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Platinum Priority – Editorial

Referring to the article published on pp. 531–538 of this issue

Developing Tissue-Engineered Solutions for the Treatment of Extensive Urethral Strictures

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Since the early 1980s when tissue-engineered skin for badly burned patients became a clinical reality [1], the field has progressed, and knowledge gained in one application has rapidly been applied to other clinical conditions. Thus it is now possible to produce several functionally competent epithelial tissues for transplantation, and our understanding of how to design tissues for particular applications is at an exciting stage.

In this issue of the journal, the article by Orabi et al. [2] presents clear data in dogs that cell-free collagenous scaffolds do not work for extensive urethral defects. In contrast, if these scaffolds are preseeded with epithelial and stromal cells in the laboratory before implantation, then wide-calibre urethras can be achieved without strictures.

We agree with the authors that more options are needed for patients with long defects of the urethra. Shorter defects can be handled successfully using the patient's oral mucosa excised at the time of surgery. The preferred options are the cheek (buccal), followed by the ventral surface of the tongue (lingual) [3]. However, if the defect is extensive, securing adequate tissue is both difficult and associated with potential postoperative morbidity, and several groups are now engaged in exploring tissue-engineered alternatives.

In designing tissue-engineered material to replace strictures of the urethra, a number of factors must be considered that are timely to review. One of the key questions in the overlapping fields of biomaterials, tissue engineering, and regenerative medicine is whether it is necessary to introduce cells onto a scaffold (whether the scaffold is natural or synthetic) to produce an effective repair. We suggest that this study helps clarify the debate about acellular scaffolds versus noncellular scaffolds. Whereas acellular scaffolds can have a role to play in small defects where one is relying on ingrowth of adjacent cells onto the scaffold, there is no evidence in the peer-reviewed literature of success in replacing large tissue defects in the urethra where the underlying problem is inevitably one of ischaemia of the corpus spongiosum [4].

We suggest there may be several combinations of both scaffolds and cells that may be useful. In the current study in dogs, the source of the natural decellularised scaffold was porcine bladder, and the source of the cells was autologous bladder biopsies from which bladder epithelial cells (urothelial cells) and bladder smooth muscle cells were cultured. Certainly allogeneic or xenogeneic bladder can provide a substrate that can support epithelial tissue reconstruction [5]. However, we suspect other natural collagenous or synthetic scaffolds will also prove viable and indeed present more attractive options in terms of safety, clinical convenience, and availability for patients and surgeons.

In 2008 we reported on a 3-yr follow-up of the use of autologous tissue-engineered buccal mucosa for extensive substitution urethroplasty in five patients [6]. We found that initial results were good in all five, and at 3 yr, three patients had patent urethras based on the use of buccal epithelial cells and fibroblasts and decellularised acellular sterilised human dermis. Although these results are promising, synthetic scaffolds are in development that may offer an off-the-shelf reproducible and risk-free alternative to the use of donor human or animal collagen-based scaffolds. The Raya-Rivera group reported a study of five boys where a bladder biopsy was taken through a suprapubic incision from each patient, and the

DOI of original article: http://dx.doi.org/10.1016/j.eururo.2012.07.041.
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http://dx.doi.org/10.1016/j.eururo.2012.09.046

muscle and epithelial cells were expanded and seeded onto tubularised polyglycolic acid/poly(lactide-co-glycolide acid) scaffolds [7]. Patients then underwent urethral reconstruction with the tissue-engineered tubularised urethras. At a median follow-up of 71 mo, the authors reported the maintenance of wide urethral calibres without strictures.

The next question is which cells can be used successfully. Stromal cells are necessary to form a good epithelial attachment and also to provide structural, renewable stromal tissue with which to replace fibrotic tissue. There are several potential options for the source of stromal cells. The authors of the current article show that smooth muscle cells from bladder can be effective. We have previously used buccal mucosal fibroblasts with reasonable clinical success, and we are currently exploring bone marrow or fat-derived mesenchymal cells because they can take on a range of useful mesodermal phenotypes. Additionally, it is quite feasible that an allogeneic-screened stromal cell could work well in this context because our current understanding is that these cells will be replaced by autologous cells over several months.

