3D Printing Applications in Tissue Engineering

NIH Center for Engineering Complex Tissues (CECT)

June 7, 2019

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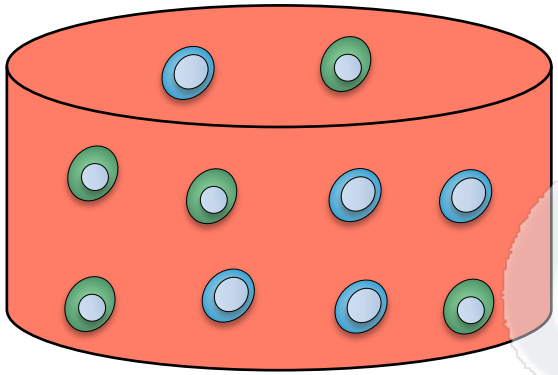
Assistant Director, CECT

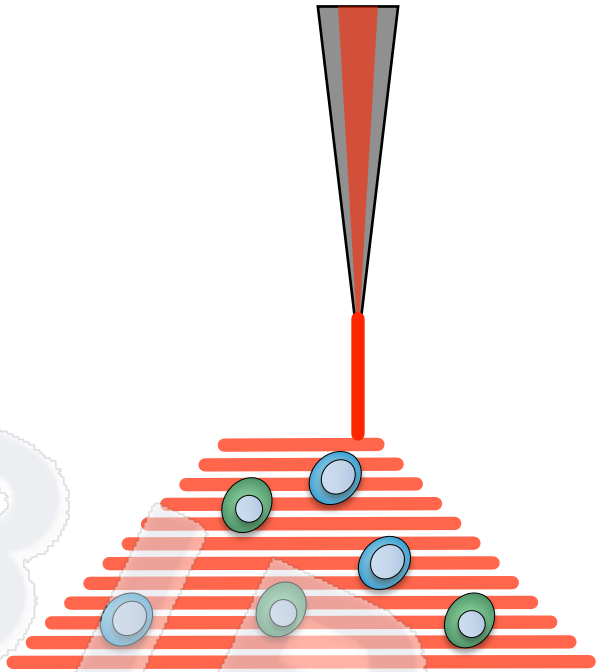
University of Maryland

CECT Center for Engineering Complex Tissues

Do you really need 3D Printing?



vs.



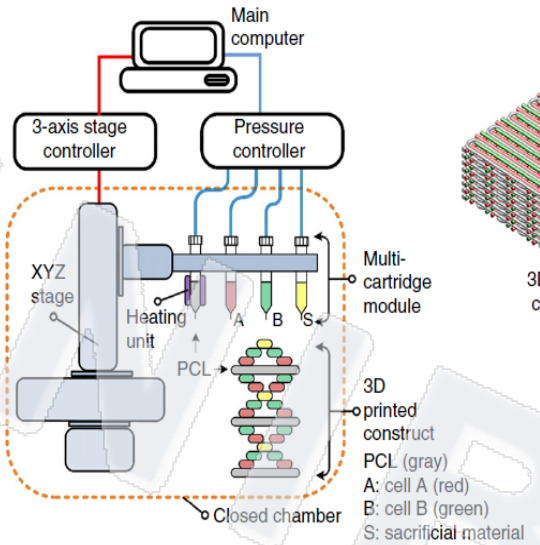
Cellular response

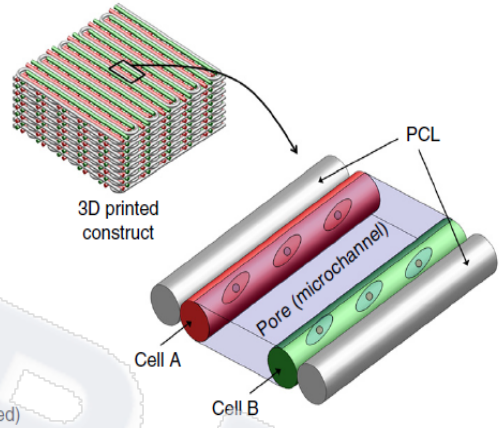
Tissue-level function

Application

Custom-made, Multi-material Platforms

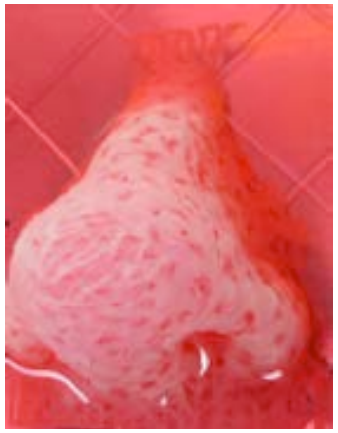
Integrated Tissue-Organ Printer (ITOP)





