Children's Wisconsin), [Dr. David Chu](#) (early-stage investigator at Lurie Children's Hospital of Chicago), and [Dr. Jing Huang](#) (biostatistician at Children's Hospital of Philadelphia). In the proposed PONY P20 Center, we address critical structural and scientific barriers that have impeded strengthening the evidence base for management of pediatric nephrolithiasis. We will accomplish our objectives by leveraging the resources generated by Dr. Tasian's research program, in particular the robust infrastructure of the Pediatric KIDney Stone (PKIDS) Care Improvement Network and data generated by the NIDDK-supported Urinary Stone Disease Research Network. Central to the PONY P20 Center is the PKIDS Care Improvement Network, which will support the Research Project and provide the means to disseminate the knowledge generated by the research directly into real-world care. In Aim 1, we will generate new knowledge responsive to patient-identified gaps in kidney stone research by conducting two distinct but complementary research studies that use data from PKIDS trial, the Prevention of Urinary Stones with Hydration (PUSH) trial, and the Study to Enhance uNderstanding of sTent-associated Symptoms (STENTS). In Aim 2, we will accelerate the research careers of early-stage investigators in benign urology. The Administrative Core will create opportunities for Drs. Ellison and Chu to lead the execution of the Research Project through operational and logistical support as well as data access. PKIDS will also provide the scientific environment to support the R01 applications led by Drs. Ellison and Chu that will arise from the Research Project. In Aim 3, the PONY P20 Center will enhance the benign urology research community. We will share our expertise in stakeholder (particularly patient and caregiver) engagement with members of CAIRIBU other benign urologic researchers. We will participate in existing CAIRIBU forums by contributing our lessons learned on stakeholder engagement in clinical investigation, patient-centered trial design, and conceptual innovations in learning health systems. Overall, the PONY P20 Center will generate knowledge that addresses critical priorities identified by youth with nephrolithiasis and accelerates the career of early-stage investigators who will be leaders in benign urological research.

Public Health Relevance Statement

PROJECT NARRATIVE. Nephrolithiasis is a common and painful condition with considerable morbidity the incidence of which is increasing among youth. The evidence base supporting management of common scenarios is weak due in part to the few urologists engaged in research. In this project, we leverage existing data and research infrastructure to accelerate the research careers of early-stage investigators and generate important knowledge of the course of non-obstructive kidney stones and the experiences after surgery to remove kidney and/or ureteral stones among pediatric patients.

Administrative Core

PROJECT SUMMARY. The central mission of the proposed Personalizing Outcomes of Nephrolithiasis in Youth (PONY) P20 Center is to generate knowledge that improves outcomes for youth with nephrolithiasis through collaborative research among established and Early-Stage Investigators. To achieve this mission, this proposal strengthens partnerships among Children's Hospital of Philadelphia, Children's Wisconsin, and Lurie Children's Hospital of Chicago. The Administrative Core will draw upon the resources of each institution, the robust infrastructure of the Pediatric KIDney Stone Care Improvement Network (PKIDS), the perspectives of the Kidney Stone Engagement Core, and data generated by the NIDDK-supported Urinary Stone Disease Research Network (USDRN) to overcome structural barriers that have impeded the generation of impactful new knowledge and have prevented the entrance and continued success of new investigators into benign urologic

research. In the proposed PONY P20 Center, we address critical structural and scientific barriers that have impeded strengthening the evidence base for management of pediatric nephrolithiasis. The Administrative Core will provide the project management support to ensure the success of the proposal. This support includes providing resources and infrastructure to complete the Research Project and facilitating the continued trajectory of Early- Stage Investigators towards future independent R01 funding. Aim 1 of the Administrative Core is to support the Research Project. The Administrative Core will create opportunities for Drs. Ellison and Chu to lead the execution of the Research Project through operational and logistical support as well as data access. Aim 2 of the Administrative Core is to accelerate the research careers of Early-Stage Investigators and enhance the clinical impact of their research. The Administrative Core will integrate the research project into the existing organizational structure, relationships, and resources of PKIDS, which includes 30 institutions in North America. The Administrative Core will actively disseminate the results of the Research Project and promote their implementation into clinical care throughout PKIDS, thereby expediting and enhancing the impact of these findings. PKIDS will also provide the scientific environment to support the R01 applications led by Drs. Ellison and Chu that will arise from the Research Project. Aim 3 of the Administrative Core is to disseminate knowledge generated by the PONY P20 Center to the CAIRIBU community and the broader research base. The Administrative Core will access bidirectional channels created by the U54 Interactions Core to share and receive new ideas and knowledge with the CAIRIBU community and the broader benign urologic research base. Overall, the Administrative Core will facilitate the generation of knowledge that addresses critical priorities identified by youth with nephrolithiasis and will accelerate the career of early-stage investigators who will be leaders in benign urological research.

