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

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Acknowledgments & Collaborators

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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 Tracheobronchial 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
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

Patient Specific Anatomic plus Functional Design

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

Optimized Density Layout

Final Integrated Design

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

Laser Sintering of Implants/Scaffolds

- PCL tracheal splint fabricated by laser sintering

PCL Laser Sintering

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 & bioreosportion -> 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

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**3D Printed PSMD:**

**Examples of the Paradigm**
**Tracheobronchomalacia (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)

**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 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
Patient 1: 
Left Bronchus; 
IRB Approval, 
Emergency through FDA 
NEJM (2013), 368:2043-2045. 
38 months post-surgery

Patient 2: 
Bilateral Bronchi; 
IRB Approval, 
Emergency through FDA 
15 months post-surgery

Patient 3: 
Left Bronchus; 
IRB Approval, 
Emergency through FDA 
13 months post-surgery

Pre-Op and Post-OP Patency

Pre-Op 
Post-Op

Pre-Op 
Post-Op

Pre-Op 
Post-Op

Patient 1: 
Left Bronchus; 
Exhalation Scans

Patient 2: 
Bilateral Bronchi; 
Exhalation Scans

Patient 3: 
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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-Op</th>
<th>Post-Op (2 months)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydraulic Diameter</td>
<td>9.0 ±1.4 mm</td>
<td>12.1 ±1.0 mm</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Area</td>
<td>82.0 ±26.1 mm²</td>
<td>134.3 ±17.1 mm²</td>
<td>&lt;0.0001</td>
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</table>
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

Post-Fab Fluid Based Functionalization

Formation (Biologic; nm-μm-mm)

Function + Formation (Mass Transport; mm-cm)

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

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)

Modular Fabrication & Post-Fab Functionalization

Fabrication: AM
Modular & Patient Specific

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

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

<table>
<thead>
<tr>
<th>CT Scan &amp; Scaffold Design</th>
<th>3D Printed Scaffold + 1mg BMP2</th>
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<tbody>
<tr>
<td>3D Printed Scaffold Imпланted in Pig Lattissimus Dorsi</td>
<td>4.45cm³ bone growth (blue) at 5 weeks</td>
</tr>
<tr>
<td>Prefabricated Scaffold, Bone, Muscle Completely Vascularized Flap</td>
<td></td>
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**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

- 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 biocompatibility 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