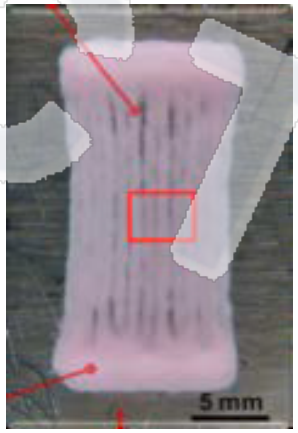
Ear

Nose



Bone

Muscle



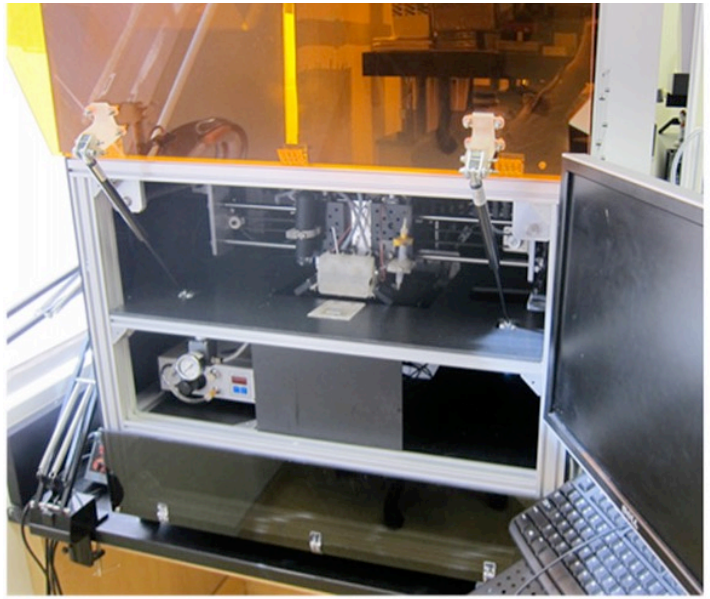
Biomask

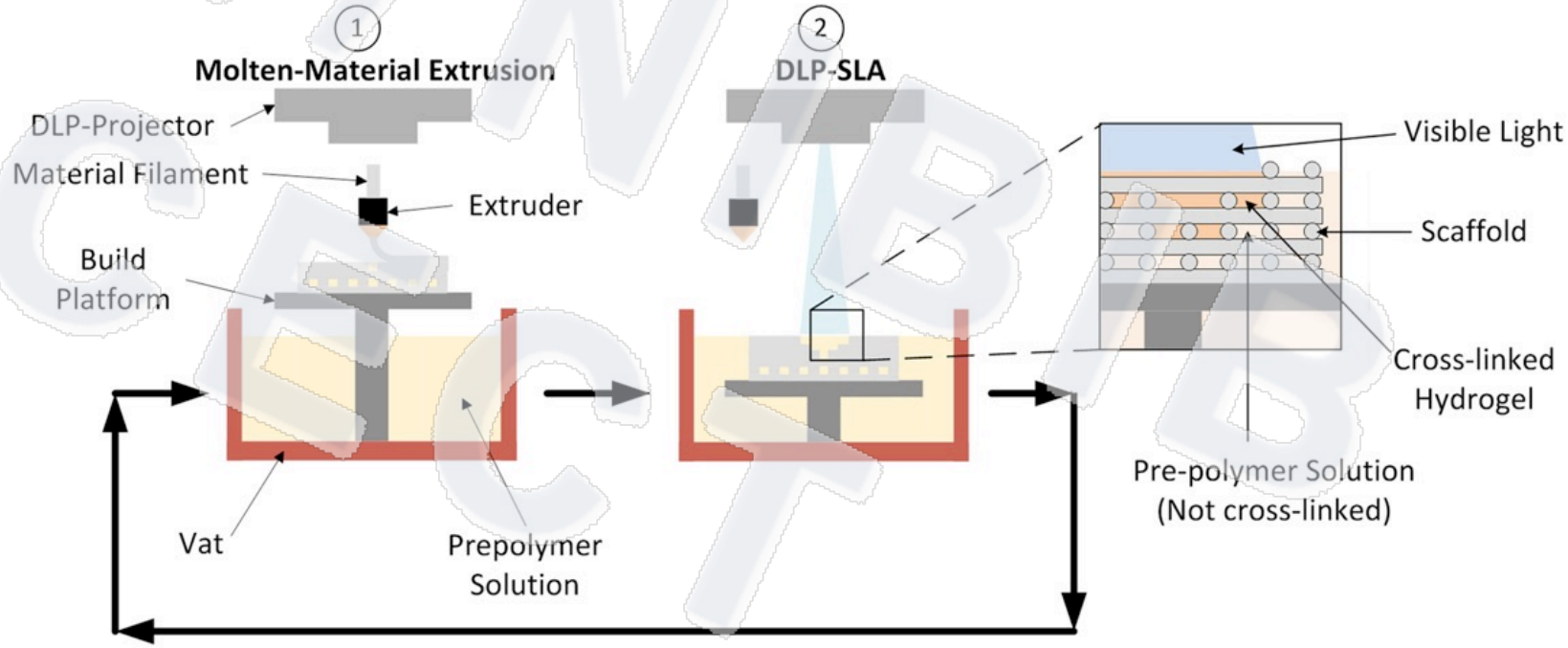
Skin

Custom-made, Multi-material Platforms

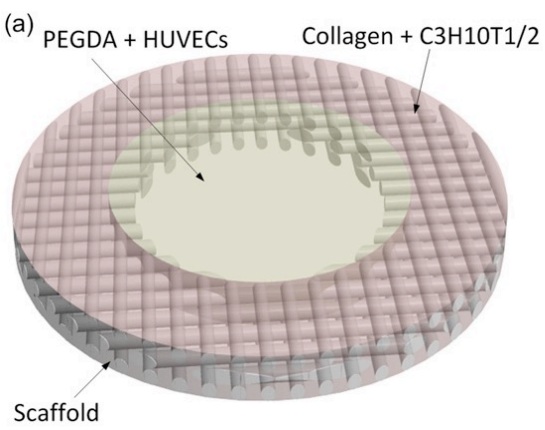
Hybprinter

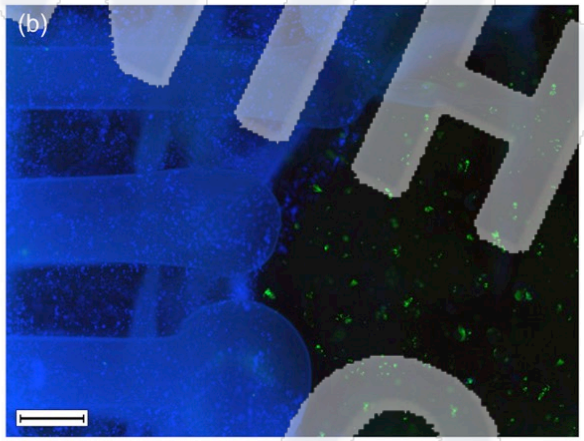
Y Shanjani *et al* 2015 *Biofabrication* **7** 045008

