Engineered Tissue “Factories”

to Enable Bench-to-Bedside Translation

Rohan Shirwaiker
Associate Professor, Industrial & Systems Engineering
Associate Faculty, Biomedical Engineering
Director, 3D Tissue Manufacturing Research Team
North Carolina State University
Email: rashirwaiker@ncsu.edu
Tissue “Manufacturing”

- Significant progress in relevant fundamental biomedical sciences not matched by advances in manufacturing science to enable scale-up and scale-out.
- Other industries are evolving towards Industry 5.0, but engineered tissue technology is still striving to make it to 2.0, for the most part.

1995
Massachusetts General Hospital (Vacanti et al.)

2016
University of Tokyo and Kyoto University (Takato and Tsumaki et al.)

https://www.smithsonianmag.com/science-nature/history-lab-rat-scientific-triumphs-ethical-quandaries-180971533/

Engineered Tissues: Clinical Needs

- Congenital Disorders
- Trauma & Injuries
- Chronic Diseases

Pharmaceuticals
Surgical Repair
Grafts & Transplants
Devices & Implants
Engineered Tissue Technology: Proofs of Concept

Able to grow cells onto biomaterials.....

with tissue-specific characteristics.....

in patient-specific 3D geometries.....
Current State of Tissue “Manufacturing”

- Bioinks (Cells + Biomaterials)
- Biomodeling (Imaging → CAD/CAM)
- Bioprinting Process Modalities
Current State of Tissue “Manufacturing”

Biomodeling (Imaging → CAD/CAM)

Bioinks (Cells + Biomaterials)

Bioprinting ≠ Tissue Manufacturing

Bioprinting Process Modalities
High upstream variability leads to more significant downstream disruptions (*bullwhip effect*)

$\Rightarrow$ Wasted resources

$\Rightarrow$ Scheduling issues in subsequent stages of bioprinting and implantation
Example: Downstream Challenges

For quality inspection

For implantation
Vision for Tissue Manufacturing

Modular Scalable Smart Factories for Mass Production of Patient-specific Tissues at Point-of-Care

- Mass production with lot sizes of one
- End-to-end sterile environment with no cross-contamination between lots
- Stochastic processes with high variabilities (pre-dominantly biology driven)
- Process cycle times and production lead times spanning up to several weeks
- Transient properties of living raw material, WIP, and finished product leading to inventory constraints
- 100% inspection
- Continuous process improvement challenging due to regulations

Pn Biopsy

Pn Data

Pn Tissue

Pn Digital Twin
Central QC/QA

- Biopsy
- Sterile coverage
- Tissue-neutral
- Self-contained (matl. hand. + data proces.)
- Reconfigurable
- Autonomous

Vision for Tissue Manufacturing

- Processing on Demand (POD)
- Material Inventory ASR
- Incubation
- Bioprinting
- Tissue Maturation
- Central QC/QA

- P1 tissue
- P2 tissue
- Pn Digital Twin

- Pn Biopsy
- Pn Data
- Waste

- Self-contained
- Sterile coverage
- Reconfigurable
- Autonomous
- Tissue-neutral
Vision for Tissue Manufacturing

Pod#1: Biopsy Processing
- P_n Biopsy
- P_n Data
- Chemicals/Media
- Pod#1 QC/QA
- Waste
- Incubation
- Media/G. Factors

Pod#2: Cell Expansion
- Cell Passaging
- Pod#2 QC/QA
- Incubation
- Media/G. Factors

Pod#3: Bioprinting
- Cell Seeding
- DLP Printing
- Pod#2 Biomaterials
- Extrusion Printing
- Flow Perfusion Bioreactor

Pod#4: Tissue Maturation
- Flow Perfusion Bioreactor
- Pod#4 QC/QA
- Waste
- Incubation
- Media/G. Factors

Pod Pod#3: Tissue Maturation
- Flow Perfusion Bioreactor
- Pod#3 QC/QA
- Waste
- Incubation
- Media/G. Factors

Pod Pod#2: Cell Expansion
- Cell Passaging
- Pod#2 QC/QA
- Incubation
- Media/G. Factors

Pod Pod#1: Biopsy Processing
- P_n Biopsy
- P_n Data
- Chemicals/Media
- Pod#1 QC/QA
- Waste
- Incubation
- Media/G. Factors

Digital Twin
- P_n Digital Twin
- P_n tissue
Vision for Tissue Manufacturing
R&D of Critical Enablers

- Cells
- Biomaterials
- Design for X (Tissue Manufacturing, Implantability)
- Process Design for Biomimicry
- Automation & Robotics
- Multi-variate Sensing
- Taxonomy & Ontology
- Cyber-physical System Architecture
- Machine Learning & AI
- Logistics & Supply Chain Design
- Data & Waste Management
- Economics & Decision-making Modeling

Education

Collaborations

Regulations

Standards
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