ICS* updates in continence care: a personal perspective on the role of basic science in urology

BY DOMINIKA BIJOS

At a urology research meeting in Sheffield a few years ago, a former post doctorate researcher in urology, Mathieu Boudes, said: "Stop calling it basic research, there is nothing basic about it. It is *fundamental* research to everything urologists do." At the time, I did not understand . . .

Norman Zinner pointed out that: "OAB is misleading because it makes it too easy for clinicians to feel that they have made a diagnosis when they have not. In so doing, it curtails further thinking and does not promote the scientific pursuit of the fact" [1]. With 70% of cases of overactive bladder (OAB) being idiopathic, we certainly need to understand the mechanisms of the disease behind it.

This is where basic research of the pathology comes in: it is an indispensable tool to control, manipulate and interrogate molecular changes behind the disease and to enable a more precise diagnosis in the future. Regarding OAB, the answer is not only in knowing how to treat people, but knowing the underlying nature of the condition itself, particularly as there are several possible mechanisms of causation of symptoms. Here, fundamental studies in animal models and test tubes can make a huge contribution to the understanding of how to tease out the different types of the condition and target therapies accordingly.

The patient vs. science

It is possible for a basic science researcher to get completely immersed in the science under study. However, one of the first things I learnt when doing my PhD in fundamental / basic science research at the Bristol Urological Institute was that the patient is central and will always be more important than research. Although this is stating the obvious, it is important for every researcher to realise that every person with a particular condition has individual needs and requirements for care which can never be solved by statistical results and experimental conclusions. The patient won't care about statistics!

As an early career researcher, I was initially disappointed to find that my exciting conclusions perhaps mattered very little to patients in the clinic next door to me, on whose lives I apparently made little impact. However, it soon became apparent that my own little contribution did matter by adding to the knowledge of the condition I was studying, and every tiny step made the late nights in the laboratory worthwhile.

Forums such as the ICS Annual Meeting are a unique opportunity for dialogue between fundamental researchers and clinical fellows.

Fundamental research may not bring immediate benefits, but it helps develop sophisticated tools and technologies that expand our knowledge-base with possible applications of research results. These are the building blocks on which everything else rests, and each piece of information is a small cog in the large machine that is the clinical condition. In this article, I will try and summarise some of the current basic research in functional urology, including some of the exciting new topics presented at recent ICS meetings.

Incontinence research and practice – key abstracts from the ICS

Tissue engineering

In the keynote address at the 2015 ICS Meeting, Christopher Chapple provided an excellent overview of the key areas of incontinence research and practice. He discussed changes in urodynamics, conservative management, underactive bladder, neural reconstruction and tissue engineering [2].

Tissue engineering promises an answer for many issues related to male and female incontinence surgery. This line of research may support the new directions shown in the choice of materials used in surgical solutions to better understand the immunological response to them as well as guide new indications for use of engineered materials in clinical care.

Currently, synthetic or biological materials are used in techniques for the surgical treatment of pelvic organ prolapse (POP) and stress urinary incontinence (SUI). Synthetic meshes like polypropylene mesh have low failure rates but are prone to complications including infection and erosion. Biological materials have lower complication rate, whereas xenografts and allografts have a high failure rate and carry infection risks. Autologous grafts have a low failure rate and low incidence of complications but may lead to morbidity at the donor site. Although there is no ideal material yet, fundamental research is aiding our understanding of the best

available options.

Two promising scaffold material candidates are electrospun poly-L-lactic acid (PLA) and porcine small intestine submucosa (SIS). Cells grown on scaffolds show more appropriate biomechanical properties for clinical implantation when subjected to a strain. Adipose-derived stem cells (ADSCs) are a suitable cell type for seeding on scaffolds. The next step required for the success of implantation of a scaffold and regeneration of tissue is an appropriate level of acute inflammation, which needs to cause moderate fibrosis and promote tissue strength. This is a great field for fundamental research which can test the use of bioactive materials, i.e. materials containing compounds that actively facilitate integration of new tissue. Tissue engineering is therefore contributing to the development of safe options for the treatment of pelvic organ prolapse and stress urinary incontinence.

Genomics

As the cost of sequencing human genomes has rapidly decreased over recent years, genomics research in urology has increased. At the 2016 ICS meeting, Rufus Cartwright presented the current state of genetics in lower urinary tract dysfunction and the promise of personalised medicine [3]. Twin studies estimate the heritability of urgency incontinence in women at 40-49% [4-5] and 49-83% for male LUTS [6-8].

