3D Printed Patient Specific Medical Devices: There is a Paradigm, but is there a Path?

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Acknowledgments & Collaborators

- Glenn Green, MD - Tracheal splint; CPAP; Ear/Nose; Fetal Facial Model
- Robert Morrison, MD- tracheal splint, CPAP, Fetal Facial Model, Ear/Nose
- Susan Garetz, MD; Helena Schotland, MD - CPAP collaborators
- David Zopf, MD - tracheal splint, Ear/Nose
- Kyle VanKoevering, MD – CPAP and Fetal Facial Model
- Sean Edwards, MD, DDS - Craniofacial reconstructive surgery planning
- Richard Ohye, MD – tracheal splint (surgery)
- Marc Nelson, MD – tracheal splint(referring)
- Maria Torres, MD; George Mychaliska, MD, Majorie Treadwell MD, Sanjay Prabhu MBBS – Fetal Facial Model
- Khaled Kashlan - CPAP
- Colleen Flanagan - Splint SLS manufacture
- Supported by the NIH/NIAMS R01 AR060892, NIH/NIDCR R01 DE0133197, NIH/NICHD R21 HD076370 and a MICHR grant

Outline

- The Paradigm of 3D Printed Patient Specific Medical Devices (PSMD):
  - Patient Specific Design & Simulation
  - 3D Biomaterial Printing
- 3D Printed PSMD: Examples of the Paradigm
  - 3D Printed Tracheobronchal Splint
  - 3D Printed Platforms for Regenerative Medicine
- 3D Printed PSMD: Is there a Path?

Note: this talk will focus primarily on clinical translation of pediatric devices

The Paradigm of 3D Printed Patient Specific Medical Devices (PSMD)

3D Printed PSMD: The Paradigm

Clinical Need

↓

Patient Data:
Photo/Scan, CT/MRI/US

↓

Patient Specific Design/Simulation:
Patient Specific, Multiscale/function

↕

Fabrication:
Multi-Material, Multi-modality – AM/Microfab

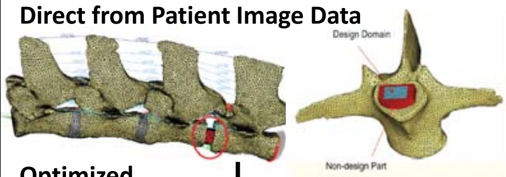
↓

PSMD
Designed Procedure, PSMD w/wo Biologics

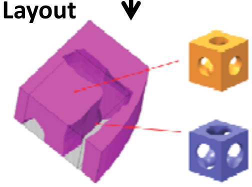
CONCEPT TO CLINIC

Patient Specific Anatomic *plus* Functional Design

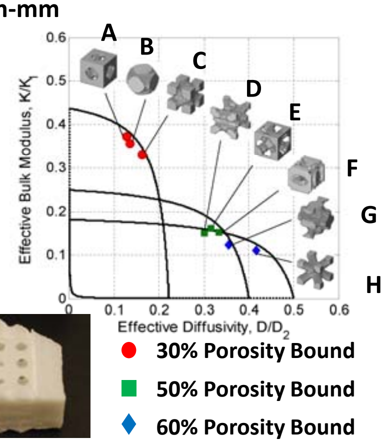
***Global Anatomic Design*: mm-cm**
Direct from Patient Image Data



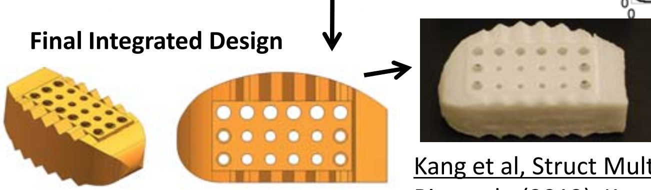
Optimized Density Layout



Porous Architecture Design:
Topology Design/Optimization for mechanical/mass transport properties (separate image data): μm-mm



Final Integrated Design



Kang et al, Struct Mult Opt, (2010), Kang et al, J. Biomech, (2012), Kang et al, J. Biomech Eng,(2013

