Tissue Engineering and Conduit Substitution

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KEYWORDS

• Urinary diversion • Radical cystectomy • Tissue engineering • Regenerative medicine • Scaffolds

KEY POINTS

- Radical cystectomy with urinary diversion is associated with significant morbidity, which could be reduced substantially with a tissue engineered substitute for bowel.
- Efforts to develop a tissue engineered urinary conduit have involved scaffolds with or without cell seeding.
- Significant hurdles remain to the development of a clinically useful tissue engineered urinary conduit.

INTRODUCTION

For centuries, regeneration observed in organisms such as amphibians and crustaceans has fueled enthusiasm for the potential of regenerative medicine. The ability to recreate functional biological structures through tissue engineering (TE) represents a substantial goal, which would have a dramatic impact across multiple fields of medicine, including organ transplantation, reconstruction, and oncology. Although pioneering work on TE has been ongoing for decades, intense media interest was ignited in 1995, when images of the "auriculosaurus" were broadcast by the British Broadcasting Company (**Fig. 1**). The now highly recognized mouse—which appeared as if it was growing a human ear along its dorsum—immediately captured the imagination of the public and many believed rapid advancements in the field of TE were forthcoming. In reality, the synthetic ear-shaped scaffold, which was seeded with bovine cells and implanted on the back of a nude mouse by Charles Vacanti and his team, represented an important proof of concept in TE, but not the advent of xenotransplantation. Nevertheless, substantial attention and lofty expectations resulted in high enthusiasm for the promise of TE and regenerative medicine. The seemingly limitless possibilities of regenerative medicine were explored in popular culture as evidenced by major motion pictures such as *The Island* (Warner Bros. Entertainment Inc), which portrayed a dystopian world where humans were cloned for producing autografts. Headlines such as *Grow Your Own Replacement Parts* were seen on mainstream media outlets, signaling an impending medical revolution.[1] Despite the initial excitement, it has now been more than 2 decades since the auriculosaurus caught our attention, and although significant advances have been made, widespread clinical applications of TE remain very limited.

Some pioneering TE efforts have come in the field of urology. In 2006, Atala and colleagues[2] published what was viewed as significant breakthrough at the time, detailing the creation and implantation of tissue engineered bladders in 7 patients with myelomeningocele. Synthetic and composite synthetic natural bladder–shaped scaffolds were seeded with bladder cells obtained via

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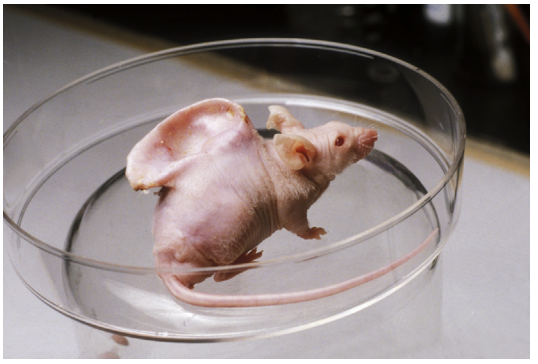

Fig. 1. Images of the "auriculosaurus," a mouse with a subcutaneously implanted ear-shaped scaffold were broadcast by the British Broadcasting Company in 1995, catapulting the prospect of tissue engineering into public consciousness. (*Courtesy of* the British Broadcasting Corporation London, United Kingdom; with permission.)

biopsy and incubated for several weeks. The engineered bladders were then used to augment the native bladder and preliminary results were encouraging—after a mean follow-up of 46 months, the bladders were functioning normally. In 2011, Raya-Rivera and coworkers[3] reported promising results in 5 boys who underwent urethral reconstruction with tissue-engineered tubular urethras. Autologous muscle and epithelial cells were seeded onto a synthetic tubular scaffold in vitro and the engineered urethras were used in posterior urethroplasty. After a median follow-up of 71 months, the urethras remained patent and biopsies confirmed normal urethral histology.

For numerous reasons, the bowel is used frequently in urinary reconstruction. Its relatively abundant supply and rich vascularization make it an attractive substitute for urothelium; however, its absorptive nature is not ideal for use in the urinary system and results in a number of metabolic disturbances. These limitations were a major motivation in efforts to design a tissue engineered bladder augment. Urinary diversion after radical cystectomy (RC) represents the most common uses of bowel in urology. RC with urinary diversion is associated with significant morbidity; nearly two-thirds of patients experience a perioperative complication, of which the majority are gastrointestinal in nature.[4] The development of a tissue-engineered substitute for urinary diversion likely would dramatically reduce the perioperative and metabolic morbidity associated with the use of bowel after RC. A fully functional, continent replacement bladder would represent a remarkable achievement in TE, but is far from clinical reality with our current technology. Recent efforts have instead focused on developing a tubular conduit for use in incontinent urinary diversion. Although there are significant challenges in any TE application, tubular structures such as a conduit represent a lower level of complexity than hollow, distensible organs such as the bladder and far less complexity than end-organs such as kidneys. In this paper, we review the current approaches for TE, limitations of current technology as well as clinical experience with the development of tissue-engineered urinary conduits (TEUC).

TISSUE ENGINEERING APPROACHES

There are several approaches that have been explored for TE. The bulk of efforts at developing a TEUC have used scaffolds with or without cell seeding. Scaffolds are an acellular matrix that provides structural support and a backbone for cells to proliferate. Cell seeding has been attempted with several different cell types, all with particular advantages and significant hurdles. Finally, and possibly most challenging, is that a suitable host environment needs to exist to promote the expansion and organization of cells. This includes adequate vascularization, appropriate growth factors, and immune regulation. There are efforts underway to understand and harness the natural self-assembly of cells for scaffold-free approaches to TE, but the majority of clinical applications now use the scaffold and cell seeding approach.

Scaffolds

A particular challenge with many TE applications is that target tissue has not have fully developed at the time of implantation, yet it must immediately perform as a functioning organ. In the case of a TEUC, once surgically implanted, it must immediately serve its basic function, passively transporting urine to the external environment and also must act as an impenetrable barrier to urine, which can diffuse into surrounding tissue, resulting in inflammation and fibrosis. Additionally, cells need a physical structure on which to migrate and guide growth into the desired tissue architecture. Scaffolds help to solve these issues as a 3-dimensional structure that provides physical support and an organizing template for cells to proliferate. The ideal scaffold would provide adequate mechanical support, allow for rapid cell ingrowth, elicit no adverse physiologic or immunologic reaction, and completely dissolve over time. Unfortunately, a material that perfectly fulfills these requirements has yet to be identified; these qualities often juxtapose one another. For example, to enhance