Research Project (David Chu, MD, MSCE)

PROJECT SUMMARY. Nephrolithiasis is a chronic disease characterized by recurrent symptomatic events that are both painful and expensive. Despite concerning epidemiological trends showing a higher incidence of disease and more frequent recurrence rates in youth aged 21 years and younger as compared to adults, a strong evidence base upon which to develop individualized management strategies for youth with nephrolithiasis is lacking. The overarching objective of the Personalizing Outcomes of Nephrolithiasis in Youth (PONY) P20 Center is to strengthen patient- centered knowledge and improve personalized management of youth with nephrolithiasis. We will generate new knowledge about two distinct but related common clinical scenarios: 1) the natural history of non-obstructive kidney stones, and 2) the post-operative patient-reported experience following ureteroscopy surgery for stones. To achieve this mission, we will leverage ongoing partnerships among Dr. Gregory Tasian (PI at Children's Hospital of Philadelphia, Dr Jonathan Ellison (early-stage investigator at Children's Wisconsin), Dr. David Chu (early-stage investigator at Lurie Children's Hospital of Chicago), and Dr. Jing Huang (biostatistician at Children's Hospital of Philadelphia). Specifically, this project will be supported by the resources generated by Dr. Tasian's research program, in particular the robust infrastructure of the Pediatric KIDney Stone (PKIDS) Care Improvement Network and data generated two NIDDK-supported Urinary Stone Disease Research Network studies: the Prevention of Urinary Stones with Hydration (PUSH) trial and the STudy to Enhance uNderstanding of sTent-associated Symptoms (STENTS). In Aim 1, we will develop and validate a risk prediction model for symptomatic stone events for youth with non-obstructive stones. Model development will leverage PKIDS trial data, which will be further augmented by linkage with the PCORnet common data model, providing an additional 18 months of follow-up beyond the PKIDS trial. The prediction model will be externally validated among youth in the PUSH trial. We expect to evaluate this prediction tool in a future R01-supported hybrid implementation- effectiveness trial within the PKIDS Care Improvement Network comparing the prediction tool against usual care for non-obstructing nephrolithiasis. In Aim 2, we will apply group-based trajectory modeling to differentiate distinct longitudinal trajectory groups of post-operative pain intensity, pain interference, and urinary symptoms following ureteroscopic surgery for stones. These unique trajectory groups will identify subgroups of youth at high risk for severe pain and urinary symptoms after surgery. We will determine the predictors and consequences of group membership to help with risk stratification. This modeling approach will be applied first to youth in the PKIDS trial, then repeated among youth in STENTS. We expect to leverage our findings in a future R01-supported pragmatic trial comparing adaptive interventions against usual care that implement individualized pre-operative strategies to enhance post-operative recovery and symptoms. This project will enrich the evidence base for youth with nephrolithiasis and support career trajectories for two early-stage instigators to carry this evidence forward.



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

University of Wisconsin-Madison K12 Urologic Research (KURe) Career Development Program

- **PI Chad Vezina, PhD** [(2023-2028); also prior iterations 2013-2018 (PI Dale Bjorling, DVM), and 2018-2023 (PI Dale Bjorling, DVM)]

Wisconsin Multidisciplinary K12 Urologic Research Career Development Program

PROJECT SUMMARY. The University of Wisconsin (UW)-Madison Multidisciplinary Urologic Career Development Program (KURe) K12 began in 2013 to attract and retain aspiring scientists into the benign urologic research field. Our rich training environment includes robust urologic research support including a George M. O'Brien Center in Benign Urology Research; a Summer Program in Undergraduate Urologic Research (SPUUR); and a U24 interactions core focused on Collaborating for the Advancement of Interdisciplinary Research in Benign Urology (CAIRIBU). The K12 scholars and cadre of outstanding mentors also benefit from UW Madison's NIH-funded Institute for Clinical and Translational Research (ICTR) and an internationally recognized Center for Improvement of Mentored Research Experiences. There has been tangible progress since 2013. In addition to five current scholars receiving training, six scholars have completed K12 training and earned investigator-initiated NIH funding. Five of these scholars are leading independent benign urology focused research programs as tenure track faculty at research-intensive institutions. Building on proven success, the program will continue to recruit and retain promising investigators through formative mentored research experiences and didactic training, as well as new initiatives to enhance professional development, with the goal of expanding the workforce in benign urology research.



