INUS Neuro-Urology News

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From the President's Desk

Prof. Thomas M. Kessler, MD (CH)
INUS President

Πάντα ῥεῖ - panta rhei - everything flows

Dear Friends and Colleagues, Ladies and Gentlemen:

It is my great honor and pleasure to invite you to attend the INUS Annual Congress to be held in Athens, Greece, from 8 to 10 June 2023.

Neuro-Urology is a highly-regarded and relevant sub-specialty wedding the fields of both neurology and urology to prevent and treat the debilitating manifestations of urinary tract dysfunction which have major impact on our patients' health and their quality of life.

The world's leading experts in Neuro-Urology will provide an overview on the latest advances in research and clinical practice of this rapidly developing and exciting discipline. This unique meeting combines state-of-the-art lectures (keynote lectures, INUS partner societies' lectures), lively panel discussions, poster sessions, and hands-on workshops (urodynamics, neuromodulation, neurosciences, translational research, pediatrics) with emphasis placed on interactive components. There will be many opportunities to exchange thoughts, experiences and ideas, and also to make new friendships.

To promote the next generation of outstanding young researchers and clinicians who represent the future of Neuro-Urology, I am excited to again announce the prestigious Swiss Continence Foundation (SCF) Award of 10,000 Swiss francs which will be awarded to the best contribution from a young Neuro-Urology talent at the INUS Annual Congress 2023 in Athens.

I am very much looking forward to seeing you all in Athens!

Best regards,

T. Kessler

Prof. Thomas M. Kessler, MD

INUS ATHENS ANNUAL CONGRESS 2023
June 8-10th

INUS Calendar

INUS Annual Congress 2023
Athens, Greece
June 8-10, 2023

INUS Lecture at Congress of the European Academy of Neurology
Budapest, Hungary
July 1-4, 2023

INUS at ICS 2023
Toronto, Canada
September 27-29, 2023

INUS Course at EAUN Meeting
Paris, France
April 6-8, 2024

Interview with the Expert

TRPM3 ion channel role in bladder pathophysiology

Wouter Everaerts, MD, PhD (BE) @EveraertsW
Associate Professor, Urology, KU Leuven, Leuven, Belgium
Consultant Urologist, UZ Leuven, Leuven, Belgium

Glenn Werneburg, MD, PhD @gwerneburg
Editor, Neuro-Urology News

Dr. Wouter Everaerts, MD, PhD, is Associate Professor in the Laboratory of Ion Channel Research, Department of Cellular and Molecular Medicine at Katholieke Universiteit (KU) Leuven, and Consultant Urologist at Universitair Ziekenhuis (UZ) Leuven in Leuven, Belgium. He received his MD and PhD degrees at KU Leuven, and performed his urological training at The Royal Melbourne Hospital and the Peter MacCallum Hospital, both in in Melbourne, Australia. He is an accomplished surgeon-scientist, having made significant advances in the understanding of the TRP family of ion channels and their clinical relevance in neuro-urology. In this month's "Interview with the Expert" we discuss his recent work on the TRPM3 channel, and its role in the urinary bladder.

Dr. Glenn Werneburg: What is known about the TRP family of channels and what is their relevance to urology? What about TRPM3, specifically?

Dr. Wouter Everaerts: The Transient Receptor Potential (TRP) family is a large family of ion channels. Twenty-seven TRP channels have been described in humans. In urology, we have been studying these channels for some time. In sensory neurons, there are several of these channels like TRPV1, which is a vanilloid receptor, and is a target for intravesical capsaicin treatments. We have studied this channel for years. Once this was cloned and identified as the receptor for capsaicin, a lot of interest developed in the TRP channels within urology.

TRPA1 is an intravesical receptor for inflammatory mediators. TRPM8 is the cold receptor responsible for the bladder cooling reflex that mediates the bladder's response to cold water intravesical instillation. Besides TRP channels in the sensory neuro-fibers, there are also TRP channels within urothelial cells. For example, TRPV4 is a mechanosensor in the bladder. We know that in pathological conditions such as inflammation in the bladder, this channel gets sensitized. We can block it during inflammation to reduce symptoms. These TRP channels play a role in normal physiology and in pathological circumstances.