Laser Sintering of Implants/Scaffolds

- PCL tracheal splint fabricated by laser sintering

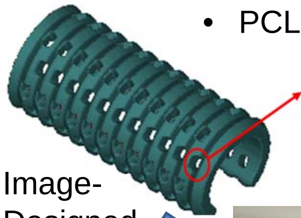
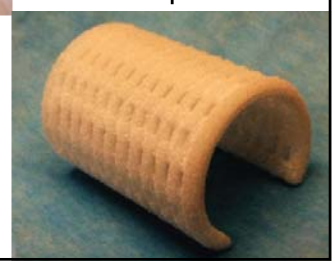


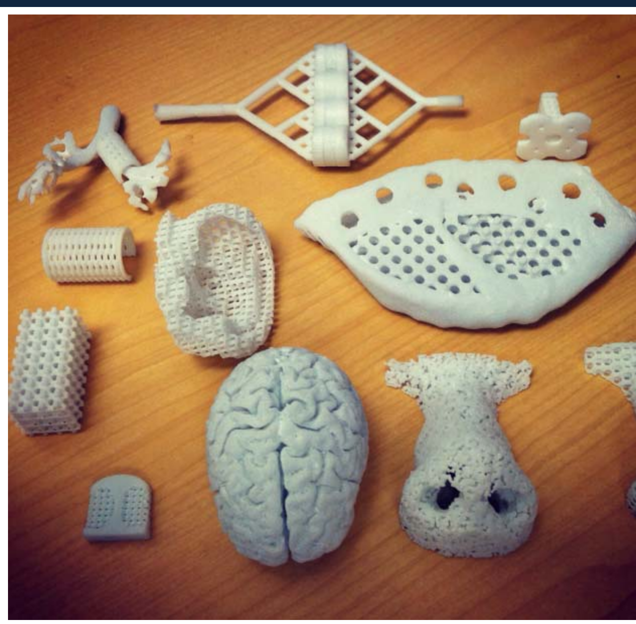
Image-Designed Implant

PCL Laser Sintering

Final Manufactured Implant



PCL Implants/Devices by Laser Sintering



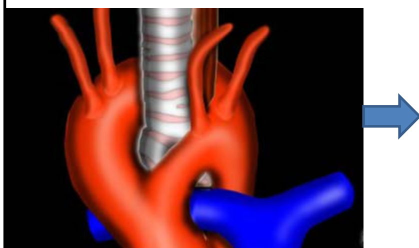
Technical issues for 3D Printing PSMD

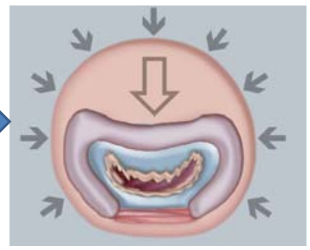
- **Design for 3D Printing: Anatomic geometry, porous structures, design for printing feature size; broader characterization of nonlinear, viscoelastic tissue properties as design targets for FDA design control**
- **Pediatric Specific Design: Account for Growth through design & bioresportion -> need to characterize and model tissue growth**
- ***Multiple, Tissue-like materials: a *range* of printable materials that mimic tissue properties and are biocompatible**
- **Processing biomaterial into appropriate form for machine (i.e. filament, viscosity, powder size, photopolymerizable)**
- **Post-processing surface finish, support removal, combine with microfab (like electrospinning) functionalization**
- **Quality control: geometry, mechanical properties, fatigue/durability**

3D Printed PSMD: Examples of the Paradigm

Tracheobronchalmalacia (TBM) in Humans

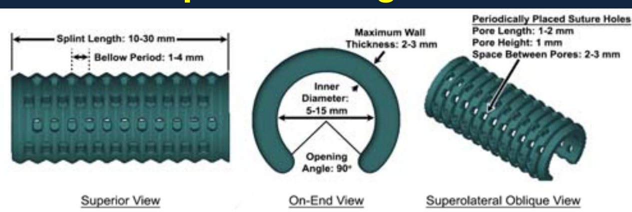
- Compression of airway, typically by malformed vascular structures
- Complete collapse on expiration
- Currently treated by tracheostomy/ventilators 1-2 years
- Significant complications, including death
- Stents have failed in children; Implanted splints external to airway found to give better results, but “Jury Rigged” in the OR
- Need for patient specific implants due to different defect geometry (length, diameter, number)