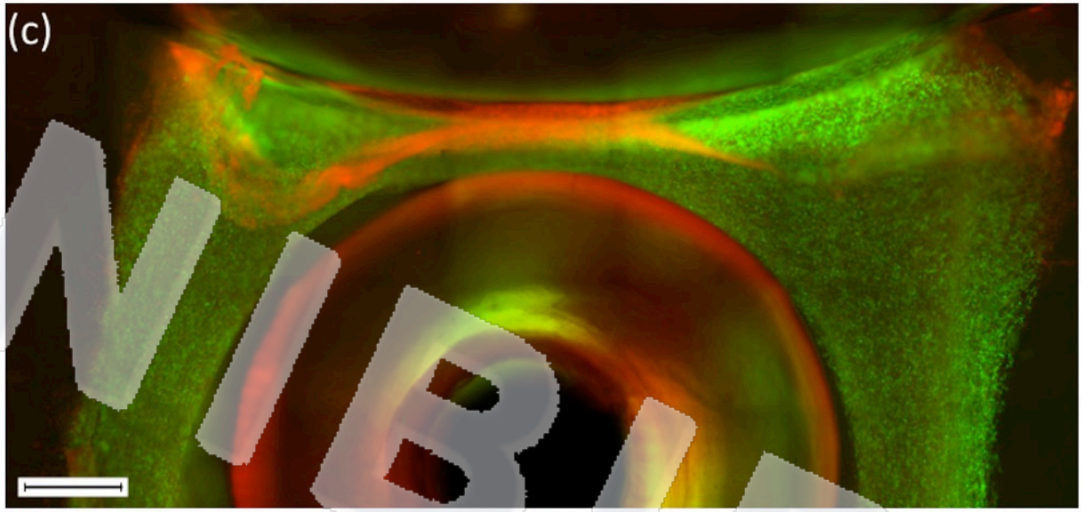


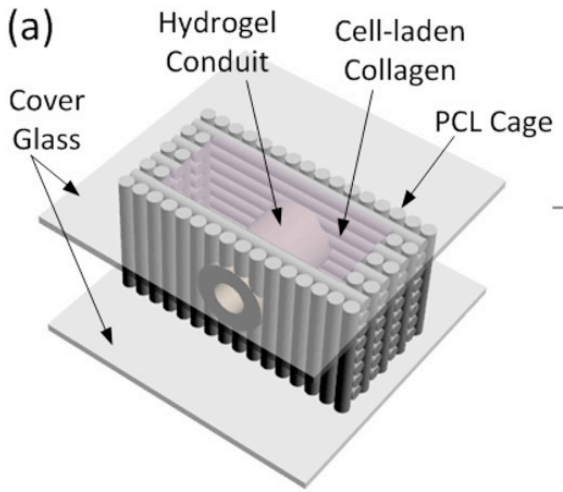


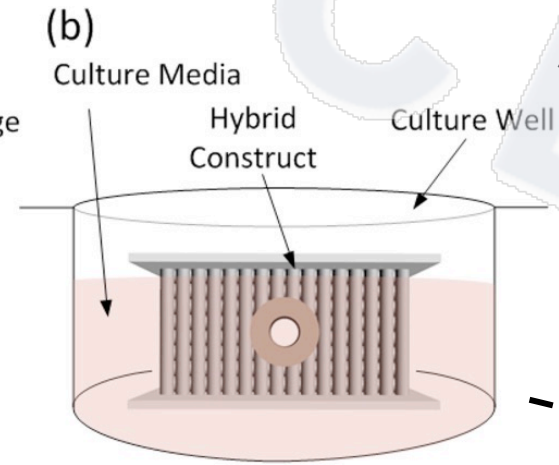
Custom-made, Multi-material Platforms

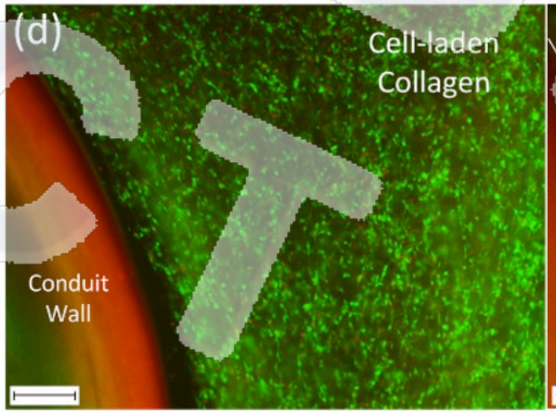


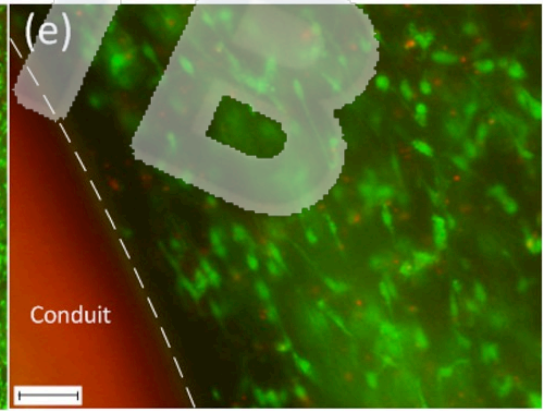








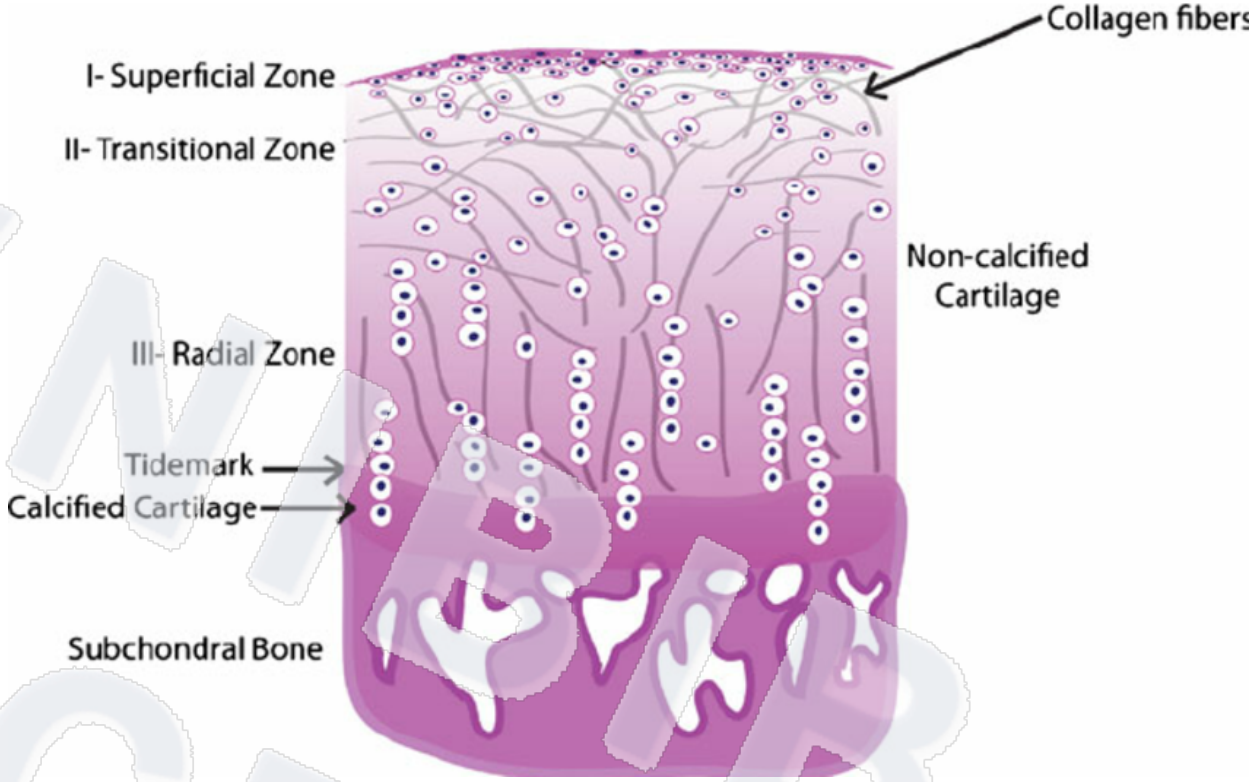




Applications in Cartilage Engineering

- Challenges in cartilage printing:
  - Avascular
  - Single cell type, low proliferation
  - Zonal architecture with a complex microenvironment
  - Mechanical properties

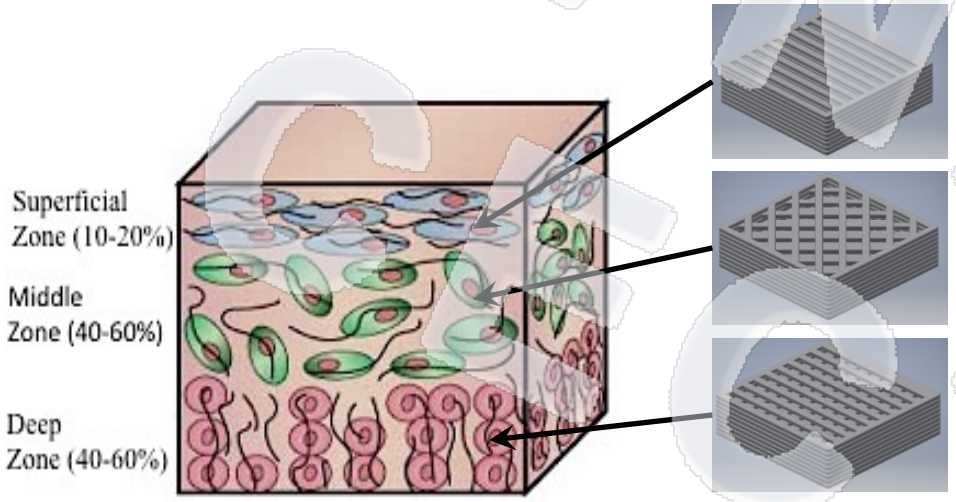
- Current medical practices lacking
  - Physical treatment
  - Microfractures
  - Auto/allo grafts



Gardjanski et al. Stem cell reviews 8(3):863-81, 2011

Cartilage Engineering: Patterned Scaffolds

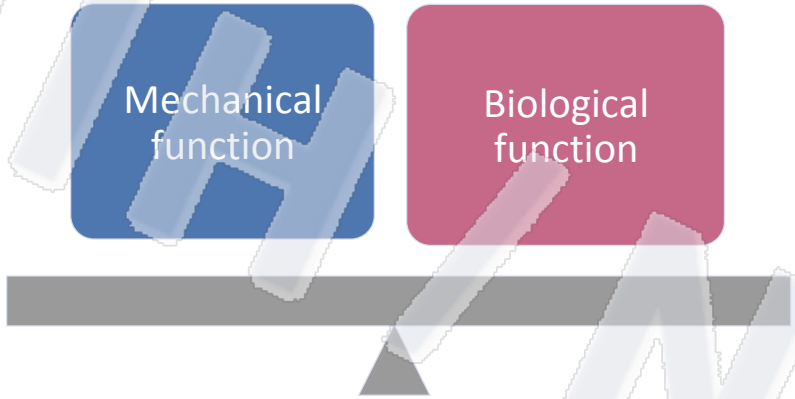
- Chondrocytes
- ECM (Collagen II, proteoglycans
- Zonal architecture

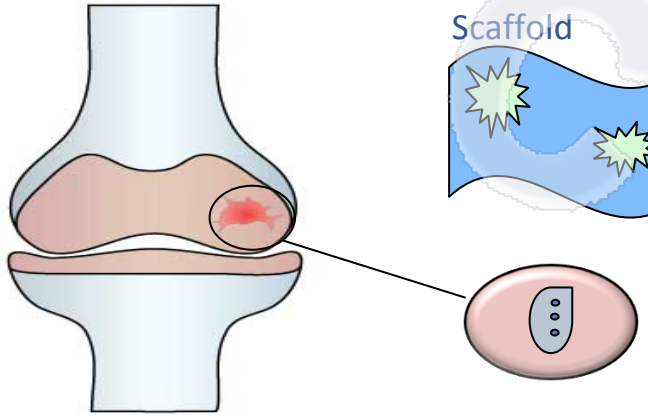


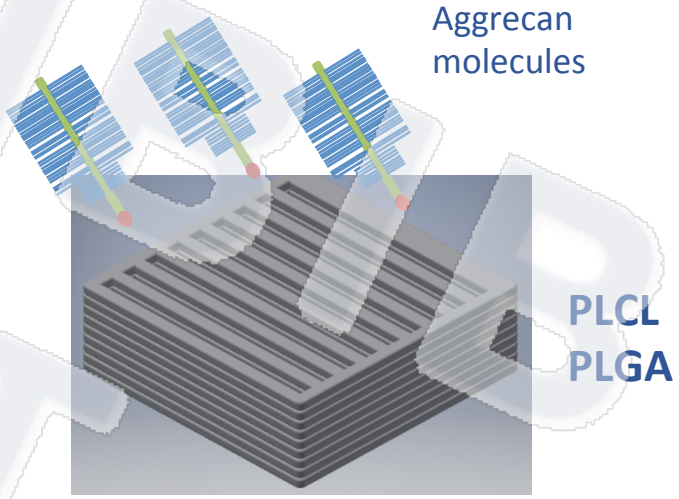
Native cartilage tissue Tissue engineering approach

T Guo, J Lembong, LG Zhang and JP Fisher. 3D Printing Articular Cartilage: Recapitulating the Complexity of Native Tissue. *Tissue Engineering Part B: Reviews.* (2017) 23(3): 225-236

