



**CAIRIBU
Annual Meeting**

**P20 Exploratory
Center Summaries**



CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

**Beaumont Hospital/ Oakland University School of Medicine/ Michigan State University
2021-2023 - Co-PIs, Bernadette Zwaans, PhD and Michael Chancellor, MD**

MICHIGAN INTERDISCIPLINARY CENTER FOR UROLOGY RESEARCH AND EDUCATION (MI-CURE)

SUMMARY. The Michigan Interdisciplinary Center for Urology Research and Education (MI-CURE) seeks to develop a world-class interdisciplinary research team comprised of scientists, clinicians, biostatisticians, and engineers to provide comprehensive and innovative approaches in benign urology. As such, we have brought together exceptional investigators with diverse expertise from Beaumont Hospital/ Oakland University William Beaumont School of Medicine and Michigan State University. The overall purpose of the MI-CURE Exploratory Center is to establish strong research foundations in bladder physiology, develop an intellectual infrastructure, and expand educational and training opportunities in benign urology research. Despite decades of research, the mechanisms by which bladder fullness is sensed are still unknown. A major barrier to developing and testing novel therapies for bladder dysfunction is our lack of understanding the mechanism of how bladder fullness is sensed. Thus, the overall goal of this initial project is to understand the basis of pressure sensing and its linkage to afferent nerve activation during bladder filling, and consequently how bladder remodeling and altered bladder wall compliance during disease can impact these mechanisms. To address this significant knowledge gap, we have assembled an interdisciplinary team of experts in physiology, cell biology, fibrosis, neurourology, statistics, and clinical urology and have recruited a promising new investigator in engineering to benign genitourinary disease, Dr. Sara Roccabianca. She has unique expertise in soft tissue mechanical characterization, microstructural quantification, and mathematical modeling of soft tissues movement. In addition to the strong benign urology research program using innovative and cutting-edge approaches, MI-CURE has an exciting Educational Enrichment Program to train and mentor all levels of adult learners, from high school students to medical students, to help expand and enhance benign urology research. MI-CURE is co-directed by the established physician-scientist team of Drs. Laura Lamb and Michael Chancellor, with clear communication and coordination plans in place. Together, MI-CURE will foster successful collaborations, education initiatives, and innovative research. Funding of MI-CURE as a P20 Exploratory Center will allow us to work with the George M. O'Brien Urology Cooperative Research Centers Program and the KURe and UroEpi career development programs through joint meetings and conference calls. Our goal is to leverage our collective resources and results into well-designed, novel projects suitable for submission as future NIH Investigator-Initiated R01s. We believe that the Michigan Interdisciplinary Center for Urology Research and Education program as a whole will be greater than the sum of its parts and will contribute to developing talented researchers in benign genitourinary disorders.





CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

**Children's Hospital of Philadelphia/ University of Pennsylvania
2020-2022 - PI, Gregory E. Tasian, MD, MSc, MSCE**

THE CHOP/ PENN CENTER FOR MACHINE LEARNING IN UROLOGY

Rilwan Babajide, Katerina Lembrikova, Justin Ziemba MD, MEd, Antoine Selman-Fermin MD, Yong Fan PhD, and P20 Center PI Gregory E. Tasian MD, MSc, MSCE

The mission of the Children's Hospital of Philadelphia (CHOP) and University of Pennsylvania (Penn) Center for Machine Learning in Urology (CMLU) is to apply machine learning to improve the understanding of the pathophysiology, diagnosis, risk stratification, and prediction of treatment responses of benign urological disease among children and adults. The CHOP/Penn CMLU addresses critical structural and scientific barriers that impede development of new treatments and the effective application of existing treatments for benign urologic disease across the lifespan. Structurally, urologic research occurs in silos with little interaction among investigators that study different diseases or different populations (e.g. pediatric and adult). To break down these barriers, the CHOP/Penn CMLU will establish a community with the research base, particularly with the CAIRIBU Community. We will build this community by providing mini-coaching clinics to facilitate application of machine learning to individual projects, developing an educational hub for synchronous and asynchronous engagement with the research base, and making freely available all source code and standalone executables for all machine learning tools. In addition, the CMLU will amplify interactions across institutions and engage investigators locally and nationally by providing summer research internships, an interinstitutional exchange program, and an annual research symposium.



