National Institute of Diabetes and Digestive and Kidney Diseases

Advancing Basic and Translational Research for Genitourinary Conditions: Female Urethral Function and Failure

Virtual

Executive Summary and Research Gaps

Description

The National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a virtual workshop series composed of seven weekly sessions on "Advancing Basic and Translational Research for Genitourinary Conditions: Female Urethral Function and Failure" from September 30, 2020, to November 18, 2020. The workshop was open to the public, and more than 200 participants logged in from 71 institutions around the world, with more than 100 attendees at each session. Physicians and researchers registered in nearly equal numbers, and approximately 20 percent of the registrants were early-career researchers.

The goal of this iterative workshop series was to generate a systems model that demonstrates what is known about the urethra's role in continence and identifies knowledge gaps that impede progress toward better treatments. Participants received, in real time, information on developing peer-reviewed publications, an iterative systems diagram, and an infographic to stimulate research ideas. The workshop planning committee—composed of basic, clinical, and translational scientists from the NIDDK, academia, and industry—moderated the sessions. Topics of the sessions were as follow:

1. The Urethra: What We Know, What We Don't Know, and Why It Matters
2. The Urethra: Current Knowledge of Urethral Function in Health and Disease
3. The Urethra: The Mucosal, Submucosal, and Sensory Aspects
4. The Urethra: Neural Control and Integration
5. The Urethra: Technologies for Translation
6. The Urethra: Lessons from Animals, Cells, and Children
7. The Urethra: Current Therapies and Future Solutions

Detailed summaries of each session can be accessed from the NIDDK-supported Collaborating for the Advancement of Interdisciplinary Research in Benign Urology (commonly known as CAIRIBU) public website.

The NIDDK anticipates that the generation of a systems model incorporating interdisciplinary perspectives will facilitate the development of meaningful research questions that can lead to novel, impactful grant applications with the important goal of improving women's health. Research questions that are informed by cross-disciplinary discussions may lead to additional fundable investigator-initiated research grants (e.g., R01s).

Background

Enormous knowledge gaps exist in understanding the function and dysfunction of the lower urinary tract (LUT). To fill these gaps, the NIDDK Division of Kidney, Urology and Hematology (KUH) pioneered a workshop series to seek out a multiperspective brain trust, including basic, translational, and clinical researchers at all stages of their careers; health professionals; patients; and industry representatives. The topic—female urethral function and failure—encouraged workshop participants to share knowledge, ask questions, and engage in real-time and asynchronous discussions regarding this understudied and not-well- understood area.

A key aim of the KUH is to increase its portfolio of R01 grants on genitourinary conditions within NIDDK's mission. Traditionally, the NIDDK has sponsored meetings and workshops held at the NIH to foster cross-disciplinary conversations, often leading to a workshop summary or the development of a research agenda for the topic, but these conversations often stop short of the granularity of solid research questions that are informed by adequate clinical perspective.

Over time it has become increasingly challenging for clinicians to take time away from clinical care to attend meetings. This virtual webinar series was piloted to determine if this series of seven webinars organized around a single topic could stimulate and sustain cross-disciplinary conversations that extend beyond institutional boundaries

and could lead to solid research questions (and approaches) that will result in a larger R01 portfolio. The NIDDK established the Stimulating Urology Interdisciplinary Team Opportunity Research (SUITOR) R01 (PAS-19-241) as one funding opportunity available for research questions that evolve from this series of meetings. SUITOR has set aside funds to support R01 grants that fall outside of the NIDDK payline.

Research Gaps, Opportunities, and Barriers

- In the absence of diagnostics and therapeutics targeting urethral failure, treatments using the two-factor model fail to achieve a higher level of success.
- The field's understanding of urethral anatomy, factors controlling function, and disease processes leading to urethral failure lags significantly behind our understanding other organs, such as the lower esophageal sphincter or pharynx.
- Diagnostic tools (e.g., magnetic resonance imaging or ultrasound) used for urology are unsophisticated, and similar tools are needed to investigate the subtleties of urethral anatomy, form, and function.
- It is critical to discover key physiologic elements in urethral dysfunction that currently are not being measured.
- Researchers should share raw data to enable standardization and improve testing and interpretation of physiologic tests.
- Although urethral closure pressure is a promising pharmacologic target, the success of such treatments is unclear.
- Computational and animal modeling, as well as advances in such technologies as high-resolution ultrasound, may provide answers to mechanistic questions regarding the functional role of the layer of longitudinal smooth muscle.
- Numerous studies have revealed that the urethra's vascular plexus, extracellular components, and smooth and striated muscle layers are promising therapeutic targets that deserve more thorough biologic investigation.
- Because existing intraurethral pressure measurements have many artifacts, better measurement methods are needed to improve the understanding of how striated muscle helps provide continence.
- The goals in urethral motor testing are not being met; additional methods are needed to measure dynamic urethral pressures with minimal artifacts to understand physiology and pathophysiology, guide treatment, predict response to treatment, address surgical failures, and predict and evaluate voiding dysfunction after surgery.
- It is important to study urethral physiology in appropriate animal models and throughout disease progression and not study the urethra in a vacuum.
- Studies frequently examine disease endpoints, but do not adequately investigate earlier stages of the disease process.
- CNS modulation of micturition and urine storage reflexes must be considered when developing electrical stimulation treatments.
- Studies investigating hormone receptor location in human urethra and bladder tissue are limited.
- Other cell types could be neural targets in the LUT, and close associations could suggest areas for further exploration.
- Studies with prostatectomy patients could provide insight into the function of the bladder neck, although results may not necessarily translate between sexes.
- The definition and boundaries of the bladder neck remain unclear, and significant work is needed on standardizing such terminology for the urethra and the bladder.
- Few incentives and extra barriers are present for clinicians, particularly urology residents interested in adding a research component to their career.

Planning Committee:

1. Dr. Tamara Bavendam, NIDDK
2. Dr. John DeLancey, University of Michigan
3. Dr. Carlos Estrada, Harvard Medical School and Boston Children's Hospital
4. Dr. Daniel Gossett, NIDDK
5. Dr. Jim Hokanson, Duke University
6. Dr. Indira Mysorekar, Washington University School of Medicine in St. Louis
7. Dr. Kristina Penniston, University of Wisconsin–Madison
8. Dr. Lynn Stothers, The University of British Columbia
9. Dr. Victoria Spruance, NIDDK