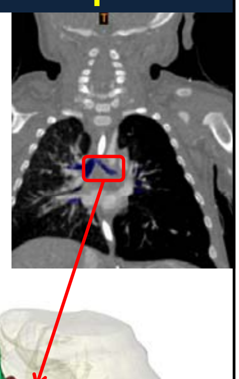




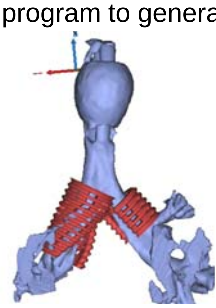
1st Patient Etiology

Patient Specific Image-Based Design for Splint

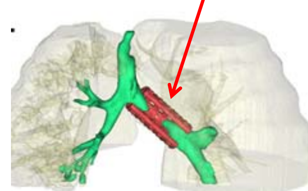




- MATLAB program to generate design w suture holes

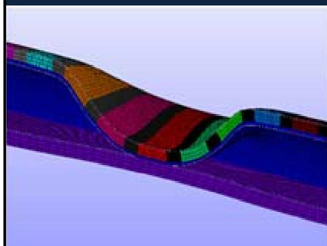


2nd Patient
2 splints, one with spiral design to accommodate both splints



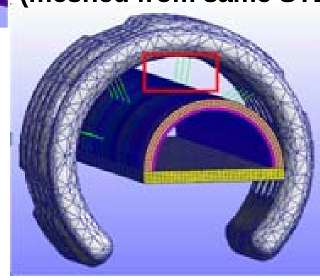
- Input parameters MIMICS Digital Model
- Fit splint to patient model in MIMICS
- Perform finite element analysis: compression, bending, opening (growth)

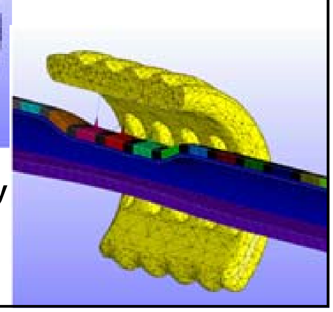
Simulating TBM Collapse & Rescue by Splint



Nonlinear Model of Airway Collapse (hyperelastic tissues & lumen collapse contact

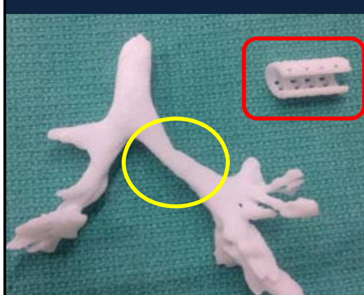
Model of surgical intervention including splint (meshed from same STL used for AM) & sutures





- **Simulation showing splint creating patent airway**
- **Model used to simulate patient outcome from exact device manufactured by AM**

Patient Specific Planning & Implantation for Splint



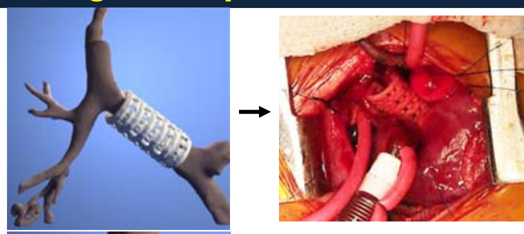
Model Showing Collapse (Yellow); Splint (Red)

Splint Fit on Printed Airway (Red)

Splint Implanted in Patient

- Printed Patient Trachea model for Implant Sizing
- Splint Fitted to Model in OR before Implantation
- Example of Surgical Planning combined with Patient Specific Implant