Scientifically, analysis of imaging and other complex data is limited by inter-observer variability, and incomplete utilization of available clinical information. The CMLU overcomes these barriers by applying cutting-edge approaches in machine learning to analyze complex imaging data that is routinely obtained for the clinical evaluation of individuals with kidney stone disease. In particular, the proper selection of medical or surgical treatments for kidney stones is contingent upon accurate assessment of stone characteristics including size and location. Current methods for quantifying these characteristics depend on manual measurement of CT images by clinicians.

This process is laborious, slow, and introduces unnecessary inter- and intra-rater variability. Therefore, effective methods to automate this process and make it more accurate and reliable would improve point of care decision making. The CHOP/Penn CMLU will develop machine learning algorithms for CT images to automate measurement of characteristics of stones (e.g. size, location, and shape) and kidneys (e.g. hydronephrosis, ureteral dilation). We will use manual measurements as a comparative gold standard. Following this first stage, we will then apply our deep learning algorithm to additional CT images, which will be supplemented with patient clinical characteristics (e.g. age, sex, BMI) to predict the spontaneous passage of stones in children and adults treated for kidney stones at CHOP and Penn. This study will introduce a new paradigm into clinical care by automating what is now an inefficient and inaccurate process. Furthermore, it will create a tool that may be used to improve clinical decision-making for patients most likely to benefit from early elective surgical intervention.



CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

**Medical College of Wisconsin
2020-2022 - PI, Kathryn Flynn, PhD**

WISCONSIN EXPLORATORY CENTER FOR INTERDISCIPLINARY RESEARCH IN BENIGN UROLOGY



OVERALL PROJECT SUMMARY. Lower urinary tract symptoms (LUTS) represent a heterogeneous set of symptoms with high economic and social costs and significant effects on patients' quality of life. The prevalence of LUTS in the United States ranges between 45% and 70% and increases with age. Medical expenditures for certain LUTS have been reported to be as high as \$65 billion per year. The guiding premise of the Wisconsin Exploratory Center for Interdisciplinary Research in Benign Urology is that LUTS can be better managed through improved collaboration between primary and specialty care. Specifically, the Wisconsin Exploratory Center investigators intend to investigate innovative strategies to target effective treatments to appropriate patients. One particularly bothersome LUTS is urinary incontinence, or the involuntary loss of urine, which is a common chronic condition affecting nearly half of adult women. While there are effective treatments for the two main types of urinary incontinence (namely, stress and urgency incontinence), there is evidence that most patients do not receive any treatment, and for those who do, treatment is often inadequate, and symptoms remain.

The first research project of the Wisconsin Exploratory Center will bring together 5 Center investigators with the necessary expertise to develop, implement, and evaluate a novel health system care pathway for treating women with incontinence. With improved identification of symptomatic patients using patient-reported outcome measures, and subsequent, stepwise initiation of available therapies, we hope to better manage incontinence, improve patients' symptoms, and reduce inappropriate referrals. The Wisconsin Exploratory Center's Administrative Core will provide oversight for all activities related to the research project and the Educational Enrichment Program. The Educational Enrichment Program will support medical student summer research experiences and a seminar series that brings invited speakers from backgrounds that are non-traditional in benign genitourinary conditions. The Administrative Core will facilitate coordination with the NIDDK and other NIDDK-funded Programs and Centers. It will ensure regulatory compliance for human subjects research. The Wisconsin Exploratory Center will solicit outside perspectives on progress and strategy from a Patient Advisory Panel and from an Advisory Committee comprising institutional leadership. By bringing together members of our local community of scientists already investigating benign genitourinary diseases and recruiting experienced scientists investigating other conditions to apply their expertise and techniques to the study of benign genitourinary diseases, the Wisconsin Exploratory Center will enhance the intellectual infrastructure of the benign genitourinary research community and foster scientific research that advances the field.

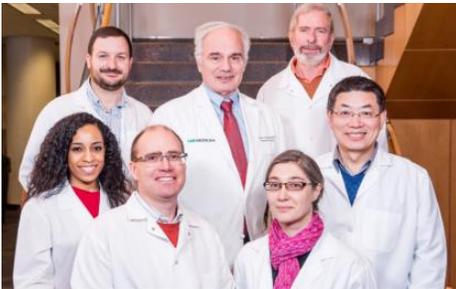


CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

University of Alabama Birmingham
2018-2020 and 2020-2022 - PI, Dean G. Assimos, MD

CENTER FOR RESEARCH ON OBESITY AND OXALATE KIDNEY STONES

The prevalence of both obesity and kidney stone disease has been steadily increasing in the U.S. over the past several decades. Calcium oxalate stones are the most common type, including within the obese cohort. There is mounting evidence that obesity is associated with increased urinary oxalate excretion, an important risk factor for calcium oxalate stone formation. The amount of oxalate excreted in urine is a risk factor for the development of calcium oxalate stones and several studies have identified that obese individuals excrete more oxalate than individuals with normal BMI. The prevalence of both obesity and stone disease is high in both Alabama and Texas, indicating that these states are ideally suited to identify whether they are inter-related.



