# Autologous Cell Seeded Biodegradable Scaffold for Augmentation Cystoplasty: Phase II Study in Children and Adolescents with Spina Bifida

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**Purpose:** Augmentation cystoplasty using gastrointestinal segments in children/adolescents with medically refractory neurogenic bladder is associated with significant complications. We evaluated an autologous cell seeded biodegradable scaffold (Tengion®) for bladder augmentation as an alternative to traditional enterocystoplasty in this population.

**Materials and Methods:** A phase II prospective study was performed in children with neurogenic bladder due to spina bifida requiring enterocystoplasty for detrusor pressure 40 cm $H_2O$ or greater despite maximum antimuscarinic medication. Following open bladder biopsy, urothelial and smooth muscle cells were grown ex vivo and seeded onto a biodegradable scaffold to form a regenerative augment as the foundation for bladder tissue regeneration. Bladder neck sling was the only concomitant surgical procedure permitted. Bladders were cycled postoperatively to promote regeneration. Primary and secondary outcomes at 12 months included change in bladder compliance, bladder capacity and safety. Long-term assessment was done with similar outcomes at 36 months.

**Results:** Compliance improved in 4 patients at 12 months and in 5 patients at 36 months, although the difference was not clinically or statistically significant. There was no clinical or statistical improvement in bladder capacity at 12 or 36 months in any patient. Adverse events occurred in all patients, and most were easily treated. Two patients had low cell growth following bladder biopsy, of whom 1 withdrew from the study and 1 underwent a second biopsy. Serious adverse events of bowel obstruction and/or bladder rupture occurred in 4 patients.

**Conclusions:** Our autologous cell seeded biodegradable scaffold did not improve bladder compliance or capacity, and our serious adverse events surpassed an acceptable safety standard.

**Key Words:** regenerative medicine; spina bifida cystica; transplantation, autologous; urinary bladder, neurogenic; urologic surgical procedures

**Abbreviations and Acronyms**

AE = adverse event
EBC = expected bladder capacity
NGB = neurogenic bladder
Pdet = detrusor pressure
SAE = serious adverse event
SB = spina bifida
UDS = urodynamic study
VUR = vesicoureteral reflux

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Regenerative medicine has been investigated as an alternative to augmentation cystoplasty in children with neurogenic bladder secondary to spina bifida.[1] Augmentation with gastrointestinal segments carries a risk of short and long-term complications.[2–4] Use of the native bladder tissue to create an autologous cell seeded construct has the potential to decrease the morbidity associated with incorporating gastrointestinal

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tissue into the urinary tract. Preclinical studies in cystectomized canines have demonstrated the feasibility of this approach, allowing the neo-organ to adapt to growth of the host.[5,6] In a pilot study of children with spina bifida Atala et al implanted cell seeded composite collagen-polyglycolic acid constructs to augment native bladders.[1] In this investigation the greatest improvement in urodynamics occurred with the use of full omental wrapping and, more importantly, adverse events associated with gastrointestinal segments were not encountered.

Based on the preclinical and clinical experience, a prospective Food and Drug Administration multicenter phase II trial was performed to establish the safety and efficacy of a regenerative autologous cell seeded biodegradable scaffold for use in bladder augmentation. The primary outcome was change from baseline compliance at 12 months, and secondary outcomes were change from baseline capacity and safety at 12 months. A long-term phase was added, monitoring the primary and secondary outcomes out to 36 months. We report our clinical experience with the autologous cell seeded biodegradable scaffold in children with NGB due to SB.

## MATERIALS AND METHODS

### Patient Population

Four centers participated in this open-label, single arm trial (Children's of Alabama/University of Alabama at Birmingham, Boston Children's Hospital, Children's Hospital Los Angeles and Wake Forest Baptist Medical Center), which was conducted between December 2006 and April 2011. An institutional review board at each center approved the protocol, with parents/guardians and patients providing written informed consent and assent. An independent data safety monitoring board assessed the benefit vs risk on an ongoing basis.