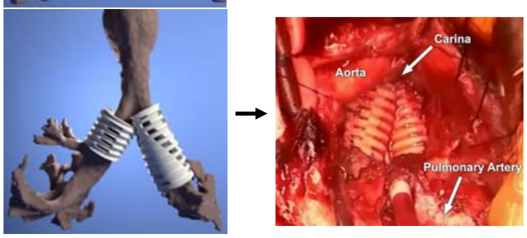
Design & Implantation of Patient Specific Splints



<u>Patient 1:</u>

Left Bronchus;

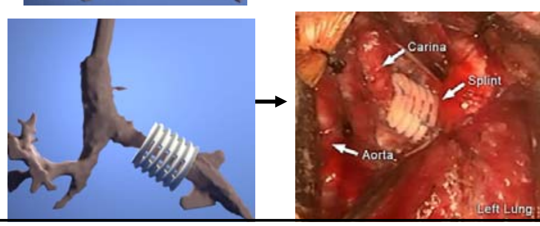
IRB Approval,
Emergency through FDA
NEJM (2013), 368:2043-2045.
38 months post-surgery



<u>Patient 2:</u>

Bilaterial Bronchi;

IRB Approval,
Emergency through FDA
15 months post-surgery



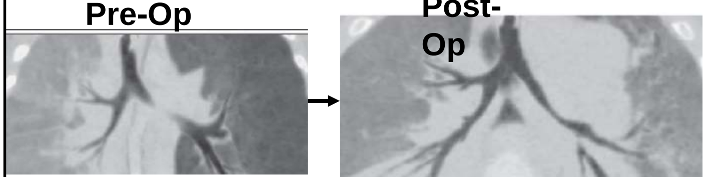
<u>Patient 3:</u>

Left Bronchus;

IRB Approval,
Emergency through FDA
13 months post-surgery

Pre-Op and Post-OP Patency

Pre-Op Post-Op

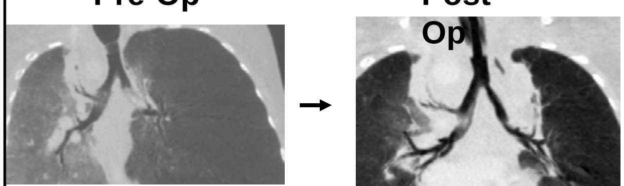


<u>Patient 1:</u>

Left Bronchus;

Exhalation Scans

Pre-Op Post-Op

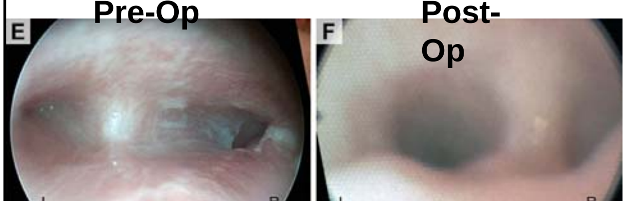


<u>Patient 2:</u>

Bilaterial Bronchi;

