

IDENTIFY RESEARCH GAPS & BARRIERS

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 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
- **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>)