Inclusion criteria consisted of age 3 to 21 years and the presence of NGB secondary to SB refractory to medical treatment. The need for bladder augmentation was based on decreased/inadequate bladder compliance with bladder pressure 40 cm $H_2O$ or greater at or below EBC for age using the formula, $(age/2 + 6)30 = ml$,[7] and/or new upper urinary tract changes (hydronephrosis, VUR) in the preceding 12 months. A steering committee consisting of the 4 principal investigators and a Tengion representative verified the eligibility of each patient. Patients with a history of bladder augmentation and those who recently underwent urological, intraperitoneal or neurological surgery as well as those who recently received injections of onabotulinumtoxin A for detrusor overactivity were excluded.

### Procedures

Eligible patients underwent screening consisting of physical examination, laboratory evaluation, renal imaging, voiding cystourethrogram and UDS. UDSs were performed in a standardized fashion. The cystometrogram component of the UDS was performed using a dual/triple lumen catheter passed per urethra. The bladder was filled via slow technique (10% of EBC ml/min) using normal saline or Cysto-Conray™ (iothalamate meglumine injection). A rectal catheter was used to record abdominal pressure. Electromyography of the external urethral sphincter was analyzed. UDS tracings were analyzed by an outside central reader. Parameters assessed included cystometric bladder capacity and percent EBC. Cystometric bladder capacity was defined as infused volume at voiding contraction, sensation of fullness, urine leakage, intravesical pressure greater than 60 cm $H_2O$ or greatest volume attained during UDS in the absence of any other criteria. Bladder compliance was calculated as change in volume divided by change in Pdet.

Patients underwent laparoscopic visualization of the omentum followed by open harvesting of a 1 $cm^2$ template guided, full thickness bladder biopsy from the apex of the bladder dome (day −60). The biopsy was placed in sterile medium containing gentamicin sulfate and shipped overnight to Tengion in a chilled insulated container. Autologous urothelial cells and smooth muscle cells isolated from the bladder sample were propagated separately in vitro during a period of 5 to 7 weeks and then seeded in a customized bioreactor onto the external (smooth muscle cells) and luminal (urothelial cells) surface of a sterile, cup shaped polyglycolide/polylactide biodegradable mesh scaffold, creating the construct for implantation (see supplementary figure, http://jurology.com/). Predesigned partially spherical constructs based on volume (250, 350 or 450 ml) were available or the investigator could request a custom size if necessary. Construct size selection was based on patient size, pelvic anatomy and EBC for age. The autologous cell seeded biodegradable scaffolds were prepared by Tengion.

Surgical implantation of the autologous cell seeded scaffold (day 0) was performed with patients under general anesthesia. The need for bladder neck surgery to improve outlet resistance was based on preoperative fluoroscopic evidence of an open bladder neck and low leak point pressure on UDS. In these cases a fascial sling was performed with implantation. No other concomitant urological surgical procedures were permitted. The construct was secured to the bladder with absorbable sutures in a "no touch" technique by handling a removable exoskeleton (supplementary figure, http://jurology.com/). Vascularization of the autologous cell seeded scaffold was optimized through mobilization and wrapping of omentum around the construct, with complete coverage achieved in all patients (supplementary figure, http://jurology.com/). Omentum was held in place with suture and Crosseal™ fibrin sealant.

Patients remained hospitalized 10 to 14 days after implantation as a precautionary measure. Fluoroscopic cystography was performed before discharge to exclude urinary extravasation. Bladder cycling via intermittent clamping of the suprapubic bladder tube was initiated on postoperative day 21, starting with 1-hour clamp duration and progressing to 4 hours to promote expansion and regeneration of the neobladder. After 1 week of cycling intermittent catheterization was resumed. Urodynamic and safety evaluations continued on an outpatient basis at 6, 9, 12, 18, 24 and 36 months.