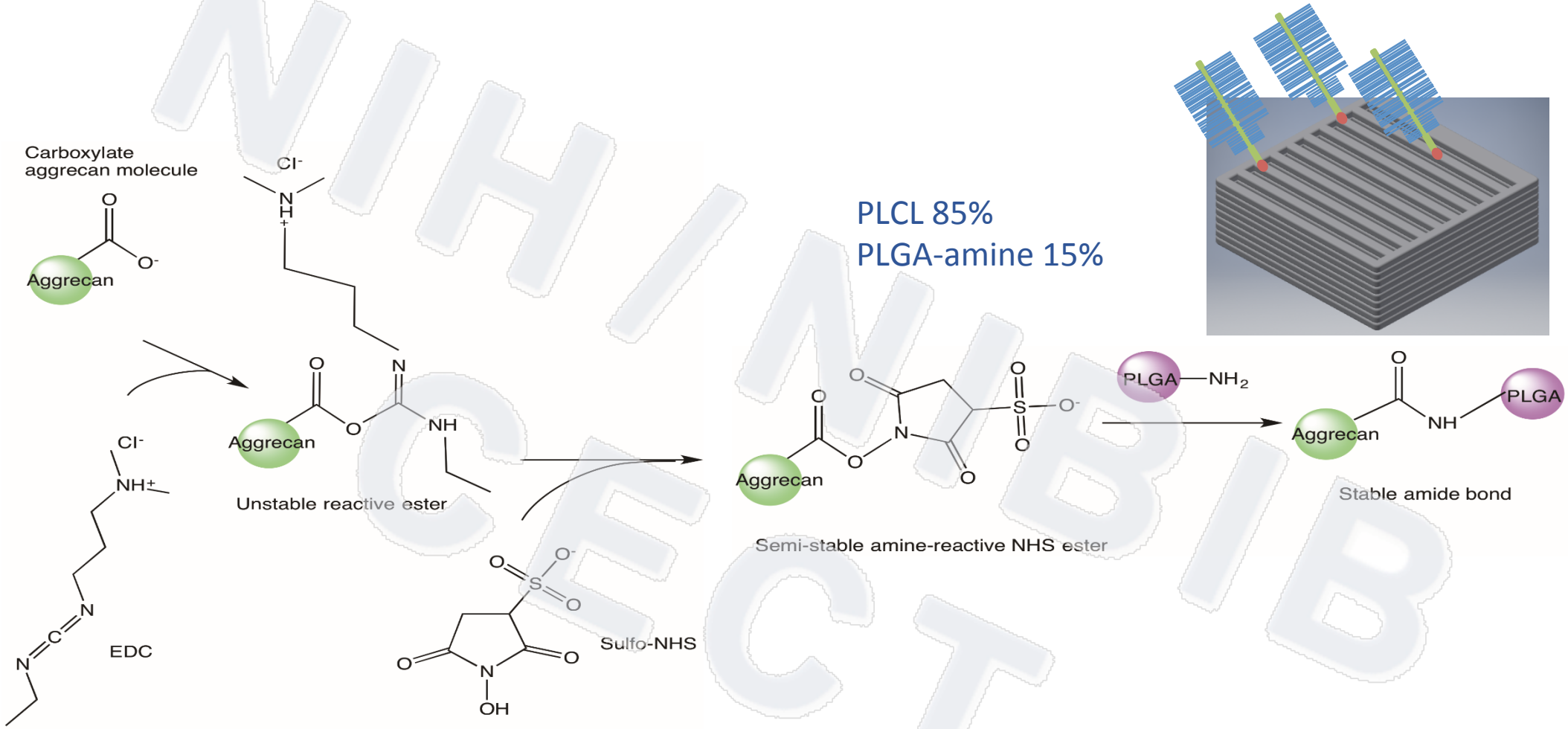
Biofunctionalization







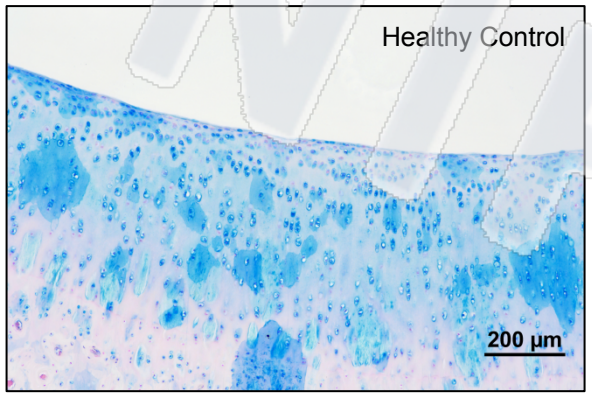
Chemical Modification

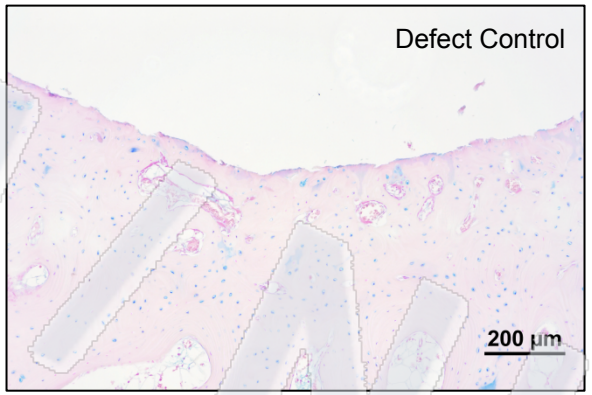


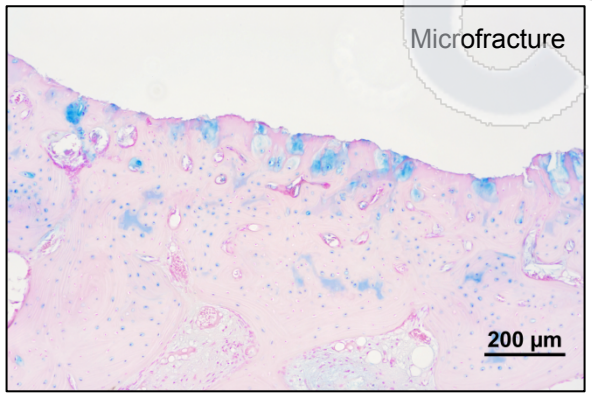
PLCL 85%
PLGA-amine 15%

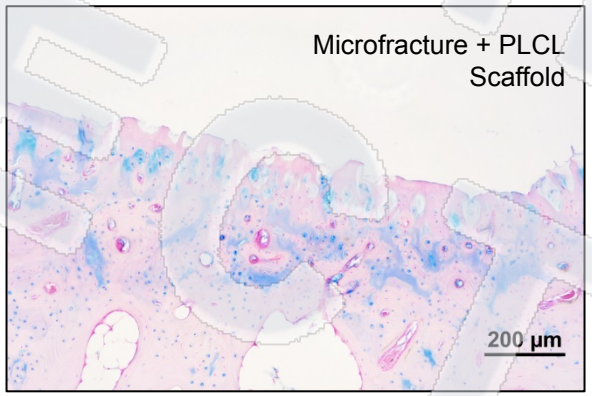
Chemical linking reaction between aggrecan and PLGA involving EDC and sulfo-NHS