To address this issue, we have established a research center (NIH/NIDDK: P20 DK119788) that was given the acronym COOKS (Center for research on Obesity and Oxalate Kidney Stones). This Center provides a platform for novel scientific research and the infrastructure for education and dissemination of information. In this project we will assess 3 possible reasons for greater oxalate excretion, including an increased contribution of endogenous oxalate synthesis to the urinary pool, enhanced net gastrointestinal oxalate absorption, and augmented renal oxalate

secretion. Both established and novel techniques will be utilized. Established techniques will include extended dietary studies where levels of oxalate, calcium and other nutrients are tightly controlled. Novel techniques will involve metabolic labelling to follow oxalate handling and synthesis, and state of the art imaging techniques. We will merge the skill sets and knowledge present on the UAB campus in the Center for research on Obesity and Oxalate Kidney Stones (<https://www.uab.edu/medicine/kidneystone/>) with those in the University of Texas Southwestern Center for Mineral Metabolism and Clinical Research in order to address this hypothesis. This joint endeavor will enhance skill sets originating in urology, biochemistry, obesity, nutrition and physiology at UAB with those in endocrinology, urology, gastrointestinal medicine/hepatology and nephrology at UTSW. The amalgamation of expertise in these Centers should be a pathway for strong future collaborative research focused on therapeutic interventions.



CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

**Albert Einstein College of Medicine
2019-2021 - PI, Kelvin Davies, PhD**

DEVELOPMENT OF A NANOTECHNOLOGY RESOURCE CENTER TO ADVANCE UROLOGICAL RESEARCH

Abstract: Novel technologies facilitate breakthroughs in scientific discovery with concomitant advances in therapy. In the case of nanotechnology, a major focus has been on optimizing its use for targeted drug delivery, imaging, diagnosis, or a combination of therapeutics and diagnosis (“theranosis”). However, the application of nanotechnology in the research and treatment of benign urological pathologies remains underexplored. At our institution (“Einstein”), the research laboratory of Dr. Joel Friedman has developed a nanoparticle- delivery system (the “Einstein” nanoparticle). We and others have applied this system to multiple research fields, including benign urology, as documented by >20 publications, several extramurally funded research projects, and licensing to a commercial entity. This nanoparticle-delivery system has intrinsic potential for modulation of its physicochemical properties, allowing use in a vast array of basic research and clinical conditions. However, the availability of these nanoparticle-delivery systems to the general urologic research community is currently limited by the absence of specific resource allocations for design and synthesis. This proposal addresses these limitations by establishing a P20 Resource Development Center with two primary goals: 1) to educate and promote the use of nanotechnology within the urologic basic and clinical research community, and 2) to create a resource development (research project) component in which the “Einstein” nanoparticle will be available for collaborative projects focused on benign urologic diseases. The proposed Resource Center will design and synthesize nanoparticles tailored to each research project until commercial entities assume this role. The Center will be highly synergistic, with investigators learning how nanotechnology can be applied to their specific field of research. Investigators will have access to resources and training, so they can apply the “Einstein” nanotechnology in their project. Investigators will require design and synthesis of novel nanoparticle formulations tailored to their specific research projects. This process would therefore lead to the development and expansion of novel nanoparticle formulations for a variety of benign urologic conditions. We anticipate that commercial entities will be positioned to synthesize nanoparticles within 2-4 years, eventually replacing the need for this P20 Resource Center.