Public Health Relevance Statement

PROJECT NARRATIVE. Building on a ten-year history of successful progress, the K12 training program will continue advanced training in clinical and basic science approaches and expand recruitment and training of scholars in population health and dissemination and implementation sciences in an environment that is ideally suited for professional skills development, building networking opportunities with researchers across the country, and matriculating independent researchers in benign urology with diverse expertise.

Current K12 Scholars (as of January 2025)

Lauren Baker, PhD, DVM

Matthew Grimes, MD

Andrew Wentland, MD, PhD

Vinaya Bhatia, MD



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

Duke University K12 Urologic Research (KURe) Career Development Program

- PI Cindy Amundsen, MD (2013-2018, 2018-2023, 2023-2028; same PI)



Duke Multidisciplinary K12 Urologic Research Career Development Program

PROJECT SUMMARY. Duke's KURe program provides structured mentoring, customized research training, and individualized career development for postdoctoral fellows and early career faculty with a doctoral level degree, who are committed to an independent research career in benign urology. Over the past nine years, we have supported 13 KURe Scholars including three from groups underrepresented in medicine. When transitioning to independence, 57% of our scholars obtained individual K awards (K01, K08, K23), and 100% received major foundation or federal funding. We request competitive renewal of the Program, which has four major goals: 1) Foster diversity by recruiting Scholars from diverse backgrounds and by providing a supportive and inclusive environment; 2) Train the next generation of benign urology researchers by fostering multidisciplinary research; 3) Address gaps in scientific knowledge by strengthening inter- and cross-disciplinary collaborations within the broader benign urology research community through active participation in Collaborating for the Advancement of Interdisciplinary Research in Benign Urology (CAIRIBU); and 4) Prepare KURe Scholars to lead their own multidisciplinary research teams and become the mentors and leaders of tomorrow. At any one time, we support up to 4 KURe Scholars who are guided by 2 mentors from our robust group of KURe core mentors. The KURe mentors have significant expertise in 5 main areas of benign urology: 1) Lower Urinary Tract Dysfunction 2) Urinary Tract Infection/Inflammation 3) Pediatric Urology 4) Stone Disease and 5) Reconstructive Urology/Regenerative Medicine and Neurourology. In addition, our mentors employ different approaches and can guide our Scholars using 1) Basic/Translational Research 2) Clinical Research 3) Health Services Research and 4) Systems Biology. Scholars are appointed for one year and can be renewed annually for up to 4 years. Scholars receive one-on-one Executive/Leadership Coaching. Their Individual Development Plans include intense hands-on research, structured mentoring, and courses/activities that increase 5 core competencies (Responsible Conduct of Research, Scientific Writing, Experimental Design/Methods, Data Management/Statistics, and Leadership). At completion of the program, Scholars are expected to have published in peer-reviewed journals and have obtained independent funding. Scholars' progress is monitored by the PD/PI and the Advisory Committee (AC). Program improvements are made based on feedback from mentors and Scholars, recommendations by the AC, and results from an independent external mixed methods longitudinal evaluation. The annual Duke KURe Multidisciplinary Benign Urology Research Symposium attracts national attendees. Scholars present their research and connect with experts. Duke KURe is a successful, vibrant program with expert mentors, experienced leadership, and the institutional commitment to ensure that a diverse pool of well-trained researchers is available to address benign urology through multidisciplinary collaborations.

Public Health Relevance Statement

PROJECT NARRATIVE. Duke University, a major research university in Durham, NC, supports a career development program focused on benign urologic conditions, a major public health concern. Early career scientists will receive formal mentoring and training to conduct multidisciplinary research relevant to benign urology. These well-trained scientists will become the future leaders researching the underlying causes of benign urologic conditions and developing better treatments.