Exhalation Scans

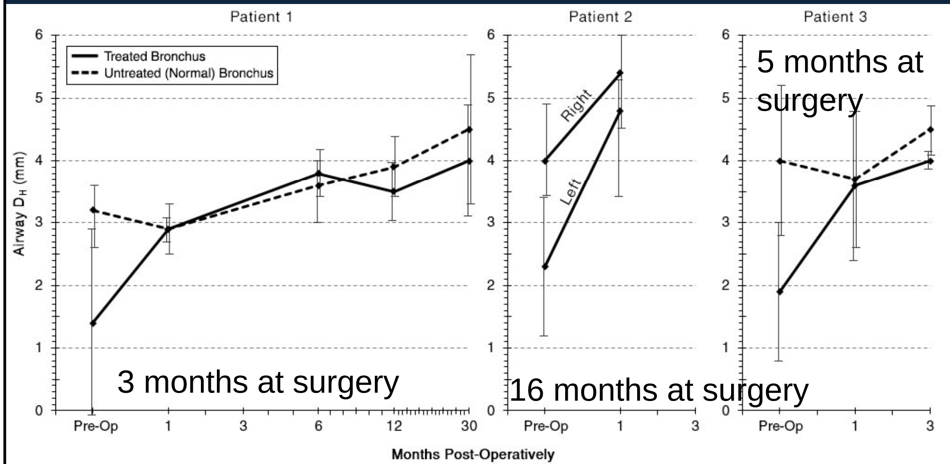
Pre-Op Post-Op



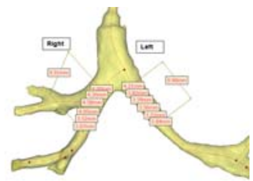
<u>Patient 3:</u>

Bronchoscopy

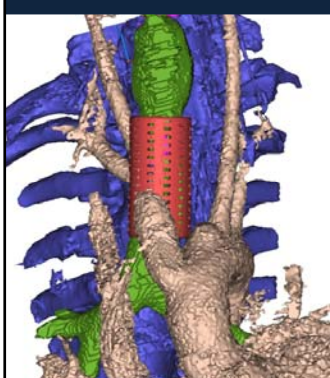
Bronchial Growth in Patients

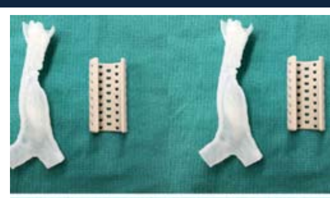


Hydraulic Diameter Measures Averaged along Bronchus in MIMICS



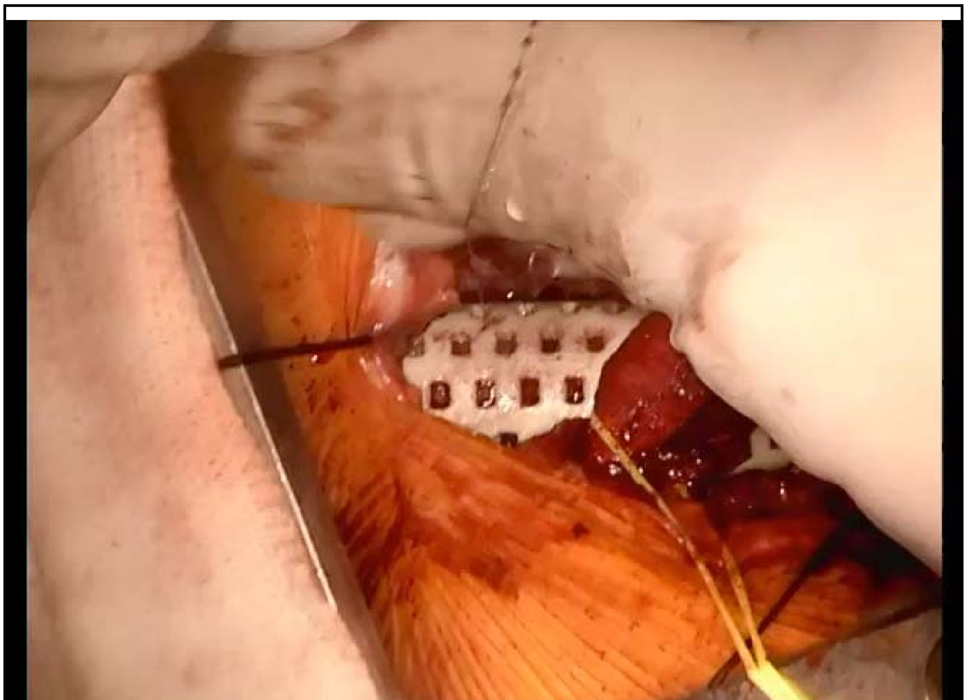
Permanent PEKK Splint for Teenager



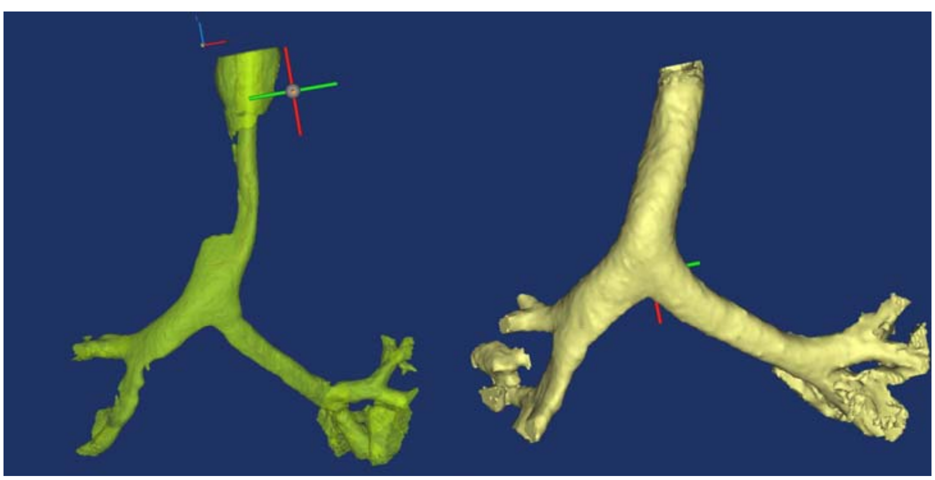


- **14-year old TM**
- **Need permanent splint**
- **Design from Image**
- **Work with OPM who printed PEKK**

Outcome	Pre-Op	Post-Op (2 months)	P Value
Hydraulic Diameter	**9.0 ±1.4 mm**	**12.1 ±1.0 mm**	**<0.0001**
Area	**82.0 ±26.1mm^2**	**134.3 ±17.1mm^2**	**<0.0001**



3D Airway Reconstruction Pre/Post Surgery



Scaffolds as Modular *Platform Systems*

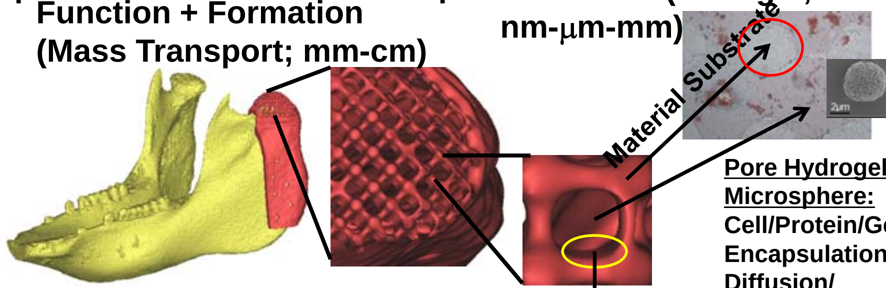