But so far candidate gene studies for a genetic association for LUTS and pelvic organ prolapse have not produced robust results. Progress is slow in this field, with millions more single nucleotide polymorphisms (SNPs) yet to be analysed. Genome-wide association studies (GWAS) look for the association of millions of common genetic variants right across the genome. They provide a novel insight into the physiology, pathology and treatment but require a very large sample size to enable multiple hypothesis testing. A few studies using this approach, including the research performed by the IGNITE consortium formed to implement genomics in practice, found genetic loci which fulfilled the criterion for a few candidates like endothelin and muscaric receptors but this requires further study.

Cartwright's keynote address concluded that although clinical advances to date have been underwhelming, novel loci discovered in GWAS may offer an entirely new insight into pathophysiology and our understanding of the interplay of genetics and environment, which may lead to future therapeutic targets for primary and secondary prevention in individual patients.

"Fundamental research may not bring immediate benefits, but it helps develop sophisticated tools and technologies that expand our knowledge-base with possible applications of research results."

The urothelium and neural interactions

At the 2016 ICS meeting in Tokyo there was a special session dedicated to cutting edge basic science which largely focused on painful bladder syndrome / interstitial cystitis and the urothelium.

The winning basic science abstract by Akiyama and colleagues presented inflammatory infiltrates specific to Hunner type interstitial cystitis (IC) [9]. Different cell types in human bladder samples from Hunner IC, non-Hunner IC, non-IC cystitis and normal controls were detected using immunohistochemistry . Their findings indicated that there was no difference in the number of masts cells / tryptase-positive cells in either areas of IC biopsy specimens compared to non-IC biopsy specimens, suggesting that mast cell infiltration may be proportional to the degree of lymphoplasmacytic infiltrations. The authors thus concluded that infiltration of inflammatory cells, but not mast cells, may be a feature of Hunner IC.

Takai and colleagues suggested that herpex simplex virus (HSV) mediated gene therapy suppression of transient receptor potential vanilloid-1 (TRPV1) could be a novel modality for the treatment of IC / BPS and / or for OAB [10]. They demonstrated their findings in a hydrogen peroxide induced model of cystitis in rats. Animal freezing behaviour representing bladder pain was reduced in rats with suppressed TRPV1, while expression of nerve growth factor (NGF), which has been proposed as an important mechanism underlying IC / BPS, was found to be lower in the mucosa. This suggests a potential therapeutic effect of this modality in a rat model of cystitis.

Specific cell interactions and their patterns were uncovered by other research in which mucosal layer and specifically urothelial cells were shown to have specific rhythm and cell interactions that may have relevance to our understanding of cystitis and nocturia [11].

Ihara and colleagues demonstrated the presence of circadian rhythm of the components of the urothelium [12]. Their study focused on the circadian regulations of genes involved in the sensation of bladder fullness by clock genes in the mouse bladder urothelium. The 'clock' mutant mouse model has a nocturia phenotype and presents an excellent model to study molecular mechanisms behind the phenotype. The investigators hypothesised that bladder fullness is regulated in a circadian fashion by expression of mechanosensors (Piezo1, TRPV4) and ATP release pathways (Connexin26 and vesicular nucleotide transporter – VNUT) that take part in the signalling to the central nervous system. Their study found that these genes are indeed regulated by the clock genes in the mouse bladder urothelium: high activity during an active phase of the animal and low during sleep. These changes are absent in the mutant clock mice. Their study links circadian expressions of mechanosensors and ATP release to bladder sensation, suggesting that the disruption in those channels could lead to hypersensitivity of bladder fullness during sleep and be one of the causes of nocturia because of hypersensitivity to bladder wall distension.

Ikeda et al. showed specifically that apical urothelial cells in the bladder interact with afferent neurons [13]. By injecting microbeads to pelvic and hypogastric dorsal root ganglia, the investigators demonstrated labelling of nerve fibres that run through the muscle layer and accumulate in the urothelium, more specifically in the apical umbrella cells. Bi-directional communication between the urothelial cells and the afferent nerves suggests a mechanism by which afferent nerves can sense luminal changes including urine composition, pH and intravesical pressure, and thereby modulate voiding function. These elegant studies provide a great foundation for further research into the role of urothelial signalling in bladder physiology and pathology.

Research on healthy bladders

What is normal bladder function remains an important and yet incompletely answered question. Basic science research holds the key to defining the physiology of the bladder, i.e. what is normal? Patients present to doctors because of their symptoms which may represent underlying pathology. In laboratory conditions, we can study the system in a

near-physiological state and introduce a controlled pathology, like in the examples of hydrogen peroxide induced cystitis or a gene mutation described above. It allows for the discovery of new therapeutic possibilities for known drugs or the improvement of our understanding of behavior such as urothelial cell-neuronal interaction.

