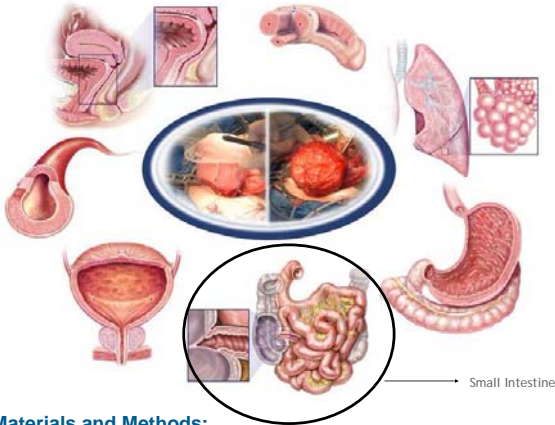


## Introduction:

Current treatment strategies for patients needing esophageal or small intestine (SI) tissue replacements are often associated with adverse effects, which negatively affect quality of life. This study seeks to apply tissue engineering principles to the regeneration of these organs. Previously, these principles have been successfully used to develop implantable cell/biomaterial composites for reconstructing bladder, another tubular organ with laminar wall architecture. In these cases, *de novo* organogenesis was catalyzed following implantation of the composite (aka, construct) and resulted in the regeneration of a functional organ<sup>1-4</sup>.

Figure 1. The bladder is a foundational platform for tubular organ regeneration. (Center, left) Implantation of Tengion's Neo-Bladder Augment (NBA) at the dome of a native bladder during augmentation cystoplasty of a patient presenting with neurogenic bladder secondary to spina bifida. (Center, right) Wrapping of omentum around NBA for vascularization. Examples of laminarily organized tubular organs that may be regenerated using the foundational platform technology demonstrated for the bladder. Top, clockwise: penis, lung, esophagus and stomach, small intestine, bladder, vessel, vagina<sup>1</sup>.



## Materials and Methods:

Biomaterials of different forms and composition were evaluated. Polycaprolactone (PCL) foams of pore sizes 23-300µm were made by a solvent cast-particle leached method as well as polyglycolide (PGA) fibers in various forms coated with poly-DL-lactide-co-glycolide (PLGA). These included coated PGA nonwoven mesh (PGAnw), woven mesh (PGAw) and braided tube (PGAb). Smooth muscle cells were expanded *ex vivo* from rat visceral adipose (Ad-SMC) and used to seed biomaterials for *in vitro* and *in vivo* evaluation. Assessment of this cell-biomaterial interaction *in vitro* was by live/dead staining, cell attachment/proliferation assay (MTS) and scanning electron microscopy (SEM). For evaluation of esophageal and SI regeneration *in vivo*, PGAw and PGAnw were trimmed to 5mm x 4mm rectangular patches and seeded with Ad-SMC to make constructs. PGAb with Ad-SMC was used to make tubular SI constructs. Patch constructs for both esophagus and SI were sutured with non-resorbable suture over a rectangular defect of approximately 5mm x 4mm that was cut into the tissue wall to expose the lumen in adult rats. Tubular SI constructs (10mm length, 4mm I.D.) were used to connect anterior and distal portions of the SI after transverse dissection. Omentum was sutured over the constructs to provide a source of vascularization. Animals were euthanized at time points ranging from 6 days to 20 weeks post-implantation. At necropsy, tissues were harvested, fixed in formalin and paraffin embedded for sectioning and staining with Trichome. The non-resorbable suture marking the defect site allowed comparison of the native and the regenerated tissue.

