W14: Current clinical status of BPS/IC and what the future holds in basic & translational science

Workshop Chair: Francisco Cruz Miranda Rodrigues, Portugal
28 September 2023 10:30 - 12:00

Start	End	Topic	Speakers
10:30	10:35	Introduction	Francisco Cruz Miranda Rodrigues
10:35	10:55	Choosing the animal model to study BPS/IC	Ana Charrua
10:55	11:00	Discussion	Ana Charrua
11:00	11:20	How do biomarkers and pathways translate back to the clinic	Dick A.W. Janssen
11:20	11:25	Discussion	Dick A.W. Janssen
11:25	11:45	How to use the power of computers in BPS/IC	Guldal Inal Gultekin
11:45	11:50	Discussion	Guldal Inal Gultekin
11:50	12:00	Questions	All

Description

Chair Prof. Francisco CRUZ - Introduction:
BPS/IC is one of the few unmet needs in the area of lower urinary tract pathology. On one side BPS/IC is a diagnosis of exclusion since no pathognomonic symptoms, signs or biomarkers exist to swiftly establish a firm diagnosis. On the other side BPS/IC has no cure yet. Most treatments that try to replenish the urothelial glycosaminoglycan layer or decrease bladder inflammation are far from showing generalised effectiveness, leaving most of the time clinicians with the necessity of combating pain. Although assumed as relevant, the identification of subgroups of patients that might respond better to a particular treatment is not yet possible due to the lack of appropriate biomarkers. Facing this scenario, it is clear that translational research, identifying key unmet needs and making smart use of animal models to test relevant questions will play an important role. In addition, bioinformatics are ready to gather clinical and experimental information to be used in the future diagnosis and treatment of BPS/IC.

Speaker 1 – Ana Charrua, PhD
Choosing the animal model to study BPS/IC:
The evolution of the concepts around BPS/IC has led to the use of multiplicity of animal models to study this syndrome, mostly using rodents and cats. The animal models began to replicate bladder centric aspects of BPS/IC, to find new treatments for the functional complaints such as frequency and pain. In addition, non bladder centric models are gaining importance due to the frequent systemic symptomatology referred by patients.

Key learning point 1 - Choosing the animal model to study BPS/IC:
The most used bladder centric model are the cyclophosphamide- and lipopolysaccharide-induced cystitis models, which are used to replicate macroscopic (such as bladder wall lesions) and/or microscopic (such as inflammatory cells infiltration) bladder changes and study their implication in the appearance of the urinary bladder functional disruption. The most recently used complex animal models have in consideration that BPS/IC symptoms surpass those exclusively related with the urinary bladder. The stress models have gained a special attention as, besides pain, they replicate systemic changes observed in BPS/IC patients, such as alterations in hypothalamic-pituitary-adrenal axis (as is the case of the maternal deprivation models - MDM) or changes in the autonomic nervous system (as is the of the MDM and of the water avoidance stress model). The advantages of each model will be listed, taking particular interest in the characteristics that replicate the systemic changes, such as those observed in the central nervous system of BPS/IC patients. Also, some of the critical points in each model will be emphasized. Suggestions for the models' improvement/refinement will be presented, such as the coordination of usage of different models, be them, or not, a mix of bladder centric models and complex models.

The advantages and disadvantages of the models, as well as the proposed improvement of each model will be discussed with the attendees.

Key learning point 2 - Methodologies to assess pain and other behavior in the animal models:
To study pain-like behavior in animals, there are a set of induced and spontaneous tests available. However, most of these tests were developed to evaluate the effects of analgesic drugs on the pain-like behavior of non-visceral/pelvic animal models. Which of those tests can be used to study BPS/IC? What are the possible refinements these tests need to be used in visceral/pelvic animal models? Is there room for international standard operating procedures? How animal models can be used to study changes in social interaction shown by patients? A list of tests available to study them will be presented, going from simple observation to more complex cognitive tests. Factors that influence tests replicability and reproducibility will be discussed with the attendees. Also, the advantages and disadvantages of performing automated home cage analysis will be addressed.