Current K12 Scholars (as of January 2025)

Michael Odom, PhD

Cassandra Kisby, MD

Em Abbott, PhD

Bin Ni, MD, PhD

Natasha Wilkins, PhD



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

Stanford University K12 Urologic Research (KURe) Career Development Program

- PIs Joseph Liao, MD and James Brooks, MD (2023-2028)

Multidisciplinary K12 Urologic Research at Stanford (KUReS) Career Development Program

PROJECT SUMMARY. The overall objective of the Multidisciplinary K12 Urology Research at Stanford (KUReS) Career Development Program is to develop the next generation of highly qualified MD, MD/PhD, and PhD scientists to emerge as independent investigators capable of obtaining funding to support their research, leading their area of research in benign urology, and ultimately bring meaningful impact to their field. During the program period, Scholars will be given the training, courses, and guidance needed to achieve this goal; key to the Program's success will be the mentoring provided by our NIH-funded faculty preceptors. Twenty-eight Faculty Preceptors drawn from 3 Schools, 6 Institutes/Centers and 16 Departments at Stanford, 8 Advisory Committee members, and 6 Near-Peer Mentoring Committee members will collaborate to train junior physician scientists and investigators (KUReS Scholars) to acquire the skills and experience needed to transition into productive, independent physician scientists able to sustain viable careers and mentor future generations. The KUReS Program bridges clinical care with excellence in basic, clinical and translational research to address the national shortage of qualified investigators in benign urology. The Program includes a structured training plan of sufficient duration to achieve independence, individualized didactic education based on skills, competencies, and needs, extensive team-based mentoring, hands-on research, and protected time with immersion in a vibrant research community. Stanford has robust mentoring systems, strong curriculum, and solid infrastructure in place to prepare KUReS Scholars for research independence. Each Scholar will have a multidisciplinary mentor team as well as access to a wealth of resources including the Stanford U54 O'Brien Center, Stanford CTSA and NIDDK CAIRIBU network. We have an excellent pipeline of diverse Scholar candidates and comprehensive collateral resources. Two KUReS Scholars will be supported each year of the 5-year Program. Duration of support for each Scholar will average 2-3 years. Leveraging on the expertise of the Preceptors and Stanford's outstanding infrastructure, Scholars will be recruited nationally to pursue one of five research thematic areas: 1) Regenerative Medicine, Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS), and Voiding Dysfunction; 2) Urologic Omics and Lower Urinary Tract Symptoms (LUTS); 3) Urologic Imaging and Engineering, 4) Urinary Stone Disease and Infections; and 5) LGBTQ+ Health and the Urinary Tract. Scholars will develop essential skills and a portfolio of research projects to propel their transition to independence. Research progress and career outcomes of Scholars are evaluated in an ongoing basis by Faculty Preceptors, Program leadership and Advisory Committee members.



Public Health Relevance Statement

PROJECT NARRATIVE. The overall Multidisciplinary K12 Urology Research at Stanford (KUReS) Career Development Program is to develop the next generation of diverse, highly trained MD, MD/PhD, and PhD scientists to emerge as independent investigators capable of obtaining funding to support their research, leading their area of research in benign urology, and ultimately bring meaningful impact to their field. Having this program embedded in Stanford's rich culture of innovation and collaboration provides an exceptional environment to empower the next generation of independent investigators who will advance reproductive health for all..

Current K12 Scholars (as of January 2025)

Kathleen Kan, MD

Alex Polasko, PhD



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

University of California San Francisco (KUroEpi) Career Development Program

- PI Alison Huang, MD (2016-2021; 2021-2026; same PI)

