Visceral Hollow Organ Reconstruction: Preclinical Experience with Silk Fibroin Grafts

The Good, the Bad, and the Translational

Joshua Mauney, Ph.D.
Associate Professor of Biomedical Engineering and Urology
Jerry D. Choate Presidential Chair in Urologic Tissue Engineering
University of California, Irvine

World Biomaterials Congress 2020

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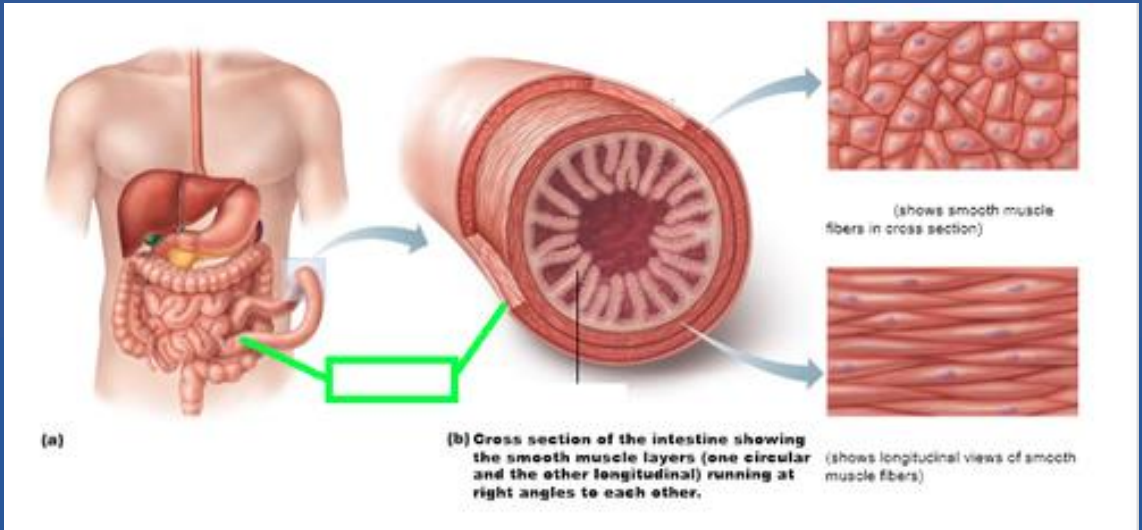
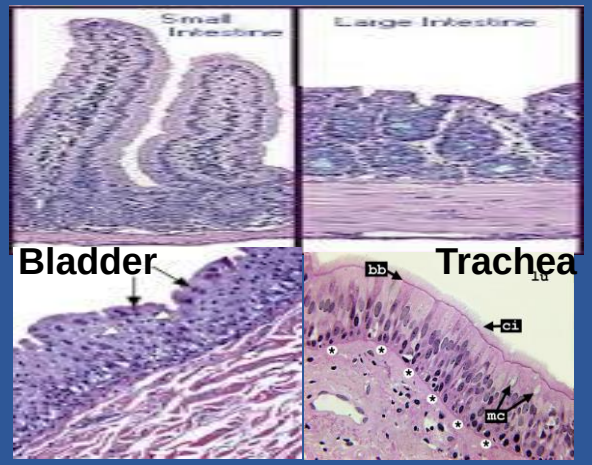
Overview of Visceral Hollow Organs

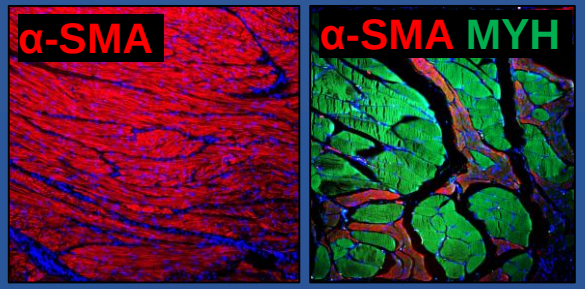
- Organs of the Digestive, Respiratory, and Urogenital Tracts
- Provide Storage and Transport Functions for Body Systems
- Tubular or Elliptical Organs with Specialized Epithelium Lining Muscular or Cartilaginous Walls.



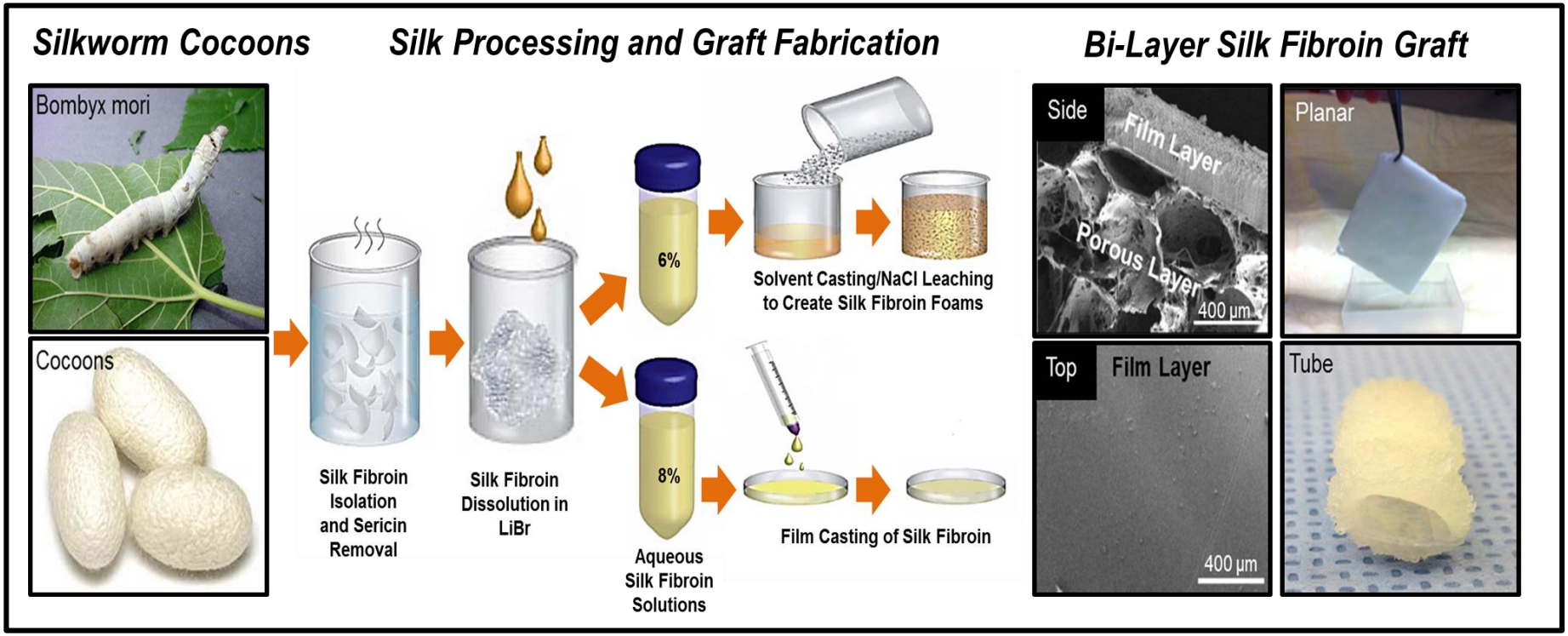
Epithelia



Muscle



Bi-Layer Silk Fibroin (BLSF) Grafts for Reconstruction of Visceral Hollow Organs



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Bladder Diseases and Consequences

