THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

4D Bioprinting Smart And Nanomaterials For Complex Tissue Regeneration

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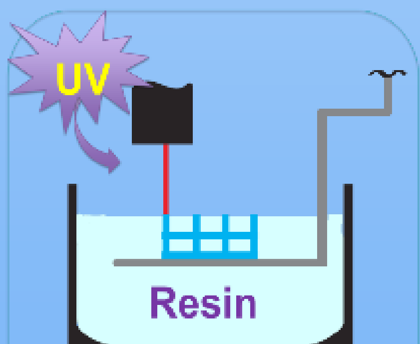
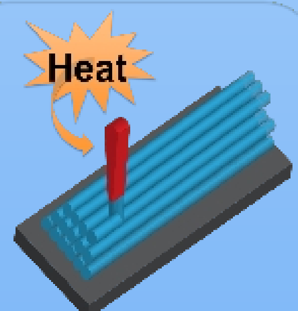
December 7, 2023

Pillar I: 3D Bioprinting

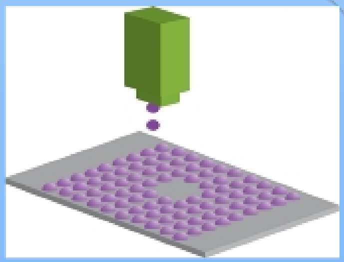
- Printing cells, bioactive factors and biomaterials
- 3D microfabrication for patient specific complex tissue and organ design