TRPM3 has been an overlooked ion channel. Our group has been interested in this channel because we identified it as the missing link for heat sensing. We know that TRPV1 and TRPA1 are important heat sensors, but if TRPV1 and TRPA1 are both knocked out in mice, the animals can still sense heat. My colleagues in the lab made a triple knockout in mice, wherein they knocked our TRPA1 and TRPV1, but also TRPM3. These mice completely lacked heat sensing. Even upon exposure to boiling water, they did not sense heat. In this way, we demonstrated TRPM3 is responsible for heat sensation. It is also upregulated in inflammatory conditions. We know that in osteoarthritis it gets upregulated, and that it is important for somatosensory pain.

In this investigation, we sought to determine whether TRPM3 is expressed in the sensory neurons innervating the bladder, and to determine its role in normal bladder function and pathological conditions such as visceral hyperalgesia.

GW: Please describe the design of the current study.

WE: We wanted to do two things. First, we wanted to know exactly where the channel was expressed. We did this by performing either immunohistochemistry, but this is not convenient for TRPM3 because there is no good antibody. We used RNA probes to analyze mRNA expression in bladder tissue and in isolated dorsal root ganglia (DRG) neurons. We not only wanted to look at structure, but also function. We isolated DRG neurons and looked at responses to known TRP channel agonists and antagonists. We wanted to look at the function of TRPM3 by exposing mice to either TRPM3 agonists and antagonists. By looking at the uro-phenotype of wild-type and TRPM3 knockout mice, we performed cystometry wherein the catheter is placed in the mouse bladder, it is filled at a constant rate, and the intravesical pressure is measured as a function of time. Secondly, we analyze the spots of urine produced by mice freely moving about a grid, to analyze their voiding habits. We did this in healthy mice and in the pathological model, where mice were pre-treated with cyclophosphamide, which is a model of acute bladder inflammation. After 24 hours, we did both structure and function analyses of these animals.

GW: What were the findings from this study?

WE: To check which neurons expressed TRPM3, we first labeled the neurons through the injection of a tracer inside the bladder. Then the tracer is transported in a retrograde fashion to the DRG neurons. We isolated the DRGs and looked in these labeled cells to determine whether TRPM3 is expressed. We did find TRPM3 expression in these neurons. We also found functional expression in the neurons. In the DRG neurons isolated from TRPM3 knockout mice, there was no response to TRPM3 agonist, but the responses to TRPV1, TRPA1, and TRPM8 were preserved. These results demonstrated that TRPM3 is expressed in sensory neurons innervating the bladder.

We also found that in mice treated with cyclophosphamide-induced cystitis, there was clear overexpression of TRPM3. This was very exciting to us in that we showed that TRPM3 was expressed in normal sensory neurons, and overexpressed in inflammation. Next, we were interested in finding a phenotype. However, we did not detect any phenotypic differences between wild-type and TRPM3 knockout mice. We did not detect any acute responses of mice treated with a TRPM3 agonist, or even an antagonist. Even in mice with a background of inflammation, we did not detect any contribution of TRPM3.

So, although we confirmed expression and over-expression in the DRG neurons, we could not find a functional phenotype or role for TRPM3 thus far. This could have to do with the limitations of the animal model used. We used mice in the study, and this may not have been the optimal model. It could also be that the model we used for cyclophosphamide-induced cystitis is a very strong model. These mice get very serious inflammation, but they also get very sick from the cyclophosphamide. So, to do behavioral tests in these mice, it is possible that a phenotype may be missed because of their overall unwell state. Or, the knockout models may have too much compensation from other TRP channels. There is another group, however, that did find a phenotype. Zhou et al. (Pain, 2022), used a rat model with cyclophosphamide. They found effects, for example, of TRPM3 antagonists on voiding behavior including reduced voiding frequency and pain behavior.

GW: Please describe your group's next steps to build on these results.