Speaker 2 – Dick Jansen, MD PhD
How do biomarkers and pathways translate back to the clinic:

Discussion on what is currently known on the pathophysiology of BPS/IC from basic and clinical science perspective. Thus to develop a better understanding of the underlying molecular mechanisms of BPS by discussing molecular pathways.
BPS/IC is a clinical diagnosis and currently consists of a heterogenous group of patients with different pathophysiological profiles. This is reflected by differences in responses to treatment amongst BPS/IC patients and the lack of molecular biomarker tests available for clinical diagnosis. This diversity has to be taken into account when using preclinical models for research. Stratification of BPS/IC subgroups has been improved with the ESSIC criteria, but this is mainly done using clinical cystoscopy and pathological evaluation on biopsy specimens. There are currently 2 types with bladder wall centric inflammatory characteristics, but also one non-inflammatory type with normal bladder wall characteristics on cystoscopy. A more refined stratification using biomarker profiling is needed to improve targeted therapy and therefore treatment success rate. Hunner´s lesion and non-Hunner´s lesion subtypes is improving. Using RNA sequencing, microbiome sequencing and protein identification techniques, we are increasingly capable of detecting the pathways affecting different BPS/IC patients. However, challenges remain. Finding the correct in vivo model representing the specific clinical BPS/IC features and pathophysiology is key. As far as currently known, only cats show a similar Hunner´s lesion type disease comparable to human BPS/IC and using cats for experimental research is problematic. Therefore the current strategy relies on models that focus on bladder centric problems representing epithelial dysfunction and inflammation and other models with a focus on the more systemic problems relating to neuroinflammation, peripheral and central pain pathways.

Key learning point 1 - Genes and proteins that are known for BPS/IC and how they are representative of the molecular pathways that lead to pathology:
For the most appropriate translational model, we can and have learned from pathway analyses from genetic fishing and other experiments from human samples and these can be translated into biomarkers such as Nitric oxide pathways, Anti-prolific factor, cytokines, Substance P pathways, neurotrophins and urothelial barrier molecules. These are our quality controls to show we can mimic these pathways in our preclinically applied in vitro and in vivo models to investigate novel treatments, but these biomarkers should also translate back and lead to improvement of clinical diagnosis and treatment outcomes.
This part of the workshop will focus on the BPS/IC associated pathways and biomarkers derived from preclinical studies and how they translate to clinical BPS/IC characteristics.
Key learning point 2 - Learning about strategies to implement biomarkers into clinical practice to improve stratification and healthcare in BPS/IC?
The main goal of this section is to give a current overview on where we stand regarding biomarkers and pathways and the research strategies to actually translate these into clinical practice.

Speaker 3 – Güldal Inal Gültekin, PhD
How to use the power of computers in BPS/IC:
The main purpose of this part of the workshop will be to propose and discuss the potential utility of bioinformatics and AI approaches to potentiate discovery of novel biomarkers and therapy targets for BPS/ IC.

Key learning point 1 - Assessing the utility of bioinformatics and artificial intelligence for BPS :
Bioinformatics is an interdisciplinary field of science which is a point of intersection of biology, computer information, and computational sciences. It allows for the analysis and interpretation of complex and numerous biological data. The computational method combines several publicly available databases, including text-mining, and employs multiple statistical analysis of 'microarray data'. High-throughput methods, such as microarray technology, create vast quantities of genomic and expression data. This massive amount of data, also called 'big data', becomes manageable with the aid of software tools and codes generated by computer scientists. Hence, the main goal of bioinformatics is to obtain a global view of biological problems at OMICS level (genomics, transcriptomics, proteomics, metabolomics), yet also to decipher molecular interactions and thus pathways at each respective level. This allows for the emergence of a more comprehensive overview of the pathology, by statistically emphasizing importance on some genes or proteins more than others. Depending on the tools utilized for analysis, protein-protein interactions, hub genes, and molecular pathways can be suggested and predicted. Hence the type of data required for bioinformatics analysis and obtained output will be discussed with the attendees.

Artificial intelligence (AI) and machine learning, however, are computer tools and software that learn from combined layers of high-throughput data. AI is increasingly utilized in medical research, and opens the opportunity to elaborate algorithms to tackle complex diseases like BPS/IC. A few examples of simultaneously utilized data sources include, age, sex, mutations, RNA expression levels, clinical data. With repetitive simulations, AI tools will learn to accurately predict disease status. The importance of the completeness of 'BPS/IC data' for AI analysis, and the differences between bioinformatics and AI will be discussed with the attendees. The overall consequence of effective biomarker acquisition through bioinformatics and AI research will pave the way for a successful diagnosis of disease with only a blood withdrawal.

