Editorial

Clinical challenges in tissue-engineered urethral reconstruction

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Urologic patients often present with congenital and/or acquired tissue and organ dysfunctions requiring surgical reconstruction to re-establish normal genitourinary system function. The field has made tremendous use of limited resources, developing creative and effective ways to reconstruct or replace inadequate tissues. Urethral reconstruction continues to be a challenging area of expertise for urologists. Whilst for some conditions, only one or a few procedures are recognized as standard of treatment, over 300 techniques are known for urethral stricture and hypospadias repair. This diversity illustrates the complexity of these conditions and indicates the lack of a gold standard procedure. In addition to the surgeon's skills, successful outcomes of any procedure depend on the availability of appropriate tissues. A wide variety of tissues, such as (vascularized) skin grafts, and bladder and buccal mucosa, have been used in urethral repair. However, all of these substitutes have limitations compared to autologous urethral tissue, which can lead to complications (e.g., stricture formation, graft failure). Furthermore, the amount of tissue that can be harvested from a donor site is limited, which can be problematic, especially in the case of long defects. To overcome these difficulties, alternative methods for urethral reconstruction have been explored.

Traditional reconstructive surgery methods are associated with varying degrees of donor site morbidity as well as inherent notable complications. Tissue engineering (TE) is an emerging field offering the possibility of providing true biological substitutes with patient-specific properties to restore the structure and function of pathologically altered tissues. TE was full of hope and promise in its infancy in the late 20th century and has truly exploded in the first decade of the 21st. In 2010, over 4,000 articles were available on PubMed when searching for "tissue engineering" or "regenerative medicine," as compared to less than 400 in the year 2000 (1). Several groups have attempted tissue-engineered urethral substitution by using acellular and cellularized matrices (2). A major issue concerning acellular matrices, as shown in rabbits by Dorin *et al.* (3), is that urothelial regeneration in acellular graft is limited to 0.5 cm, which compromises success in more complex cases, such as long strictures. Tissue-engineered matrices containing autologous cells in addition to extracellular matrix are more promising. The main advantage of this method is that a large autologous-cell graft having the ability to grow *in vivo* without rejection can be created with only a limited amount of material, such as a piece of oral mucosa. Moreover, studies have reported that stem cells can simply be obtained from urine (4,5), making this approach even more attractive.

Despite significant progress in the urethral TE field, very few teams have proceeded to clinical trials and published their results to date. However, the four clinical trials so far conducted present encouraging results. Indeed, Engel *et al.* (6) have seeded oral keratinocytes on collagen-based matrices (MukoCell®) and grafted their substitutes in 10 patients with a success rate averaging 90%. Fossum *et al.* (7) rather used bladder urothelial cells seeded on decellularized dermal matrices to treat six patients and were 83% successful at a mean follow-up of 87 months. Bhargava *et al.* (8) chose the recellularized matrices approach by seeding oral keratinocytes and fibroblasts in donor dermal matrices that were then grafted in five patients. Within the first nine months of follow-up, two patients had graft complications. One patient had to undergo excision of the entire graft due to scarring, whereas another had to have partial excision due to graft hyperproliferation. In a recently

published update of their study commenting on long-term results with a mean follow-up of 111.8 months (9), they reported that of the original five patients, four had a normal-looking urethra and still retained their graft *in situ* nine years post-implantation. Finally, Raya-Rivera *et al.* (10) reported the success of performing an open-bladder biopsy to harvest 1 cm^2 of full thickness bladder tissue, which was then divided into urothelium and smooth muscle. Urothelial and smooth muscle cells were then grown separately in culture, and subsequently seeded on the luminal and outer surface of a tubularized polyglycolic acid mesh scaffold. Their constructs were prepared over the course of four weeks prior to being used as urethral replacement grafts for gaps of 4 to 6 cm in five pediatric patients aged 10 to 14 years who had a history of either a failed posterior urethral repair or complete posterior urethral disruption from pelvic trauma. They reported excellent success over a median follow-up of 71 months. These are outstanding results in a limited number of patients with long-segment and/or complex stricture disease. Although this is certainly far from an "off-the-shelf" alternative, with consistently reproducible outcomes, this could offer an alternative that would be superior to current approaches to long-segment urethral replacement.

