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CAIRIBU

Round Robin – Friday, July 18
Uro-Voiding & Dysfunction

Introduction

Nathan Tykocki, PhD.

Associate Professor

- Michigan State University
- Dept. of Pharmacology & Toxicology

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Research Interests & Goals

Research Focus Areas

- Sensation of Bladder Fullness
- Mechanotransduction in the Bladder Wall
- Urinary Bladder Vascular Physiology

Primary Topics

- Aging (pediatric bladder dysfunction)
- Neuro-urology (sensation of fullness)
- Biomechanics (ECM mechanical properties)

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Key Expertise & Methods

Core Knowledge & Expertise

- Benign lower urinary tract dysfunction due to stress
- Bladder wall biomechanics during filling
- Regulation of bladder blood flow
- Ion channel physiology

Skill Set

- Instrumentation fabrication and design
- Ex vivo and in vivo imaging
- Electrophysiology
- Smooth muscle pharmacology

Everything I build I will share with you all. My Core Facility (MSU Cubi^{3}c) can make almost anything…plus my team can bring your idea to fruition!

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Ongoing/Recent Projects

Bladder Wall Stiffness Drives Sensation of Fullness

12/2023-12/2027

- This project seeks to understand how the mechanical properties of the urinary bladder wall influence sensory outflow to the brain during bladder filling.
- NIDDK R01-DK135696
- Dr. Sara Roccabianca, Ph.D.

TRPV1 Mediates Progressive Stress-Induced Bladder Dysfunction

7/2019-6/2025

- This project investigated how the duration/intensity of social stress causes bladder dysfunction and determined the role TRPV1 channels play in the progression of stress-induced bladder dysfunction.
- NIDDK R01-DK119615
- Gerald Mingin, M.D. & Gerald Herrera, Ph.D.

Your Thoughts:
Major Knowledge Gaps in the Field

How Fullness is Sensed

- The signal itself is unknown, let alone the mechanisms that transduce it to the CNS
- Engineers, neuroscientists, and physiologists could hit from all angles
- Literature supports a differential sensor located in the bladder wall

Regulation of Blood Flow

- Loss of blood flow alone leads to overactive bladder, but no mechanism
- Cross-disciplinary collaborations with vascular biologists and CV researchers
- Possibility of treating some LUTS as a vascular problem instead

Urothelial Signaling

- Growing evidence that umbrella cells can be "excitable" cells
- Physiologists, pharmacologists, and biochemists could identify key players without using cultured cells

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Introduction

Margot Damaser, PhD

Position

- Professor, Cleveland Clinic Lerner Research Institute, Dept of Biomedical Engineering
- Senior Career Scientist & Deputy Director, Advanced Platform Technology Center, Cleveland VA Medical Center

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Research Interests & Goals

Research Focus Areas

- Female Pelvic Floor Disorders
- Regenerative Medicine
- Device Development

Primary Topics

- Technologies for individuals with neurogenic bladder
- Neuromuscular and ECM regeneration for pelvic floor disorders
- Technologies for improved in vivo functional LUT outcomes in humans & animals

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Key Expertise & Methods

Core Knowledge & Expertise

- LUT physiology, function, and dysfunction
- Interpretation and improvement of clinical & animal model Urodynamics data
- Development of animal models of LUT & pelvic floor dysfunction
- Biomechanics

Skill Set

- Survival pelvic surgery in large & small animals
- In vivo outcomes & necessary instrumentation and analysis in animals and humans
- Quantitative morphometry for nerves, muscles and ECM
- Translation of Intellectual Property

- Wireless catheter-free ambulatory monitoring of bladder function for large animals and humans

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Ongoing/Recent Projects

Matrix Regenerative Nanotherapeutic Platform for Pelvic Organ Prolapse

Oct 2025 – Sept 2030

- We will use a KO model of prolapse and waste human vaginal tissue to test an elastin regenerative nanoparticle to delay prolapse
- NIH 1R01 HD119910-01
- Anand Ramamurthi, PhD, Lehigh University

Wireless Mechano-Electrical Stimulation of Pudendal Nerve using a Piezoelectric Platform for Stress Urinary Incontinence

April 2023 – March 2028

- We are developing a piezoelectric material-based biodegradable and implantable platform that can generate wireless, local, and on-demand mechano-electrical stimulation of the pudendal nerve upon applied mechanical forces for nerve regeneration to treat stress urinary incontinence
- NIH R01 DK135472
- Metin Uz, PhD, Cleveland State University

Ongoing/Recent Projects

Center for Advanced Platform Technology

Jan 2005 – Dec 2029

- This technology center advances development and support of novel technologies to benefit rehabilitation of Veterans and trains the next generation of researchers
- VA RR&D 2 I50 RX001871-10
- Ron Triolo, PhD, Case Western Reserve University
- https://www.aptcenter.research.va.gov/
- https://www.linkedin.com/company/aptcenter/

Feasibility of Monitoring Bladder Pressure at Home in Veterans with Neurogenic Bladder

Oct 2024 – Dec 2025

- In this feasibility study, er are using our wireless catheter-free bladder monitor system (the Urodynamics Monitor) to compare bladder pressures at home with those measured during clinical Urodynamic testing
- APT Center Garverick Innovation Award
- Steve Majerus, PhD, Case Western Reserve University

Your Thoughts: Major Knowledge Gaps in the Field

Detailed physiological phenotyping

- Broad symptom complexes are inadequate for precision medicine; therefore we need more precise phenotyping to enable detailed differential diagnoses and precision therapy
- Different aspects could be tackled by different teams; validation with current methods is key; translation, dissemination, and commercialization is crucial; big data (AI/ML) analysis methods will be necessary

Mechanistic Basis of Disease

- We have little understanding of mechanistic processes that lead to incontinence and voiding dysfunction, limiting precision of therapy development or ability to intervene to prevent these conditions
- We need experts in multiple areas to produce clinically significant results
- Overlap with the Uro-Aging group

Development of 21st Century Treatments

- Regenerative Medicine, Gene Therapy, Patient controlled treatment, etc hold great potential for improving incontinence and voiding dysfunction
- Need to recruit experts from other medical fields and disciplines; need a variety of testbeds and outcomes

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Introduction

Anne "Hanneke" Verstegen, PhD

Assistant Professor

- Beth Israel Deaconess Medical Center/ Harvard Medical School
- Department of Medicine, Nephrology division

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Research Interests & Goals

Research Focus Areas

- Barrington's nucleus in the brainstem
- Neural circuits
- Neuronal populations and LUT function

Primary Topics

- Neuro-Urology
- Mapping neural circuits, Neural activity dynamics, Identifying the neuronal populations (in male and female (mice), and with aging)
- Brain, spinal cord and interaction/connections focus