Scaffolds as modular platform systems: adaptable to different clinical scenarios, with sliding scale of complexity (Hollister/Murphy, Tissue Eng.C, 2011)

Topology Design + AM
Controlled architectures enable rigorous tests of design hypotheses

Function + Formation (Mass Transport; mm-cm)

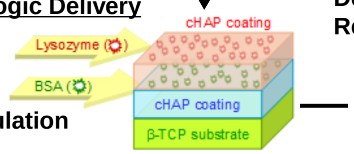
Post-Fab Fluid Based Functionalization

Formation (Biologic; nm-μm-mm)



Pore Hydrogel/ Microsphere:
Cell/Protein/Gene Encapsulation – Diffusion/ Degradation Release

Interface Layers for Biologic Delivery
- CaP Nanoscale coating
- Electrostatic Binding
- Chemical Conjugation
- Layer-by-Layer Encapsulation

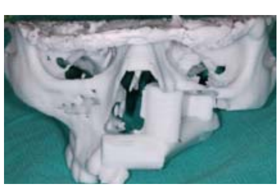


μsphere/ Layer cartoon Courtesy Bill Murphy

Modular Fabrication & Post-Fab Functionalization

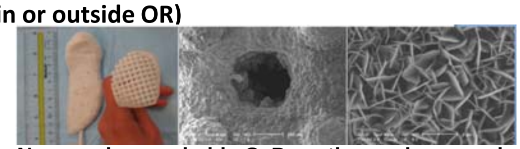
Fabrication: AM
Modular & Patient Specific