Neurogenic Bladder
Spina Bifida,
0.7 per 1000 births;
Spinal Cord Injury,
~250,000 in US

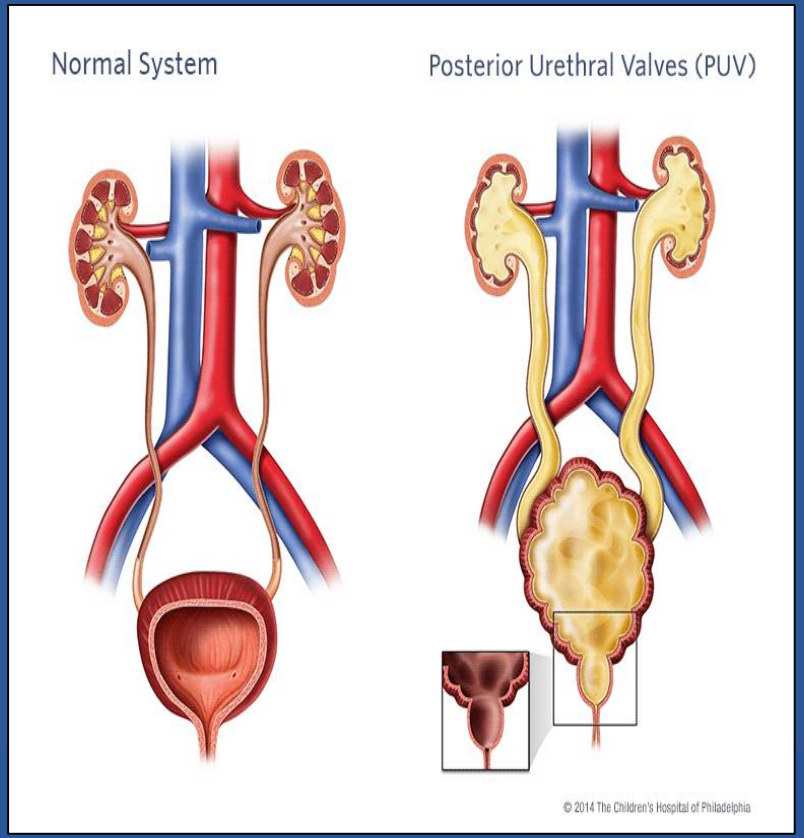
Bladder/Cloacal Exstrophy
1 per 50,000 births

Posterior Urethral Valves
1 per 5,000 male births

Severe Voiding Dysfunction
BPH/LUTS,
~35 million in the US


Exstrophy


Spina Bifida



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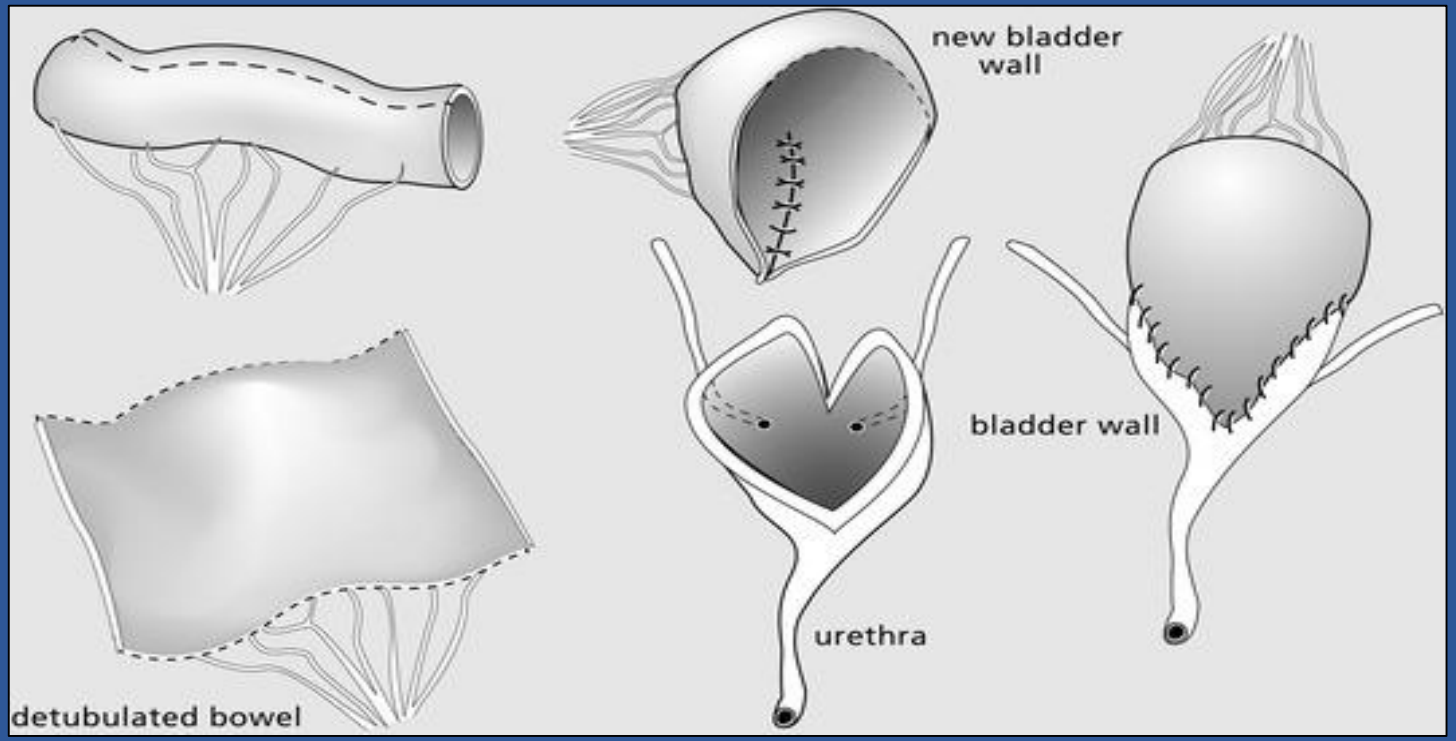
Enterocystoplasty: Current Standard of Care



Complications: chronic urinary tract infections, stones, metabolic abnormalities, bowel dysfunction, malignancy

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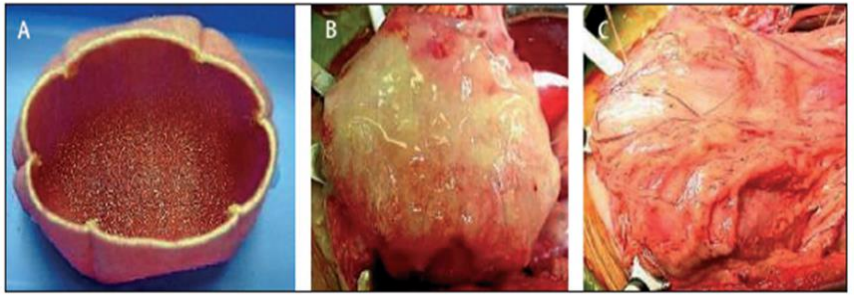
Limitations in Acellular and Cell Seeded Grafts for Bladder Augmentation: Clinical Trials



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

David B. Joseph,* Joseph G. Borer, Roger E. De Filippo,† Steve J. Hodges‡ and Gordon A. McLorie

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

0022-5347/14/1915-1389/0
THE JOURNAL OF UROLOGY®

Bladder augmentation with small intestinal submucosa leads to unsatisfactory long-term results

M. Schaefer [a,*], A. Kaiser [b], M. Stehr [a], H.J. Beyer [a]

Conclusion: Bladder augmentation with SIS in humans failed to fulfill the hopes raised by animal studies. Due to the insufficient increase in bladder compliance and therefore failure to accomplish sufficient protection of the upper urinary tract, bladder augmentation with SIS cannot be recommended as a substitute for enterocystoplasty.