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Key Expertise & Methods

Core Knowledge & Expertise

- Neuroscience
- RNA sequencing, functional studies
- Neuronal subtypes and their roles

Skill Set

- Optogenetics, chemogenetics and experimental design
- Calcium imaging; fiber photometry for measuring neural activity (population-wide)
- Viral tracing

To share: Our published Video Thermography VSA (PMID: PMC6942227)
Circuit tracing expertise - using viruses (AAV, PRV, HSV etc.)
"Anatomy reference" and Barrington's nucleus (environment) "resource"

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Ongoing/Recent Projects

The Neural Control of Continence

Project 1 Date: 2020-2025

- Barrington's nucleus (Bar) in the brainstem sends an excitatory signal to the motor neurons in the spinal cord. We are studying the inputs to Bar to reveal what controls its activity.
  - Labeled afferent sites in the brain,
  - PAG^{Vgat} neurons can delay voiding via their projections to Bar.
- NIDDK -
- Mark Zeidel at BIDMC

Ongoing/Recent Projects

The Neural Control of Continence

Project 1 Date: 2020-2025

- Barrington's nucleus (Bar) in the brainstem sends an excitatory signal to the motor neurons in the spinal cord. We are studying the inputs to Bar to reveal what controls its activity.
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- NIDDK -
- Mark Zeidel at BIDMC

Mapping Mechanosensory Circuits from the Bladder to Barrington's Nucleus

Project 2 Date: 2025-

- Unraveling the circuits and activity patterns of neurons in the circuit – from the bladder to the spinal cord, up to the brain, and in Barrington's nucleus subpopulations.
  - Reveal the neuronal identities,
  - Map how the bladder signals end up in and are being processed in the brain
- NIDDK -
- Kara Marshall at Baylor

Your Thoughts:
Major Knowledge Gaps in the Field

Neural control – (fundamental) – in healthy state

- How is the LUT controlled from the brain?
- Many components underexplored (afferent (via DRGs), within brain, efferent (to) spinal cord)
- Under healthy and pathological conditions

Spinal populations involved in LUT control

- (Too) Little knowledge/ Transcriptomic profiling
- 1. Identify, 2. Characterize, 3. Functional studies
- (Lumbo)sacral spinal cord focus

Differences in LUT function between males and females

- Male, female differences in LUT innervation, and with aging.
- Changes in voiding behavior as mice age? Do they become incontinent/retaining?
- Study sex differences

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Introduction

Kimberly Keil Stietz, PhD

Assistant Professor

- University of Wisconsin-Madison
  - Dept. of Comparative Biosciences

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Research Interests & Goals

Research Focus Areas

- Environmental Toxicant Impacts on Lower Urinary Tract Function
- Genetic Influences on Lower Urinary Tract Function
- Gene x Environment Interactions
- Rodent models of urinary dysfunction

Primary Topics

- Neuro-urology
- Toxicology
- Voiding assessments in mouse models

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Key Expertise & Methods

Core Knowledge & Expertise

- Mouse models/voiding assessment
- Toxicology/developmental toxicology
- Gene x environment interactions
- Autism spectrum disorder mouse models
- Developmental Biology (UGS)

Skill Set

- Voiding physiology assays, ex vivo bladder tissue strip assays
- Mouse models
- Toxicology assays
- ASD mouse models and neurotoxicology

Use of the Rodent Urinary Function Testing Core (RUFT) at UW Madison, includes VSA, uroflow, cystometry, bladder bath assays

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Ongoing/Recent Projects

PCBs and bladder contractility

2024-2029

- Developmental PCB exposure alters bladder smooth muscle contractility pathways
  - Receptor mediated functions
  - Calcium pathways
- NIEHS R01
- Hans Lehmler, PhD (U of Iowa)

Mutations in Shh signaling pathway affect continence

2024-2025

- Mouse model of female incontinence
  - Hypomorphic Shh signaling in female mice increases incontinence and alters urethral cell organization
  - Postnatally bladder and urethral epithelial boundaries are disrupted
- CAIRIBU Collaboration Award
- Walid Farhat MD.

Ongoing/Recent Projects

Voiding dysfunction in mouse models of Autism Spectrum Disorder

2025-2030 Lindsey Felth Tanaka (Postdoc in my lab)

- Genetic and environmental influences on ASD and LUTD
  - Genetic mouse models of ASD and LUTD
  - Brain, pelvic nerve, bladder smooth muscle
- NIDDK K12
- Lindsey Felth Tanaka (Postdoc in my lab)
  - Michael Cahill
  - Cara Westmark
  - Hanneke Verstegen
  - Nick Burgraff

PCBs and estrogenic effects on bladder smooth muscle function

2025-2027

- Determine whether PCBs which lead to LUTD in mice have estrogenic activity
  - ER reporter assays
  - ER KO mice +/- PCBs
- NIEHS F31
- Monica Ridlon PhD student in my lab.

Your Thoughts:
Major Knowledge Gaps in the Field

Assessment of Environmental Chemicals and LUTS in humans

- Correlative data on chemical exposure and LUTS classification is limited
- Many large cohorts have either chemical analysis data or LUTS data but not both – though biobank samples are available.

Assessment of LUTS etiology in ASD or other NDDs

- Lack of basic science and mouse models addressing LUTS in the context of ASD
- Leverage existing mouse models and assess LUTS along with other commonly performed behavioral ASD related assays

Gene x Environment interactions

- Gene and environment interactions studies are complex, expensive and long
- Capitalizing on convergent pathways

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Introduction

Sara Roccabianca, PhD.

Associate Professor

- Washington University in St. Louis
- Mechanical Engineering and Material Science Dept.

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Research Interests & Goals

Research Focus Areas

- Mechanobiology of Sensing Fullness
- Mechanophysiology of the Bladder Wall
- Effects of Sex Hormones on Bladder Function

Primary Topics

- Biomechanics (mechanical properties of the bladder wall)
- Female Urology and Aging (menopause, pregnancy, PCOs)
- Neuro-urology (mechanobiology of sensing)

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Key Expertise & Methods

Core Knowledge & Expertise

- Biomechanics of the bladder wall
- Effect of sex hormones on bladder mechanics
- Biomechanics of the vasculature

Skill Set

- Quantification of material properties
- Mechanical modeling of soft biological tissue
- Image analysis and 3D reconstruction
- Quantification of histology

We are happy to share custom codes that allow for 3D reconstruction of the bladder during filling (ex vivo), mechanical analysis, and histological analysis

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Ongoing/Recent Projects

Bladder Wall Stiffness Drives Sensation of Fullness

12/2023-12/2027

- This project aims to explore how the biomechanical properties of the urinary bladder wall affect sensory signals sent to the brain during bladder filling

- NIDDK R01-DK135696
- Dr. Nathan Tykocki

Michigan Interdisciplinary Center for Urology Research and Education (MI-CURE)

7/2021-7/2024

- MI-CURE aims to create a top-tier interdisciplinary research team to advance benign urology through collaboration, education, and innovation.
- Multi-Institution Project

- NIDDK P20-DK127554
- Chancellor M., Zwaans B.

