W7: LIVE WEBINAR: Bladder wall surface science; the relevance of a entrapped water microenvironment. GAG's, receptors, microbiome and novel therapeutic developments

Workshop Chair: Dick A.W. Janssen, Netherlands

Start	End	Topic	Speakers
		Prof Dr. Scott Glickman; Introduction	Scott Glickman
		Dr. Dick A.W. Janssen; 'What do we know about the function of different GAG's and proteoglycan-GAG complexes in the bladder wall?'	Dick A.W. Janssen
		Prof. Dr. Wouter Everaerts; Urothelial cell membrane receptors and their response to local intravesical treatment? An underexplored area of treatment.	Wouter Everaerts
		icw Prof. Dr. Robert Hurst; Creation of proteoglycan-GAG complexes and their therapeutic potential for drug-vehicle or coating for intravesical treatment.	Dick A.W. Janssen
		Dr. Sajjad M.S. Rahnama'i ; Bladder microbiome; should we rethink how the bladder wall works in health and disease?	Sajjad Rahnama'i
		Interactive Panel session and questions from the audience (chair prof S. Glickman; panel members: Prof. Wouter Everaerts, prof. Dr. R. Hurst, Dr. DAW Janssen, Dr. M.S. Rahnama'i	Scott Glickman
		Time for feedback/ evaluation via app by audience	Dick A.W. Janssen

Aims of Workshop

This workshop provides the latest insights in preclinical science on bladder wall surface functions. The aim is to better understand: 1) How glycosaminoglycan-proteoglycan complexes function in the bladder 2) How proteoglycan-GAG complexes could be used as therapy or drug vehicle for intravesical therapy 3) Which urothelial cell membrane receptors respond to intravesical treatment and 4) How benign bacterial flora interact to keep the bladder healthy. We want to get scientists and clinicians together to educate them about the complexities and implications that these structures have on bladder (patho)physiology and show the therapeutic potential of this microenvironment to improve bladder health.

Learning Objectives

Learn about the complexities and functions of different GAG's and proteoglycan-GAG complexes create a water-retaining microenvironment on the bladder wall surface and how GAG's can be used for intravesical therapies

Target Audience

Urology, Pure and Applied Science

Advanced/Basic

Intermediate

Suggested Learning before Workshop Attendance

See the references section from the presenters

Dick A.W. Janssen
What do we know about the function of different GAG's and proteoglycan-GAG complexes in the bladder wall?

Gaining more insight in the function of different GAG's and and other cell surface molecules on and in the bladder wall is crucial if we are to advance anti-inflammatory treatments for the urinary bladder. There has been a considerable research focus on uroplakins and GAGs as barrier enhancing molecules, but there is a whole array of underexplored mucins and lectins that could have potential therapeutic properties.

Even the role of GAGs has for a long time been unclear. GAG replacement therapies have been applied for decades to treat bladder inflammatory conditions such as bladderpain syndrome. Despite this, there is a common lack of understanding on how these individual molecules and their target receptors actually work to repair the inflammed bladder wall.

Different GAGs play separate roles and even molecule chain lenghts can lead to a different function. This presentation will update you on the most recent findings from preclinical studies concerning the effects of different GAGs on bladder wall barrier and repair and will highlight where we may be able to improve our treatments.

Wouter Everaerts
Urothelial cell membrane receptors and their response to local intravesical treatment? An underexplored area of treatment.

In addition to their crucial role in maintaining a highly impermeable barrier, the specialized cells of the urothelium play an important role in the sensory function of the bladder. The bladder is able to determine its degree of filling (mechanosensation), as well as the presence of intravesical irritants, including bacterial toxins and inflammatory mediators. This sensory function is important to coordinate the interplay of urine storage and evacuation.

Urothelial cells express a number of cellular sensors, like Transient Receptor Potential channels, Piezzo's and G-protein coupled receptor that enable them to detect chemical and physical changes in the intravesical milieu. Via the release of messengers like purines (ATP, ADP and AMP) and nitric oxide, urothelial cells can communicate these signals to neighboring urothelial cells and underlying sensory nerve fibers, that will relay the sensory signals to the Central Nervous System.