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**Duke University, Department of Mechanical Engineering and Materials Science
2019-2021 - PI, Pei Zhong, PhD**

DUKE UNIVERSITY P20 EXPLORATORY CENTER FOR INTERDISCIPLINARY RESEARCH IN BENIGN UROLOGY

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 a healthcare cost over \$2 billion annually. LL is typically performed using Holmium (Ho):YAG laser operating at wavelength (λ) of 2.1 μm with a pulse repetition frequency (F) < 10 Hz. In recent years, new Ho:YAG lasers and technologies, such as the Lumenis H120 with MOSES technology, have enabled LL at high power (120 W)/high frequency (80 Hz), while offering new treatment modes, such as dusting, popcorning and pop-dusting. In 2020, Olympus launched the Soltive SuperPulsed Thulium Fiber Laser (TFL), operating at $\lambda = 1.94 \mu\text{m}$ with $F > 200 \text{ Hz}$, further expanding the armaments for USD management. Despite the rapid technology advances and growing clinical enthusiasm about the new lasers, the fundamental knowledge of LL has not changed commensurately in the past two decades.



The Duke University P20 Exploratory Center for Interdisciplinary Research in Benign Urology has created a comprehensive program to investigate the mechanism of stone damage in LL through a combination of experimentation and numerical modeling. This is an important endeavor because better understanding of the mechanism of stone destruction is the first step in developing improved and even less invasive surgical technologies for managing patients with USD. Most importantly, we have discovered that cavitation, i.e., the formation of an elongated vapor bubble at the laser fiber tip, plays a significant and, in some cases, even dominant role in stone damage. This finding is in distinct contradiction to the prevailing theory that stone damage in LL is predominantly produced by photothermal ablation. This paradigm-changing observation opens up opportunities to improve LL treatment strategy and patient outcome based on optimization of bubble dynamics, instead of maximizing laser energy delivery to the stone. The overarching goal of our P20 program is to promote multidisciplinary collaborations from basic to translational and clinical research applied to improve the efficiency and safety of LL treatment for USD.



CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

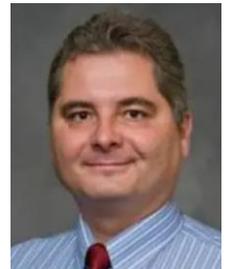
University of Tennessee Health Science Center
2019-2021 - PI, Georgi Petkov, PhD

NOVEL APPROACH IN UROLOGICAL RESEARCH REVEALS DIFFERENTIAL ION CHANNEL SUBCELLULAR LOCALIZATION IN HUMAN URINARY BLADDER SMOOTH MUSCLE

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INTRODUCTION AND BACKGROUND: Contraction and relaxation of detrusor smooth muscle (DSM) control micturition. DSM cell excitability and contractility depend on synchronized activity of multiple ion channel types. Our group, in collaboration with urologists, has the unique advantage to study the expression, function, and regulation of human DSM ion channels. Here, we have focused on two key DSM channel families: the TRPM (activation causes membrane depolarization and contraction) and voltage-gated Kv7 (activation causes hyperpolarization and relaxation). To exert their regulatory role, these channels would be expected to be localized to the DSM plasma membrane but so far investigations confirming this are lacking. To test this hypothesis, we selected the three most important family member representatives, the TRPM4, Kv7.4 and Kv7.5 channels in order to investigate their cellular localization.



METHODS: We have employed a novel technique called 'surface biotinylation' in conjunction with immunocytochemistry to examine the overall plasma membrane versus intracellular localization of these three ion channels. Human DSM tissue strips were incubated with non-cell permeable biotin tagged reagents that specifically bind to cysteine and lysine protein residues. Biotinylated surface proteins were then separated using avidin beads, eluted and Western blotting performed to determine the overall surface (plasma membrane) to intracellular localization of these channel proteins. Immunocytochemistry analyses for Kv7.4 and Kv7.5 channels were also performed on freshly isolated human DSM cells.

RESULTS: Surface biotinylation revealed that >85% of total TRPM4 protein was localized to the surface of human DSM cells, with only ~15% appearing in the intracellular fraction. Similarly, >82% of total KV7.4 and ~66% of total Kv7.5 proteins were also localized on the surface of DSM cells. Interestingly, the Kv7.5 distribution surface/intracellular (~66%/34%) ratio was the lowest among the three channels studied. Immunocytochemistry data analyses revealed that Kv7.4 channels were predominantly surface localized while Kv7.5 displayed a uniform distribution.

CONCLUSION: By employing surface biotinylation, a novel approach in urological research, along with immunocytochemistry, we revealed differential expression of ion channel subunits in human DSM. These exciting new data offer vital clues to the relative importance of the TRPM4 and Kv7 channels in regulating human bladder function.