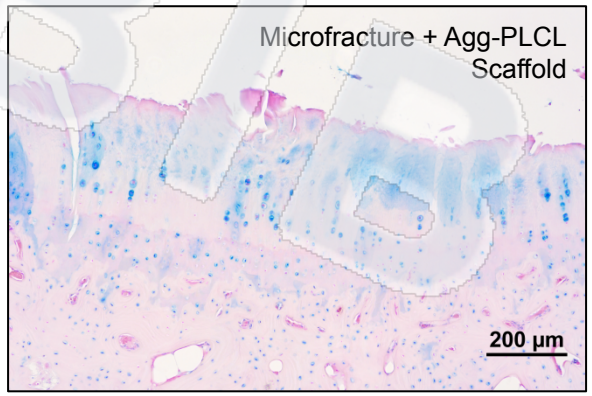
In vivo Evaluation: Rabbit Model







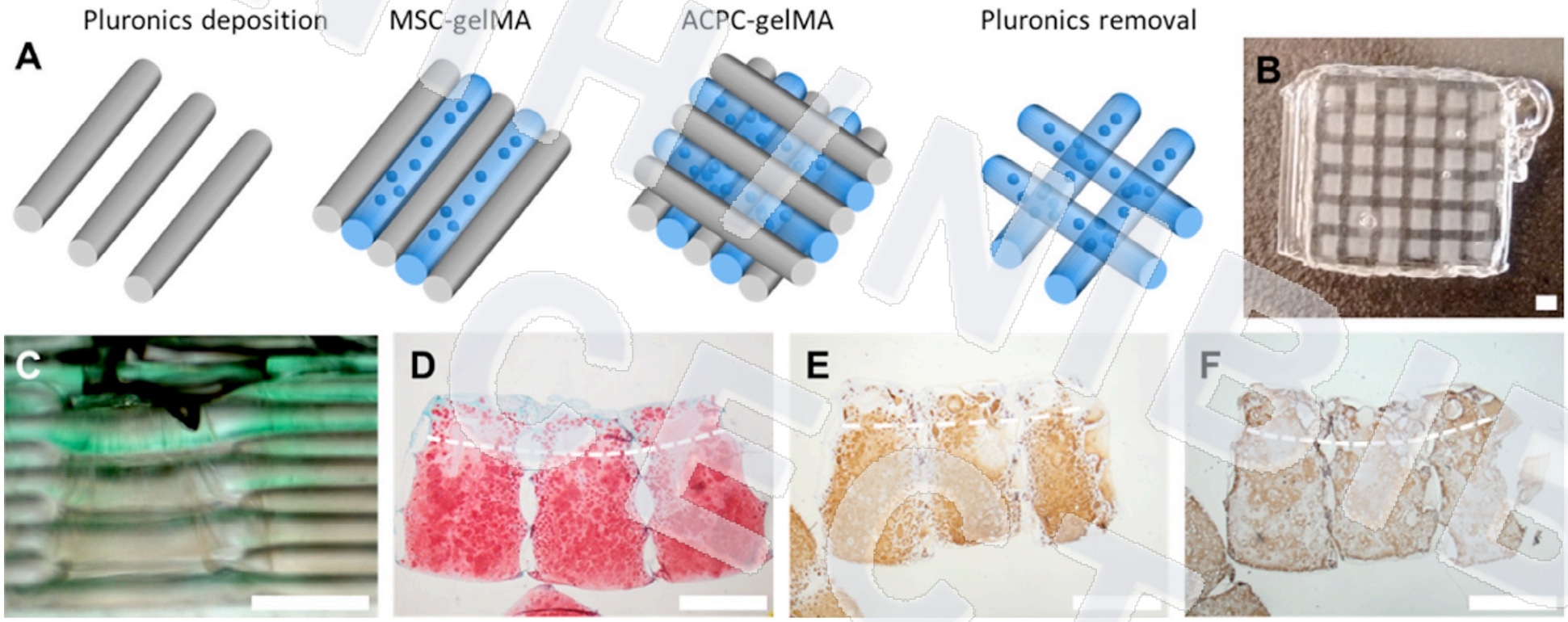




Alcian Blue Staining

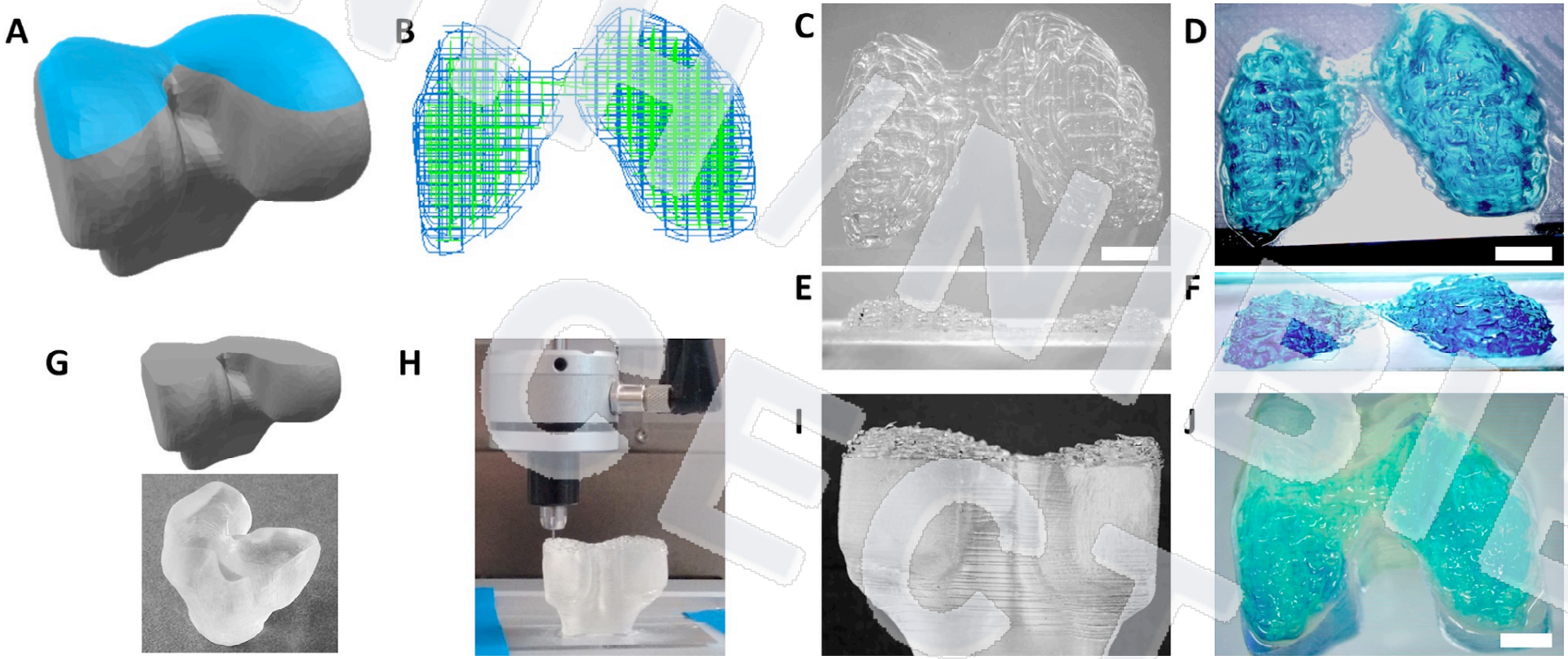
- Pink: cartilage or bone ECM
- Purple: cell nucleus
- Blue: proteoglycans (blue background indicates cartilage layer)