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Your Thoughts:
Major Knowledge Gaps in the Field

How Fullness is Sensed

- Sensing fullness is inherently a mechanobiological process, but we don't understand it
- The lost or diminished ability to sense fullness is at the core of bladder dysfunction
- A range of expertise is required to unravel this mystery

Sex and Bladder Dysfunction

- It remains unknown whether the mechanophysiology of the bladder is identical in men and women
- Bladder dysfunction manifests differently in men and women
- Investigating this issue necessitates collaboration

Female Urology

- Hormonal fluctuations (pregnancy, menopause, PCOS) affect women's biology, especially the bladder, but mechanisms are unclear
- Bladder dysfunction is common in women due to these hormonal changes
- Further research is needed to understand and treat this

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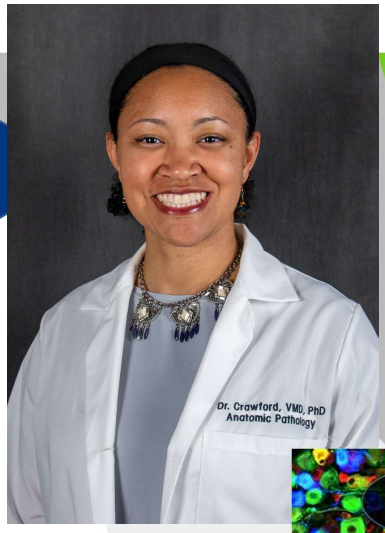
Introduction



LaTasha K Crawford, VMD, PhD

Assistant Professor

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Research Interests & Goals

Research Focus Areas

- Visceral Pain and Models of Bladder Inflammation
- Peripheral Mechanisms of Chronic Pain
- Comparative Neuropathology (DRG, Neuropathy, NeuroAging)

Primary Topics

- Sensory Innervation of the Bladder, Neuro-urology
- Mechanistic studies of how disease alters sensory ganglia (DRG)
- Collaborative studies of pain and neurologic disease in veterinary patients (Multinstitutional Veterinary NeuroBiobank, Ganglionitis & Pain in Horses, Sheep Tail Docking Neuromas, Cat Dementia as model of Alzheimer's)

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Key Expertise & Methods

Core Knowledge & Expertise

- Sensory Neurobiology, Neurophysiology
- Sensory ganglia pathology and peripheral neuropathies
- Comparative Neuropathology (Veterinary Medicine)
- Veterinary Biobanking (familiarity with biofluid biomarkers)

Skill Set

- Multiplex immunofluorescence, whole mount staining, image analysis
- Intravesicular acrolein and CYP-based mouse models of cystitis (female and male)
- Ex vivo DRG neurophysiology platforms: Whole DRG prep; Skin-Nerve_Ganglion-Cord prep
- Board certified veterinary pathologist w/ ample experience in animal models of human disease

Upright Thunder 3D Tissue imaging microscope with deconvolution, electrophysiology rig for calcium imaging (extracellular, whole-cell patch clamp capabilities), pathology insights in any species (neuro- and uro- histopathology, specialized dissection skills, etc).

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Ongoing/Recent Projects

Tools and models for the study of sensory neural drivers of bladder pain and urinary dysfunction

- TrkB genetic tools to label and silence CGRP-negative bladder mechanoreceptors
- Phenotyping the intravesicular acrolein cystitis modelafferent
  - Modality-specific 2ndary allodynia
  - Void dysfunction peaks at 2 days
  - Histologic lesions last > 8 days, mirror IC
- UW KURe (K12DK-100022), Pre-doctoral NRSA (mentee, F31DK135392), UW OVCRGE+WARF
- Kim Keil-Stietz (Dale Bjorling)

The effect of cystitis on neuron excitability and receptor-mediated responses in the DRG

- The effect of cystitis extends beyond the bladder afferent
  - Incr excitability in neighboring L3 >> L5, L6 DRGs
  - Incr several nerve injury and pain molecules; macrophage change morphology @ L5, L6 and L3 (L4)
- UW KURe (K12DK-100022), Pre-doctoral NRSA (mentee, F31DK135392), CAIRIBU collaboration award (U24-DK-127726), UW OVCRGE+WARF
- Robert Pearce (Richard Lennertz, Chad Vezina)

Your Thoughts:
Major Knowledge Gaps in the Field

Bladder /Urethral Mechanosensation

- Cell-specific details of LUT mechanoreceptor roles in healthy urinary function + dysfunction
- Confirmation of bladder /urethral nerve terminals from patients + controls
- Age-related changes in mechanoreceptor innervation?

Long Term Fx of Induced Models and/or Initial Etiopathogenesis of IC/BPS

- Lack of 'omics insight into how bladder disease alters sensory ganglia in models, patients
- Effects extend beyond bladder afferents (@DRG: neuro-immune, neighboring neurons)
- Need cell-specific molecular mechanisms, neurophysiologic, & behavioral validation
- Major challenge in translation + reverse translation: DRG = post-mortem samples

Fx of Neuromodulation on Bladder Afferents

- Knowledge gap may underlie untapped opportunity to hone / combine therapies
- Sensory axons that innervate the bladder are, in fact, axons (can release NT, factors)
- DRG "circuitry" (and effects of neuromodulation?) could change in health vs disease

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Introduction

Johanna Hannan, PhD.

Associate Professor

- University of Wisconsin-Madison
- Urology
- *previously at East Carolina University*

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Research Interests & Goals

Research Focus Areas

- Male and female sexual dysfunction
- Smooth muscle physiology
- Pelvic nerve regeneration
- Impact of cancer therapies on urogenital dysfunction

Primary Topics

- Pelvic radiation induced urogenital dysfunction
- Aging, obesity, diabetes and metabolic disorders and urogenital dysfunction
- Bioenergetics of bladder (dys)function

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Key Expertise & Methods

Core Knowledge & Expertise

- Broad knowledge of pelvic organ (dys)function (genital, bladder, urethra, pelvic floor, vasculature, nerves)
- Vascular/smooth muscle signaling
- Nerve regeneration
- Bioenergetics of the bladder

Skill Set

- Small animal surgeries
- Smooth muscle physiology – tissue bath
- Primary pelvic ganglia neuronal cultures
- Mitochondrial respiration

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Ongoing/Recent Projects

Localized SDF-1 mRNA nanoparticle delivery for treating erectile dysfunction

May 2022-April 2026

- This project optimized a nanoparticle-based platform to deliver SDF-1 mRNA to the penis to recover erectile function following bilateral cavernous nerve injury.