Key learning point 2 - Evaluating data repositories and bioinformatic graphics and pathway tools:
Biomarker research for diagnosis, follow-up, and also treatment of BPS/IC is receiving growing interest but still needs more work-up. Furthermore, the genetic basis of BPS/IC is not fully elucidated. Thus a key area of collaborative work space for BPS/IC research is in the field of molecular biology. Studies producing massive amounts of publicly available OMICS data can be re-analyzed using various methods and statistical approaches. The addition of clinical data, such as imaging, pathology, blood work, pain levels etc., will empower even more the accurate estimations of disease predictions. Thus computer based tools can

increase the chance to discover putative biomarkers for BPS/IC. Therefore, following a brief introduction to the notion of bioinformatics and AI, this workshop will discuss the benefits and expansions that computerised approaches will provide for BPS/IC research.

Take home messages:
1. The choice of the animal model to study BPS depends on the scientific question
2. The link between in vivo and in vitro studies are essential to understand BPS/IC
3. Understanding the molecular complexity of the disease
4. Defining what is needed in the clinics for optimized treatment and patient care
5. Acquiring a basic knowhow on bioinformatics

Aims of Workshop

This workshop aims to:
- Discuss the animal models used to study BPS/IC, and the limits of how they mimic the disease
- To discuss how chronic pain and other symptoms may be evaluated in the BPS/IC animal models.
- To discuss the available bioinformatic tools to study BPS/IC
- To understand some basic notions of computational analysis
- To discuss current molecular pathways and biomarkers for BPS/IC subtypes

Educational Objectives

Since its first definition in the late 17th century, there have been no major advancements in the treatment of BPS/ IC. This could be partly explained by the lack of an organized, multidisciplinary and multinational effort to understand disease mechanisms and underlying pathophysiological pathways.

The science of bioinformatics can offer unique opportunities in processing clinical data that can facilitate understanding of underlying pathologies.

There have also been recent studies on developing better animal models that can replicate pathophysiological pathways in BPS/IC in humans.

This course will gather clinicians and scientists from different disciplines to take a snapshot of the current clinical status of BPS/IC treatment and define the available trends in biomarker search and translational medicine. The potential contribution of findings of computational science and bioinformatics will be explored by a multidisciplinary group of researchers. Developments in search for a more representative source of animal models will be explored.

Learning Objectives

1. At the end of the workshop the attendees will know the available animal models of BPS/IC and choose among them the best to test the hypothesis at stake.
2. At the end of the workshop the attendees will understand where translational research is needed to fill unmet needs in the fields of diagnosis and treatment.
3. At the end of the workshop the attendees will acquire basic notions of computational analysis and will recognise the importance of bioinformatic tools in BPS/IC basic and clinical research.

Target Audience

Urology, Urogynaecology and Female & Functional Urology, Bowel Dysfunction, Pure and Applied Science

Advanced/Basic

Basic

Suggested Learning before Workshop Attendance

Nunez-Badinez et al. Preclinical models of endometriosis and interstitial cystitis/bladder pain syndrome: an Innovative Medicines Initiative-PainCare initiative to improve their value for translational research in pelvic pain. Pain. 2021;162(9):2349-2365.

Inal-Gultekin G, Gormez Z, Mangir N. Defining Molecular Treatment Targets for Bladder Pain Syndrome/Interstitial Cystitis: Uncovering Adhesion Molecules. Front Pharmacol. 2022;13:780855.

Akiyama Y, Luo Y, Hanno PM, Maeda D, Homma Y. Interstitial cystitis/bladder pain syndrome: The evolving landscape, animal models and future perspectives. Int J Urol. 2020 Jun;27(6):491-503.

Ueda T, Hanno PM, Saito R, Meijlink JM, Yoshimura N. Current Understanding and Future Perspectives of Interstitial Cystitis/Bladder Pain Syndrome. Int Neurourol J. 2021 Jun;25(2):99-110.