UCSF-Kaiser Urological Epidemiology Research Career Development Program

PROJECT SUMMARY. The University of California San Francisco-Kaiser Permanente Northern California Urological Epidemiology (UCSF-KPNC UroEpi) K12 Program provides rigorous training, multidisciplinary mentoring, and career support to junior faculty developing high-impact epidemiological research programs in non-malignant urological conditions. Our institutions will continue to collaborate successfully to provide faculty with the mentoring, skills, and experience they need to achieve success as epidemiologic investigators. Scholars will continue to be based at UCSF and the KPNC Division of Research, both with robust scientific infrastructures, where they will be able to access an unparalleled set of data resources, including data from the entire KPNC patient population. The history of collaboration between our institutions and Program Directors will perpetuate our superb track record of developing future leaders in urological epidemiology. Training and Pipeline: This highly structured program includes comprehensive mentoring, rigorous didactic training, career development activities, and hands-on research. Each Scholar benefits from an individually- tailored, multidisciplinary training program, with available programs including a certificate program, masters or PhD degree program in research methods and/or epidemiology, mentored work-in-progress and career development seminar series, and diverse specialized courses. We have also identified over a dozen Research Program Areas in non-malignant urology that leverage the UCSF-KPNC environments' diversity, direct access to real-life clinicians and patients, and mentors' methodological and content area strengths. With UCSF's diverse array of training programs, including multiple earlier-stage research training programs directed at the resident and postgraduate fellow level, we have an excellent pipeline of future, diverse K12 scholar candidates. Program Progress: Since this program was launched less than four years ago, it has already been successful in identifying exceptional Scholars from diverse backgrounds and guiding them to success in epidemiology research. Our past and current UCSF Scholars have not only been productive in publications and research accolades, but have also competed successfully for NIH funding. Along with our recently appointed and pending Scholars, they also contribute to diverse perspectives in urological epidemiology research. Innovation and Impact: This program's innovative pairing of a top tier academic center with a learning and integrated health care system represents an excellent investment of NIDDK resources to catalyze the growth of urological epidemiology research in a uniquely fertile environment. We will continue to build upon our long history of collaborative, multidisciplinary research that complements other large projects supported by NIDDK, such as O'Brien, MAPP, and LURN Centers. Thus, our environment enables our UroEpi Scholars and their mentors to make unique research discoveries with important implications for clinical practice and public health.



Public Health Relevance Statement

PROJECT NARRATIVE. In this career development program, the University of California, San Francisco (UCSF) and Kaiser Permanente Northern California (KPNC) will provide rigorous interdisciplinary training and robust career development support to junior faculty developing research programs in urological epidemiology. Our leadership and faculty at UCSF and KPNC have a superb track record of producing accomplished, independent scientists in urology, epidemiology, and related fields. This program will leverage the unique environment of KPNC, a large learning health care system with a diverse population and extensive electronic clinical data, numerous prospective cohorts, and the rich investigative and educational resources of UCSF to develop emerging leaders in epidemiology of non-malignant urology conditions.

Current K12 Scholars (as of January 2025)

Abigail Shatkin-Margolis, MD

Rachel Wattier, MD, MHS

Jennifer Yarger, PhD



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

University of Michigan (KUroEpi) Career Development Program

- **PIs Aruna Sarma, PhD and Quentin Clemens, MD** (2016-2021; 2021-2026; same PIs)

University of Michigan UroEPI Career Development Program

PROJECT SUMMARY. New medical discoveries and health care reforms are emerging at a pace that far exceeds our current capacity to translate new tests and treatments into an ever-evolving clinical environment. As such, while training in the skills required for bench to bedside translation remains fundamental, there is also a compelling need to expand the pool of epidemiological scientists capable of performing the clinical, health services, comparative effectiveness, dissemination and implementation research necessary to translate scientific discoveries not only into clinical practice but into population health benefits as well. This UM Urological Epidemiology (UroEPI) Institutional Research Career Development Program (K12) inspires and provides junior investigators/scholars with the necessary technical skills so that he/she can initiate and sustain an independent research program in the study of the epidemiology of benign urological conditions and embrace the interdisciplinarity of our institution. The UroEPI K12 consists of two principal components: 1) one year of didactic course work with concentrations in epidemiology and biostatistics; and 2) one year of applied experience in the conception, execution, and dissemination of a well-designed research project. Guided by their faculty mentor, scholars will be instructed in the philosophy, ethics and theory behind epidemiological research, as well as methodological techniques derived from a broad array of clinical, public health and social sciences. The Director and Co-Director will undertake administration of this program while progress will be monitored continuously by mentors, and biannually by the Mentor Steering Committee (MSC). Scholars will be expected to present their work to the MSC as well as at national scientific conferences. By the end of the training program, scholars will have completed both the requirements for an advanced research degree and a mentored research project, including publication of their findings in the peer-reviewed literature. Graduates of this training program will be well positioned to establish a longitudinal research agenda and to pursue an independent research career in academic Urology with a focus on the epidemiology of benign urological conditions.