- NIDDK R01 - DK132425
- NIH R43 – DK130750
- Jun Soo Suk, PhD, University of Maryland; Nikolai Sopko MD, PhD

Novel SDF-1 mRNA therapy for prostatic radiation-induced erectile dysfunction

March 2023 – March 2026

- This study examined neuroinflammation and penile fibrosis following prostatic radiation and androgen deprivation and determined the efficacy of SDF-1 mRNA therapy to recover erections.

- DOD Idea Award - PC220484
- Trinity Bivalacqua, MD, PhD, University of Pennsylvania

Ongoing/Recent Projects

Targeting mitochondrial function to prevent obesity induced bladder dysfunction

Nov 2017 – May 2019

- This project assessed mitochondrial respiration in the urothelium and detrusor in parallel with bladder function in high fat diet fed mice.

- NIDDK-sponsored DiaComp Pilot and Feasibility Program
- Espen Spangenburg, PhD, East Carolina University and Kelsey Fisher-Wellman, PhD, Wake Forest University

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Your Thoughts:
Major Knowledge Gaps in the Field

Integrated whole organ physiology

- Often focused on one aspect of bladder physiology and need to collaborate with multiple experts, integrating whole bladder function (multidisciplinary bladder teams)
- Need more clinical samples for multi-omic assessments (lots done in bladder cancer but few in benign bladder conditions and incorporating urethra)

Underactive bladder (UAB)

- Few therapies to improve function when patients have UAB (often with aging)
- Fully understand the mechanism behind pathophysiological progression of UAB and are there critical times to intervene
- Multidisciplinary team (basic scientist, clinicians) to follow disease progression

Pelvic radiation induced bladder dysfunction

- Bladder dysfunction following prostatic or rectal radiation (not radiation induced cystitis)
- How radiation to the bladder's neurovascular supply can impact function
- Preventative therapies

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Introduction

Jim Hokanson, PhD

Assistant to the Professor

- Medical College of Wisconsin & Marquette University
- Joint Department of Biomedical Engineering

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Research Interests & Goals

Research Focus Areas

- Neuromodulation, primarily electrical stimulation
- Personalized Medicine
- Cross-over of symptoms/conditions (interest)

Primary Topics

- neuro-urology (role of nerves in controlling LUT)
- urgency urinary incontinence (treatment, diagnostics)
- neurogenic bladder dysfunction (treatment, diagnostics)

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Key Expertise & Methods

Core Knowledge & Expertise

- electrical stimulation
- human urodynamic testing
- neuroanatomy
- signal processing

Skill Set

- Electrophysiology
- Programming
- Talking with clinicians

We're working on making our extensive library of code for analyzing urodynamics data available, but I'm always open to offering some free advice on the topic. I have lots of other code on GitHub (stimulator control code, LabChart reading, etc.)

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Ongoing/Recent Projects

Neuroanatomical basis for tibial neuromodulation

Aug 2024 - July 2025

- We are characterizing neural connections between the tibial nerve and the lower urinary tract.
- CAIRIBU collaboration award
- Kajana Satkunendrarajah, PhD (U. Miami) and Aaron Mickle, PhD (MCW)

Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN)

Sept 2019 – Aug 2026

- As part of NIDDK LURN I'm involved on a project that has conducted physiological testing in women with UUI and healthy controls, and a project that is using Fitbit data to track nocturia events. Studies were done at 6 sites across the US.
- U01DK097780, U01DK100011
- Claire Yang, MD (U. Wash), John DeLancey, MD (U. Mich), Cate Bradley, MD (U. Iowa), many others

Your Thoughts:
Major Knowledge Gaps in the Field

Ways to link human dysfunction to animal "realm" – e.g., urothelial dysfunction, specific molecular dysfunction

- Feels like there is a disconnect between studying humans and animals
- Genetic testing in humans? Physiological markers of molecular dysfunction in animals (that can be translated to human testing).

Animal models with treatment failure

- Therapies that work well in animals fail to work well in humans
- We lack animal models where the therapy sometimes work (opportunity for improvement and learning)

How to optimize diagnostics in humans to personalize medicine

- Treatment is largely agnostic of testing
- Unclear what best tests are to inform therapy response
- Role of genetics, advanced imaging, various physiological tests
- How to enable big data?

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Report, Friday, July 18, Day 1
Uro-Voiding & Dysfunction

Voiding Control

Uro-voiding & Dysfunction

Co-Leaders: Margot Damaser and Nathan Tykocki

Understanding the gaps in knowledge (and ways to fill them) with regard to voiding behavior. This includes:

- Normal physiology
- Pathophysiology
- Environmental impacts
- Neuological control of voiding
- Pathogenesis of disease, including genetics
- Translation to clinical outcomes and diagnoses

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Day 1 report, continued (Uro-Voiding)

Critical Gap: We Need More Than Symptomology

Bi-Directional Neural Regulation of Fullness and Voiding

- Central to understanding both the physiology and pathophysiology of disease
- Foundational to the understanding of disease and disease progression

Sex Differences in the Lower Urinary Tract

- Clear differences in anatomy, physiology, and regulation of function
- Woefully under-researched, especially given the epidemiology of LUTS/LUTD

Human Data Mining: from the Brain to Bladder

- Our current understanding is piecemeal (at best) and incorrect (at worst)
- Imperative for generating new models to interrogate mechanism in animal models

Mechanistic Understanding of Disease Subtypes

- The lumping together of "LUTS" dilutes our ability to understand pathogenesis of each
- Physiological dysfunction/testing is needed, yet still not being undertaken

Research Questions

How are we going to get a "human baseline" of the complete bladder system?

- Everything thus far focuses on pieces and components, but never from the same person in totality
- Foundational insights that would influence how we ask EVERY question about LUT function

How is estrogen affecting the entire lower urinary tract – from brain to urethra?

- Also foundational to understanding sex differences and modeling mechanisms for further study
- Uncovering better targeted therapies, pathophysiology, and pathogenesis

Does urinary dysfunction predict molecular patterns in the bladder-innervating nervous system?