However, with respect to the epithelial cell component, the choice of source material is going to be more limited. Current evidence suggests that one can replace one epithelial cell with a similar morphology epithelial cell to some degree. Thus the choice is likely to be bladder (necessitating a bladder biopsy), urethra (where accessing a biopsy from the patient who needs the tissue reconstruction makes this unlikely), or buccal mucosa (very easy to biopsy). Oral epithelial cells and bladder epithelial cells can both be made into three-dimensional tissue-engineered models in vitro (using a variety of natural or synthetic scaffolds with stromal cells) and can achieve a physiologic barrier function. However, we suggest the field has now moved on to the point where we need to address the clinical challenges and ask to what extent these tissues can replace ischaemic fibrotic strictures in humans and how effective they will be in the longer term. Here it is also important to consider the aetiology of these patients' conditions and how they are managed because one must acknowledge there will be a likelihood of recurrent fibrosis for some, particularly where there is inadequate vascularisation of the graft or there is an underlying disease process such as lichen sclerosis (LS). We suggest this problem will occur whether native tissue (eg, buccal mucosa) or tissue-engineered alternatives are used irrespective of the composition of the tissue-engineered grafts.

When does failure occur? Tissue engineering for the urethra has one major advantage: The wound bed is very well vascularised. Hence loss of tissue-engineered grafts due to delayed vascularisation (as we have previously reported to occur in tissue-engineered skin) was not found to be an issue in our series of five patients [6]. In the study by el-Kassaby et al. [4], failure of the cell-free grafts occurred in longer strictures and where there was a poor wound bed. In our clinical study we found that the recurrence of fibrosis occurred within 9 mo in two of five patients. In one patient, we encountered marked extensive fibrosis necessitating complete removal of the graft. In another patient, only partial fibrosis occurred with half of the grafted area remaining unaffected. Because the procedures were in patients with significant LS, it was unclear whether this was related to the technique or the underlying disease process. We did suspect more of a local reaction to the cadaver-derived matrix than we normally see with native oral mucosa, however, which led on to our current programme of developing an absorbable synthetic matrix [8].

Clearly the issue of fibrosis with any tissue engineering is a challenging one. Reconstructive surgeons are historically cautious and conservative in treating any scar conditions, particularly hypertrophic or keloid scarring where there is a clear history of recurrence after excision, a difficult problem also encountered in some patients with LS after grafting. Essentially it appears that the immune system, for reasons not yet understood in these patients, declares war on the part of the body that has suffered some tissue damage.

We have in fact utilised the propensity towards scarring in tissue engineering in another research programme where we believe a degree of fibrosis may be beneficial in managing pelvic organ prolapse (POP), which when treated with surgical techniques using biologic grafts has proven in many series to have poor long-term results. This led to the increasing use of synthetic cell-free mesh. However, there has been increasing concern expressed over the morbidity resulting from the use of these materials that are designed as permanent implants. The US Food and Drug Administration highlighted these concerns in a 2011 safety alert [9]. Indeed, a recent systematic review assessing data from 110 studies including 11 785 women concluded that approximately 10% of women undergoing transvaginal POP repair with mesh experienced mesh erosion within 12 mo of surgery [10]. In this context it is clear that tissue-engineered solutions to this clinical challenge merit exploration.

In conclusion, more studies are needed in urogenital reconstruction to explore alternatives with respect to scaffolds and cell sources. The current study strongly supports that scaffolds without cells will not be appropriate for long urethral strictures. We also 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. It is also evident that understanding the aetiology of fibrosis in response to any transplantation surgery for these patients presents the next considerable clinical and scientific challenge.

Conflicts of interest: The authors have nothing to disclose.

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