In OR modular scaffold

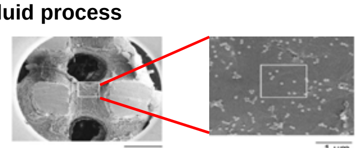


Patient Specific PCL Scaffold

Post-Fab Functionalization: Fluid & Gas Approaches (in or outside OR)



Nanoscale resorbable CaP coating on large scale scaffolds – protein/cell delivery (Bill Murphy; Biomaterials (2012); Scientific Reports (2013)) – SBF fluid process

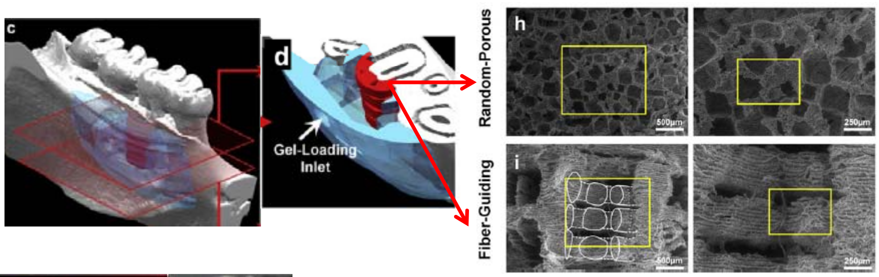


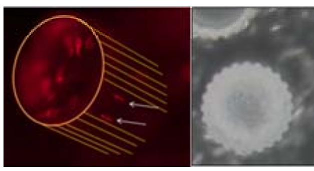
Direct attachment of viral vectors to PCL scaffolds – CVD Gas process Joerg LaHann, Paul Krebsbach Biomaterials (2009)

IntraOR: Cell Loading (left), BMP2 Loading (right)

Designed Oriented Pores Enhance PDL formation

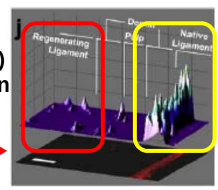
- Designed scaffold compartments for bone (BMP7) and PDL (hPDL cells)
- Designed oriented PDL interface pores vs random PDL interface pores
- More oriented ligament structure oriented pores (Park et al, Biomaterials, 2012)



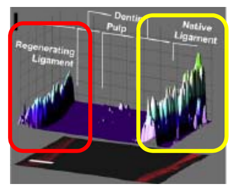


Next Step: MicroFab interfaces to further align PDL cells

PDL (Ligament) Orientation Results 6 weeks

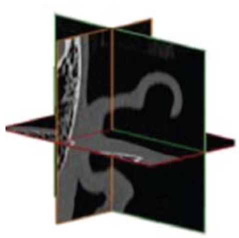


Random (red)
Native: (yellow)



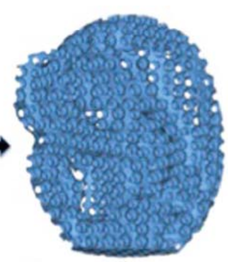
Oriented (red)
Native: (yellow)

Auricular 3D Patient Specific 3D Printed Scaffolds



CT Scan

External Anatomy Design

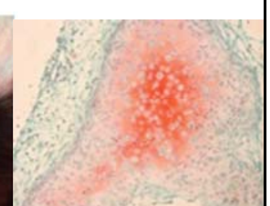


Final Scaffold Design

3D Printed PCL Scaffolds

Scaffolds seeded with 30 million chondrocytes

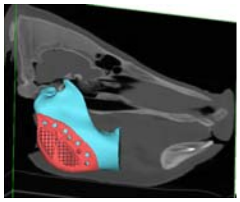
Scaffold Implanted Under Skin in Pig



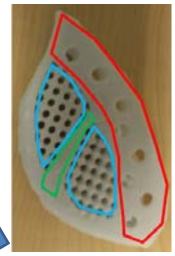
Cartilage Regenerated

Prefabricated Flaps: 3D Designed/Printed Scaffolds/Biologics for Craniofacial Flaps

