**National Institutes of Health**
**National Institute of Diabetes and Digestive and Kidney Diseases**

# Neurourology: Bridging Basic and Clinical Science to Understand Urologic Disease

**Virtual Meeting**
**August 22–23, 2021**

## EXECUTIVE SUMMARY

### Background and Overview

Neural mechanisms underlie a range of benign urologic diseases and conditions. Altered innervation of the bladder, urethra, ureters, prostate, erectile tissue, or other pelvic structures has a range of effects—including pain, dysfunction, and cross-sensitization—contributing to a spectrum of urologic diseases and conditions. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored a workshop in May 2019—the "Neuroscience in Urology Think Tank"—that engaged participants with complementary expertise in urology, neurology, neuroscience, developmental neurobiology, and neuroimmunology. This follow-on 2-day workshop—"Neurourology: Bridging Basic and Clinical Science to Understand Urologic Disease"—provided an opportunity to reconvene leading experts and evaluate the existing body of basic and translational research and the more recent advances in the field.

NIDDK's leadership recognizes that neurologic conditions and diseases are extremely common, chronic, and consequential and that they remain poorly understood. New evidence suggests a role of neural mechanisms. The National Institutes of Health (NIH) and the NIDDK have funded several large-scale projects that touch upon this research area, some of which were highlighted in this workshop. These include the GenitoUrinary Development Molecular Anatomy Project (GUDMAP), Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN), and Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium. Furthermore, the NIDDK is interested in neurourology and bladder sensation, new mechanics (e.g., sensing channels), the role of afferent/efferent nerves, and circuits and feedbacks, including the immune system and the brain. Treatments and ways to use these mechanisms of normal physiology and pathophysiology to help patients also are of wide interest to the NIDDK.

The goals of this workshop were—

- Identify persistent gaps in knowledge related to the interaction between the nervous system and the genitourinary system.
- Understand how that interaction contributes to benign urologic diseases and disorders.
- Determine how multidisciplinary basic, translational, and clinical research can fill these gaps and ultimately enhance the prevention, diagnosis, and therapy of benign urologic conditions.

The focus areas were—

- Sensory and autonomic innervation, neuroimmune mechanisms, interoception, and cross-organ sensitization in genitourinary function and pathophysiology
- Clinical and translational tools and technologies informing research and management strategies, including optogenetics, neuroimaging, and neuromodulation therapies

- Strategies to connect neurobiology to social, behavioral, or psychosocial factors
- Targeting neurobiological etiologies of urologic disease with novel therapies

Five scientific sessions composed the workshop. Invited speakers updated workshop participants on the state of the science; highlighted neural concepts and their relevance to research models and disease; elaborated on clinical and translational tools and technologies; shared on the intersection between neurobiology and social, behavioral, and psychosocial factors; and described targeting neurobiological etiologies of disease with novel therapies. These leading experts in the field identified gaps in knowledge and research opportunities, which were discussed in detail and are presented later in the Breakout Discussion.

The agenda also included panel discussions, lightning talks of emerging science, and breakouts to better understand the challenges, gaps, opportunities, and common themes. NIDDK staff, the Planning Committee and moderators took part in the discussions. More than 80 participants registered and attended worldwide.

This workshop leveraged other NIDDK programs, including Stimulating Urology Interdisciplinary Team Opportunity Research (SUITOR) and Collaborating for the Advancement of Interdisciplinary Research in Benign Urology (CAIRIBU). For SUITOR, the NIDDK is soliciting R01 applications focusing on neurourology. CAIRIBU is a thriving community, and the NIDDK convenes the Directors of the U54 O'Brien Urology Centers and their research teams annually. The O'Brien Urology Centers Program Interactions Core manages CAIRIBU and related activities.

**Panel Discussions**

The workshop focused on the five main discussion topics. Examples of research opportunities identified on each topic are summarized here.