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CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

Vanderbilt University Medical Center
2019-2021 - PI, Maria Hadjifrangiskou, PhD

THE VANDERBILT UROLOGIC INFECTION REPOSITORY, A RESOURCE FOR PERSONALIZED CLINICAL DISCOVERY

SUMMARY. In personalized medicine, the care of each patient is guided by his/her unique clinical circumstances. At its foundation, however, this paradigm holds a concurrent need for personalized science, in which technologies are developed and hypothesis explored in light of individual diversity. Critically, this diversity also includes unique microbial populations, which can augment the onset, progression, and treatment of disease. Within the field of benign urology, one of the most common pathologies—urinary tract infections (UTIs)—is also one of the most heterogenous, as the risk factors, symptomatology, and outcomes can vary significantly from patient to patient. Not surprisingly, the complexity of UTIs extends beyond the host, with tremendous genotypic and phenotypic diversity among the species/strains of microbes that elicit these infections. To better align the management of UTIs with the goals of precision care, our understanding of pathophysiology must become more nuanced, as we network in tandem the inherent diversity of host and microbe. To these ends, we propose a resource that provides an interconnected picture of both components, the Vanderbilt Urologic Infection Repository (VUIR). With our institution's unique foundation in medical informatics, we will create a searchable database of clinical parameters from bacteriuric patients (many thousands of cases annually), together with microbiologic data on the organisms. In parallel, the paired microbial strains will be stored permanently as a biobank for analysis and experimentation, together with linkage to anonymized versions of patient records within Vanderbilt's Synthetic Derivative (a filtered version of our electronic health data). The logistical infrastructure for clinical biobanking is also already in place at Vanderbilt via the institutionally-supported microVU initiative, in which microbial isolates from the diagnostic laboratory are repurposed as academic resources. As a basic expansion of these efforts, the VUIR will represent a first-in-kind tool for developing technologies to combat UTIs, while also investigating their underlying pathogenesis. In particular, it could facilitate functional genomic studies that bridge host and pathogen. Demonstrating the resource's value, we will conduct whole-genome sequencing of clinically underrepresented bacterial species, together with genome-wide association studies that focus on the infection phenotypes of the source-patients. In addition to novel virulence factors, we seek to identify elusive genomic determinants that distinguish cases of asymptomatic bacteriuria (ASB) and symptomatic UTI. The molecular basis of UTI-versus-ASB epitomizes a clinical challenge that requires integration of host and pathogen, as provided by the VUIR. Finally, to support the program and its discoveries, we propose an organizational structure of multidisciplinary content-area experts and dedicated support staff. Along with coordinating daily activities and assuring seamless dissemination of data/specimens, this Administrative Core (AdCore) will champion educational activities and additional pilot projects that build upon the resource. In sum, the VUIR stands to generate actionable discoveries from the human and microbial diversity of UTIs—not in spite of it.





CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

Beth Israel Deaconess Medical Center/ Harvard University
2018-2020 - PI, Mark Zeidel, MD

SINGLE CELL TRANSCRIPTOME PROFILING TO DEFINE CELL TYPES IN BRAIN NUCLEI CONTROLLING BLADDER FUNCTION

Harvard Medical School P20 Center for Interdisciplinary Research in Benign Urology (DK119789).

Scientifically the goal of our P20 Center was to identify subpopulations of neurons critical to the control of bladder function. While it is now possible to manipulate specific neuron populations (e.g. glutamatergic neurons) in specific brain regions (e.g. the pontine micturition center, PMC), neurons which utilize a common neurotransmitter still consist of many different subpopulations, each of which has a different set of inputs, distinct projections, and different functions. Single cell transcriptome profiling is a powerful approach for identifying these subpopulations, because information from rare cell types is not lost among the many. Unlike approaches that analyze DNA from a population of cells, single-cell analysis captures the heterogeneity of cells in a tissue.

Our first aim sought to use single cell RNA-seq to define all the neuron subtypes in the periaqueductal gray and in the PMC and to create a cellular atlas. The second aim proposed to map the connections of specific bladder controlling neurons using anterograde and retrograde tracing, while the third hopes to define the most functionally important neurons based on their response to a bladder stress model in mice. Administratively, the goals were to establish an educational enrichment program, to train young investigators through summer research projects and to establish a website for disseminating scientific findings.