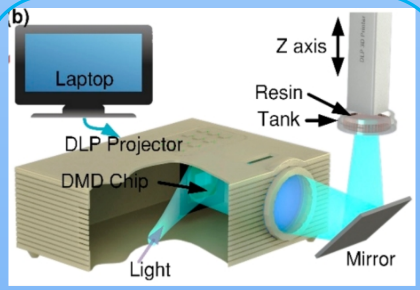


Stereolithography



Fused Deposition Modeling


Bioplotting or Inkjet bioprinting

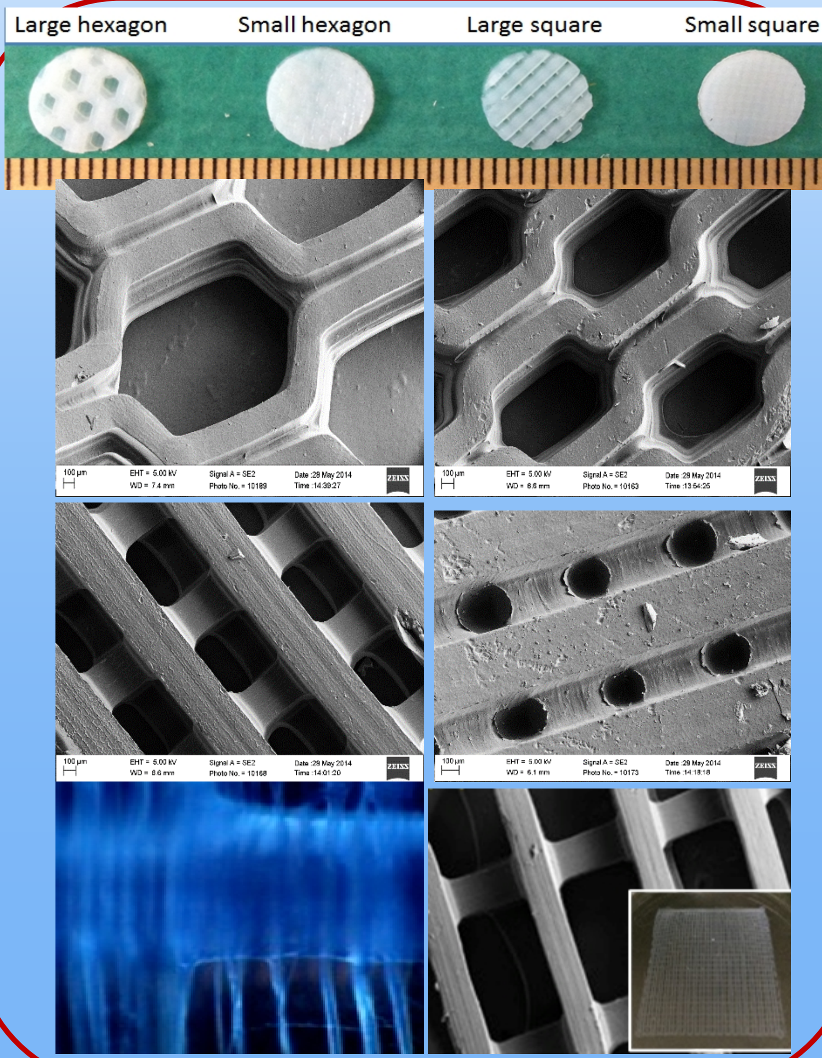


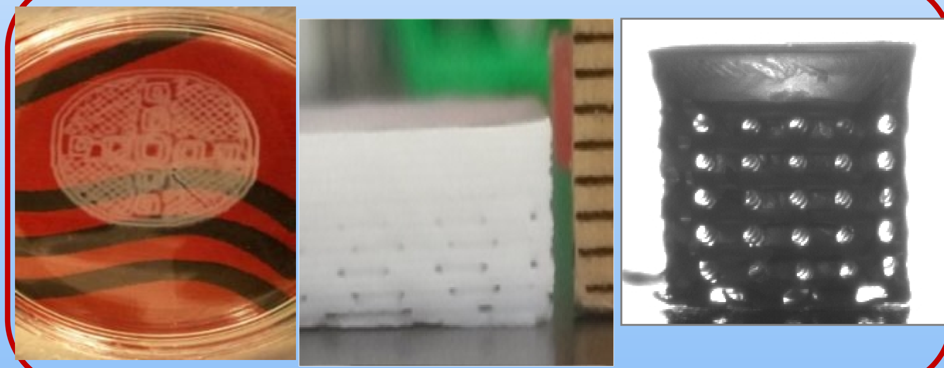
Digital light processing based printing

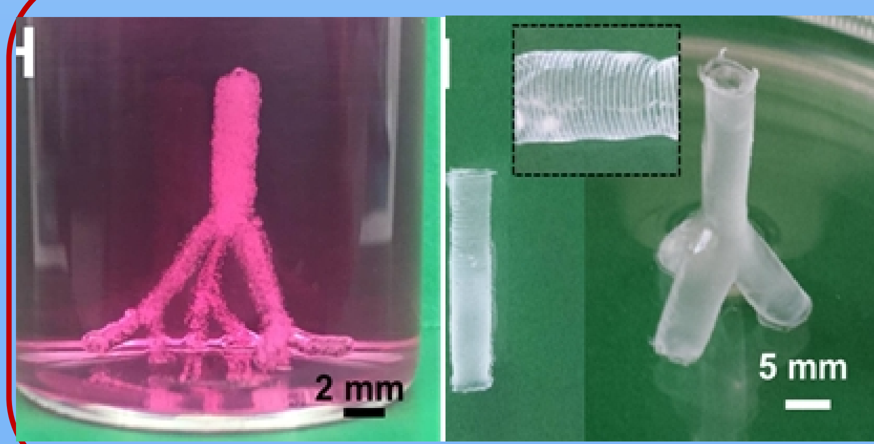
Y. Wang, H. Cui, et al., ACS Applied Materials & Interfaces, 13(11):12746–12758 (2021).

C. O’Brien, B. Holmes, S. Faucett and L.G. Zhang. *Tissue Engineering*, 21(1): 103-114, (2015)

3D Printed Tissue Scaffolds





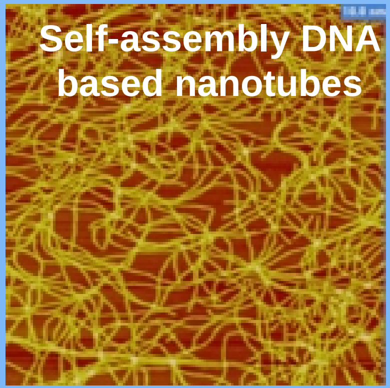


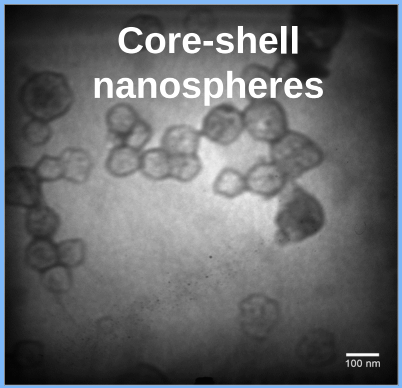
Pillar II: Nanotechnology

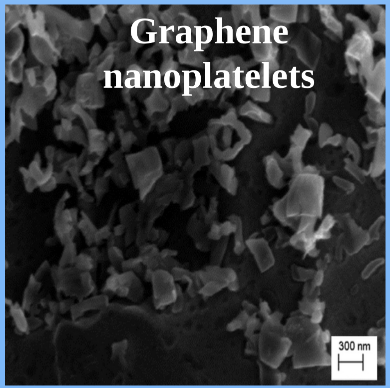
- Nanomaterials are materials with basic structural units, grains, particles, fibers or other constituent components smaller than 100 nm in at least one dimension.