- Lots of other diseases that this could be done with and correlated together
- Can we use this to predict therapeutic response?
- Use urine biomarkers, genetic markers, and standardized tests to drive future investigation
- Pair post- and antemortem information/samples to derive relevant information and future study

Uro-Voiding Breakout Day 1

Zoom transcript, edited by kp

This research interest group focused on advancing research in urinary dysfunction. Kristin Ebert, MD (pediatric urology, UW-Madison) highlighted the need for better diagnostic tools and personalized medicine, emphasizing the variability in neurogenic bladder phenotypes. Nathan Tykocki, PhD (Michigan State University) discussed the importance of bladder blood flow and urothelial signaling. Jim Hokanson, PhD (Medical College of Wisconsin) emphasized the crossover of symptoms in urological conditions and the need for better diagnostics. Sarah Roccabianca, PhD (Washington University) focused on mechanical biology and sex hormones in bladder dysfunction. Joanna Hannan, PhD (UW-Madison) highlighted the impact of pelvic radiation on bladder function. LaTasha Crawford, VMD, PhD (UW-Madison) discussed the role of sensory innervation in bladder pain. Kim Keil Stietz, PhD (UW-Madison) stressed the impact of environmental toxicants on bladder function. Anneke Verstegen, PhD (BIDMC/Harvard) focused on neural control of continence. Margot Damaser, PhD (Cleveland Clinic) emphasized translational research and device development.

The group focused on improving diagnostics and treatments for bladder dysfunctions. Key themes included multi-modal monitoring, gene therapy, and regenerative treatments. **The group identified four research gaps: bi-directional neural regulation, sex differences in the lower urinary tract, human data mining from brain to bladder, and mechanistic understanding of disease subtypes.** Specific research questions addressed predicting adverse outcomes, understanding disease progression, and identifying physiological fingerprints. The goal is to develop more precise treatments and better characterize bladder diseases.

Action Items

- Reflect on individual knowledge gaps and research interests to share with the group.
- Come prepared on Saturday to discuss specific aims and hypotheses for potential research projects.
- Assign individuals to specific research projects and strategize on grant submission plans.

Kristin Ebert's Introduction and Overview of Urinary Dysfunction Research

- Kristin Ebert introduces herself as a pediatric urologist at the University of Wisconsin.
- She explains the focus of her talk on the clinical perspective of urinary dysfunction research.
- Kristin describes the spectrum of lower urinary tract dysfunction, including overactive bladder, stress incontinence, and underactive bladder.
- She highlights the importance of understanding neurogenic bladder and the need for better diagnostic tools.
- Kristin discusses the challenges of current diagnostics and the need for more precise methods to categorize patients.

Detailed Analysis of Bladder Dysfunction in Spina Bifida Patients

- Kristin presents examples of bladder dysfunction in spina bifida patients using urodynamics tracings.
- She explains the differences between safe and problematic bladders, including bladder diverticula and detrusor sphincter dyssynergia.
- Kristin emphasizes the importance of early intervention to prevent kidney damage.
- She discusses the limitations of current diagnostic methods and the need for better biomarkers and imaging tools.
- Kristin highlights the potential benefits of personalized medicine based on individual patient characteristics.

Research Gaps and Opportunities in Urinary Dysfunction Research

- Kristin identifies key research gaps, including the need for better biomarkers and imaging tools.
- She discusses the challenges of using animal models to study pediatric diseases.
- Kristin emphasizes the importance of integrating urodynamic data with molecular or neurophysiologic data.
- She calls for collaboration between basic scientists and clinicians to develop personalized medicine approaches.
- Kristin challenges the basic scientists to design studies that reflect variability in human disease.

Introduction to the Day's Agenda and Research Roadmaps

- Margot provides an overview of the day's agenda, focusing on developing research roadmaps.
- The goal is to address the public health burden of disease through advanced science.
- The objectives include identifying current knowledge gaps, prioritizing research ideas, and developing specific research questions and hypotheses.
- Margot emphasizes the importance of team science and the collective intelligence of the participants.
- The deliverables include individual and collaborative grant applications and multiple PI projects.

Round Robin Introductions and Research Focus Areas

SEE SLIDES FOR ROUND ROBIN INTRODUCTIONS

Collaboration and Future Directions

- Participants discuss the importance of collaboration and team science in advancing research.
- The need for better diagnostic tools and personalized medicine is emphasized.

- The potential benefits of integrating urodynamic data with molecular or neurophysiologic data are highlighted.
- The importance of addressing knowledge gaps and developing new research approaches is discussed.

Funding and Research Tools for Improved Diagnostics

- Speaker 3 discusses the funding through 2029 and the use of wireless devices to compare bladder pressures at home with clinical urodynamic testing.
- Emphasis on the need for multi-modal monitoring at home, including bladder measurement, EEG for nocturia, and environmental toxin monitoring.
- Speaker 3 mentions the potential for 21st century treatments like gene therapy and regenerative therapy, using diabetes as an example.

Research Gaps and Barriers

- Speaker 1 outlines the plan to discuss research gaps and barriers and categorize them, with a focus on detailed physiological phenotyping.
- Speaker 3 suggests using the last slide to detail research questions instead of barriers, emphasizing the need for more productive focus.
- Speaker 5 notes the addition of headlines for gaps in a Google Doc and invites participants to move things around to identify four gaps.
- Speaker 1 and Speaker 3 discuss the importance of narrowing down broad areas to fundable aspects for grants.

Identifying Research Questions and Gaps

- Speaker 5 explains the goal of identifying about four themes and generating research questions related to each theme.
- Speaker 1 and Speaker 3 discuss the importance of understanding the normal mechanisms of continence and voiding, and the need for detailed physiological phenotyping.
- Speaker 7 adds the importance of understanding how emptiness is sensed and the need for appropriate braking and loosening mechanisms.
- Speaker 1 emphasizes the need to know the normal mechanisms to influence disease treatment and the potential for basic science grants.

Challenges in Data Collection and Analysis

- Speaker 7 highlights the need for sacral spinal cord and dorsal root ganglia samples for comparative studies between humans and animal models.
- Speaker 8 suggests designing studies to correlate disease states with available biobank tissue.
- Speaker 1 mentions the challenges of getting comprehensive data from living people and the potential for prospective studies.
- Speaker 3 and Speaker 7 discuss the need for phenotyping and clinical data to support research questions.

Breakout Sessions for Research Questions

- Speaker 1 and Speaker 3 discuss the importance of understanding the origin of symptoms and the need for better tools to characterize the disease.
- Speaker 7 emphasizes the need for a physiological fingerprint to predict adverse outcomes and treatment response.
- Speaker 4 and Speaker 1 discuss the importance of understanding sex differences in the lower urinary tract and the need for comprehensive data mining.