On the other side, there is an increasing understanding of the complexity underlying the use of *in vitro* techniques and their translation into clinical studies with reliable and consistent outcomes that can be scaled to achieve true clinical successes (11-14). The extensive culture time required for TE models could limit their clinical application, but as reconstructive urethral surgeries are usually performed on an elective basis, this would be a minimal inconvenient. High cost of production and lack of off-the-shelf availability are the major disadvantages of the technique, but appropriate scientific development and careful commercialisation will help circumvent these aspects.

These and other limitations have been discussed in an editorial published by Barbagli and Lazzeri (15) in European Urology, in which they highlighted that "the gap between technical success in the laboratory or animal experiments and clinical application of tissue-engineered materials for the human bladder has been reported in the literature" and that "the same gap between investigative *in vitro* studies and clinical use of tissue-engineered materials in patients is evident for urethral reconstruction." The authors also mentioned that while there is a plethora of publications describing diversified TE products, solely three papers have reported clinical results on the use of these products in urethral stricture disease (16).

This triggered a letter to the editor by Osman *et al.* (17) in which they questioned various elements. First, they criticized Barbagli and Lazzeri for pointing out a recent publication as "the most important step in the clinical use of a tissue-engineered material for urethral reconstruction" as Barbagli is a coauthor of this specific paper and since it only includes preliminary data from work realised with the pharmaceutical company Urotiss. Secondly, referring to Barbagli and Lazzeri's inquiry about the future of TE urethral reconstruction when looking at if from a worldwide perspective, Osman *et al.* commented that currently, the main focus should be on the achievement of high-quality phase 1 and 2 studies and on long-term follow up, notably to avoid safety issues such as the recent saga with polypropylene mesh, rather than on commercialisation and globalization of a TE technique for urethral surgeries. They also noted that significant costs and expertise required for TE would add to the challenge of making it accessible to developing countries.

In their editorial, Barbagli and Lazzeri also wondered about what would be the optimal use of TE technology for different urethral conditions (simple *vs.* complex). At the present time, available TE models are promising, but in simple cases where local tissues or buccal mucosa are available, these less troublesome options should remain the gold standard. We agree that using TE models only in complex cases harbouring higher complication rates will place TE in a difficult position to prove itself, but these are the situations where patients can benefit the most from it and where the cost-effectiveness risks to be the greatest. Osman *et al.* believe that academic centers should ally and share the strengths of their regenerative scientists and clinicians to enhance even more the expertise on TE.

Barbagli and Lazzeri (18) replied to Osman *et al.* and suggested studying the "new world" of TE in simple cases. They concluded by asking for "tight collaboration, sharing experiences and knowledge among everyone working on and dedicating time to TE" and acknowledged that there is a "need to increase our efforts to conduct high-quality clinical trials for TE in urology." Those last two comments go along the same line. Undeniably, there should be more cooperation in urologic TE because the purpose of optimizing this technology is to improve patients' health and quality of life, and although the sphere has progressed remarkably in the last fifteen years, it is still not enough. Experts and leaders in the field should call for a focus

meeting on the subject to set objectives for the next 5 to 10 years. An upcoming European or American Urologic Association (EAU or AUA) meeting would be perfect for that!

Knowledge on TE in the field of urethral repair is expanding and still finding its way into clinical implementation. Although experience with differentiation of stem cells (either isolated from urine or from adipose tissue) towards different lineages is gaining ground, protocols with *in vitro* expansion of original tissues are better established at this moment. It is noteworthy that no research has yet been performed with pseudostratified urethral epithelium. Tissue-engineered buccal mucosa has been used in urethral reconstruction and good results have been obtained with this easily available cell source. In contrast to harvesting a full graft of buccal mucosa for reconstructive surgery, TE only requires a very small biopsy, making the harvest relatively non-invasive.

In conclusion, more studies are needed in urethral reconstruction to explore alternatives with respect to scaffolds and cell sources. Orabi *et al.* study (19) strongly supports that scaffolds without cells will not be appropriate for long-segment urethral strictures. Finally, Osman *et al.* (17) suggest that several options for scaffolds and stromal cells, and even epithelial cells, exist and merit investigation, with respect to clinical efficacy whilst considering safety issues and convenience to the patient in making any choices.

