

Total urinary bladder regeneration with restoration of native structure and pharmacological response

Timothy A Bertram, George J Christ, Belinda J Wagner, Deepak Jain, Tamer Aboushwareb, John Ludlow, Richard Payne, Yagna Jarajapu, Chanda Turner, Manuel J Jayo

Abstract:

Neo-bladder histology was investigated in 21 canines at 30-79 days (n=9) and 80-180 days (n=9) after radical cystectomy and implantation of a Neo-Bladder Replacement Construct (Construct). Pharmacological responses of neo-bladder tissue strips from 9 retrieved neo-bladders (n=1, 30-79 days; n=8, 80-180 days) were compared to age-matched native bladder tissue (n=17).

In both groups, regenerated bladder was histologically consistent with native bladder including mucosal and serosal linings, detrusor muscle, vascular, and nerve composition. Logistic analysis revealed similar EC50 and slope factor values for contraction of bladder tissue strips derived from both groups induced by carbachol (Car) and electrical field stimulation (EFS). A progressive increase in the mean Emax values and slope factor values for contraction of bladder tissue strips derived from both groups induced by carbachol (Car) and electrical field stimulation (EFS) increased over time in the neo-bladder tissue, they were lower than native bladder responses in the 30-79 day group. Car-induced contractions, but not EFS-induced contractions, became equivalent to native tissue in 80-180 days post-implantation (p.i.)

The Neo-Bladder Replacement Construct is capable of regenerating urinary bladder *in vivo* with histology similar to native bladder in 30-79 days p.i. and pharmacological responses became similar to native bladder in 80-180 days p.i. with no evidence of abnormal cell growth, immune response, or adverse systemic effects.

Tengion is currently conducting a GLP study to support clinical trial studies in 2009.

Introduction:

Bladder cancer is the fourth most common cancer in men in the United States (US) and the 8th most common cancer in women, with an estimated 64,420 new cases diagnosed and 13,060 deaths in 2006 (Konety, 2007). More than 70% of all newly diagnosed bladder cancers are superficial, meaning that they are localized to the mucosal luminal epithelium. Radical cystectomy with urinary diversion by ileal conduit is used to treat superficial bladder cancers, notably carcinoma in situ, where the risk of progression can approach 80%; high grade T1 tumors that recur despite topical Bacillus Calmette-Guérin; Stage T2 cancers; and more advance T3 and T4 cancers.

From 1985-2000 the number of patients diagnosed annually with bladder cancer increased by 33%. Patients would benefit from a regenerative alternative to the current standard of radical cystectomy followed by urinary diversion with incontinent ileal conduit to avoid the numerous complications that arise from surgical manipulation of the bowel as well as chronic exposure of gut mucosa to urine. In this study, a neo-bladder construct comprised of a scaffold of synthetic lactide/glycolide polymer mesh plus bladder smooth muscle cells was tested for safety and efficacy as a template for regeneration and formation of a neo-bladder organ in a canine model of total bladder replacement.

Jayo, M. J., Jain, D., Wagner, B. J., & Bertram, T. A. (2008). Early cellular and stromal responses in the regeneration of a functional mammalian bladder. *J Urol*, *in press*.

Konety, B. R., Joyce, G. F., & Wise, M. (2007, May). Bladder and upper tract urothelial cancer. *J Urol*, *177*(5), 1636-1645.

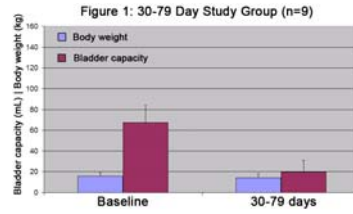


Figure 1: Scaffold degradation phase (<80-days). Lower than native capacity is transiently observed in the regeneration process. A similar finding is observed with bladder augmentation and linked to scaffold degradation (Jayo, et al., 2008).