There are many research questions regarding healthy bladder function that remain unanswered. For example, what is the pattern of detrusor contraction and relaxation that determines compliance, and when it results in non-voiding contractions that may result in sensations? Urodynamic traces provide information on gross pressure parameters but it is suspected that there is a potential role of unregulated autonomous bladder micromotions in urinary storage and voiding dysfunction, including overactive bladder and detrusor underactivity. Peripheral 'patchy' denervation causing loss of efferent inhibition, may enable unregulated micromotility, and afferent stimulation predisposing to urinary urgency. Depending on the extent of the denervation, the impact on voiding function may be low as neighbouring areas may overcome the insufficiency. In a more severe denervation the micromotility of the bladder wall is no longer capable of propagating and thus the denervated regions can no longer contribute to voiding, showing signs of detrusor underactivity [14].

What are the barriers for surgeons in the scientific world?

In urology, and in particular continence care, the patient will always be the most important factor. And we also need clinical research. So why not simply have urologists do lab-based research? Basic research projects usually require substantial time commitments, protected time and funding.

Let's look at the challenges. In the largest survey of academic surgeons to date, Keswani et al. found that the biggest barriers for surgeons considering basic investigation were:

- Pressures to be clinically productive;
- Excessive administrative responsibilities;
- Difficulty obtaining funding;
- Desire for work-life balance.

This survey in the US found that 68% did not believe surgeons can be successful basic scientists [15]. This echoes Elberli and Atala's concerns that the number of urologists involved in basic science research is falling and educational opportunities need to be supported [16].

Basic research contributions beyond the knowledge base

In my opinion, basic research contributes more than just knowledge base. Here are a few ways, some of them unexpected, in which basic research benefits clinical research and researchers:

- *Pairing clinical experience with scientific laboratory research teams:* In some centres clinicians pair up with a fundamental researcher to get a return from the amplified strength of the group, including clinical and laboratory perspectives, without the commitment of doing research full-time. This combination can result in clearly designating the available expertise; on the one hand physiology, engineering or statistics / mathematics and on the other the clinical direction. There are several good examples of the fruits of such combined efforts such as research into what urodynamic traces tell us about the physiological detrusor contractility [17], the effects of transdermal amplitude modulated signal (TAMS) in OAB treatments [18], how does the movement propagate in animal bladder [19].
- *Basic science forums:* Although only 1-2% of ICS members identify themselves as basic scientists, a much greater proportion of fundamental research papers are presented at ICS annual meetings, largely by clinical fellows who undertake great basic research projects around the world. Consequently, forums such as the ICS Annual Meeting are a unique opportunity for dialogue between fundamental researchers and clinical fellows from which new collaborations can spark. The basic research discussed above is very urology centred, but basic scientists who research the field are able to bridge specialties to tap into knowledge and expertise gained from other areas which may have applicability in urology. There are other meetings where scientists present their work which research-orientated clinicians should be aware of. In the UK urology researches attend the Physiological Society annual meetings and usually present papers under the vascular and smooth muscle section of physiology. In neuroscience meetings, there is a good representation of bladder research at the Society for Neuroscience Meeting in the USA. There is also a Young Urology Meeting dedicated to the academic fundamental researchers working in urology – their numbers are reversed as opposed to ICS or European Association of Urology meetings, with over half of delegates actively engaged in fundamental research.
- *Open access publications:* In research, publications are the main means in disseminating research findings and ideas, of progressing careers, and as a measurable output of academic activity. These very important fruits of research activity are unfortunately not available for everyone to read due to a lack of access. In smaller hospitals, where extended academic journal subscriptions are not in place usually as a result of funding constraints, access to literature is a barrier. In the UK, in order to address this problem, all publicly funded research must now be available for open access which means that after paying publication charges, anyone can view the publication. This positive shift in funding will allow fundamental research publications to be available to the smaller, and primarily clinical, research centres.
- *Raising awareness:* Advancing the fundamental knowledge base is the main role of scientists, but I have also found myself raising awareness of bladder dysfunction issues. Public interest and the recognition of this taboo has been met with interest and discussions with the public at a number of events, such as an ICS Bladder Diary Day promotion event or a TEDx talk about bladder issues. Such science communication activities not only extend contacts and collaborations with other researchers across the globe, but also extend funding sources for research to organisations like Age UK, Multiple Sclerosis Society or Parkinson's UK. Opening the network and developing collaborations across different fields has brought molecular biologists, pharmacologists, physiologists, neuroscientists, engineers and physicists working together to solve issues. With such a huge range of expertise contributing to the field we can only advance further in our discoveries.

What makes good research?