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Footnote

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References

1. Fisher MB, Mauck RL. Tissue engineering and regenerative medicine: recent innovations and the transition to translation. Tissue Eng Part B Rev 2013;19:1-13.
2. Atala A, Danilevskiy M, Lyundup A, et al. The potential role of tissue-engineered urethral substitution: clinical and preclinical studies. J Tissue Eng Regen Med 2015. [Epub ahead of print].
3. Dorin RP, Pohl HG, De Filippo RE, et al. Tubularized urethral replacement with unseeded matrices: what is the maximum distance for normal tissue regeneration? World J Urol 2008;26:323-6.
4. Zhang Y, McNeill E, Tian H, et al. Urine derived cells are a potential source for urological tissue reconstruction. J Urol 2008;180:2226-33.
5. Bharadwaj S, Liu G, Shi Y, et al. Characterization of urine-derived stem cells obtained from upper urinary tract for use in cell-based urological tissue engineering. Tissue Eng Part A 2011;17:2123-32.
6. Engel O, Ram-Liebig G, Reiß P, et al. 15 Tissue-engineered buccal mucosa urethroplasty. Outcome of our first 10 patients. J Urol 2012;187:e6.
7. Fossum M, Skikuniene J, Orrego A, et al. Prepubertal follow-up after hypospadias repair with autologous in vitro cultured urothelial cells. Acta Paediatr 2012;101:755-60.
8. Bhargava S, Patterson JM, Inman RD, et al. Tissue-engineered buccal mucosa urethroplasty-clinical outcomes. Eur Urol 2008;53:1263-9.
9. Osman NI, Patterson JM, MacNeil S, et al. Long-term follow-up after tissue-engineered buccal mucosa urethroplasty. Eur Urol 2014;66:790-1.
10. Raya-Rivera A, Esquiliano DR, Yoo JJ, et al. Tissue-engineered autologous urethras for patients who need reconstruction: an observational study. Lancet 2011;377:1175-82.
11. Roth CC, Kropp BP. Recent advances in urologic tissue engineering. Curr Urol Rep 2009;10:119-25.
12. Olson JL, Atala A, Yoo JJ. Tissue engineering: current strategies and future directions. Chonnam Med J 2011;47:1-13.
13. Hollander AP. Cell therapies and regenerative medicine - the dawn of a new age or more hype than hope? Clin Transl Med 2012;1:12.
14. Oerlemans AJ, Feitz WF, van Leeuwen E, et al. Regenerative urology clinical trials: an ethical assessment of road blocks and solutions. Tissue Eng Part B Rev 2013;19:41-7.
15. Barbagli G, Lazzeri M. Clinical Experience with Urethral Reconstruction Using Tissue-engineered Oral Mucosa: A Quiet Revolution. Eur Urol 2015;68:917-8.
16. Ram-Liebig G, Bednarz J, Stuerzebecher B, et al. Regulatory challenges for autologous tissue engineered

products on their way from bench to bedside in Europe. Adv Drug Deliv Rev 2015;82-83:181-91.
17. Osman NI, Chapple CR, MacNeil S. Re: Guido Barbagli, Massimo Lazzeri. Clinical Experience with Urethral Reconstruction Using Tissue-engineered Oral Mucosa: A Quiet Revolution. Eur Urol. In press. http://dx.doi.org/10.1016/j.eururo.2015.05.043. Eur Urol 2015;68:e99-100.
18. Barbagli G, Lazzeri M. Reply to Nadir I. Osman, Christopher R. Chapple, Sheila MacNeil's Letter to the Editor re: Guido Barbagli, Massimo Lazzeri. Clinical Experience with Urethral Reconstruction Using Tissue-engineered Oral Mucosa: A Quiet Revolution. Eur Urol. In press. http://dx.doi.org/10.1016/j.eururo.2015.05.043. Eur Urol 2015;68:e101-2.
19. Orabi H, AbouShwareb T, Zhang Y, et al. Cell-seeded tubularized scaffolds for reconstruction of long urethral defects: a preclinical study. Eur Urol 2013;63:531-8.

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