Cartilage Engineering: Zonal Approach



Acta Biomaterialia, Volume 61, 1 October 2017, Pages 41-53

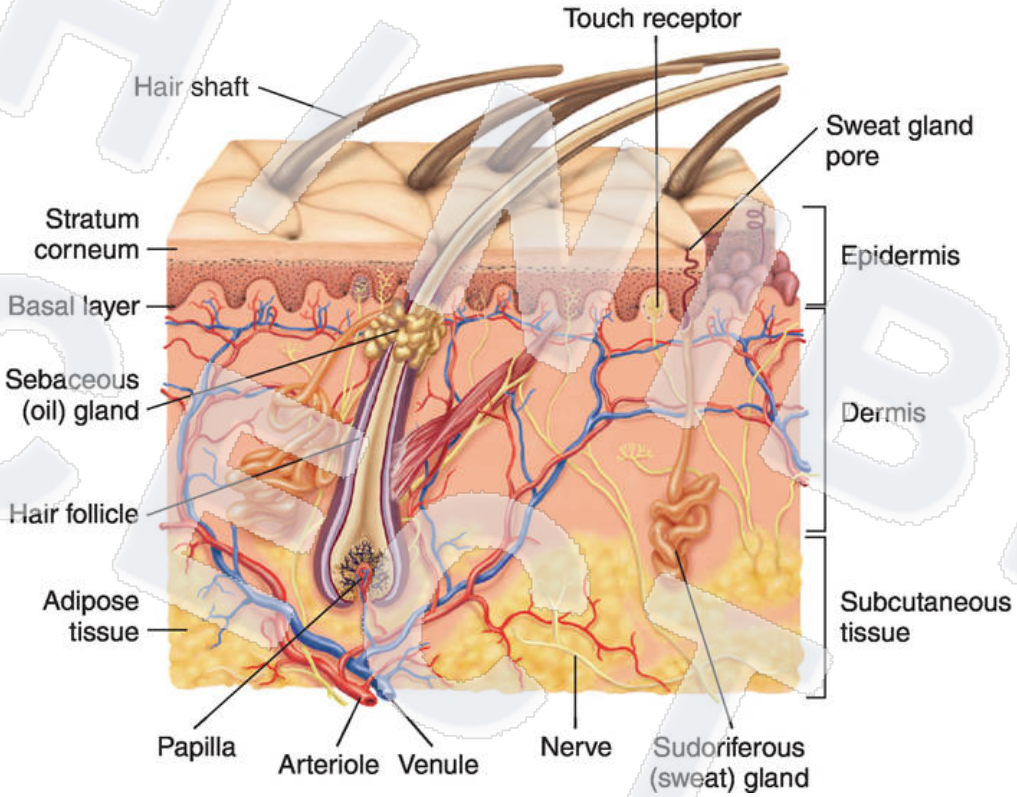
Cartilage Engineering: Zonal Approach



Acta Biomaterialia, Volume 61, 1 October 2017, Pages 41-53

3D Printing Skin

- Stratified tissue similar to cartilage

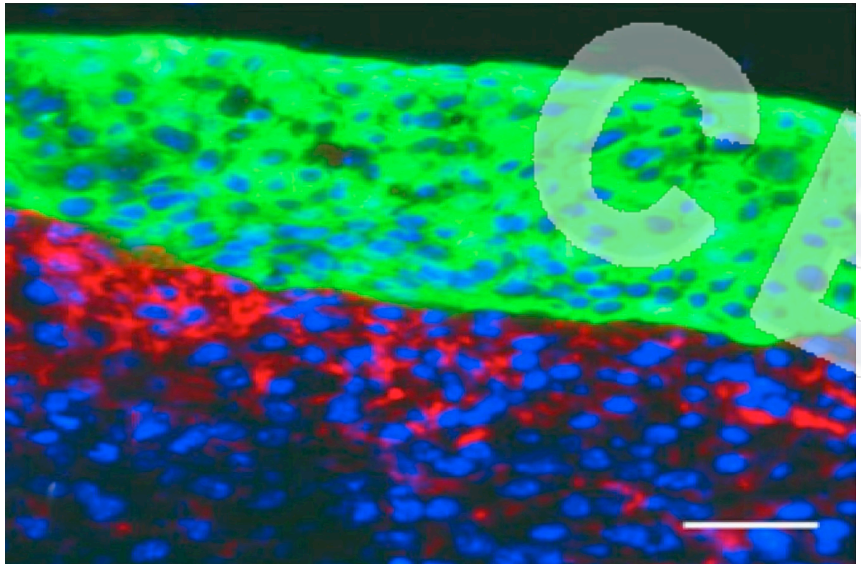


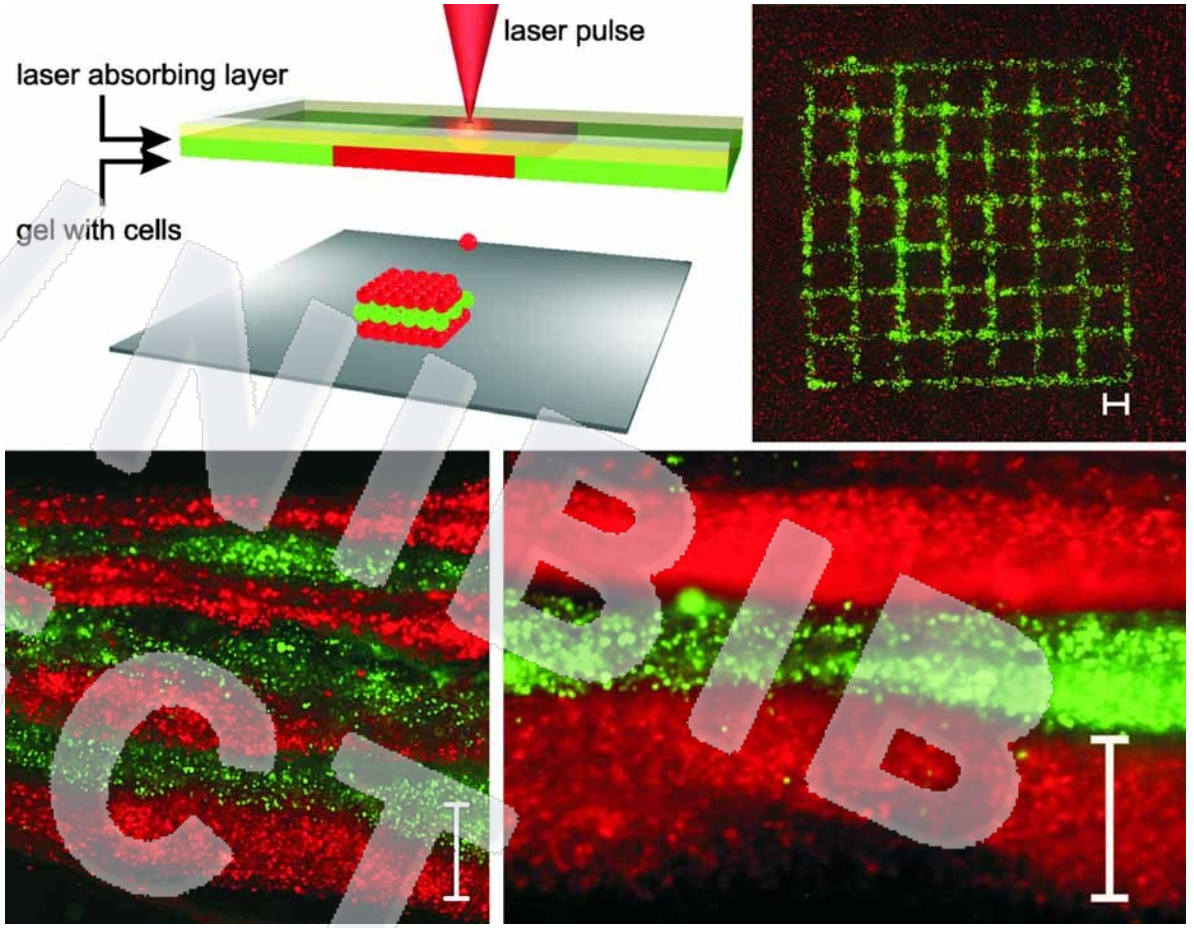
Skin, Farlex Partner Medical Dictionary, 2009

3D Printing Approaches for Skin

- Recapitulating the various layers of skin using different biomaterials and cell types

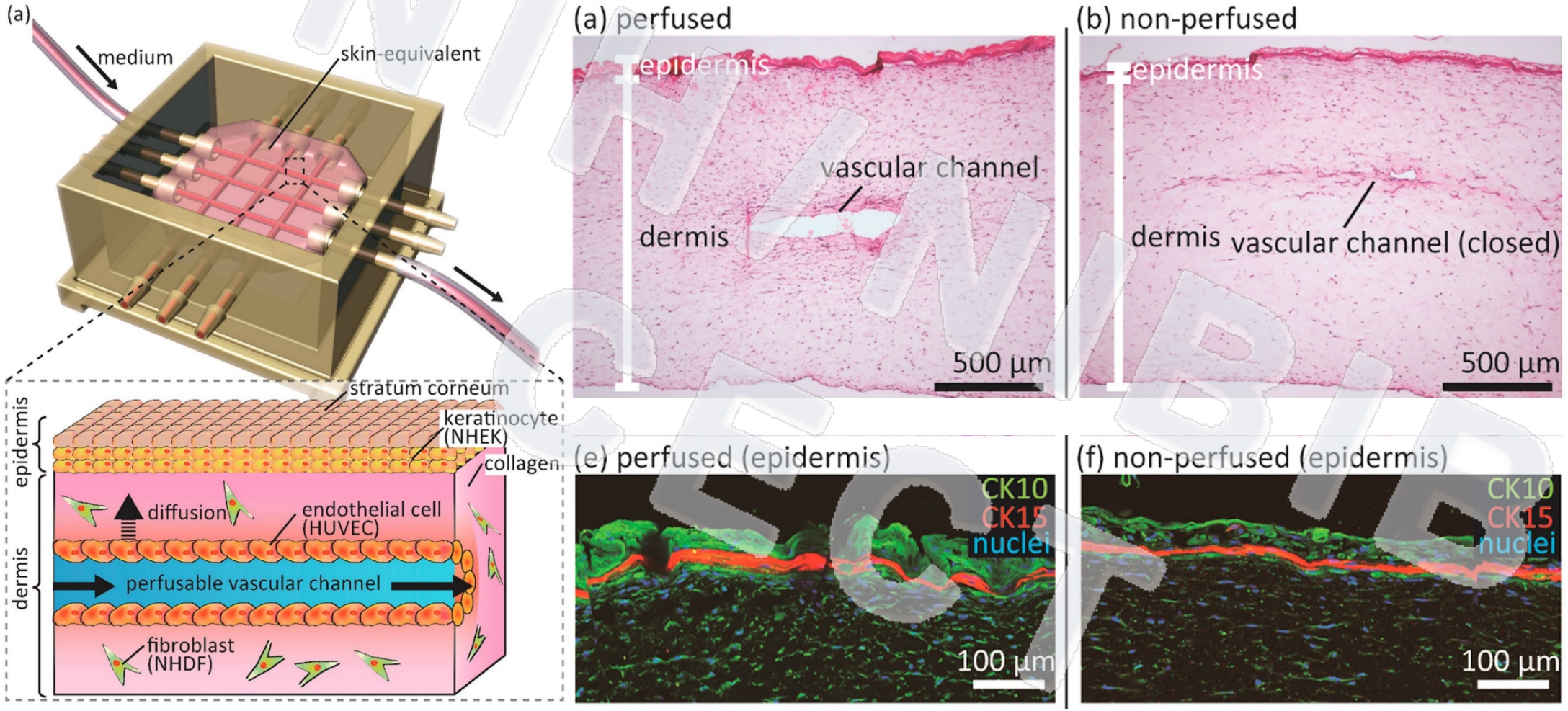
- Keratinocytes (keratin) and fibroblasts most commonly used