Journal of Pediatric Urology (2013) 9, 878–883

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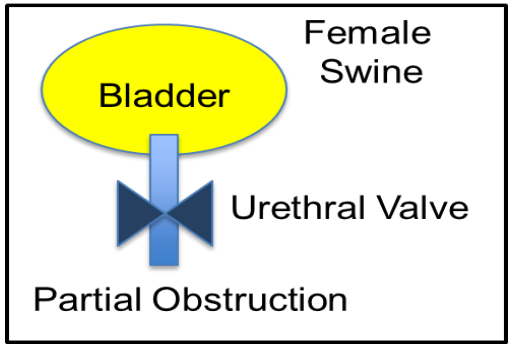
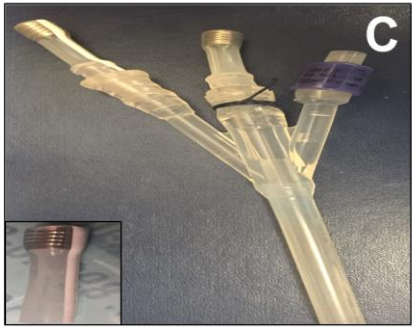
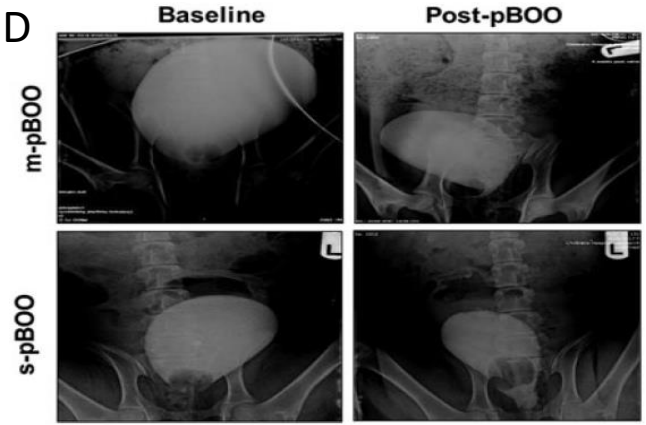
Porcine Partial Bladder Outlet Obstruction (pBOO) Model

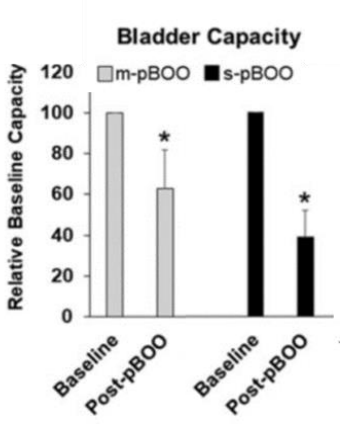


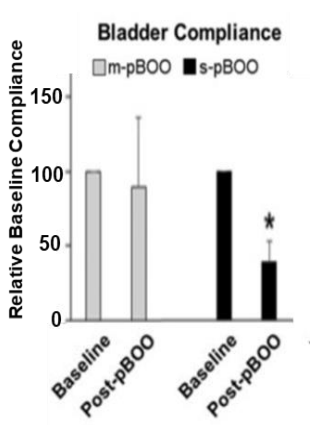


Acute and Chronic pBOO
Mild pBOO , 35 cmH20
Severe pBOO, 70 cmH20

Normal Bladder Resting Pressure
20 cmH20







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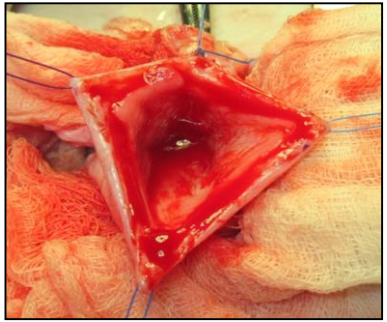
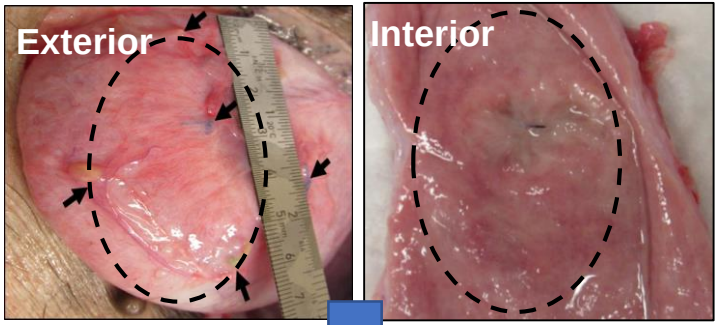
Bladder Augmentation with BLSF Grafts in a Porcine pBOO Model

Bladder Defect

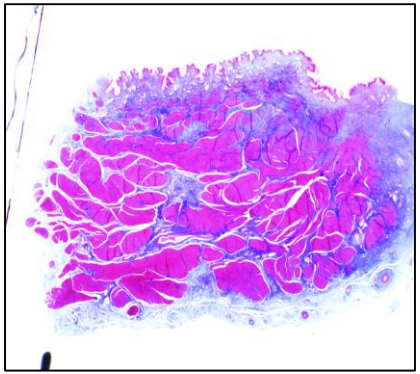


Graft Implantation

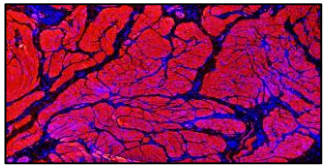
New Bladder Tissue (3 months)



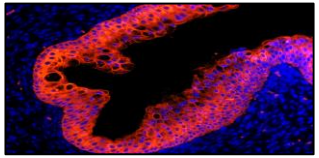
Cross-section of New Bladder Tissue



Muscle



Epithelium



Post-pBOO

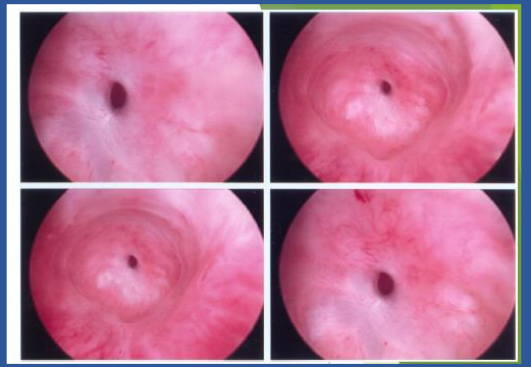
Repair (3 months)

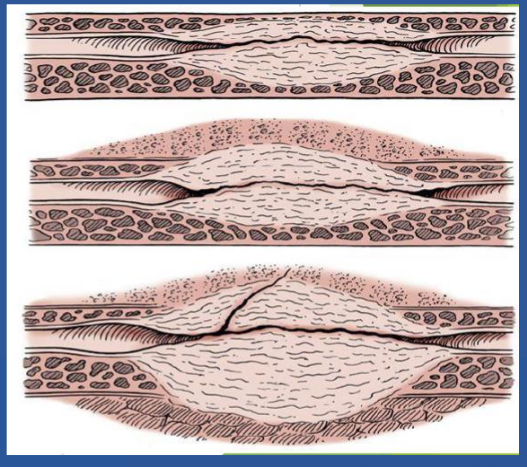
100% Increase in Bladder Capacity over pBOO
330% Increase in Bladder Compliance over pBOO

Tissue Eng Part A. 2018 Oct 26.