***Gaps and New Opportunities in Clinical and Translational Neurourology***

- Increase understanding in sensory and afferent signaling in genitourinary conditions.
- Investigate all aspects of autonomic innervation, including the pathways, neurosignaling, identification of nerves, and the resultant neurophysiology of autonomic pathways.
- Develop additional animal models (e.g., marmoset) that are structurally similar to humans in terms of the nervous system, social behaviors, and anatomy to examine the genitourinary neurophysiology and for future lower urinary tract studies.
- Leverage existing research that is studying the bladder to address different research questions (e.g., cancer, physiology) to share tissue samples that can be used to support ancillary studies.
- Improve knowledge on how to induce the overactive bladder in a clinically relevant manner that can be validated.
- Promote neonatal neurology studies.
- Consider using an animal model that provides more information about the development of lower urinary tract innervation, neurophysiology, and pharmacology.

***Enhancing the Relevance of Research Models to Disease***

- Ensure that the questions being asked are relevant to what a particular model can provide.
- Use animal models to study the fundamental attributes of the reflex in the lower urinary tract, for example, which cannot be investigated in human patients.
- Acknowledge the limitations and highlight the value of using animal models.

- Consider using non-disease models in a basic science grant to better understand normal function and normal physiological conditions.

***Leveraging State-of-the-Art Technologies to Inform Translation of Neurourology Concepts***

- Evaluate microstimulators for performing multi-region neuromodulation, which is beneficial in identifying target regions for noninvasive brain stimulation of the bladder.
- Promote studies on small-fiber neuropathy involvement (e.g., through punch biopsy) for the development of diagnostic tools for interstitial cystitis.
- Consider functional magnetic resonance imaging (MRI) studies to provide insight on the effects of spinal cord lesions on bladder function.

***How Can Neuroscientists and Clinical Scientists Collaborate to Identify the Most Relevant Variables and Targets?***

- Adopt a systems-level understanding of signal interactions regarding interoceptive accuracy.
- Explore studying the distinction between interoception and somatosensory function in the context of age-related cognitive disorders, in which incontinence results from the loss of central processing function, and consider gender differences.
- Define metrics for the evaluation of perception in animal models.

***What Are the Most Promising Interventions to Prioritize?***

- Design future studies to use multiple cohorts targeting different areas to simultaneously contract the bladder and relax the sphincter.
- Evaluate a drug capable of decreasing the general tone in an overactive bladder; the nervous system may be able to adjust to the drug and maintain control.

**Emerging Research**

Established researchers in the neurourology field and their trainees, some of whom were NIDDK K01 awardees, presented posters highlighting emerging topics. Key findings are summarized here.

***Preclinical Studies***

- The obese-prone rat is a novel animal model that can be used to study the pathophysiology of detrusor underactivity, and restoring external urethral sphincter bursting is a novel therapeutic approach to the restoration of efficient voiding.
- In a mouse model of urinary tract infection, the intravesical inoculation of *Escherichia coli* strain UTI89 promoted the sensitization of bladder afferent sensory neurons of both Aδ- and C-fiber origin.
- In the urinary bladder smooth muscle of non-diseased mast cell–deficient C57BL/6 mice, the mast cell activator, Compound 48/80, is suggested to be increasing phasic contractions via activation of urothelial cell signaling. This resulted in the release of adenosine triphosphate and activation of a cyclooxygenase-mediated pathway to increase the synthesis of pro-contractile mediators. In a separate study, Compound 48/80 significantly increased the amplitude and leading slope of transient contractions while increasing mouse bladder wall compliance.
- Genetic mouse models of urofacial syndrome, *Hpse2* and *Lrig2*, revealed a peripheral neuropathy in the bladder in the first study of vector-mediated gene therapy for a congenital bladder disease.

### *Clinical Studies*

- Current perception threshold testing confirmed poor sensation in the urethra and bladder in humans with underactive bladder symptoms.
- A new alternative, noninvasive intervention called transcranial rotating permanent magnet stimulation (TRPMS) was successful in treating voiding dysfunction in women with multiple sclerosis.
- A systematic review of 125 abstracts on managing pelvic floor disorders revealed that noninvasive transcranial neurostimulation for lower urinary tract symptoms and pelvic pain is emerging as an effective tool for physicians to utilize in the future.

## Breakout Discussions

Workshop participants identified gaps and opportunities relevant to the main theme of the scientific sessions, touching on areas that the NIDDK should address. Participants also discussed potential strategies to address those gaps. Guiding questions were provided to frame the discussions. Examples of roadblocks, gaps, and strategies are summarized here.