Reconvening and Finalizing Research Questions

- Speaker 1 and Speaker 3 discuss the importance of understanding the progression of disease and the need for predictive molecular patterns.
- Speaker 7 highlights the need for a battery of tests to collect comprehensive data and the potential for post-mortem samples.
- Speaker 5 emphasizes the importance of understanding the disease to develop targeted therapies and the need for comprehensive data collection.

Uro-Voiding Breakout Day 2

Zoom transcript, edited by kp

The discussion focused on integrating sex differences and hormonal effects in uro-voiding models, emphasizing the need for comprehensive data collection and predictive models. Key points included the importance of considering estrogen's role in stress incontinence and breastfeeding, the potential use of tamoxifen in rodents, and the necessity of diverse animal models. The group debated the feasibility of large-scale, longitudinal studies to understand bladder dysfunction, suggesting the use of RNA sequencing and environmental exposure analysis. They also explored the potential of machine learning and predictive models to enhance clinical outcomes, highlighting the need for interdisciplinary collaboration and well-defined research questions. The meeting focused on prioritizing research questions and projects related to uro-voiding. Key points included the need to clarify the "complete bladder system" as "from brain to urethra" for better understanding. The group discussed the importance of accessing human and animal tissues, particularly from veterinary patients, to study bladder

dysfunction and hormonal influences. They emphasized the potential of using urodynamics data to predict disease progression and treatment response, particularly in conditions like spina bifida. The team also considered the development of predictive models to identify necessary data collection and the role of mechanistic models in guiding research.

Action Items

- Discuss the possibility of incorporating more mechanistic, computational, and predictive modeling approaches into the research plan, while considering the challenges of obtaining buy-in from clinicians and reviewers.
- Explore the feasibility of a longitudinal study to monitor the progression of underactive bladder in a cohort of at-risk individuals and identify factors associated with worsening symptoms.
- Investigate the potential role of environmental exposures, such as PFAs or Bisphenol A, in the development of lower urinary tract dysfunction, potentially leveraging existing cohorts with relevant data.

Sex Differences and Hormonal Effects on Uro-Voiding

- KS discusses the importance of considering sex differences and hormonal effects in uro-voiding models.
- KS suggests adding estrogen manipulation to basic models to study its effects on the urethra to brain pathway.
- Speaker 2 mentions various models used in Wisconsin, including those for prostate hyperplasia, and the lack of RNA sequencing data on bladder tissue.
- KS highlights the clustering of different models (obstruction, diabetic, inflammation) based on voiding assays and the need for new data collection methods like pelvic nerve recordings and calcium imaging.

Animal Models and Hormonal Regeneration

- Speaker 3 raises a question about the regenerative effects of estrogen on nerves and muscles during breastfeeding.
- Speaker 4 mentions vaginal estrogen prescriptions for women in a hypoestrogenic state due to vaginal atrophy.
- Speaker 2 and Speaker 3 discuss the potential use of tamoxifen post-parturition to prolong hypoestrogenic states in rodents.
- Speaker 2 inquires about methods to mimic stress incontinence in mice and the need for engineering solutions to measure intra-abdominal pressure.

Clinical Studies and Tamoxifen Side Effects

- Speaker 4 discusses the use of tamoxifen in breast cancer patients and its negative effects on sexual and bladder function.
- Speaker 5 suggests exploring other naturally occurring hormonal modulations like PCOS for their dysfunctional effects.
- Speaker 2 emphasizes the importance of writing specific aims for grants and the common practice of writing in increasing levels of complexity.
- Speaker 6 and Speaker 5 share their approaches to organizing aims, with Speaker 6 starting broad and focusing in and Speaker 5 starting with in vivo characterization and ending with a mathematical model.

Predictive Models and NIH Interests

- Speaker 5 discusses the potential of predictive models and the historical resistance from NIH to numerical models.
- Speaker 2 mentions the NIDDK/NIH FDA meeting and the various acronyms for animal models and novel approaches.
- Speaker 5 suggests that predictive models can be a useful tool for hypothesis generation and moving away from animal models.
- Speaker 7 highlights the importance of selling ideas to review panels and the potential for NIH to be interested in new approaches.

Multi-Site Efforts and Prediction Modeling

- Speaker 8 presents a vision for personalized therapy through diagnostics, treatment, and outcome collection, with a focus on prediction modeling.
- Speaker 8 suggests measuring a variety of factors simultaneously to understand treatment outcomes better.
- Speaker 2 and Speaker 8 discuss the challenges of using questionnaire data and the need for more effective measures.
- Speaker 8 emphasizes the importance of a multi-site effort to gather large numbers of data points and optimize for time, cost, and setting.

Environmental Exposures and Predictive Modeling

- KS discusses the potential of using environmental exposures to predict LUTS risk, mentioning ongoing investigations with PCB chemicals.
- Speaker 4 highlights the work being done in North Carolina on PFAs exposure and its impact on bladder disorders.
- Speaker 5 suggests exploring the use of machine learning to combine statistical models with mechanistic models for better predictions.
- Speaker 3 emphasizes the need for a clinical parallel to mechanistic models and the potential for machine learning to guide research.

Methodology and Translational Approaches

- Speaker 3 discusses the importance of translational research and the long-term goals of improving clinical outcomes.
- Speaker 8 suggests starting with intermediate steps to develop tests and understand their informative value.
- Speaker 4 emphasizes the need for focused models to gain clinical buy-in and the potential for expanding research later.
- Speaker 8 highlights the importance of understanding the progression of bladder disorders and the need for longitudinal studies.

Research Questions and Project Development

- Speaker 2 suggests focusing on specific research questions to develop hypotheses and inform grant proposals.
- Speaker 6 proposes a more general approach to include the whole translational part and testing the completeness of models.
- Speaker 2 and Speaker 6 discuss the potential for using core facilities to support multiple R1 grants.
- Speaker 8 mentions the possibility of applying for an RC2 grant to support the development of a human-mouse model.

Collaborative Efforts and Data Collection

- Speaker 7 discusses the challenges of finding dorsal root ganglia (DRG) for research and the potential benefits of a multi-institutional collaboration.
- Speaker 5 suggests writing a white paper to justify the need for a broad data collection approach due to the lack of existing data.
- Speaker 2 and Speaker 7 discuss the importance of full-thickness biopsies for understanding bladder and urethra disorders.
- Speaker 5 emphasizes the need for a comprehensive approach to collect data from various levels of biological organization.

Final Thoughts and Next Steps

- Speaker 2 and Speaker 1 discuss the importance of prioritizing research questions and developing focused projects.
- Speaker 8 emphasizes the need for a multi-site effort to gather large numbers of data points and optimize for time, cost, and setting.