WE: We are looking at combinations of TRP channels. As we know, the triple knockout is needed for complete insensitivity to heat. We are looking at either phylogenetically or pharmacologically blocking these channels, and their combinations, and whether we can completely eliminate mechanosensation. In this way, we are blocking the TRP channels, but also Piezo channels and others. Our research group has a strong focus on somatovisceral sensation. In bowel function, blocking TRPM3 worked very well. We are now investigating how TRPM3 can be used in reducing somatovisceral pain in the bowel, and how it may be expanded for such pain in the bladder.

GW: What advice do you have for early-stage INUS members interested in a career as a surgeon-scientist in neuro-urology?

WE: You need to be really into science. You have to accept that there is a lot of work and a lot of persistence needed to move a project forward as a surgeon-scientist. You should celebrate your successes, because often there are few. You have to love the science and love doing it. Don't get fooled by the rush for publications. In the current scientific environment the push for publication quantity is very strong. We are all rushing toward more papers. I tell my junior people that I think it is much more important to move one little stone than to write ten articles that haven't changed a thing. Make sure you have time. It's important to have dedicated time to do this. Combining basic science with clinical work is very difficult. For some, taking a few years out of one's clinical training to do this work may be a good option. Collaborating with a group that has in-depth knowledge of basic scientific techniques is also important. For example, I collaborate closely with a TRP group with strong expertise in electrophysiology, molecular biology, and animal behavior. They can help ensure that the research you're doing is rigorous and correct. Then, it is up to the clinician to determine the relevant questions and translations. This is how we work, and I think this is how we can be successful. I think the TRPM3 story for us was, in many ways, one of success. We had some good results, but also some disappointing results. I think publishing negative results is as important as positive results.

Further reading:

Everaerts, W., Zhen, X., Ghosh, D., Vriens, J., Gevaert, T., Gilbert, J. P., ... & Voets, T. (2010). Inhibition of the cation channel TRPV4 improves bladder function in mice and rats with cyclophosphamide-induced cystitis. Proceedings of the National Academy of Sciences, 107(44), 19084-19089.

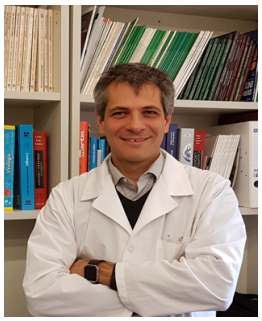
Vanneste, M., Mulier, M., Nogueira Freitas, A. C., Van Ranst, N., Kerstens, A., Voets, T., & Everaerts, W. (2022). TRPM3 Is Expressed in Afferent Bladder Neurons and Is Upregulated during Bladder Inflammation. International Journal of Molecular Sciences, 23(1), 107.

Vanneste, M., Segal, A., Voets, T., & Everaerts, W. (2021). Transient receptor potential channels in sensory mechanisms of the lower urinary tract. Nature Reviews Urology, 18(3), 139-159.

Zhao, M., Liu, L., Chen, Z., Ding, N., Wen, J., Liu, J., ... & Zhang, X. (2022). Upregulation of transient receptor potential cation channel subfamily M member-3 in bladder afferents is involved in chronic pain in cyclophosphamide-induced cystitis. Pain, 163(11), 2200-2212.

Literature Review

Brendan Frainey, MD (US) @bfrains
Urology Resident, Cleveland Clinic, Cleveland, OH, USA
Christian Sager, MD (AR) @Cristian_Sager
Department of Urology
National Hospital of Pediatrics Dr. J. P. Garrahan, Buenos Aires, Argentina



Foreword
Dr. Christian Sager

For some years we have witnessed the paradigm shift in the treatment of pediatric neurogenic bladder with botulinum toxin in patients refractory to anticholinergic drugs. This fact has contributed to delaying the indication for augmentation cystoplasty with intestinal segments. Although the most noticeable therapeutic effect occurs in those patterns of neurogenic bladders with detrusor overactivity, some benefit is also observed in patterns with a preponderance of hypertonic bladder wall. It is reasonable to think that the next step would be to use botulinum toxin as the first-line therapy in younger children in which an overactive bladder prevails, thus delaying development towards patterns with hypertonia, which are more difficult to treat.

