

A Regenerative Urinary Diversion Tissue-Engineered From Autologous Smooth Muscle Cells and a Biodegradable Scaffold

Deepak Jain, Craig Halberstadt, John W Ludlow, Rich Payne, Tom Spencer, Dominic Justewicz, Manuel J Jayo, Belinda J Wagner, and Timothy A Bertram

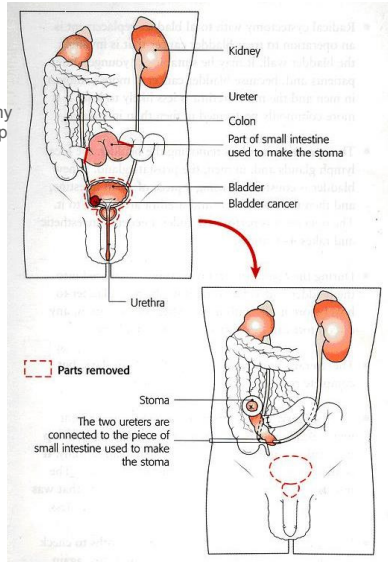
Tengion, Inc., Science & Technology, Winston-Salem, NC

Abstract:

Cystectomy or surgical removal of the bladder requires reconstructing a channel to eliminate urine from the body. While several surgical options for a urinary diversion exist, they all use a segment from the gastrointestinal (GI) tract. Harvesting GI tissue to form the diversion and exposure of GI tissue to urine can result in multiple acute and chronic complications, including GI and metabolic abnormalities. Tengion is developing autologous regenerative products such as the Neo-Urinary Conduit™ (NUC) for urinary diversion and other urologic applications as potential alternatives to the use of GI tract segments. The NUC is produced by seeding autologous smooth muscle cells (SMC) on a biodegradable scaffold to form a NUC Construct. Earlier products for regenerating urinary tissue (e.g., Tengion's Autologous Neo-Bladder Augment™) used SMC isolated from urinary bladder (1). For bladder cancer patients, a SMC source other than the bladder is preferred; therefore, sourcing of autologous SMC from an alternate tissue for use in the NUC was evaluated. Adipose tissue was determined to be a suitable source of SMC. In a porcine model, the NUC Construct regenerated an incontinent urinary diversion composed of native-like urinary tissue.

Figure 1. Diagram of cystectomy and construction of an ileal loop urinary diversion

Taken from *Cystectomy and Ileal Loop Diversion (Urostomy)*, Patient Information Book. (n.d.). Dublin, Ireland: The Adelaide and Meath Hospital.



Product Description:

The NUC is made up of the following components:

1. Scaffold: Polyglycolic acid (PGA) polymer mesh scaffold fashioned into the required tubular shape and coated with a 50:50 poly-DL-lactide-co-glycolide (PLGA) copolymer.
2. Cellular: Autologous smooth muscle cells sourced from adipose tissue, peripheral blood or bladder tissue

Results:

Figure 2. Example of a NUC scaffold illustrating the tube-like shape that is compatible with human anatomy. The scaffold is placed in a bioreactor, seeded with SMC and matured into a NUC for implantation.

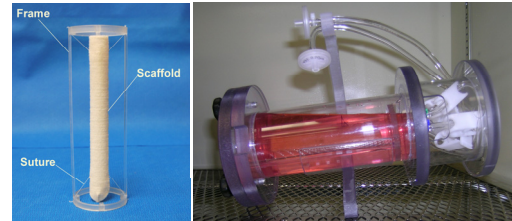


Figure 3. Expression of smooth muscle phenotype markers smooth muscle α -actin, calponin, and transgelin (SM22) assayed by immunostaining in cultures of adipose-derived SMC.