### *Incorporating Neural Concepts into Models of Disease*

*Roadblocks/Gaps*

- Comprehensive understanding of sex differences, species differences, autonomic input, and lower urinary tract physiology is lacking.
- Improved methods are needed for imaging of lower urinary tract structures to visualize neural components (i.e. bladder innervation, *ex vivo*), particularly for adults.
- Better subtyping of interneurons controlling lower urinary tract circuitry in CNS and PNS is needed.
- A general lack of critical mass of professionals in the neurourology field exists compared with other fields, particularly urologic cancer.
- The issue of sample heterogeneity and clinical heterogeneity within patient populations needs to be addressed.
- Improved communication is needed among the diverse fields of neuroscience, neurology, immunology, and sexual dysfunction research.

*Strategies*

- Expand the workforce at all levels—including at the basic, clinical, and translational levels—to overcome the barriers in neurourology research.
- Engage graduate students who are actively involved in urology research and develop a mechanism for trainees to absorb neurological topics at scientific meetings or bootcamps.
- Leverage the O'Brien Urology Centers to facilitate learning new techniques that take time to master.
- Identify mechanisms to better recruit and retain clinicians in the neurourology field and address barriers to research, such as funding.
- Sponsor neurourology sessions at major conferences hosted by scientific societies, such as the American Academy of Neurology and American Physiological Society.
- Broaden awareness in the general medical communities by promoting panel discussions and submitting abstracts to meetings not strongly focusing on neurourology topics.
- Develop a more organized, comprehensive roadmap or atlas of the pelvis, regarding neuroanatomy that extends from micro to the macro level.

- Expand GUDMAP to focus on mechanisms that change throughout development.
- Develop better ways to store and share data and resources.
- Improve access to human samples, accept and leverage heterogeneity among human samples and in preclinical models used to answer research questions

***Clinical and Translational Tools and Technologies***

*Roadblocks/Gaps*

- Better neurourology phenotyping, technologies, methods, and informative techniques are needed to improve understanding the current condition of the patient.
- Wearable or ambulatory imaging systems are needed to improve experimental data (e.g., voiding patterns) that are challenging to collect in large-scale, complex, imaging systems (e.g., MRI or functional near-infrared spectroscopy).
- A cost-effective analysis of the different technologies is needed to evaluate their advancing the care pipeline.
- Improved understanding is needed of the feeding versus the voiding phase, as well as the technologies being developed that are applicable to both phases. Researchers evaluating one phase are not communicating with those studying the other phase.
- Opportunities are needed to collaborate outside of individual, narrow silos (e.g., overactive bladder or neuromodulation) to address the broader problem of phenotyping.

*Strategies*

- Sponsor large clinical studies empowered by new technologies, particularly wearable technologies (e.g., Apple Watches, Android wearable devices, Fitbit) and data sharing technologies.
- Leverage existing resources, including studies in the NIH *All of Us* Research Program cohort, in which hundreds of thousands of people share their medical data via an online data browser, with access through respective institutions.
- Continue to convene meetings and workshops to discuss the state of the science and address research gaps.
- Consider convening a group that is interested in understanding phenotyping rather than a particular technology or subsystem.

***Connecting Neurobiology to Social, Behavioral, and Psychosocial Factors***

*Roadblocks/Gaps*

- Demand exists to learn more about the bladder in the context of the brain and connections from neurology to social, behavioral, and psychosocial factors. These can entail ecological models about the environmental impact and other factors that can affect perception and translating bladder function into whether it is about the healthy or disease condition.
- New opportunities are needed to collaborate with other disciplines, particularly behavioral neuroscience, to better understand these connections.

*Strategies*

- Endorse additional research in the neurourology area, particularly collaborating with local institutions about shared interests and shared learning in the translational space. The NIH Institutes can assist in this effort.

- Improve understanding of mechanisms in the real world, particularly in urodynamics clinics.
- Integrate the social impact across different domains.
- Encourage the field to learn more about the lower urinary tract as it relates to sensations, access to toilets, and the real world, including how these perceptions of sensations may represent on a map of the human body.
- Build on existing NIH longitudinal cohorts (e.g., *All of Us*).
- Investigate new pediatric populations and leverage the PLUS RISE FOR HEALTH cohort.