Koch et al., Biotech & Bioeng, 2012

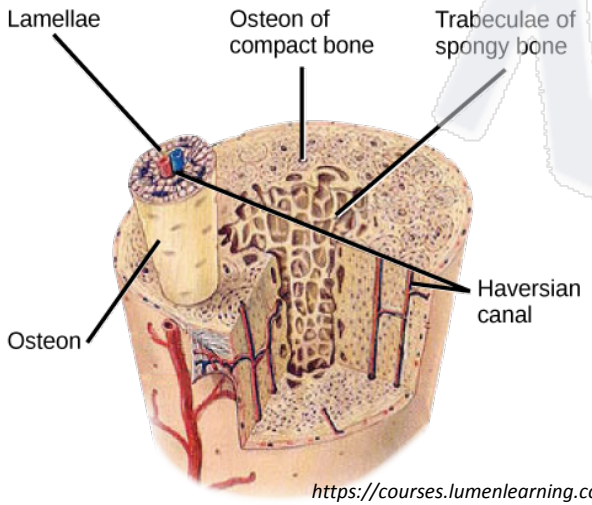
3D Printing Approaches for Skin



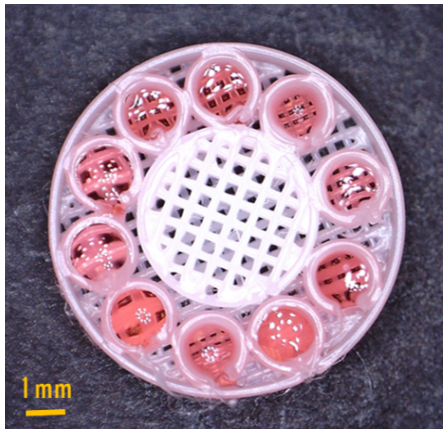
Mori et al, *Biomaterials* 2017,

Center for Engineering Complex Tissues

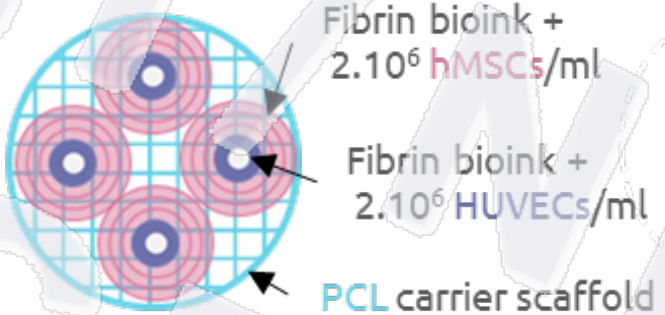
3D Printing Bone Constructs

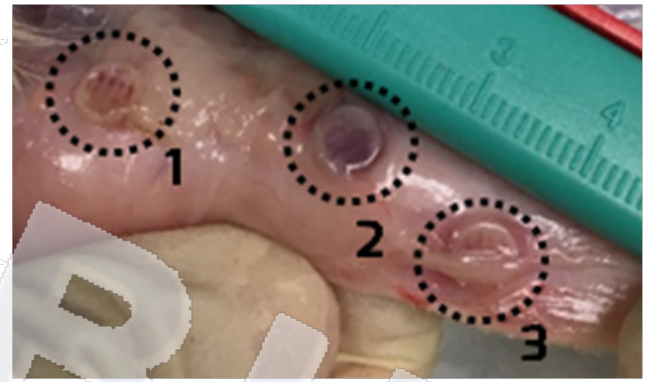


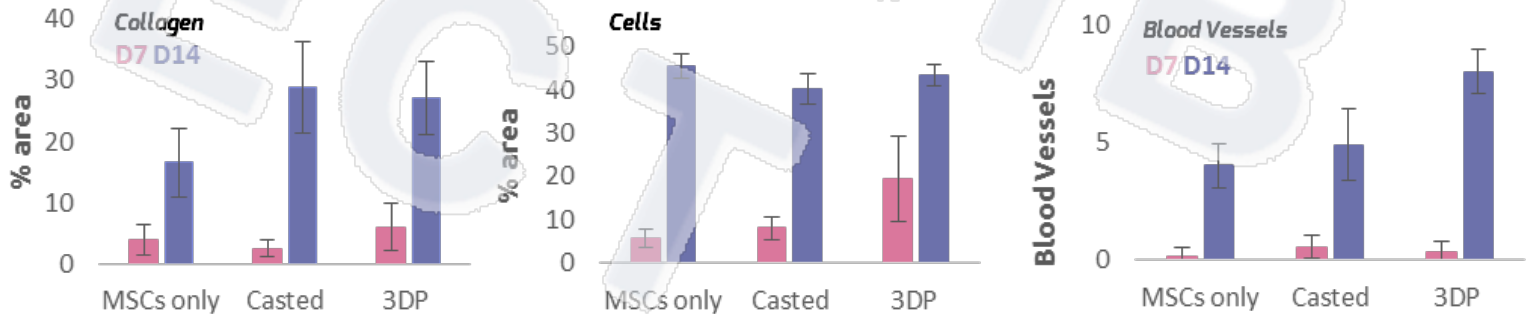
https://courses.lumenlearning.com/wm-biology2/chapter/structure-of-bones/



- Co-printing stiff (PCL) and soft (Fibrin) components for bone biomimicry



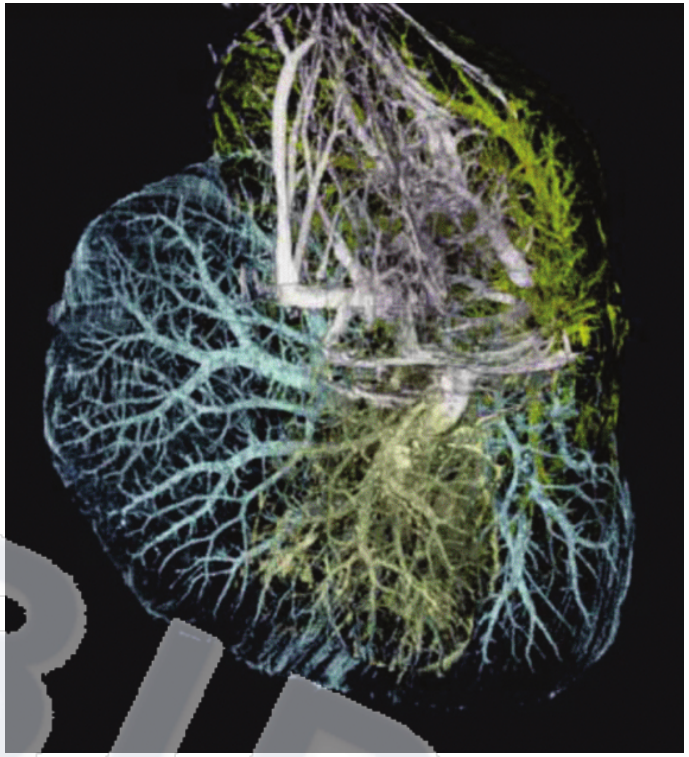




Biofabrication. 2019 Mar 28;11(2):025013

Vascularization Strategies

- Critical for large constructs
  - Diffusion restrictions
  - Nutrient availability, waste disposal
- Cancer metastasis
- Dysfunctions in vascular barriers
  - Blood brain (Alzheimers, MS)
- Drug transport
  - ADME, Toxicology, and PK/PD studies for drug development

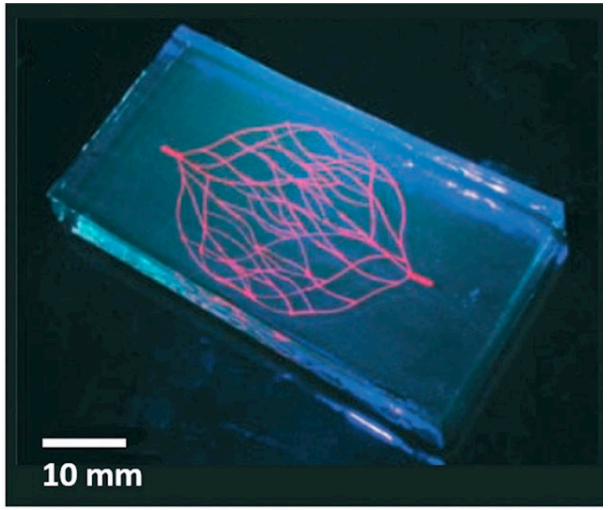


MRI of hepatic vasculature
(Malarkey et al., Toxicologic Pathology, 33:27-34, 2005