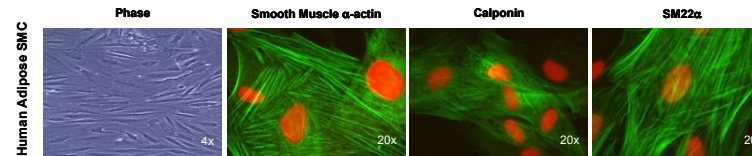
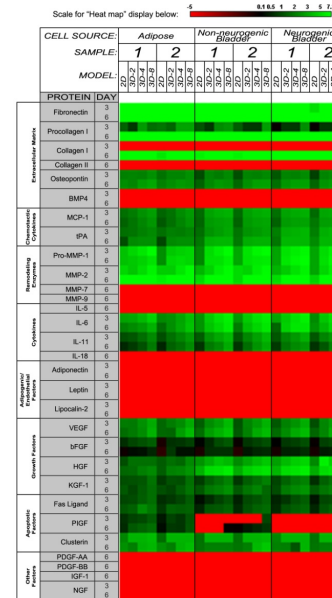
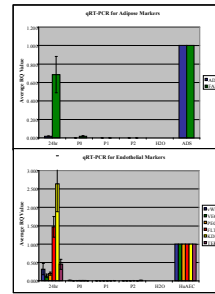


Figure 4: Secretome profile of adipose-derived SMC and bladder SMC expanded from neurogenic and non-neurogenic tissues. A hierarchy of expression in the secretome profile of SMC derived from adipose or bladder tissue was observed. In general, extracellular matrix (ECM) proteins > remodeling proteases > chemotactic cytokines > growth factors > apoptotic factors. Expression levels of 16/17 detected proteins increased in Day 6 media relative to Day 3. Adipose-derived SMC and Bladder-derived SMC secretome profiles exhibited significant correlation.

Figure 5: Adipocytic and Endothelial gene expression is virtually absent after passage 1 in adipose-derived SMC culture. SMC Phenotype (by gene expression) in Human Adipose-derived SMC persists during cell expansion (data not shown)



Abbreviations:
2D = 2D tissue culture plates; 3D = seeded scaffold coupon constructs.
3D-1 = 3D with 3x10⁶ seeded cells; 3D-4 = 3D with 4x10⁶ seeded cells; 3D-8 = 3D with 8x10⁶ seeded cells

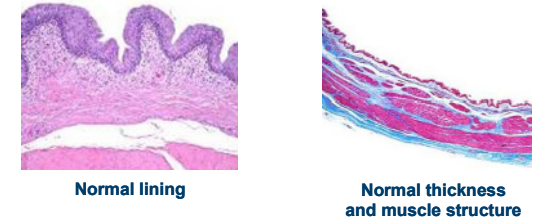


Figure 6: Histological evaluation of adipose-derived SMC seeded NUC implants at 3 months post-implantation in a porcine animal model.

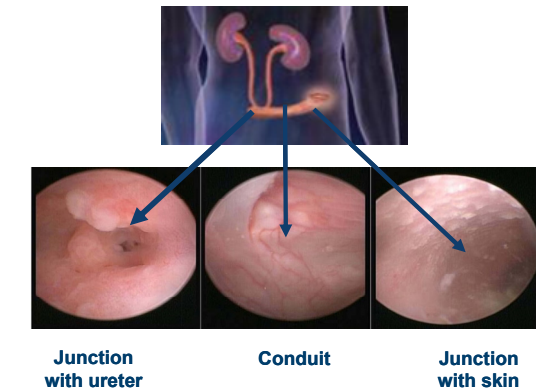


Figure 7. Radiographic image of NUC at 6 weeks post-implantation in a porcine animal model.

Conclusions:

- Neo-Urinary Conduit seeded with autologous SMC sourced from adipose tissue was capable of establishing a patent incontinent urinary diversion for post-cystectomy management of urine elimination in preclinical studies and is currently being evaluated in Phase I clinical trials.
- Neo-Urinary Conduit may represent an alternative to using GI tissue for post-cystectomy management by incontinent urinary diversion.