Urethral Stricture Disease

- A urethral stricture is scarring in or around the urethra that narrows or blocks urine flow.
- Urethral strictures can result from trauma (straddle injury), infection (STD), and chronic inflammation (lichen sclerosus).
- Relatively common disease in males (~400 per 100,000) with increased incidence after 55 years of age.
- 1.5 million outpatient visits per year. Complications including stones, incontinence, infertility, and renal damage.



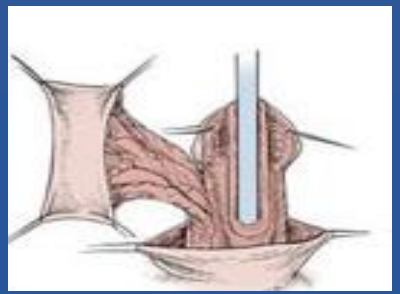


Gallegos MA & Santucci RA. Advances in urethral stricture management. *F1000Research* 2016, 5:2913.

Surgical Strategies for Urethral Repair

- Endoscopic approaches for urethral stricture repair
  - Dilation or incision (cold knife internal urethrotomy)
  - 100,000-235,000 procedures performed annually in the US*
  - Success rate of dilation is low and typically unsuccessful for >1 cm strictures
  - Repeat internal urethrotomy offers no chance of cure after 3rd treatment or restricture in 3 months.

- Open Urethroplasty
  - Approach based on length and severity of the defect
  - End to end anastomosis (stricture) versus onlay urethroplasty with autologous tissue grafts (stricture and hypospadias)
  - Treatment limited to highly specialized centers, ~2500 procedures in the US annually

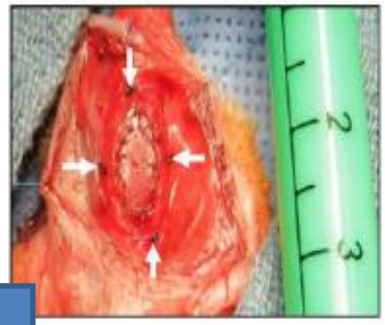


*Extrapolated from: Blaschko SD, et al. Trends, utilization, and immediate perioperative complications of urethroplasty in the United States: Data from the national inpatient sample 2000-2010. *Urology* 2015, 85:1190.

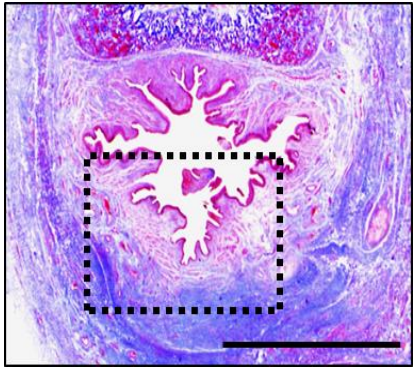
Preclinical Trials for Urethral Reconstruction

Rabbit Stricture Model

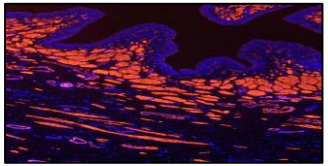
Urethral Implantation



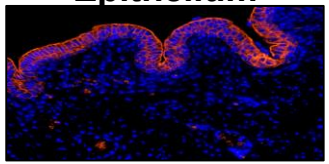
Cross-section of New Urethral Tissue



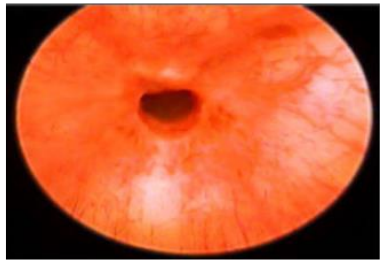
Muscle



Epithelium



Stricture



Repair (3 months)

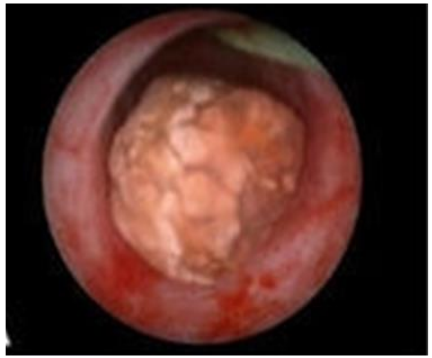
J Surg Res. 2018 Sep;229:192-199.