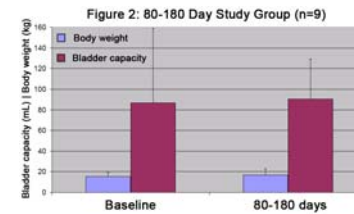


Figure 2: Regeneration of baseline or greater capacity occurs within 6 months of implantation of a Neo-bladder Replacement Construct. A similar finding is observed with bladder augmentation and linked to tissue regeneration (Jayo, et al., 2008).

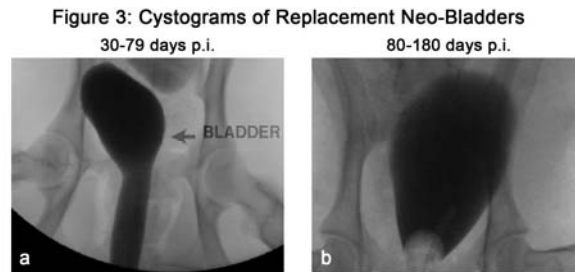


Figure 3. Cystograms of neo-bladders at (a) 30-79 days and (b) 80-180 days p.i. Both are water-tight, bladder-shaped neo-organs. All animals were continent after Foley catheter removal.

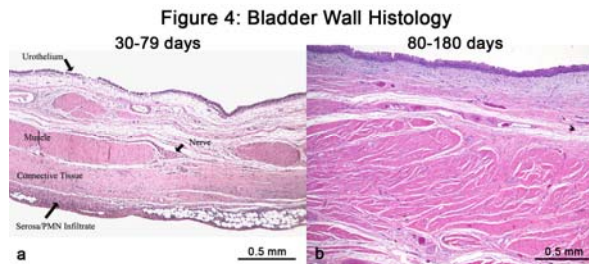


Figure 4. Although the bladder wall is thinner at the 30-79 day timeframe, all three layers of the bladder wall were present: Urothelial, muscular and serosal layers. (a) Scaffold material is present during early stages of regeneration (51 days p.i.). (b) Detrusor muscle has reached mature thickness by 6 mo p.i. (179 days p.i.).

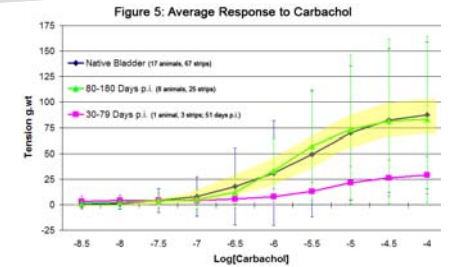


Figure 5: Response of regenerated bladder to carbachol became equivalent to native tissue by 6 months post-implantation (mean \pm std). Note: 16/22 bladders were evaluated at cystectomy but only 1/9 and 9/12 samples in each group were available for carbachol response evaluation. Yellow area represents 95% confidence interval of native bladder measurements.

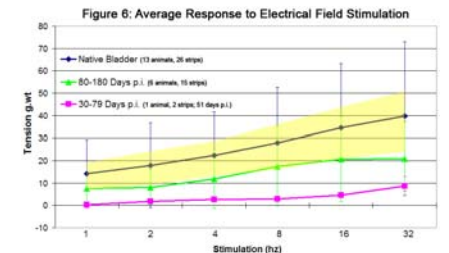


Figure 6: Response of regenerated bladder to electrical field stimulation increases over time, but does not reach equivalence with native tissue (mean \pm std). Note: 12/22 bladders were evaluated at cystectomy but only 1/9 and 7/12 samples in each group were available for EFS evaluation. Yellow area represents 95% confidence interval of native bladder measurements.

Conclusions:

A Neo-Bladder Replacement Construct:

1. Can regenerate an entire urinary bladder within 6 months post-implantation
2. Has baseline bladder capacity and cystography by 6 months post-implantation
3. Has native bladder wall structure with 3 layers: urothelial, detrusor, and serosal, by 79 days post-implantation
4. Has near native pharmacological response and electrical physiological function by 6 months post-implantation