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ABSTRACT:

Introduction: Biomechanical stimulation is a process known to promote tissue regeneration and optimal healing. Bladder regeneration is biomechanically stimulated by cycling (filling, storage and evacuation), a process initiated in utero that contributes to the development of a functional bladder in humans. Interruption of cycling in patients with neurogenic bladder from either congenital (e.g., spina bifida) or acquired (e.g., spinal cord injury) impairment leads to significant functional and structural alterations.

Methods: Cycling impacts on bladder tissue regeneration in cystectomized animals implanted with cell-seeded PLGA-based scaffolds were evaluated and learnings applied to outcomes of a Phase II clinical trial of the Tengion Autologous Neo-Bladder Augment™ (NBA) in patients with neurogenic bladder due to spina bifida.

Results: Post-implantation (p.i.) neo-bladder cycling was initiated in animals at 2 weeks p.i. for 3 days/week. Three cycling parameters were collected: total weeks, hr/day, and total hrs. Urodynamic assessments from three cycling cohorts based on mean parameters were evaluated: HIGH (10 weeks, >3.75 hr/day, >60 hrs), LOW (10 weeks, <2.25 hr/day, <25 hrs), and NO cycling. The HIGH cohort developed neo-bladders with improved compliance and capacities that were on average 3-fold higher than the LOW cohort ($p < 0.0001$). The HIGH cohort achieved 90% of native baseline capacity by 6 mo p.i., while the LOW cohort regained only 40%. Animals not cycled (incontinent) developed tubularized urinary tract diversions. Histology of the neo-bladder wall revealed native-like tissue structure and extracellular matrix composition (e.g., elastin) in cycled bladders. Early Phase II data studying the NBA suggest that patients with challenges in postoperative cycling (e.g., open bladder necks and low pressure high grade reflux) had inferior clinical and urodynamic outcomes to patients without those challenges.

Conclusions: Early post-implantation cycling is essential for promoting regenerative healing following implantation of autologous cell-seeded PLGA based scaffolds in animals and humans. Insights from Preclinical studies are consistent with early insights from the Phase II clinical trial of the Tengion Autologous Neo-Bladder Augment and confirm the importance of cycling in bladder regeneration.

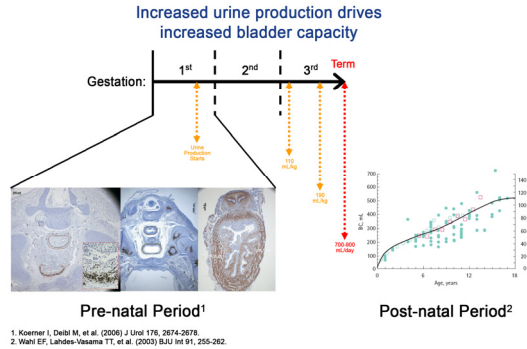
INTRODUCTION:

Bladder cycling, the process of sequential expansion and contraction, is important in the anatomic and physiologic development of the normal bladder. Cycling, triggered by the production of urine, begins in utero. This process was believed to be essential in the development of a normal regenerated bladder; to that end, cycling regimens were implemented postoperatively in preclinical and clinical trials of the Tengion Autologous Neo-Bladder Augment™ (NBA).

OBJECTIVES:

In a manner consistent with human organogenesis (Figure 1), regeneration of bladder tissue is biomechanically stimulated by cycling. Cycling is the filling, storage and evacuation of urine in the bladder. We sought to evaluate the role of cycling in preclinical models of bladder tissue regeneration, and to apply learnings from these preclinical models to a Phase II study of the Tengion NBA in patients with neurogenic bladder due to spina bifida.

Figure 1: Effect of urine production on bladder capacity during pre-natal and post-natal development



METHODS:

Cycling impacts on bladder tissue regeneration in cystectomized animals implanted with cell-seeded PLGA-based scaffolds were evaluated and learnings applied to outcomes of a Phase II clinical trial of the Tengion NBA in patients with neurogenic bladder due to spina bifida.

RESULTS:

Figure 2: Preclinical cycling - effect of cycling on capacity at necropsy

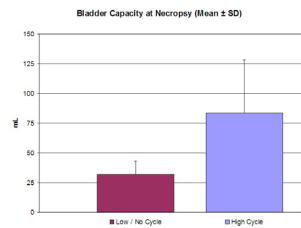


Figure 3: Preclinical cycling - total days and hours cycled in low/no cycle and high cycle groups

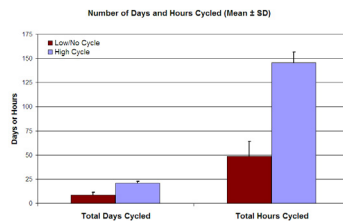
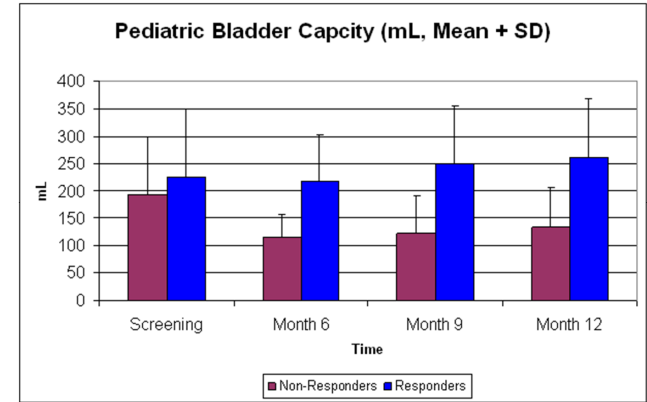


Figure 4: Clinical experience - Pediatric bladder capacity of responders and non-responders over time



Non-Responders (n=4)

Responders (n=6)

- Of the four patients with challenges to cycling, all had at least one concomitant anatomic abnormality that could interfere with their ability to cycle effectively
 - 3 patients had open bladder necks; all underwent bladder neck slings at the time of bladder augmentation
 - 2 of the 3 bladder neck slings failed
 - 1 bladder neck successfully closed; this patient developed reported improvements in continence but no urodynamic improvement
 - 1 patient had severe low pressure, high grade reflux, impeding her ability to retain urine in her bladder in order to cycle

CONCLUSIONS:

- In preclinical and clinical studies of the Tengion Autologous Neo-Bladder Augment, effective cycling appears to be essential for regeneration*
- Bladder cycling after augmentation with the Tengion NBA recapitulates bladder cycling in organogenesis*
- Patients with concomitant anatomical abnormalities experienced cycling challenges and had less robust improvements in capacity*
 - alternative approaches to cycling are being explored*
- All patients are currently in long-term follow up phase of study*