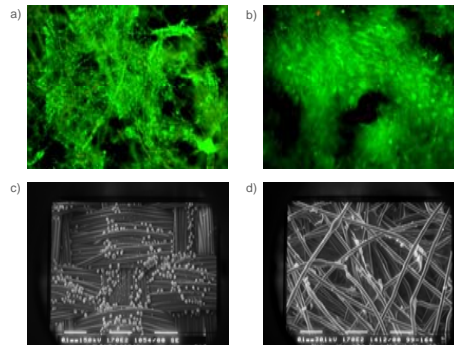


Figure 2: Images of rat Ad-SMC on different biomaterials

Live/Dead staining of AdSMC on:  
(a) PGAnw - 5x and  
(b) PCL foam - 10x

SEM images of AdSMC on:  
(c) PGAw mesh - 170x and  
(d) PGAnw mesh - 170x

Figure 3: Stages in surgical implantation of tubular SI constructs by anastomosis to resected native SI of adult Lewis rat. Left, start of implantation; right, completed anastomosis of construct

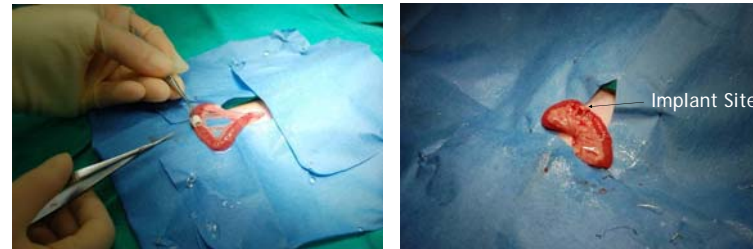


Figure 4. Regeneration of esophageal tissue at 10 weeks post-implantation

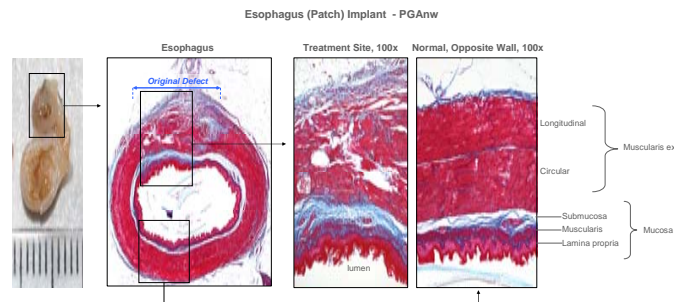
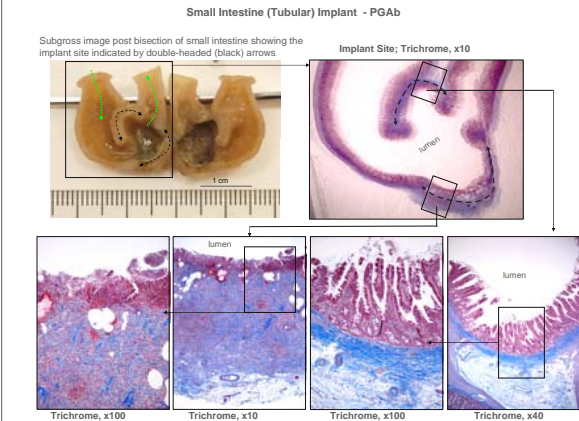


Figure 5: Regeneration of small intestine at 20 weeks post-implantation



## Results:

*In vitro* assays showed all materials had acceptable cell viability, proliferation, and morphology (Figure 2). Lower cell viability and proliferation were seen on the smaller-pore PCL foams (data not shown). *In vivo*, sectioning through the defect sites of the PGAnw esophagus patch construct at 10 weeks post-implant (Figure 4), the PGAw SI patch construct at 16 weeks post-implant (not shown), and PGAb SI tubular construct at 20 weeks post-implant (Figure 5) showed nearly complete reconstitution of mucosal layers characterized by re-epithelialization/regeneration of the luminal surface and submucosa with partial regeneration of the muscularis externa. There was minimal, remnant chronic inflammation, mild fibrogenic response and complete degradation of biomaterial without evidence of calcification.

## Conclusions:

- PGA and PCL biomaterials showed biocompatibility with Ad-SMC *in vitro*. PGA materials were suitable for making esophageal and SI patches and SI tubular constructs
- *In vivo* implantation of PGA patch constructs resulted in esophageal and SI tissue regeneration within 10 and 16 weeks respectively.
- *In vivo* implantation of PGAb tubular constructs resulted in SI tissue regeneration within 20 weeks.

## References:

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