It is well known that after the artificial urinary sphincter (AUS) placement the bladder can behave at high renal risk and therefore may require an augmentation cystoplasty due to high intravesical pressures. This behavior is not necessarily predictable in AUS pre-placement urodynamic studies and requires close postoperative follow-up. In turn, in most cases after an augmentation cystoplasty, it is possible to protect the upper urinary tract and achieve urinary continence without the need for AUS. Therefore identifying what each patient needs continues to be a priority, considering the limitations of financial access to AUS in low-income regions.

Despite the fact that we have protected many urinary tracts with augmentation cystoplasty, not all neurogenic bladders will need reconstruction after botulinum toxin or AUS placement, since this reconstruction is not exempt from important complications such as lithiasis, urinary tract infections, potential perforations, among others.

These issues are addressed in this month's Literature Review by Dr. Brendan Frainey and will be extensively addressed at the upcoming INUS Congress in Athens focused on the pediatric and adolescent population. There will be a workshop on neurogenic bladder (urodynamic/therapeutic evaluation) and a plenary session on sphincter incompetence with different scenarios and opinions from internationally renowned experts.

Literature Review
Dr. Brendan Frainey

Long Term Safety and Tolerability of Repeated Treatments With Onabotulinumtoxin A in Children With Neurogenic Detrusor Overactivity

Franco I, Hoebeke PB, Dobremez E, Titanji W, Geib T, Jenkins B, Yushmanova I, Austin PF. J Urol. 2023 Apr;209(4):774-784. doi: 10.1097/JU.0000000000003157. Epub 2023 Jan 19. PMID: 36655470.

Despite OnabotulinumtoxinA's (BTXA) approval for treatment of neurogenic detrusor overactivity in children, studies on intradetrusor BTXA in pediatric subjects have been limited by duration of follow up and size. This study recently published in Journal of Urology by Franco et al in 2023 was a multi-center, double-blind, repeat-treatment extension study (NCT01852058) in patients who entered a preceding single-treatment, Phase 3 study (NCT01852045). The primary objective of the study was to assess long-term safety of repeated BTXA injections. Descriptive statistics were also used to report on the key efficacy endpoints (i.e. change from baseline in daytime urinary incontinence episodes) for the approved 200 U dose.

The study included subjects from 30 sites across 8 countries (US, Canada, Europe). Children ages 5-17 were enrolled in the study who had urinary incontinence (UI) secondary to detrusor overactivity associated with a neurologic condition which was confirmed on pre-study urodynamics. Patients in the preceding study were randomized to 1 of 3 groups (50 U, 100U, 200U [not to exceed 6U/kg]) and received a single administration of the medication (cycle 1). In this extension study, subjects could receive repeat treatments at patient/caregiver request and fulfillment of pre-specified requirements (> 2 UI episodes over a 2-day voiding diary). Retreatment was considered at week 12 of follow up onward. At the time of treatment, patients could receive dose escalation based on their prior response or remain on the same dose at the provider's discretion (not exceeding 200 U or 6U/mg).

All subjects received peri-operative antibiotic prophylaxis. Subjects were followed with regular outpatient and telephone visits and exited the study once 48 weeks had elapsed since study entry and at least 12 weeks of follow up had occurred since their last study treatment. Of the 100 patients enrolled in the initial study, 95 subjects enrolled in the extension study and received at least 1 treatment with BTXA.

Overall, 95, 90, 55, and 11 patients received 1, 2, 3, and 4 treatments, respectively. Median (quartiles) follow-up was 82 weeks (65,94). The overall safety profile was similar across doses and with repeat treatments. 90 (95%) patients reported at least 1 treatment-emergent adverse event (TEAE) during the study period, but only 3 serious treatment-related TEAEs (3.2%) were reported, all of which were UTIs. The annualized UTI rate for each treatment group was similar to the rate during the 24 weeks prior to study entry. There were no cases of autonomic dysreflexia, renal failure, or distant spread of toxin. Across all 3 treatment cycles, patients who received repeat BTXA 200 U showed improvement in daytime UI episodes with >75% of patients also noting "improved" or "greatly improved" response on the modified treatment benefit scale.