Lessons Learned from the Urinary Tract Reconstruction

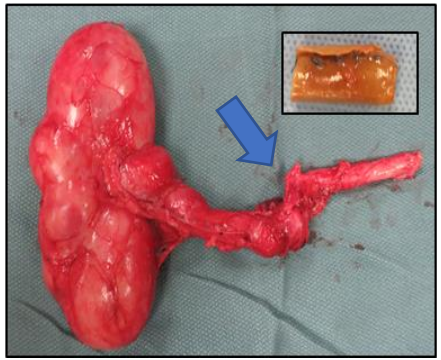
Incomplete Degradation

Stone Formation/ Obstruction

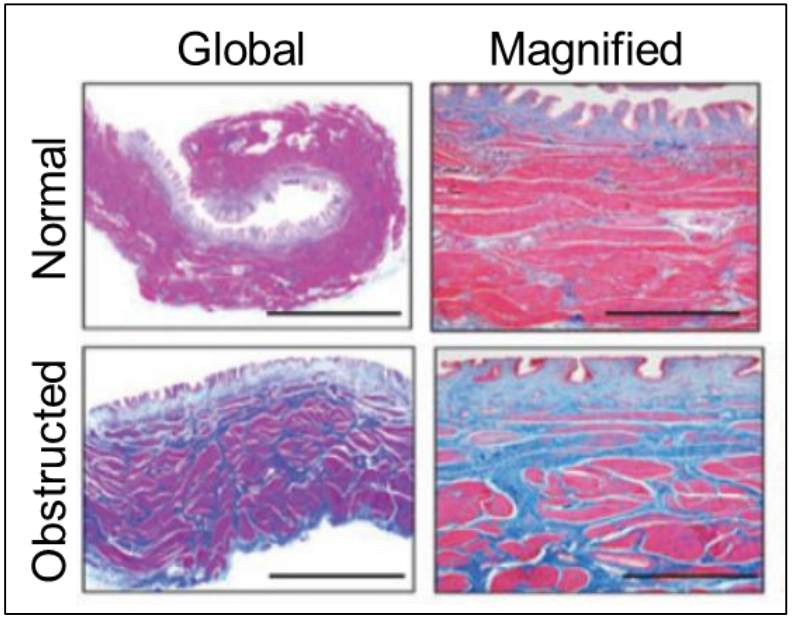
Bladder



Ureter



Persistent Fibrosis

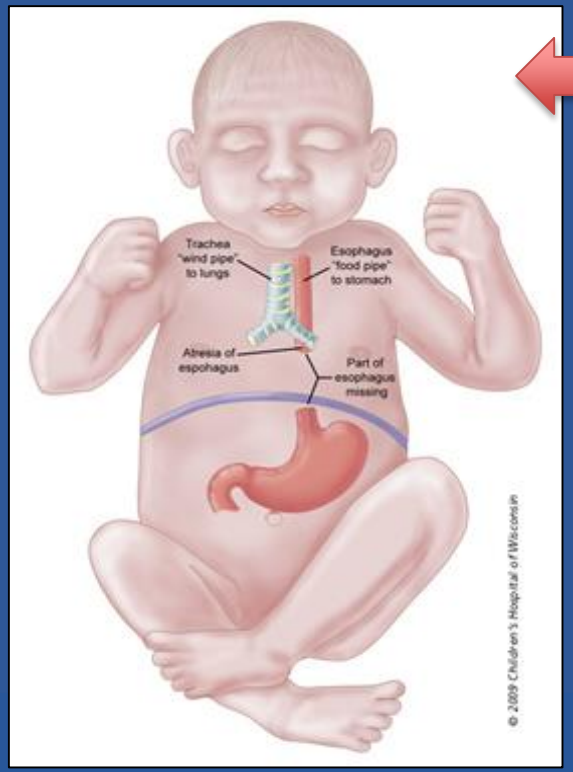


Next Generation Prototypes

Enhanced Degradation Kinetics

Anti-fibrotic Drug Delivery Capacity

Esophageal Diseases and Prevalence

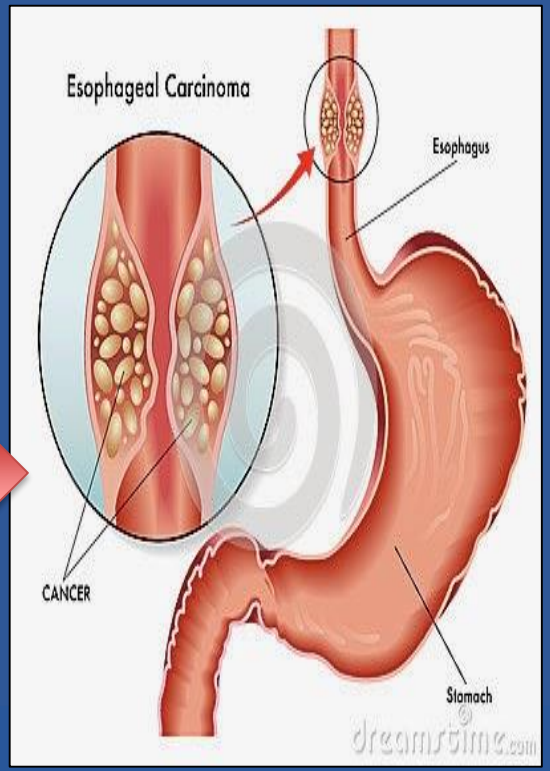


Atresia/TEF
1 in 4425 births

Strictures
23% of patients with reflux

Esophageal Cancer
6th leading cause of cancer death

Barrett's Esophagus
20% of patients with reflux



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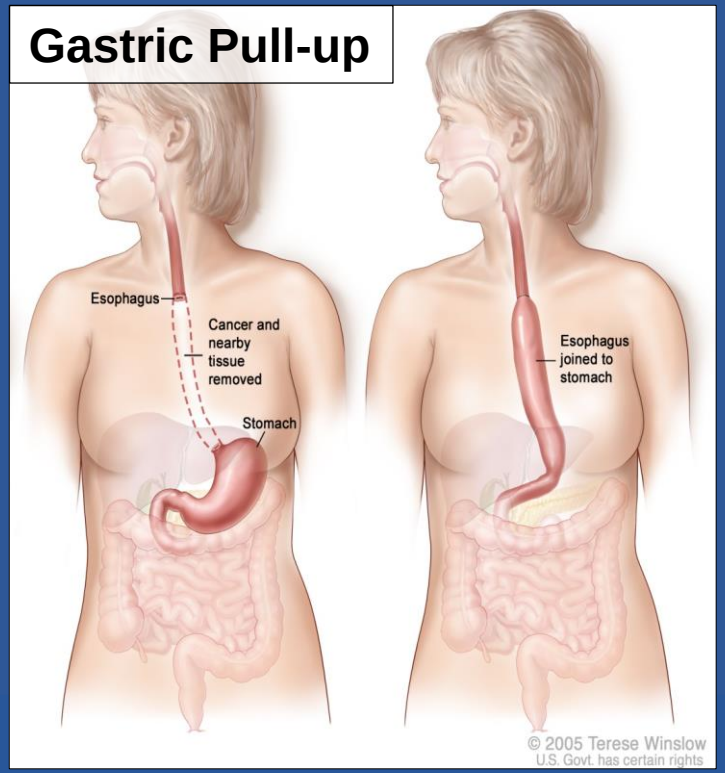
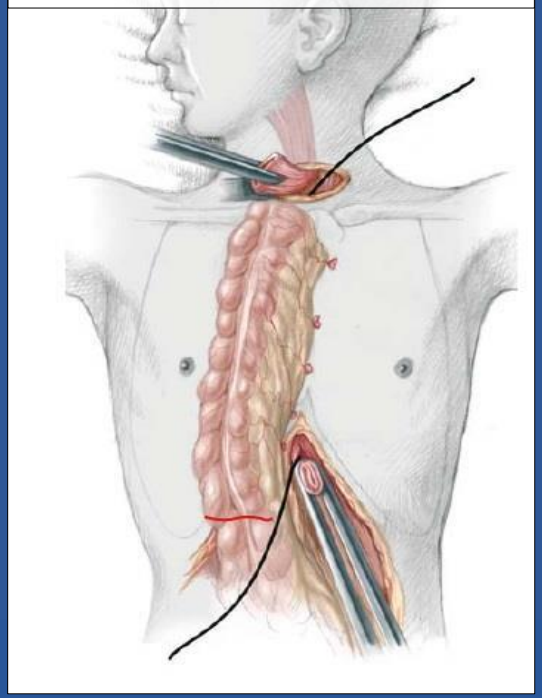
Current Treatment Options and Complications

Gastric Pull-up



Colonic Interposition



- **Anastomotic leakage** *(12-29%)*
- **Strictures** *(19-53%)*
- **Dysmotility and dysphagia** (*5-25%)*
- **Donor site morbidity** *(26-55%)*
- **Death** (*3-6%)*

~700 procedures/year in US

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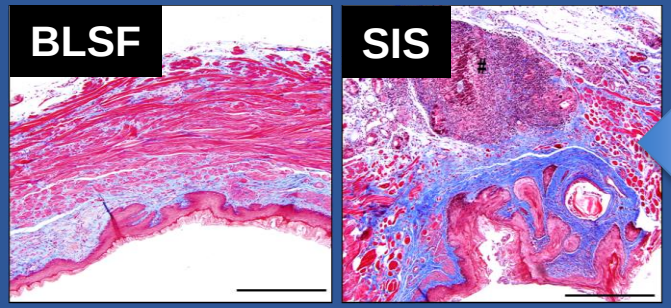
Performance of BLSF Grafts in Animal Models of Esophageal Repair