Public Health Relevance Statement

PROJECT NARRATIVE. The University of Michigan's UroEPI program (K12), directed by Drs. Aruna V. Sarma and J. Quentin Clemens, brings together the necessary mentors, resources and units to inspire and train urologists to pursue an academic career in the epidemiology of benign urological conditions. As a K12 program that is focused on training urologists and scientists in epidemiological methods, the demand for training will be considerable. This program will offer a two-year training track to meet the needs of scholars. With this support, we will provide the next generation of physician-scientists with the essential skills to address important clinical and translational epidemiological research questions.

Current K12 Scholars (as of January 2025)

Kristian Stensland, MD, MPH

Oluwaferanmi Okanlami, MD, MS

Giulia Ippolito, MD, MS

Golena Fernandez Moncaleano, MD



Collaborating for the Advancement of Interdisciplinary Research in Benign Urology

CAIRIBU Community Urology Centers and K12 Programs

University of Wisconsin-Madison Urology Centers Program Interactions Core

- PI Kristina Penniston, PhD, RD (2020-2025)



University of Wisconsin-Madison CAIRIBU Interactions Core

PROJECT SUMMARY. The critical need remains to advance our understanding of benign genitourinary (GU) diseases – their etiology, pathophysiology, and mechanisms of progression. The phenotypic expressions of many common benign GU diseases are yet to be defined. Clinical gaps in knowledge include objective diagnostic tests and criteria for many symptomatic benign GU conditions and the efficacy of multidisciplinary and interdisciplinary approaches to management. The impact of these conditions on other disease processes and whole-body health; productivity, functioning, and quality of life; and public health overall is virtually unknown. The impact of disparities in healthcare and health outcomes on patients with benign GU disease is understudied. The potential power of prevention is unexplored. The proposed Interactions Core for the Community of NIDDK-funded benign GU Centers and Programs known as CAIRIBU (Collaborating for the Advancement of Interdisciplinary Research in Benign Urology) will foster and support integrated basic and translational science that answers critical questions in benign GU disease and builds the breadth and depth of benign urologic investigators. Our mission is to provide intellectual leadership and logistic support for the CAIRIBU Community by identifying and facilitating opportunities for cross-CAIRIBU collaboration and promoting research findings and resources to the broader benign GU research community. Specific Aims are to: 1) provide scientific leadership to the CAIRIBU Community by enabling the full potential of NIDDK staff and CAIRIBU leaders to provide guidance that results in highly meritorious convergent research and highly-trained new investigators in benign GU diseases; 2) provide leadership in team science by identifying and fostering opportunities for transdisciplinary interaction and collaboration within CAIRIBU and among the broader benign GU research community; 3) provide administrative support by building the CAIRIBU infrastructure to maximize communication, collaboration, coordination, and resource sharing; and 4) develop internal and external evaluation mechanisms to maximize the performance, transdisciplinary nature, productivity, and effectiveness of the Interactions Core and CAIRIBU Community. Our Interactions Core is led by a Principal Investigator who is an established benign GU disease investigator and has functioned in a pilot capacity as Director of Interactions for CAIRIBU since July 2018. Our Co-Investigator is an expert in the science of team science and has experience in collaboration-building and measuring collaborative science efforts. The University of Wisconsin School of Medicine and Public Health provides the ideal environment for supporting the Interactions Core due to its multiple resources. The Department of Urology is the idea “home” for the Interactions Core due to its strong commitment to and track record in benign GU research. Our Core will use innovative approaches to leverage CAIRIBU members’ common passion for addressing critical gaps in knowledge in benign GU disease.

Public Health Relevance Statement

PROJECT NARRATIVE. The overarching goal of the Interactions Core at the University of Wisconsin School of Medicine and Public Health is to foster and support collaborative transdisciplinary scientific research to enhance our understanding of the causes, development, progression, and personal, societal, and environmental impacts of non-cancerous urologic conditions, including urinary tract infection, kidney and bladder stones, prostatic enlargement, lower urinary tract symptoms (pain, incontinence, neurogenic bladder, and other voiding dysfunctions), male reproductive disorders, and developmental (congenital) abnormalities of the urinary tract. We will provide intellectual leadership and logistic support to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Urology Centers and Programs collectively known as CAIRIBU – Collaborating for the Advancement of Interdisciplinary Research in Benign Urology. Specifically, the Interactions Core will identify and facilitate opportunities for cross-CAIRIBU interactions and collaborations with new urology investigators, promote research findings and resources to the broader benign urology research community, and build the community and diversity of benign urology basic, clinical, and population scientists that are actively studying benign urologic diseases.