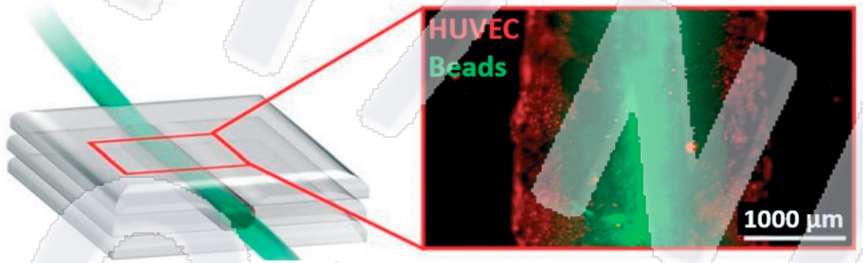
Vascularization Strategies

- Open channel formation and endothelialization at various scales

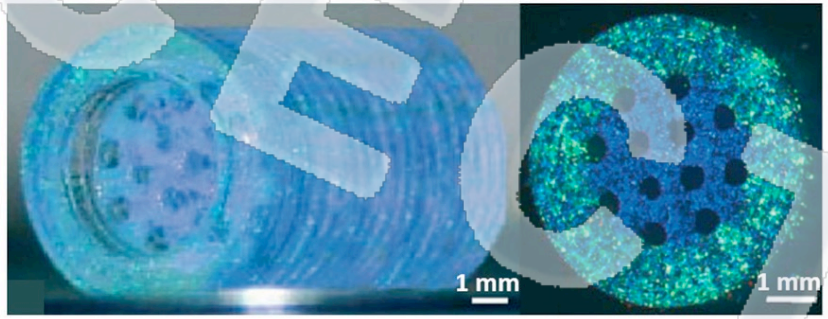
Sacrifical Pluronic Templating



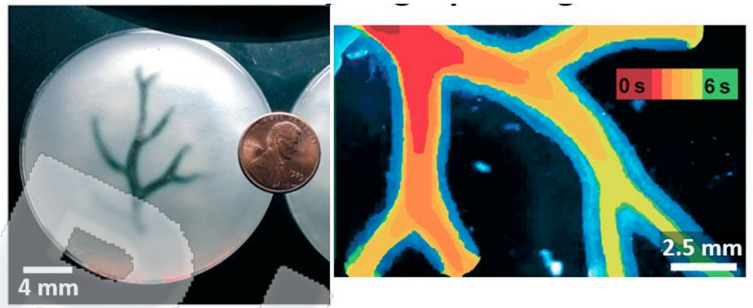
Sacrifical Gelatin Templating



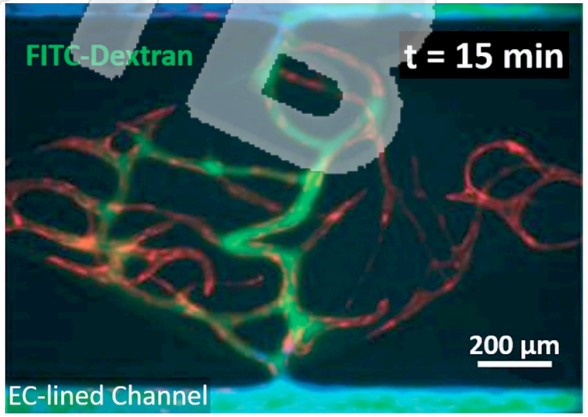
PEG Hydrogel Stereolithography



FRESH Printing



Microchannels

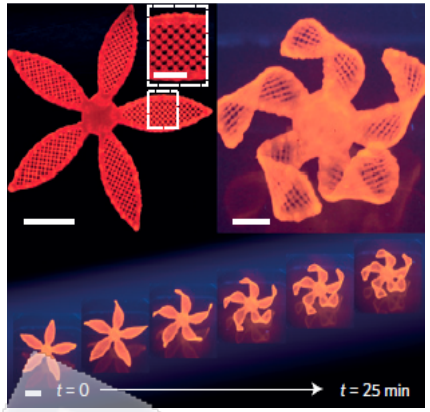


Lab Chip, 2016, 16, 2025

Potentials and future scope of 3D printing

Accounting for temporal changes: 4D printing

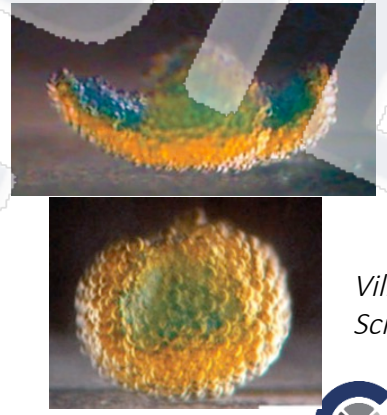
- Cellular constructs continue to evolve over time, changing the local microenvironment and consequently cell response
  - Smart biomaterials: response to external stimuli
  - Engineered biomaterials: response to temporal maturation



Lewis et al., Nat. Matls., Vol 15, April 2016

Advanced drug delivery mechanisms

- Release of drugs or cells in a programmable manner, depending on changes in body physiology
- 3D printed self-folding hydrogel layers loaded with different drugs and release profiles
- Making them implantable?



Villar, G. et al. (2013) Science 340, 48–52

CECT Center for Engineering Complex Tissues

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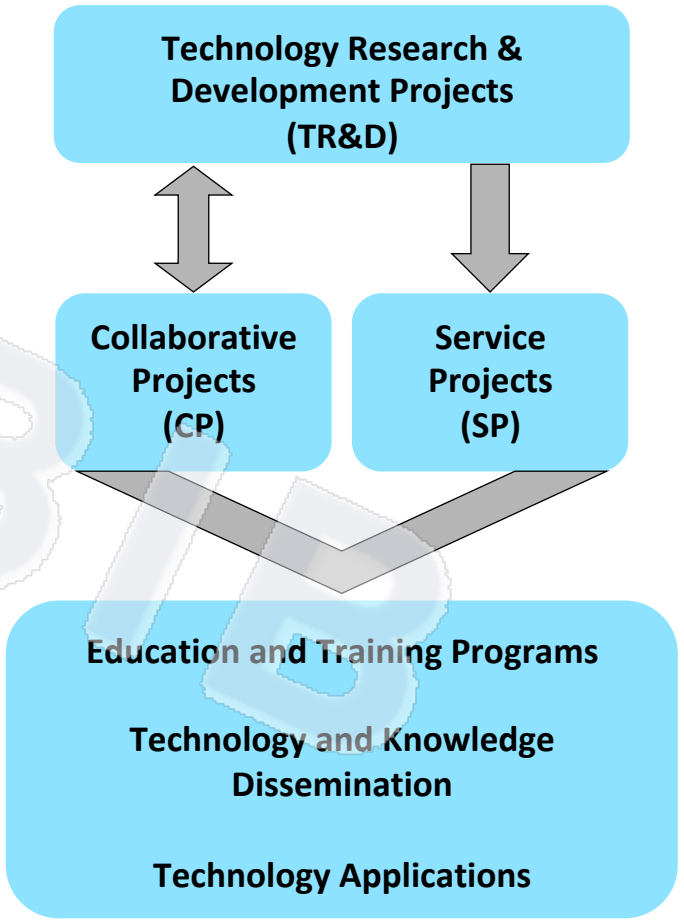
- The fabrication of complex engineered tissues remains a grand challenge in regenerative medicine
- CECT will pioneer the engineering of complex tissues by developing and disseminating techniques in bioreactor culture, cell printing, and complex scaffolds
- CECT will also establish a community of investigators in these endeavors through disseminating technologies and growing new technologies for fabricating complex tissues



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Center for Engineering Complex Tissues

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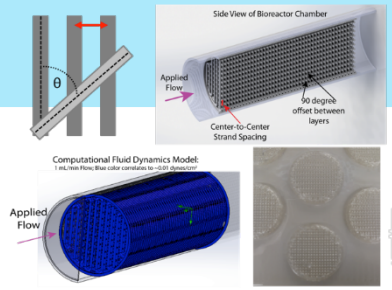
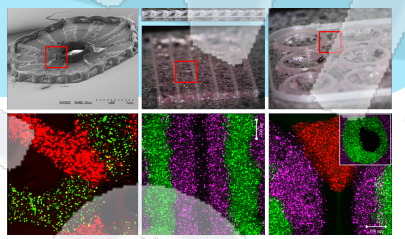
TR&D1: Bioreactor Culture

- 3DP Bioreactor Chambers
- Dynamic Coculture in Bioreactor Chambers
- Dynamic Coculture of 3DP Bone Mimetic



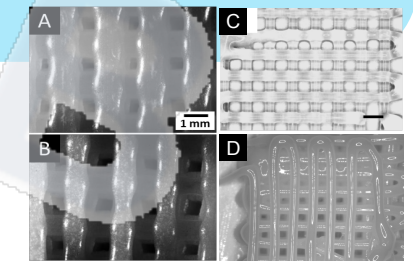
TR&D2: Cell Printing

- Cell Positioning in 3DP Tissues
- Cell-Substrate Printing to Control Microenvironment
- Bioprinting of Multiple Cell Populations



TR&D3: Complex Scaffolds

- Composite 3DP Scaffolds
- 3DP Scaffolds with Controlled Release
- Heterogeneously Distributed Growth Factors for Tissue Repair



TR&D 1: 3D Printed Bioreactors for Cell Culture
Dr. John P. Fisher, University of Maryland

TR&D 2: Bioprinting Patterning for Cell-Laden Constructs
Dr. Anthony Atala and Dr. James J. Yoo, Wake Forest University

TR&D 3: Bioprinting for Complex Scaffold Fabrication
Dr. Antonios G. Mikos, Rice University

Center for Engineering Complex Tissues

Acknowledgements

Tissue Engineering & Biomaterials Laboratory

Lab Members

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Sachiko Kaihara, PhD
Kyobum Kim, PhD
Anthony Melchiorri, PhD
Jennifer Moreau, MS
Bao-Ngoc Nguyen, PhD
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Jesse Placone, PDF
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Diana Yoon, PhD
Andrew Yeatts, PhD
Martha Wang, PhD

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Dr. Eric Brey, UT San Antonio
Dr. John Caccamese, Maryland
Dr. Yu Chen, Maryland
Dr. Curt Civin, Maryland
Dr. David Kaplan, US FDA
Dr. Peter Kim, Children's National
Dr. Maureen Dreher, US FDA
Dr. Antonios Mikos, Rice
Dr. James Yoo, Wake Forest

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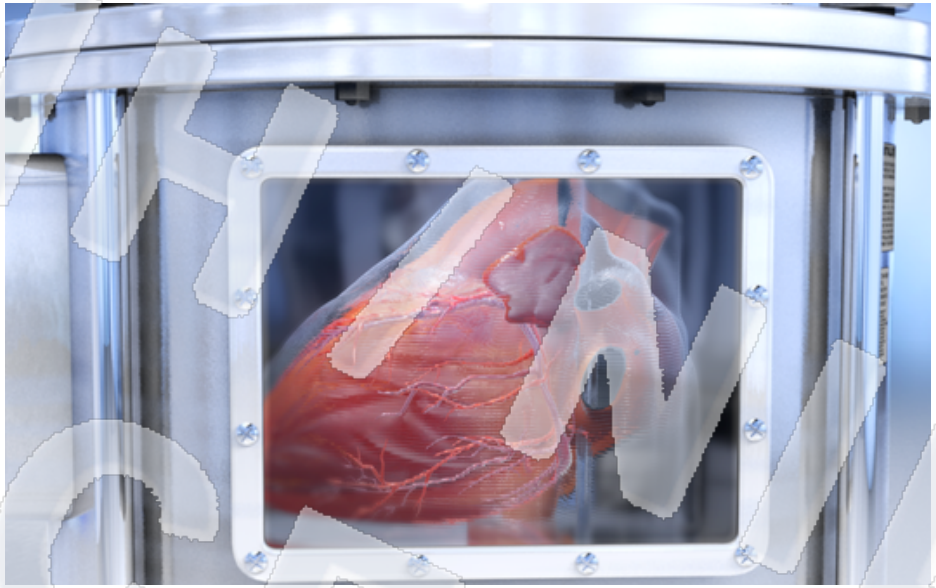
Thank you



A tool for engineering the ideal conditions to ask key biological questions