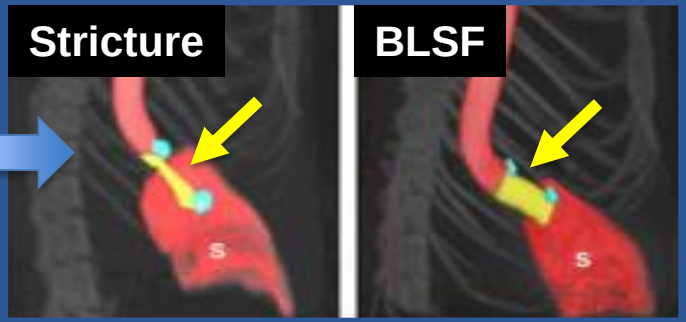
Onlay Esophagoplasty



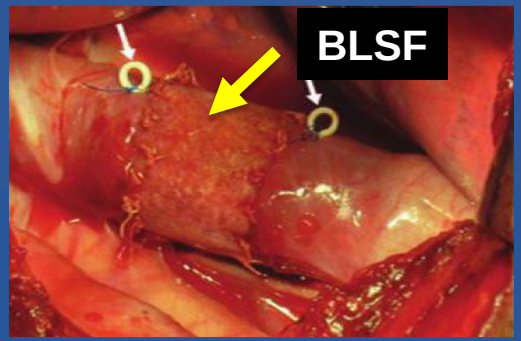
Rat Models

Algarrahi et al., 2015
Algarrahi et al., 2018a

Stricture Reconstruction



Onlay/Tubular Esophagoplasty

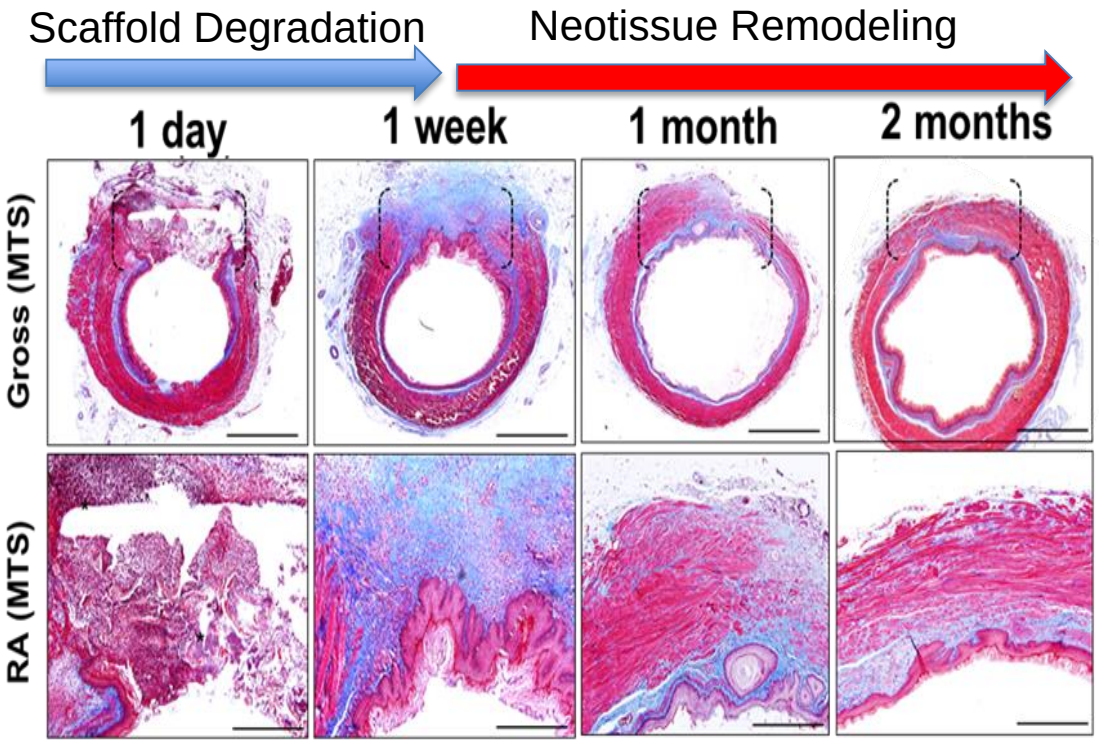


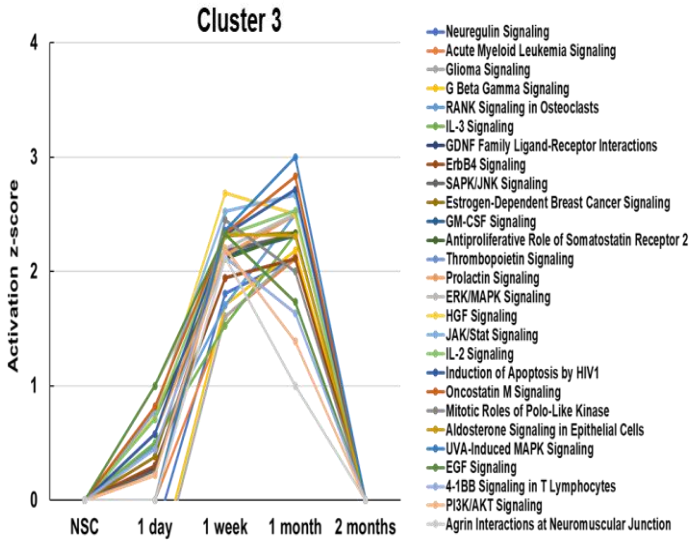
Swine Models

Algarrahi et al., 2018b
Gundogdu et al., 2020

BLSF Repair- 3 months

Understanding Mechanisms of Neotissue Remodeling and Identifying Scaffold Independent Control Points are Key to Maximizing Functional Performance





Rat Onlay Esophagoplasty

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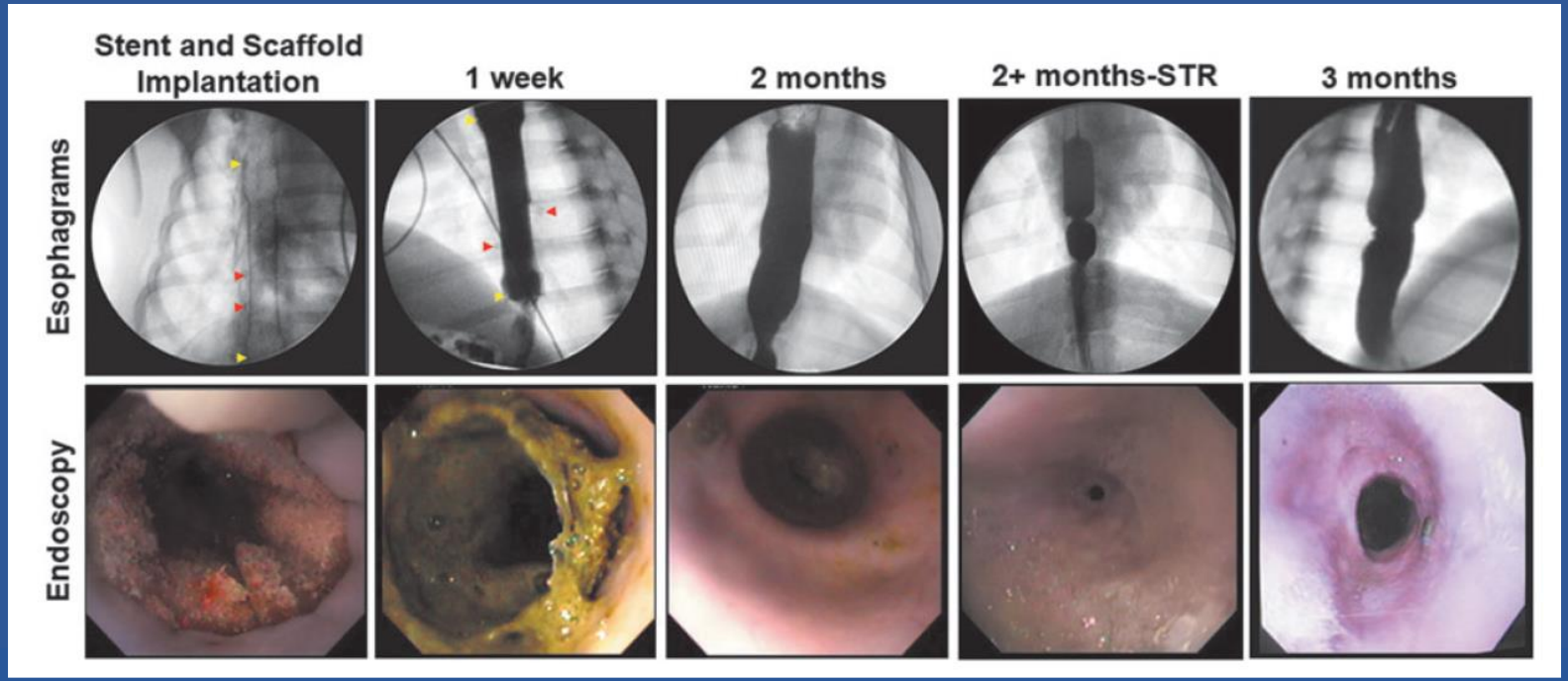
Transient Stenting is Necessary to Support Remodeling of Tubular BLSF Grafts