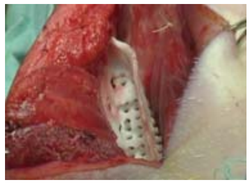
CT Scan & Scaffold Design



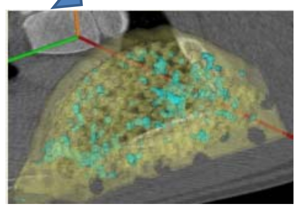
3D Printed PCL Scaffold + 1mg BMP2



3D Printed Scaffold Implanted in Pig Lattissimus Dorsi



4.45cm^3 bone growth (blue) at 5 weeks



Prefabricated Scaffold, Bone, Muscle Completely Vascularized Flap

PSMD: Is there a Path?

PSMD in Pediatrics: the Promise of a Path

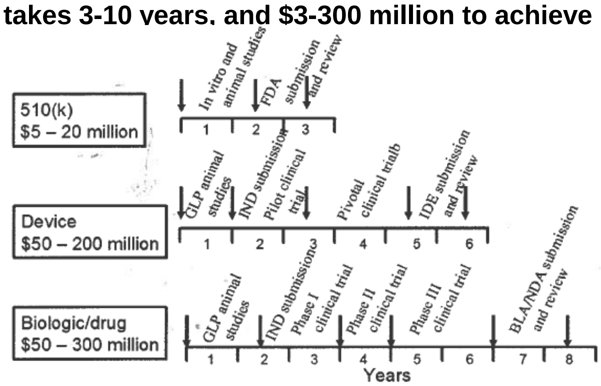
- Pediatric conditions are not commonplace:
  - TBM: 1 in 2200 births, 1500 cases per year in the US
  - Esophageal Atresia: 1 in 3000 births, ~800-1000 cases/year in US

- Pediatric conditions require PSMD for:
  - wide variations in anatomy
  - design for growth
  - simulate patient function,
  - 3D print a range of bioresorbable materials

- 3D Printing allows rapid development and manufacturing of low volume, high customizable, and highly complex devices – perfect for pediatrics

Pediatric PSMD: Facing Regulatory Hurdles

- It takes 3-10 years, and $3-300 million to achieve regulatory approval



From A. Ratcliffe

- Tracheal Splint Pre-Clinical:
  - ISO 10993: ~$600K, 2 years
  - Long Term Fatigue/Degradation: ~$2-3 million, ~ 3 years
  - GLP Large Animal Study: ~$600K
- Tracheal Splint Clinical (Feasibility/HDE):
  - ~ 3-4 years, ~ $5 million

PSMD: View from Academics, a difficult Path

- Pursuing complete clinical translation of PSMD is difficult from an academic environment due to costs and reward structures
- Typical path is to develop technology and license to company – Pediatric colleague noted he “begged” companies to develop device
- Institutions (at least UM) have been reticent to support GMP facilities for 3D printing PSMD
- Funding opportunities are not geared towards to support work associated with regulatory approval of PSMD
  - NIH study sections criticize lack of basic hypothesis driven proposal in PSMD
  - “Translational” funding like Coulter programs don’t fund low market but often high risk devices; TBM Coulter proposal denied at UM due to “low impact” market
- Publishing favors new discovery/technology; not biocompatability or fatigue studies of PSMD needed for translation

Conclusion: PSMD

- PSMD can effectively develop treatments for low volume pediatric cases – improving childrens lives
- We have used PSMD to treat 5 patients with life threatening TBM, 5 patients with custom CPAP – expanding to microtia, ASD, EA
- PSMD with expanded range of biomaterial printing could address more pediatric conditions: the paradigm
- Companies (understandably) find it difficult to pursue low volume, custom pediatric markets
- Academics/Research institutions do not provide a highly conducive environment to pursue clinical translation of PSMD – difficult to fund; institutional support for GMP; rewards not geared to work filling regulatory needs
- Paradigm for PSMD is there, need to find the path