Prioritizing Research Questions and Projects

- Speaker 1 emphasizes the importance of prioritizing tasks and making clear what the priorities are.
- Speaker 2 suggests starting with the prioritized projects and research questions, referencing a Google document.
- Speaker 8 mentions having a different version of the third research question and asks for it to be copied.
- Speaker 3 proposes adding molecular phenotyping to the research questions, highlighting the need for explanation in presentations.

Clarifying the Complete Bladder System

- Speaker 7 asks for clarification on the term "complete bladder system," suggesting "from brain to urethra" for better understanding.
- Speaker 2 agrees, noting the concept stemmed from looking at BPH and the prostate.
- Speaker 5 confirms the clarity of the phrasing, and Speaker 2 acknowledges the mistake in the initial wording.
- Speaker 8 questions the need for all the bullet points, expressing concern about overwhelming the group.

Identifying Research Leads and Collaborators

- Speaker 1 suggests keeping one bullet from the initial page to identify who could be involved and who will take the lead.
- Speaker 2 proposes keeping the prioritized research questions as an overview and addressing the need for access to human tissues.
- Speaker 6 suggests a multi-center bio banking approach, including both animal and human tissues.
- Speaker 7 highlights the feasibility of veterinary patient populations for hormonal and environmental influences studies.

Exploring Veterinary Models and Data

- Speaker 7 discusses the benefits of veterinary patient populations for studying hormonal and environmental influences.
- Speaker 4 mentions the aging dog project and its potential relevance to the discussion.
- Speaker 7 shares insights from a cat study on neurodegenerative disease, noting the feasibility of getting post-mortem samples.
- Speaker 2 expresses interest in the potential for learning from veterinary models and the importance of lifelong information for veterinary patients.

Developing Predictive Models

- Speaker 2 asks for another research question, focusing on the impact of sex hormones on bladder function and dysfunction.
- Speaker 8 suggests using urodynamics data to understand the progression of neurogenic bladder in spina bifida.
- Speaker 3 proposes a question about the data needed to create a predictive model, emphasizing the importance of preclinical work.
- Speakers 8 and 3 discuss the need for a mechanistic model to identify the information needed for a predictive model.

Assigning Leads and Collaborators

- Speaker 3 nominates Jim to take the lead on the predictive model question.
- Speakers 8 and 3 discuss the importance of a mechanistic model in developing a predictive model.
- Speaker 2 suggests assigning leads and collaborators for each research question to ensure coverage and expertise.
- Speakers 4 and 6 express interest in collaborating on specific research questions, highlighting their relevant expertise.

IDENTIFY RESEARCH GAPS & BARRIERS

From Google worksheet

KNOWLEDGE GAPS & RESEARCH NEEDS	RESEARCH QUESTIONS
1. Neural control (fundamental) in healthy state (HV) 2. How fullness is sensed (NT) 3. How fullness is sensed (SR) 4. How is emptiness sensed 5. Bladder/Urethral Mechanosensation (LC) 6. Spinal populations involved in LUT control (HV) 7. Regulation of blood flow (NT) 8. Urothelial signaling (NT) 9. Integrated whole organ physiology (JoH) 10. Ways to link human dysfunction to animal "realm" (e.g., the urothelial dysfunction, specific molecular dysfunction) (JiH) 11. Long term effects of induced models and/or initial etiopathogenesis of IC/BPS (LC) 12. Animal models with treatment failure (JiH) 13. Sex and bladder dysfunction (SR) 14. Differences in LUT function between males and females (HV) 15. Female Urology (SR) 16. Gene x environment interactions (KKS) 17. Underactive bladder (UAB) (JoH) 18. Mechanistic basis of disease (MD) 19. Pelvic radiation induced bladder dysfunction (JoH) 20. Effects of neuromodulation on Bladder afferents (LC) 21. Assessment of environmental chemicals and LUTS in humans (KKS) 22. Assessment of LUTS etiology in ASD or other NDDs (KKS) 23. Detailed physiological phenotyping (MD) 24. Development of 21st century treatments (MD) 25. How to optimize diagnostics in humans to personalize medicine (JiH)	1. How does an insult at pelvic level affect afferent signalling in which nerve populations from peripheral to brain? 2. How can we identify brain dysfunction based on proxies elsewhere (e.g., measure a bladder dysfunction on urodynamics and say "this is because of some silent stroke in this brain area"). This could incorporate animal models to work on correlations and diagnostic strategies. 3. Molecular subtyping? Cell types in brains of humans and animal models? Barrier is not well phenotyped physiologically (or even via symptoms, surveys) in biobanks, insufficiency of normals - Doug Strand as having needed expertise/samples 4. Based on what we know from preclinical studies, what diagnostic tests would we want to enact clinically (given limited time/money) that we think may inform those with symptoms vs those without, or treatment response vs. failure? What does the ideal test "suite" look like for condition "X" Or in practice, sit down and design this "testing suite", then study the impact of these things on classifying symptoms or treatment response. 5. We need a better characterization of the "disease" etiopathogenesis 6. Can we take people that we think are at high risk for UAB and try to identify things that eventually lead to UAB? Impact of environment? Impact of vascular function. Prospective study, measure things years in advance and then see who develops bladder dysfunction. How early can you predict people will have UAB before being officially diagnosed with UAB?

SHARE SPECIFIC AIMS AND/OR HYPOTHESES & PRIORITIZE

Research question 1: How are we going to get a "human baseline" of the <u>complete</u> bladder system?

- Everything thus far focuses on pieces and components, but never from the same person in totality
- Foundational insights that would influence how we ask EVERY question about LUT function

- **Specific aims**
  - **Determine the different afferent and efferent pathways** that are required for the development of volitional control of voiding
  - **Assess how well things are conserved between species** - to strengthen the translatability from animal to human models. (By comparing neuro-imaging, or neural activity patterns, or neuronal subtypes. To be used as a starting point for questions or aims using human models).
  - **Define cell types in human bladder, DRGs, spinal cord** that are involved in LUT function, then compare tissues (biopsies) of patients of whom the bladder or (disease) history is known to this "baseline". *(Rationale: Investigating parts/components (baseline, non-pathological) – human bladder, DRGs, sacral spinal cord, brain tissue (post-mortem or neuro-imaging); possibly also comparing and contrasting to other species (to enhance translational studies)).*

- Note to consider: Full thickness biopsy of bladder is logistically challenging, and one would need muscle layers to evaluate mechanoreceptor and autonomic motor innervation. Rapid autopsy specimens (organ donor networks) are another resource that could be useful for obtaining full-thickness bladder, and would certainly be useful for DRG, spinal cord, brain.
- **Can we get physiology or results from LUTS, pain surveys from these same patients** (may be an approach for addressing research question 3, build a database for secondary correlation analysis and for the next grant)
- **Prediction model aim**: Develop a physics-informed, multi-scale ML model to predict bladder physiological remodeling. Combine cell-, tissue-, organ-level mechanistic information with population datasets. This tool has the potential in the short term to function as a hypothesis generating tool (which factors have the largest impact on remodeling?) and long term to become a diagnostic and predictive patient-specific tool (what is the likely progress of the disease? What is the likely effect of treatment?)
- **Utilizing canine and feline patients as a way to compile insights from LUTS symptoms, biosamples, genetic, and post-mortem samples for histologic/molecular analyses**, can eventually produce a meaningful contribution to research Q 2 (effects of hormones, environmental toxicants) and Q 3 (urinary incontinence in FS dogs, non-infectious cystitis in cats)

- Hypothesis…….