Transient Stenting for 2 months reduced the rate of esophageal strictures from 100% to 60%

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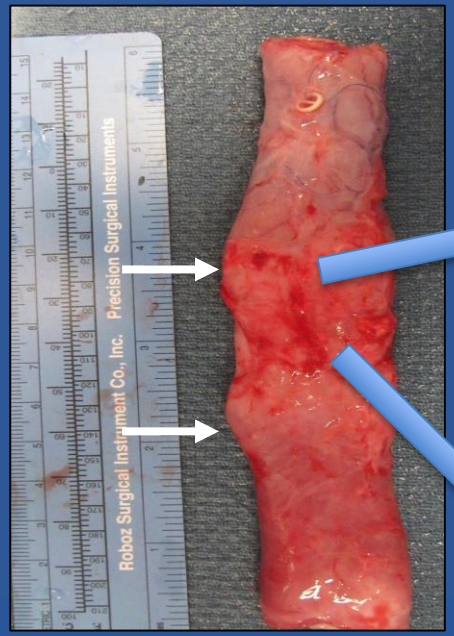
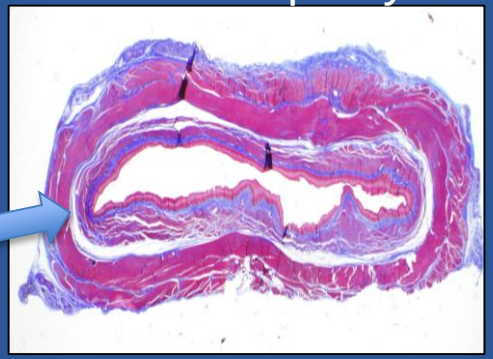
Not all implant sites are created equal and regeneration is often heterogeneous

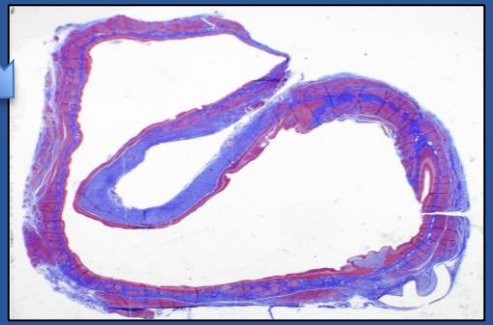


Tubular Esophageal Implant

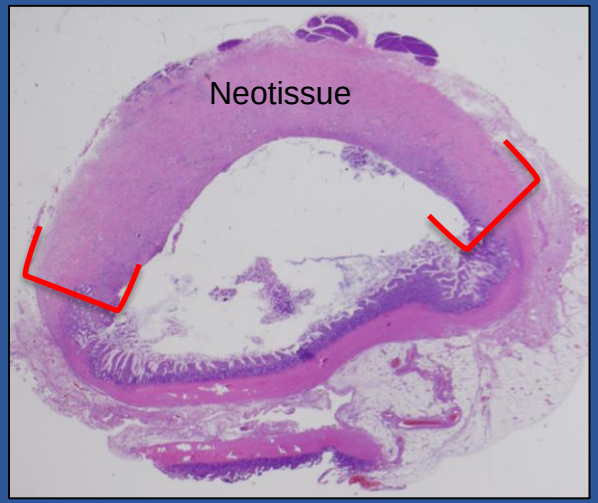
Graft Periphery



Graft Center



Rat Onlay Ileoplasty
2 months



Scar Tissue Formation

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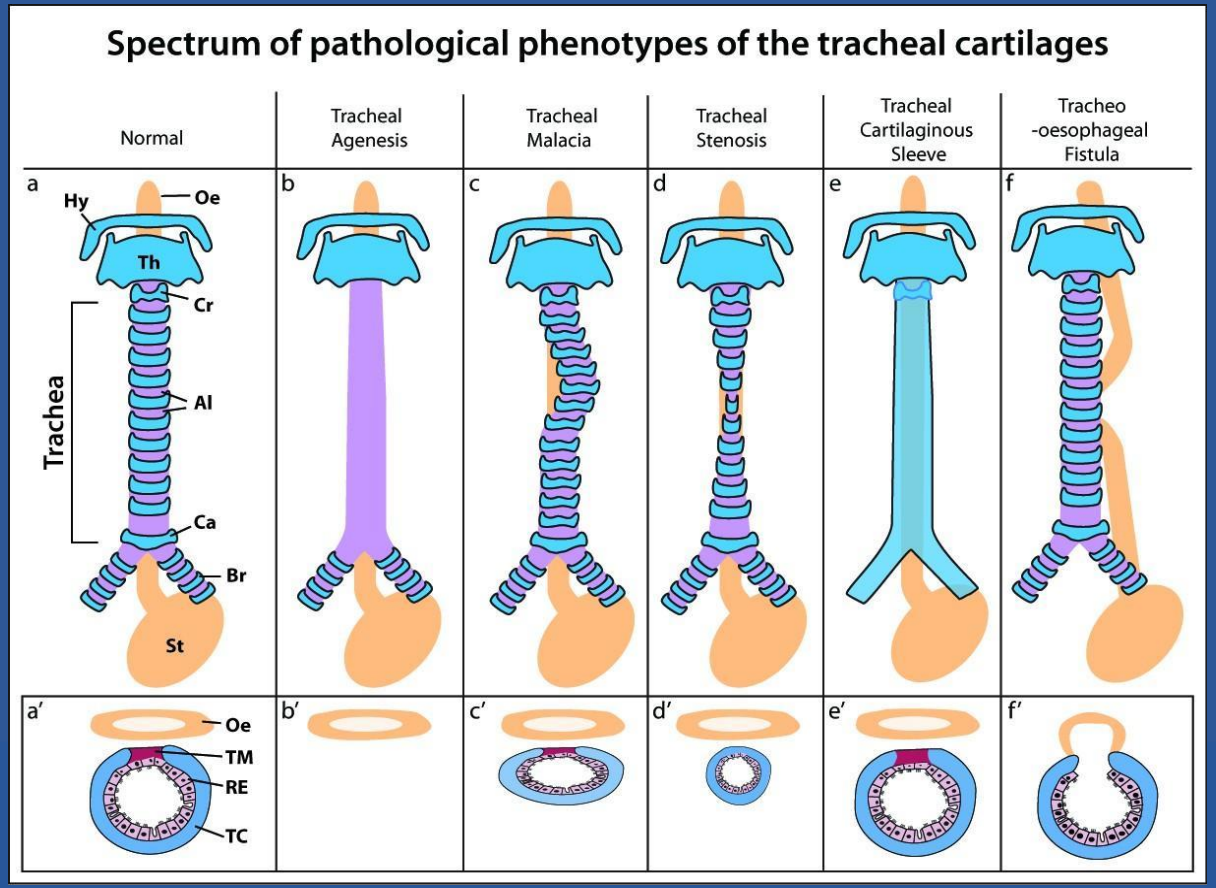
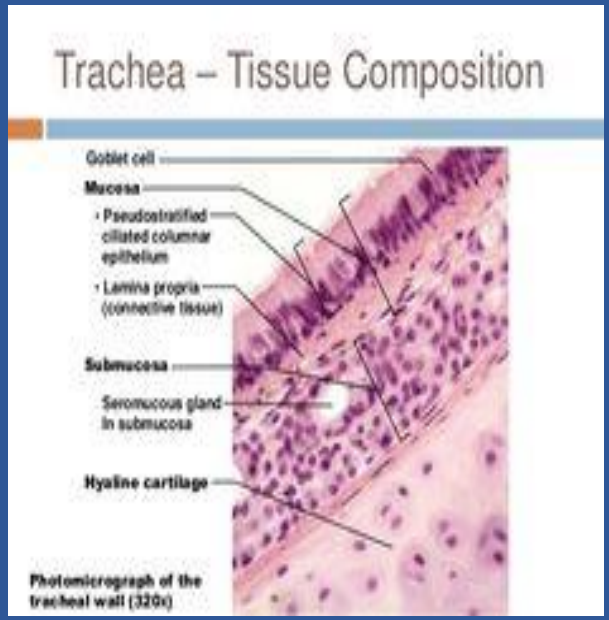
Pediatric and Adult Tracheal Diseases