In this presentation, we will discuss the different cellular sensors that are present in urothelial cells, their functional role is in bladder(patho) physiology and the potential therapeutic benefit of pharmacologically targeting these receptors.

Sajjad Rahnama'i
Bladder microbiome; should we rethink how the bladder wall works in health and disease?

Until recently, the urine of healthy individuals was assumed to be sterile. However, improvement of bacterial detection methods has debunked this assumption. Recent studies have shown that the bladder contains microbiomes, which are not detectable under standard conditions. In this review, we aimed to present an overview of the published literature regarding the relationship between urinary microbiota and functional disorders of the genitourinary system.
The urine microbiome is a newly introduced concept, which has attracted the attention of medical researchers. Since its recent introduction, researchers have conducted many fruitful studies on this phenomenon, changing our perspective toward the role of bacteria in the urinary tract and our perception of the genitourinary system health.
Analysis by 16S rRNA sequence and expanded quantitative urine culture provided evidence for the presence of live bacteria in urine, nondetectable by standard culture protocols. Moreover, differences in the urinary microbiota between healthy individuals and patients with lower urinary tract dysfunction were demonstrated.
A deeper understanding of the urinary microbiome can help us to develop more efficient methods for restoring the microbiota to a healthy composition and providing symptom relief. Modification of the urinary microbiome without antibiotic use can be a possible venue for future research.
In the near future, urologists must consider urinary dysbiosis as a possible cause of different functional lower urinary tract disorders, with potential clinical implications in their diagnosis and treatment.

Robert E Hurst
Novel proteoglycan-like glycosaminoglycan (gag) derivatives to treat ic/bps by restoring bladder impermeability.

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Much evidence supports the theory that a deficit in the luminal GAG layer of urothelium plays an etiologic role in Interstitial cystitis/Bladder pain syndrome (IC/BPS) by increasing bladder permeability to urinary solutes to pathologic levels. Intravesical chondroitin sulfate (CS) and hyaluronan have been used with limited success. Our hypothesis is that these therapies have failed for two reasons; (1) these are linear polymers whereas the natural GAG layer provides a much thicker bound water layer at the urothelial surface because the natural proteoglycans present the GAG chains bound to protein cores and (2) these therapies have never been optimized to provide continuous coverage of the damaged urothelium to allow healing.

We have synthesized several derivatives of CS that are more proteoglycan-like than CS. SG1 is a large (200 KD-2,000 KD vs 15KD CS monomer), crosslinked CS polymer with a dendritic structure that should bind to the same targets as CS. SG2 is similar except that it contains hexylamino moieties that allow it to bind covalently to the urothelium, thereby providing not only a more durable coating but a thicker bound water layer as well. Both together with vehicle and CS controls were tested in an animal model of IC for efficacy using magnetic resonance imaging (MRI) to directly assess bladder permeability and immunohistochemistry (IHC) to assess duration of binding. The animal model is the URO-MCP-1 mouse that develops bladder permeability with a dose of lipopolysaccharide (LPS) that is not toxic to normal mice.

Our findings showed that at 3 days following treatment with CS, SG1 or SG2 were approximately equal in restoring normal bladder impermeability, but by 5 days, both of the SG derivatives showed significantly more efficacy in restoring normal impermeability than did CS. This animal model, like all models of IC/BPS suffers from the same deficiency, namely that after about 7 days the bladder normally heals and normal impermeability is achieved by normal healing processes. Moreover, when the amount remaining on the urothelium was assessed using IHC, the CS was significantly reduced whereas the amount of SG2 had decreased only about 10%.

We conclude that the SG derivatives offer advantages over CS as a therapeutic for IC/B{S for restoring bladder permeability. MRI, which we earlier showed in a pilot study to be able to assess bladder permeability in humans, should be effective in optimizing treatment with SG2. We plan to initiate clinical trials using SG2 and MRI to asses permeability with the aim of maintaining normal impermeability throughout the course of treatment.