- Collaborators
  - **SR:** happy to contribute the predictive model, in vivo mechanical testing
  - **Doug Strand** and the tissue biobank he has for non-cancerous humans. Lots of RNA-Seq and potential for RNA-Scope
  - **Kim** Happy to have the UW RUFT (Rodent Urinary function testing core) help in any way
  - Rapid autopsy / organ networks, biobanks
  - Veterinary biobanks
  - Neurodegenerative research centers (experts in paired clinical information + post mortem CNS samples)

Grant mechanisms: U54? RC2?

Possible approach: parallel the efforts by research teams to create the multi-institutional human DRG biobank needed for research (white paper summarizing the need for the biobank): Renthal et al Neuron 2021 PMID 33957072

Research question 2: How is estrogen affecting the entire lower urinary tract – from brain to urethra?

- Also foundational to understanding sex differences and modeling mechanisms for further study
- Uncovering better targeted therapies, pathophysiology, and pathogenesis

- **Specific aims**
  - **Explore the effect of testosterone** on urethral contractility and biomechanics in adult female mice.
  - **Explore the effect of estrogen** on urethral/bladder contractility and biomechanics in adult female mice
    - Use genetic and pharmacological approaches to alter the hormones (They have done this in prostate, castration, chemical castration and genetic KO leading to castration phenotype PMID: 31390231, PMID: 31904290)
  - **Establish the effect of estrogen** on extracellular matrix remodeling (fibrosis) and how the changes in the extracellular matrix affect SMCs phenotype
  - **Establish a blueprint/fundament**; high estrogen levels predict xyz,/ high testosterone levels predict xyz, and thereby therapeutic effectiveness.
  - **Determine the effects of hormone signaling at a specific level on LUT function** (urodynamics) or on downstream targets. Selectively targeting the brain by knocking out Esr1 in Barrington's nucleus for example, and determining changes in voiding behavior or on postsynaptic cell activity, or up or down-regulated genes in the spinal cord, bladder, urethra….(and DRG please :0)
  - **Test whether an environmental estrogen, linked to LUTS, mimics effects of any/all of the above endpoints.**
    - Determine the effect of aromatase inhibitors/SERMs on bladder/urethra physiology (can be broken into 3 aims exploring different components)

- Hypothesis……..

- Collaborators
  - Happy to have the UW RUFT (Rodent Urinary function testing core) help in any way

- LKC is happy to help evaluate DRGs in any model or species :0)
- NT and SR have the tools to assess biomechanics and tissue composition
- JoH can help with smooth muscle assessments (urethra, bladder, vascular supply)
- JoH can work with Ricke lab to evaluate other tissues than prostate in T/E2 model
- Rapid autopsy / organ networks, biobanks
- Veterinary biobanks

Research question 3: Can physiological/histological phenotyping be used to "explain" symptoms or predict disease/symptom progression or treatment response?

- For example, if we measure parameters in spina bifida
- Can we use this to predict therapeutic response?
- Use urine biomarkers, genetic markers, and standardized tests to drive future investigation
- Pair post- and antemortem information/samples to derive relevant information and future study
- Is there a physiologic "fingerprint" amongst patients with disease X (e.g. spina bifida) that predicts adverse outcome Y (e.g. hydronephrosis/progression to unsafe bladder)? Or predicts successful response to treatment Z? How does this fingerprint compare to that of other types of disease?
- How to measure mechanics in an effective way? How to quantify mechanical remodeling directionally (changes in shape) and localized (changes in specific locations)? Do localized changes affect mechanobiological sensing of peripheral neurons?

- **Specific aims**
  - **Explore umbrella cell genotype** as a predictor of LUTS.
  - **Using biomarkers, genetic markers that predict a disease and define consequential molecular/cellular/activity patterns**. *(Rationale: Point 3: Use urine biomarkers, genetic markers, and standardized tests to drive future investigation: (**reverse translation**) if we know the phenotype of the disease> go after what is going on mechanistically ("fingerprint").*
  - **Identify better models** (not only ones that resemble symptoms); with knowledge about the mechanisms underlying disease the disease pathogenesis can be modeled rather than pathology-only.
  - **Predictive modeling for multiple PCB environmental exposures and impact on LUT along with sex differences** (can pick any envt chemical that is most relevant to the pathways leading to the phenotype)
    - Mine literature to feed into predictive modeling
    - Epigenetic map to predict exposure and resultant consequences
  - **Do Alzheimer's disease (or dementia) patients with urinary incontinence show distinct anatomic and molecular patterns in the bladder innervating nervous system compared to those without urinary incontinence?** (Evaluate the bladder, DRG, spinal cord, brain; partner with UroAging researchers, Wisc ADRC and other centers to distribute LUTS and bladder pain surveys to patients/caretakers; partner with ADRC and other centers for rapid post-mortem tissue procurement of brain, to include lumbosacral spinal cord, DRG, and bladder)
  - **Underactive bladder as an example of a condition that is not well treated**, Can we take people that we think are at high risk for UAB and try to identify things that eventually lead to UAB? Impact of environment? Impact of vascular function. Prospective study, measure things years in advance and then see who develops bladder dysfunction. How early can you predict people will have UAB before being officially diagnosed with UAB?

- Hypothesis……..

- Collaborators
  - **Cathy Mendelsohn**: CAIRIBU member and expert in umbrella cell developmental biology/genetics
- Happy to have the UW RUFT (Rodent Urinary function testing core) help in any way
- UroAging folks
- Rapid autopsy / organ networks, biobanks
- Veterinary biobanks
- Neurodegenerative research centers (WiscADRC etc.) (experts in paired clinical information + post mortem CNS samples)

Re. Research Question 1: "**RC2** at NIDDK is a single project using an interdisciplinary team approach that generates a research resource for the community.." (https://www.niddk.nih.gov/research-funding/process/apply/funding-mechanisms/rc2)