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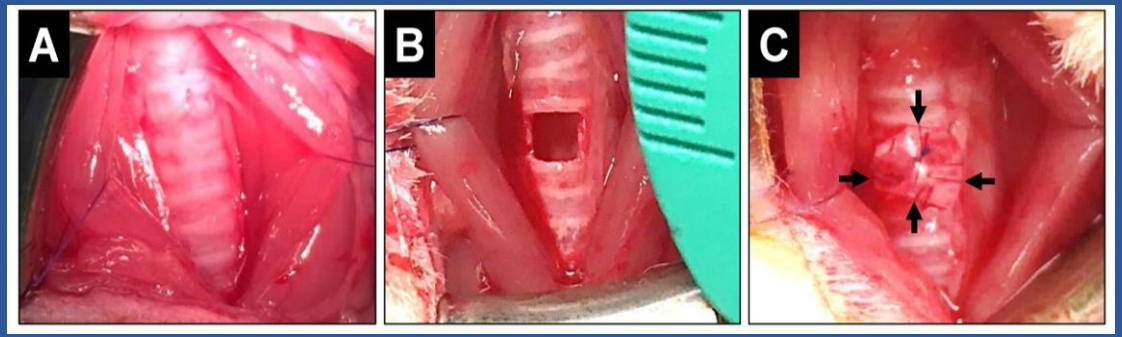
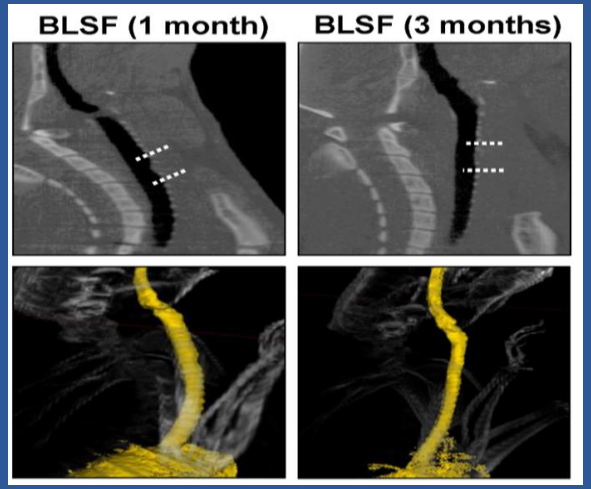
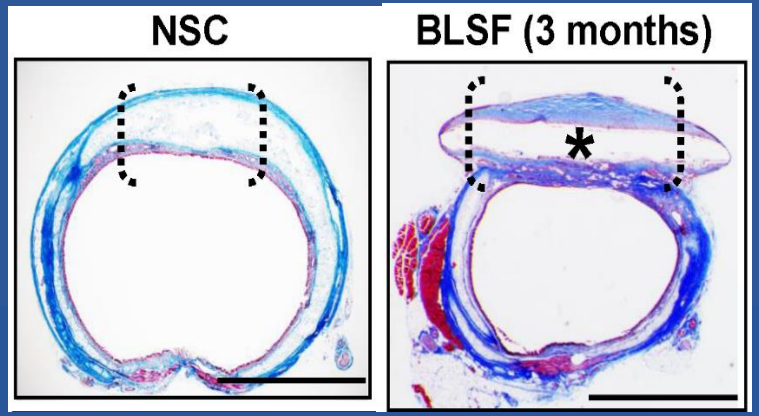
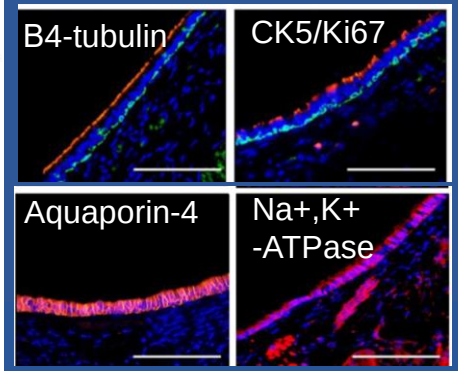
Rat Onlay Tracheoplasty with BLSF Grafts: Success and Challenges









Next Generation Prototypes
Enhanced Degradation Kinetics
Improved Cartilage Formation

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Conclusions

- BLSF grafts are capable of supporting the formation of innervated, vascularized tissues across multiple preclinical models of hollow organ reconstruction.

- Validation of silk fibroin grafts in preclinical models mimicking patient pathology is necessary to optimize functional performance.

- Enhanced control of in vivo scaffold degradation, improved anti-fibrotic properties, and increased understanding of signaling mechanisms responsible for neotissue formation is crucial in developing translational matrix prototypes.

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Acknowledgements

Project Team
Gokhan Gundogdu
Duncan Morhardt, MD, PhD
Ali Hashemi Gheinani, PhD
Khalid Algarrahi, MD
Xuehui Yang, MSc
Kyle Costa, BSc
Cinthia Galvez Alegria, MD

Collaborators
David Kaplan PhD
Carlos Estrada MD
Jaime Landman MD
Rosalyn M. Adam, PhD
Wei Yang, PhD

NIDDK

NIBIB

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