The authors concluded that repeat doses of up to 200 U BTXA were well tolerated with continued improvement in efficacy. They also conclude that BTXA injections overall do not result in increased UTI rates due to the comparable annualized UTI rates before and after treatment. This study provides much needed longer-term data to validate the use of the FDA approved 200 U dosing for the treatment of pediatric neurogenic detrusor overactivity not adequately managed with anticholinergics and CIC alone.

Simultaneous bladder augmentation and artificial urinary sphincter placement in children with neuropathic urinary incontinence. Is it safe to perform? Long term results

Delgado-Miguel C, Muñoz-Serrano A, Amesty V, Rivas S, Lobato R, Martínez-Urrutia MJ, López-Pereira P. J Pediatr Urol. 2023 Feb 10:S1477-5131(23)00027-X. doi: 10.1016/j.jpurol.2023.01.019. Epub ahead of print. PMID: 36813690.

The authors of this study sought to report their postoperative complications and long-term outcomes of simultaneous bladder augmentation (BA) and artificial urinary sphincter (AUS) placement in children with congenital neurologic lower urinary tract dysfunction (NULTD) and compare them to a staged approach for these two procedures.

This was a retrospective cohort study from a single institution from 1994 to 2020. Subjects were categorized into two groups: AUS and BA performed simultaneously (SIM) group and AUS and BA performed sequentially (SEQ) group. Subjects with congenital NLUTD who failed to become dry with CIC, medical therapy, or previous bladder/outlet procedures and had the dexterity to operate an AUS were included in the study. Elevated detrusor pressures during filling (>15 cm of H20 at 50% or less of expected bladder capacity) as well as sphincteric incompetence on urodynamics were also required for inclusion.

In total, 39 patients (21 male, 18 female) were included with a median age of 14.3 years (Q1-Q3: 12.8-15.8 years) at time of surgery. There were 27 subjects in the SIM group and 12 in the SEQ group which were similar demographically. Median follow up was 17.2 years (Q1-Q3: 10.3-23.9). In the SEQ group, median time between AUS implantation and BA was 18 months. Subjects in the SEQ group had a significantly longer length of stay as compared to the SIM group (15 days vs 10 days, p=0.032). Mechanical and non-mechanical complication rates were similar between groups. The rate of infection-related complications was 7.7% (3/39 subjects) due to device erosion and infection requiring explant: two in the SIM group (7.4%) and 1 in the SEQ group (8.3%). Adequate urinary continence was attained in 90% of patients with no statistical difference between groups.

Based on these data, the authors conclude that simultaneous BA and AUS placement is safe and effective in pediatric patients with congenital NLUTD with much lower postoperative infection rates than previously reported in the literature. They also note shorter length of stay and no difference in postoperative complications or long-term outcomes when compared to performing the procedures in a staged fashion. While single-center and retrospective in nature, this study provides the largest series with the longest follow up of this cohort and challenges the notion that AUS cannot be performed simultaneously with BA due to theoretical risk of device infection. However, the decision regarding when and who to perform these procedures simultaneously still remains nuanced.

INUS ATHENS ANNUAL CONGRESS 2023
June 8-10th

Workshops OVERVIEW

Register Now

Thursday

Urodynamics

Chairpersons:
Stefania Musco &
Lorenz Leitner

Neuromodulation

Chairpersons:
Stefan de Wachter &
Howard Goldman

Friday

Neurosciences

Chairpersons:
Bertil Blok &
Jalesh Panicker

Translational Research

Chairpersons:
Katia Monastyrskaia &
Naoki Yoshimura

Pediatrics

Chairpersons:
Anastasios Karatzas
& Cristian Sager

Saturday

Saturday: Nurse Workshop
Nursing care of neuro-urological patients needs special knowledge

Chairpersons: Archontia Nikolia, Charalampos Konstantinidis, Helmut Madersbacher, Stefano Terzoni

Again, INUS chose a venue right in the historic centre of its host town. The **Royal Olympic Hotel** is situated right in front of the famous Temple of Zeus and the National Garden. Enjoy the grand view of the Acropolis from the rooftop bar or visit the Acropolis Museum which is just a two-minute walk away.

Royal Olympic
ATHENS

Venue location:
28-34 Athanasiou Diakou Str.
117 43, Athens, GREECE

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