



# UNIVERSITY OF TENNESSEE P20 CENTER: HUMAN URINARY BLADDER MYOGENIC MECHANISMS BY ION CHANNELS IN HEALTH AND DISEASE



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## ABSTRACT

The goal of this NIH P20 grant is to establish the Developmental Center for Human Urinary Bladder Myogenic Mechanisms by Ion Channels in Health and Disease (DC-HUB) focused on the role of detrusor smooth muscle ion channels in overactive bladder (OAB) etiology and related detrusor overactivity (DO). The DC-HUB Center is based at the University of Tennessee Health Science Center (UTHSC) where the proposed studies will benefit from the robust clinical and basic science environment. Dr. Georgi V. Petkov - an established investigator with multidisciplinary training in biochemistry, physiology, pharmacology, electrophysiology, and urological research - provides project leadership by serving as the DC-HUB Center Director. A major strength of this strategic program on ion channel research that puts UTHSC at the forefront is the conduct of this research in collaboration with an impressive cadre of clinical scientists including faculty and urology residents. Dr. Robert Wake, a well-established UTHSC clinical urologist, is coordinating the urology team effort. The collaboration is supported by Dr. Eric Rovner, an internationally renowned OAB urology expert and his clinical team based at the Medical University of South Carolina. This project makes regular use of human bladder specimens to study ion channel function and correlate basic science findings with patient clinical profiles. It uses bladder tissues both from patients without an OAB clinical history (controls) and from subjects with OAB or urodynamically proven DO (idiopathic/neurogenic). These novel investigations within the DC-HUB Center provide fertile ground for future establishment of a George M. O'Brien Urology Research Center at UTHSC. This will have a major impact on improving healthcare with strong potential to better understand OAB etiology and provide novel therapeutic approaches to help OAB/DO patients. This research is highly significant given OAB/DO prevalence and the need for new therapies.

## OVERALL AIMS OF THE DEVELOPMENTAL CENTER FOR HUMAN URINARY BLADDER (DC-HUB) MYOGENIC MECHANISMS BY ION CHANNELS IN HEALTH AND DISEASE

- Aim 1:** Create a multidisciplinary collaborative structure to facilitate effective communication and interactions among program members, integrate all research endeavors, and establish an Administrative Core to coordinate DC-HUB activities.
- Aim 2:** Hold regular, monthly meetings and workshops among DC-HUB members to further develop our working hypotheses and design our research strategies.
- Aim 3:** Establish research projects for the DC-HUB multidisciplinary collaborative program.
- Aim 4:** Establish an Educational Enrichment Program through a website-based portal at UTHSC, open to the public, that will pool and share information about the Educational Enrichment Program and research results among DC-HUB program members.
- Aim 5:** Develop a research plan and prepare a George M. O'Brien Urology Research Center (U54), multi-PI, or a Program Project (P01) application.

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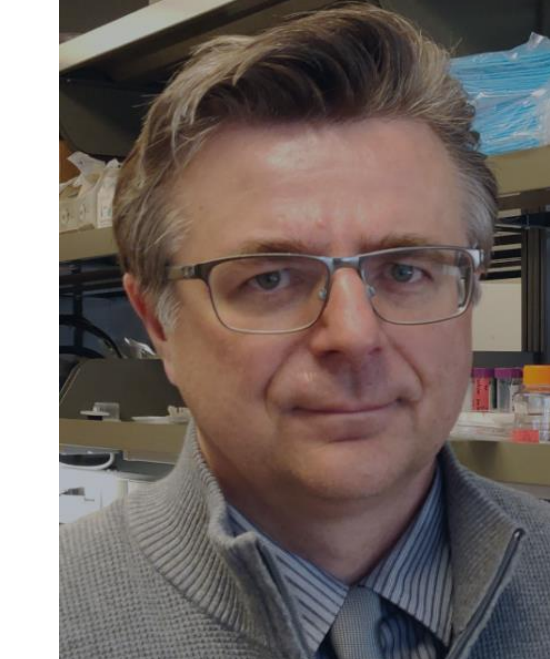
## P20 CENTER LEADERSHIP



**Georgi V. Petkov, PhD**  
Principal Investigator  
Program/Center Director



**Robert Wake, MD**  
Associate Director  
Clinical Collaborator



**John Malysz, PhD**  
Associate Director

**The specific aims of the Administrative Core are:**

**Aim 1:** To maintain oversight of activities in the scientific project. This will include facilitating interactions among investigators, supporting investigators in their research, and disseminating results as they become available to the scientific community.

**Aim 2:** To maintain oversight of the Educational Enrichment activities. This will include establishing and maintaining a Center website and coordinating diverse educational opportunities for students and other faculty.

**Aim 3:** To manage the overall budget and reporting requirements of the Center. The Administrative Core will track all project expenses, make periodic budget audits, and coordinate all internal and NIDDK report submissions.

## INTERNAL ADVISORY BOARD



**Alex M. Dopico, MD, PhD**  
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## EXTERNAL CLINICAL COLLABORATORS



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## NEW PROGRAMMATIC FACULTY HIRES



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**M. Dennis Leo, PhD**  
Assistant Professor  
Dept. Pharmaceutical  
Sciences, UTHSC



**Udai Singh, PhD**  
Associate Professor  
Dept. Pharmaceutical  
Sciences, UTHSC

## OBJECTIVE AND GOALS

- To organize a multidisciplinary collaborative program based at the University of Tennessee Health Science Center (UTHSC)
- To illuminate the roles of ion channels and their regulatory mechanisms in the human urinary bladder under normal and benign pathological conditions.

## CENTRAL HYPOTHESIS

- Specific myogenic Kv (Kv2 and Kv7) and TRP (TRPA1 and TRPV2) channels are key regulators of urinary bladder physiology, and changes in their expression, function or regulation lead to DO/OAB. We further hypothesize that pharmacological or genetic manipulation of bladder specific Kv and TRP channels could provide safe and effective therapies for DO/OAB.

## RESEARCH PROJECT - SPECIFIC AIMS

- Aim 1: Elucidate the function and regulation of Kv channels in human detrusor physiology and pathophysiology**
  - Aim 1.1: Elucidate the expression and function of the Kv2 and Kv7 channel family members in human DSM (from control non-OAB and OAB patients).*
  - Aim 1.2: Elucidate the functional links between  $\beta$ 3-AR/PDE4, and their roles in the regulation of Kv2 and Kv7 channels in DSM from control (non-OAB) and OAB patients.*
- Aim 2: Elucidate the role of TRP channels in human detrusor physiology and pathophysiology**
  - Aim 2.1: Determine the molecular expression of TRPA1 and TRPV2 channel in human DSM from control non-OAB and OAB patients.*
  - Aim 2.2: Elucidate the cellular roles of TRPA1 and TRPV2 channels in DSM single cells isolated from control and OAB patients.*
- Aim 3: Elucidate the *in vivo* role of Kv and TRP channels in control animals and animal models of voiding dysfunction**
  - Aim 3.1: Determine *in vivo* effects of Kv channel modulators on the micturition pressure and voiding parameters.*
  - Aim 3.2: Determine *in vivo* efficacies of TRPA1 and TRPV2 modulators in rats identifying TRP channel subtypes displaying greatest potential for therapeutic intervention.*