Cutting-edge technology and innovations in research can be tested in a controlled environment before being trialled on patients. Examples of translation from basic science to clinical applicability are found in tissue engineering which tests new approaches that can be used in patients, and genomics which has moved from being a predominantly research technique to a clinically useful diagnostic and predictive tool.

Curiosity fuels investigators in their pursuit of answers. But in the current set-up and research environment, scientific

or medical success is not achievable in isolation and requires collaborative expertise from different fields.

I invite you to join me at ICS 2017 in Florence, which promises to be an excellent scientific meeting. The ICS is a multidisciplinary association pertaining to the highest scientific standards and brings together a wide spectrum of the very best minds who present research on incontinence and pelvic floor disorders, both clinical and basic science. Submit your abstract by 3 April for consideration and view the programme to see the many activities specifically targeted to basic scientists.

References

1. Zinner NR. OAB. Are we barking up the wrong tree? A lesson from my dog. *Neurourol Urodyn* 2011;**30**:1410-1.
2. Chapple CR, Osman NI, Mangera A, et al. Application of tissue engineering to pelvic organ prolapse and stress urinary incontinence. *LUTS* 2015;**7**:63-70
3. Cartwright R. The genetics of LUTD and the promise of stratified medicine. *Neurourol Urodyn* 2016;**35**:S19
4. Rohr G, Kragstrup J, Gaist D, et al. Genetic and environmental influences on urinary incontinence: a Danish population-based twin study of middle-aged and elderly women. *Acta Obstet Gynecol Scand* 2004;**83**:978-82.
5. Altman D, Forsman M, Falconer C, et al. Genetic influence on stress urinary incontinence and pelvic organ prolapse. *Eur Urol* 2008;**54**:918-22.
6. Partin AW, Page WF, Lee BR, et al. Concordance rates for benign prostatic disease among twins suggest hereditary influence. *Urology* 1994;**44(5)**:646-50.
7. Meikle AW, Bansal A, Murray DK, et al. Heritability of the symptoms of benign prostatic hyperplasia and the roles of age and zonal prostate volumes in twins. *Urology* 1999;**53**:701-6.
8. Rohrmann S, Fallin DM, Page WF, et al. Concordance rates and modifiable risk factors for lower urinary tract symptoms in twins. *Epidemiology* 2006;**17**:419-27.
9. Akiyama Y, Maeda D, Niimi A et al. Inflammatory infiltrates specific to Hunner type interstitial cystitis ICS 2016 abstract. *Neurourol Urodyn* 2016;**35**:S243.
10. Takai S, Majima T, Shimizu T, et al. The therapeutic effects of gene therapy with replication-deficient herpes simplex virus (HSV) vectors encoding poreless TRPV1 or protein phosphate 1α (PP1α) on bladder overactivity and nociception in a rat model of cystitis induced by hydrogen peroxide. *Neurourol Urodyn* 2016;**35**:S245.
11. Negoro H, Kanematsu A, Doi M, et al. Involvement of urinary bladder Connexin43 and the circadian clock in coordination of diurnal micturition rhythm. *Nat Commun* 2012;**3**:809.
12. Ihara T, Nakamura Y, Mitsui T, et al. Circadian regulations of PIEZO1, TRPV4, connexin26 and VNUT by clock genes in the mouse bladder urothelium. N*eurourol Urodyn* 2016;**35**:S240.
13. Ikeda Y, Zabbarova I, Kullmann FA, et al. Bladder afferent neurons selectively interact with apical urothelial cells. *Neurourol Urodyn* 2016;**35**:S242
14. Drake MJ, Kanai A, Bijos DA, et al. The potential role of unregulated autonomous bladder micromotions in urinary storage and voiding dysfunction; overactive bladder and detrusor underactivity. *BJU Int* 2017;**119**:22-9.
15. Keswani SG, Moles CM, Morowitz M, et al. The future of basic science in academic surgery: identifying barriers to success for surgeon-scientists. *Ann Surg* 2016 [Epub ahead of print].
16. Eberli D, Atala A. Basic science research in urology training. *Indian J Urol* 2009;**25**:217-20.
17. Fry CH, Gammie A, Drake MJ, et al. Estimation of bladder contractility from intravesical pressure-volume measurements. *Neurourol Urodyn* 2016 [Epub ahead of print].
18. Slovak M, Barker AT, Chapple CR. The assessment of a novel electrical stimulation waveform recently introduced for the treatment of overactive bladder. *Physiol Meas* 2013;**34**:479-86
19. Lentle RG, Reynolds GW, Janssen PW, et al. Characterisation of the contractile dynamics of the resting ex vivo urinary bladder of the pig. *BJU Int* 2015;**116**:973-83.

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