***Therapeutic Targets and Strategies***

*Roadblocks/Gaps*

- Gaps exist in the field's ability to phenotype diseases leading to gaps in treatments and care.
- Subphenotyping is needed at the level of anatomical characterization of the central and peripheral nervous systems, followed by precise characterization of target populations with targeted treatments.
- Knowledge is needed of the mechanism of action of current therapeutics to better target treatment to the patient population.
- Better understanding is needed of why certain interventions are not fully successful.
- Improved insight is needed into the neurology of the underactive bladder.
- Continued exploration is needed of sex differences in mechanisms of disease and mechanisms of treatment action. Sex differences in normal circuitry can lead to differences in treatment efficacy.

*Strategies*

- Fund more large-animal studies, from anatomy to neurophysiology, and broaden the mechanism-of-action studies to larger animals.
- Conduct well-documented, rigorous case studies to characterize responders versus nonresponders to treatments.
- Improve the phenotyping of disease states and conditions.
- Facilitate targeted therapies and research to better understand urinary physiology.
- Develop condition-specific urinary biomarkers.
- Encourage interdisciplinary collaboration to explore investigations of the interplay between the central nervous system, peripheral nervous system, and the organs.
- Move from a unidirectional approach toward a multidirectional approach.

**Emerging Themes: Prioritizing Research Needs**

Participants highlighted several specific emergent themes of the workshop that build upon the NIDDK-sponsored GUDMAP, MAPP, LURN, and PLUS initiatives:

- Create a complete organ/cell/cell parts list (e.g., bladder, urethra, prostate, pelvic floor, neurons, spinal cord, brain, glia, immune system) that includes external components (e.g., ecological factors, stressors).
- Create complete wiring diagrams or functional connectomes of nerve fibers for both health and disease that incorporate interoception; threat, stress, and anxiety pathways; biopsychology and uropsychology pathways; hardwired reflexes and feedback loops; and functional brain centers.
- Create a list of internal and external adaptations (e.g., water intake, allosteric changes).
- Create new tools for deep phenotyping (e.g., real time, ambulatory, wearables, patient-reported outcomes, imaging) at all levels (e.g., bladder, urethra, sphincters, prostate, nerves (all types),

spinal cord, brain). Start with users; pursue minimally invasive methods; and anticipate further development of single-cell, -omics, and spatial methods.
- Use new tools to better subphenotype healthy humans, as well as those with urologic disorders.
- Use new information to build better animal (i.e., larger, non-rodent) and computational mechanistic/prediction models; triangulate between human and animal phenotyping to improve predictive validity of animal models.
- Develop a precision urology approach for personalized (i.e., level-specific) interventions; identify intermediate biomarkers to assess if hitting target/pathway; compare responders and non-responders (e.g., humans, animal models: which predict what).

In discussion, workshop participants provided feedback on the general and specific emergent themes. The following points were noted:

- Perspectives on health and disease vary across clinical disciplines. To change the paradigm and promote collaboration between urologists and neurologists, fundamental cross-training and education must occur. A multi-systems perspective of lower urinary tract system function would be beneficial. Additionally, the American Academy of Neurology can play a role in promoting awareness of neurourology within the neurology community. Urologists also might consider publishing relevant work in neurology-focused journals.
- Physiological systems are dynamic, and defects are likely to undergo temporal and spatial changes. Therefore, an emphasis on anatomic localization might be limiting, and a broader perspective might be needed. Both spatial and temporal heterogeneity should be considered because both factors are likely to affect patient outcomes.
- Multiple wiring diagrams likely will be needed to account for expected heterogeneity among individuals. Some basic reflexes, however, are well characterized within the central nervous system and can be evoked reliably. A review article on connectomes would be valuable for investigators.
- A recent study examined responders and nonresponders in previous nonselective studies. In this work, a retrospective analysis of previous clinical trial data was performed using heterogenous patient populations and global response elements. Phenotypic subgroups were identified from the data, and responses to urologic and pain symptoms were characterized. This work serves as a proof of principle for the importance of targeting therapies in well-identified subgroups.

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