Thus far we have performed RNA-seq on the PMC. Initial studies optimized the isolation of nuclear RNA transcripts (Drop-seq with nuclei; DroNc-Seq) to obtain high quality RNA transcripts, followed by transcriptomics. DroNc-Seq offers advantages over traditional cell dispersion and lysis approaches. We have identified ten clusters of Vglut2 neurons (Figure 1) and eight clusters of Vgat neurons in the PMC region.

We are now performing retrograde labeling with retro AAV2 (from sacral cord to PMC) to identify PMCVglut2 neuron subpopulations in addition to the Crh neurons, which project to the sacral cord. We anticipate that 3 – 5 of the glutamatergic non-Crh clusters will project to the sacral cord. We plan to selectively express Cre recombinase in each of these PMCVglut2 which project to the sacral cord, and then use this Cre expression to drive selective expression of channelrhodopsin2 in each subpopulation. Use of optogenetics paired with conscious cystometry will then determine what role each subpopulation plays in bladder contraction and voiding.

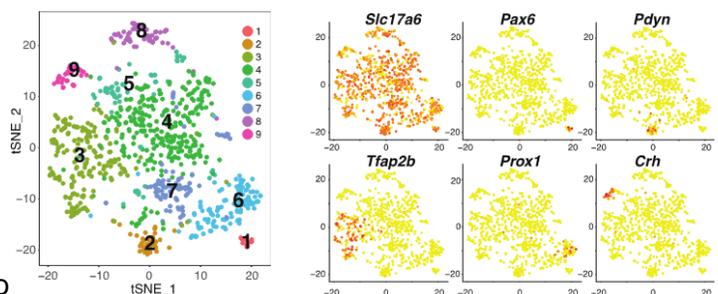


Figure. Single cell Drop-seq on isolated PMC cells. We initially clustered major cell types and then subclustered neuron subtypes to glutamatergic and GABA-ergic subpopulations. Shown is a third round of clustering of the glutamatergic populations.



CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

Columbia University Health Sciences
2018-2020 - PI, Simone Sanna-Cherchi, MD

NOVEL GENOMIC AND TRANSCRIPTOMIC TOOLS TO STUDY HUMAN CONGENITAL ANOMALIES OF THE KIDNEY AND URINARY TRACT

Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT) represent a collection of congenital abnormalities that deform the urinary system and lead to organ failure. In fact, CAKUT accounts for about half of the cases of end-stage renal disease requiring dialysis or transplantation in children. CAKUT pathogenesis results in abnormal growth, differentiation, and connectivity between different organs and tissues that comprise the urinary system. The causes of CAKUT have long been thought to be the sole result of misalignment of ureteric bud and metanephric mesenchyme, but the advent of human genetics has provided a glimpse into the myriad of genes that may direct the CAKUT phenotype; these genes are found to be expressed throughout the urinary system and the developmental timeline. Our genetic knowledge to date is incomplete because the genetic diagnosis often derives from simple searches of genetic mutations, it does not ascertain the damaged embryonic tissue itself, and it has profound limitations to connect the genome with the cellular readout. We believe we have developed novel approaches and tools that can solve these challenges by: 1) using whole-genome sequencing, rather than exome sequencing or candidate approaches, of parents and fetuses with CAKUT to comprehensively capture all sources of genetic variation; 2) evaluating the genome of families suffering termination of pregnancy rather than live births because early CAKUT manifestations are likely referable to rare mutations with large effect size that are more amenable to functional interpretation; 3) accessing the affected tissues themselves so that the consequences of the genetic abnormality can be determined by an investigation of the transcriptome and its sequelae. In fact, given the complexity of the cell types in the kidney, ureter, bladder, and lower urinary tract, often manifesting gradients of gene expression, we have worked out the conditions to derive the transcriptome from individual cells from frozen tissues. This involves the entirely novel technique of single nuclear sequencing and downstream informatics. In sum, we are now in a position to understand the subtypes of CAKUT by pairing a specific mutation, with a specific cellular or tissue lesion, with specific transcriptomic readouts. These efforts, consequently, bridge the gap between human phenotype, human genotype, and the defective developmental program leading to CAKUT and organ failure.



CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

**NorthShore University HealthSystem/ Purdue University
2018-2020 - Co-PIs, Simon Hayward, PhD and Timothy Ratliff, PhD**

LEUKOCYTIC PHENOTYPES ASSOCIATED WITH BPH PROGRESSION

The goals of this Center for Benign Urological Diseases are: 1) to create and maintain an environment that supports important and innovative research in the field of benign urology by focusing on a Scientific Research Project examining “Leukocyte phenotypes associated with BPH progression,” 2) to educate and inform young scientists and physicians about BPH, and 3) to develop new interactive projects and collaborations involving other groups in the benign urology research community. The program brings together expertise in basic science, bioinformatics, and clinical urology to apply new technologies in the field of benign urologic research. The research team includes members from the benign and malignant urology fields as well as from non- urologic cancers. Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) are highly prevalent and will become increasingly more frequent with an aging demographic. Approximately one- third of BPH patients are resistant to current medical therapy, and a further third of initial responders (around 10% of the total patient population) subsequently develop therapy resistance after an initial positive response. So, for around 40% of the patient population there is no effective medical therapy, leaving surgery as the sole treatment option. Approximately 120,000 surgeries are performed annually in the United States to treat men who are resistant to the available medical interventions. Many of these are elderly patients often with significant co-morbidities who are often not ideal surgical candidates. BPH is closely associated with pro- inflammatory co-morbidities. However, the characteristics and pathways linking immune/inflammatory changes to BPH progression are unclear. We show in preliminary data that TNF α antagonists can reduce the incidence of BPH in patients with autoimmune inflammatory conditions suggesting that a more complete understanding of the leukocyte signaling network in the prostate could elucidate new therapeutic targets. This proposal will utilize single-cell (sc)RNA-seq to fully characterize the leukocyte population in patients with small prostates and low IPSS scores vs. those with large prostates, high symptom scores, and progression to surgery specifically for a BPH indication. This will provide a comprehensive picture of the cells that are present and will allow for the application of bioinformatics approaches to define the extracellular signaling pathways that are activated in these inflammatory cells as disease progresses. The Administrative Core coordinates all Center activities, maintains financial and administrative oversight, manages the Educational Enrichment Program charged with the education of the next generation of scientists, and informs scientists and clinicians of our work. The Administrative Core also coordinates with the NIDDK and the other IR-BU Centers and integrates our approaches with the wider benign urologic research community.



CAIRIBU P20 Exploratory Centers for Interdisciplinary Research in Benign Urology

Washington University
2018-2020 - PI, Indira Mysorekar, PhD

MOLECULAR AND NEURO-INFLAMMATORY BIOLOGY OF AGING BLADDER IN NORMAL AND DISEASE STATES

PROJECT SUMMARY. Nearly 50% of post-menopausal women suffer from urinary tract infections (UTIs), and over 25% of post-menopausal women experience burdensome lower urinary tract symptoms (LUTS), including urinary urgency, incontinence, and painful urination. Given that nearly 1.5 billion people will be ≥ 65 years old worldwide by 2050, we must determine the pathophysiologic basis of these disorders so as to treat and prevent them. Solving this challenge will require an interdisciplinary approach. Thus, this is a proposal to establish an Interdisciplinary Research Center in Benign Urology focused on "Molecular and neuroinflammatory biology of aging bladder in normal and disease states". The overarching, long-term goal of the Center is to catalyze the rapid translation of breakthroughs in our understanding of chronic inflammation in the aged bladder from the preclinical to the clinical setting. The Center will accomplish this by bringing together an interdisciplinary team of physicians and scientists with diverse areas of expertise to systematically investigate markers and mechanisms driving chronic inflammation and its effects in mouse models and in human patients. The team includes practicing urogynecologists and basic and translational scientists interested in infections, age-associated immune dysfunction, and neurobiology of the bladder. The scientific research project proposes that the culprit behind many recurrent UTI and LUTS cases is a chronic neuro-inflammatory process of the bladder mucosa that can present as cystitis cystica, characterized as aggregates of lymphocytes that appear raised on cystoscopy. The Project has three Aims to define the cellular, molecular, immunological, and neurobiological changes that accompany infection and chronic inflammation in the aged bladder in mice and humans. The Center will include an Administrative Core responsible for fostering synergistic collaborations, integrating with existing NIH-sponsored O'Brien Centers in Urological diseases and urology training programs, and overseeing an Educational Enrichment Program. This Program will arrange visits to Washington University by outside speakers to present seminars relevant to the goals of the Center. The Program will also initiate didactic and practical Summer Scholar Research Experiences in Urogynecology-relevant labs for high school, college, and medical students. Together, the research and educational activities supported by the Center will allow the Team to increase interest in urology research and make substantial inroads into understanding the pathophysiology of recurrent UTIs and LUTS.