Human tissue structure: nanostructured extracellular matrix (ECM) and various cells

Nanoinks： Nanoparticles, Nanotubes, Nanofibers, Nanocrystals, Nanorods…





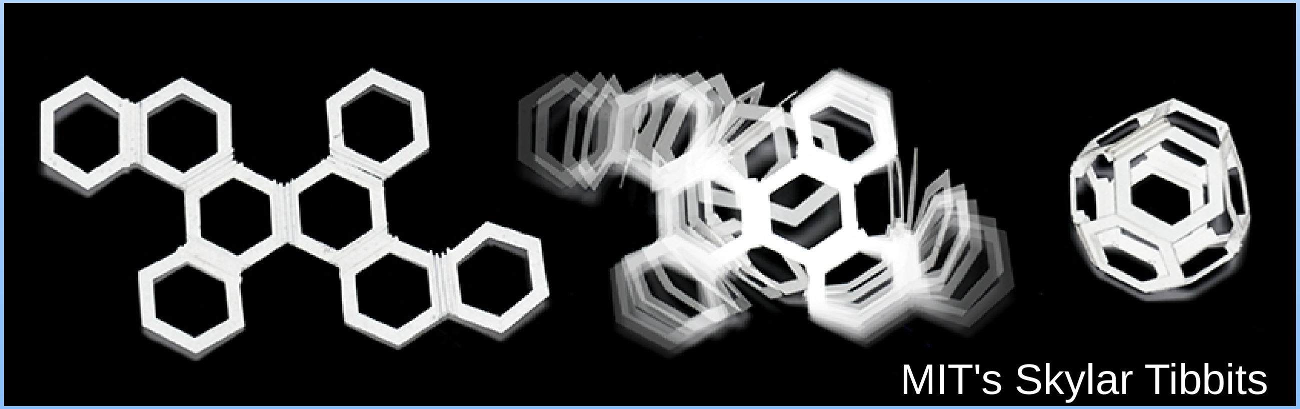


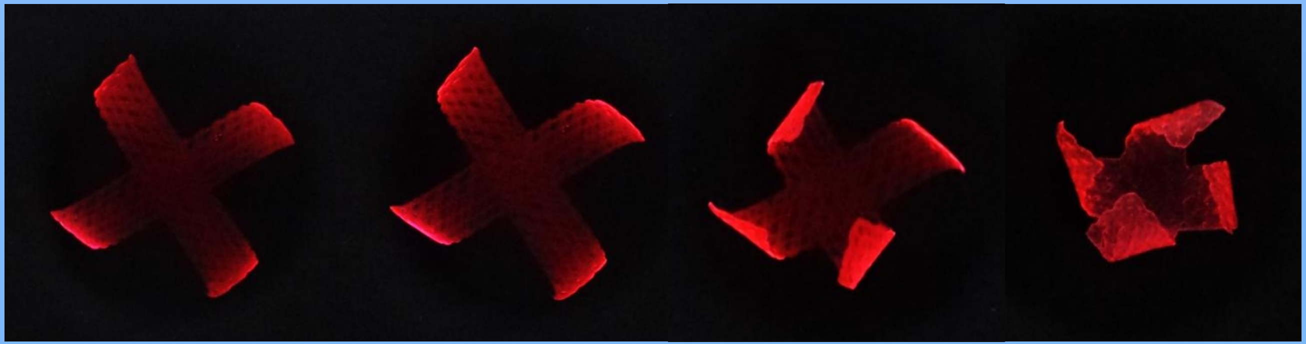
NEW FRONTIER:

4D BIOPRINTNG

4D Printing

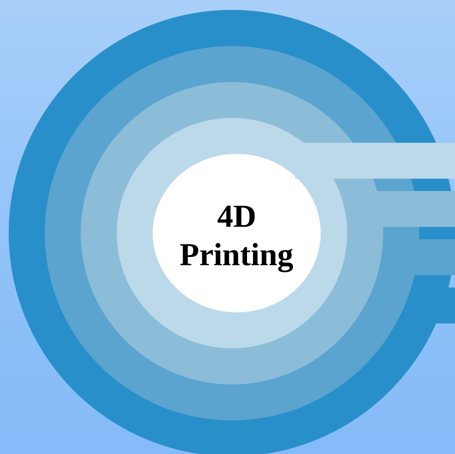
- The printed constructs are able to change and mutate **over time.**





S. Miao, et al. 4D printing of polymeric materials for tissue and organ regeneration. *Materials Today*, 20(10):577-591 (2017).

4D Printing

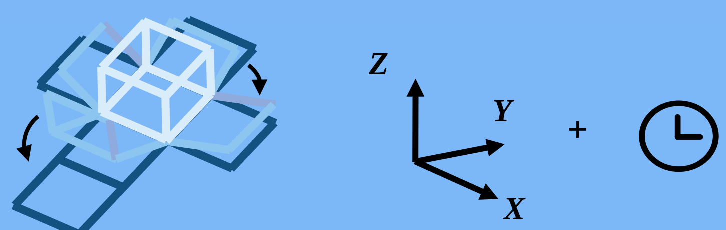


Printing Platform
Fused Deposition Modeling, Direct Ink Printing, Stereolithography, Digital Light Processing, Inkjet Printing, Digital Light Processing and etc.

Polymeric Printing Material
Shape Memory Polymers, Shape Memory Alloys, Hydrogel, Liquid Crystal Elastomers, Smart Composites and Other Responsive Materials

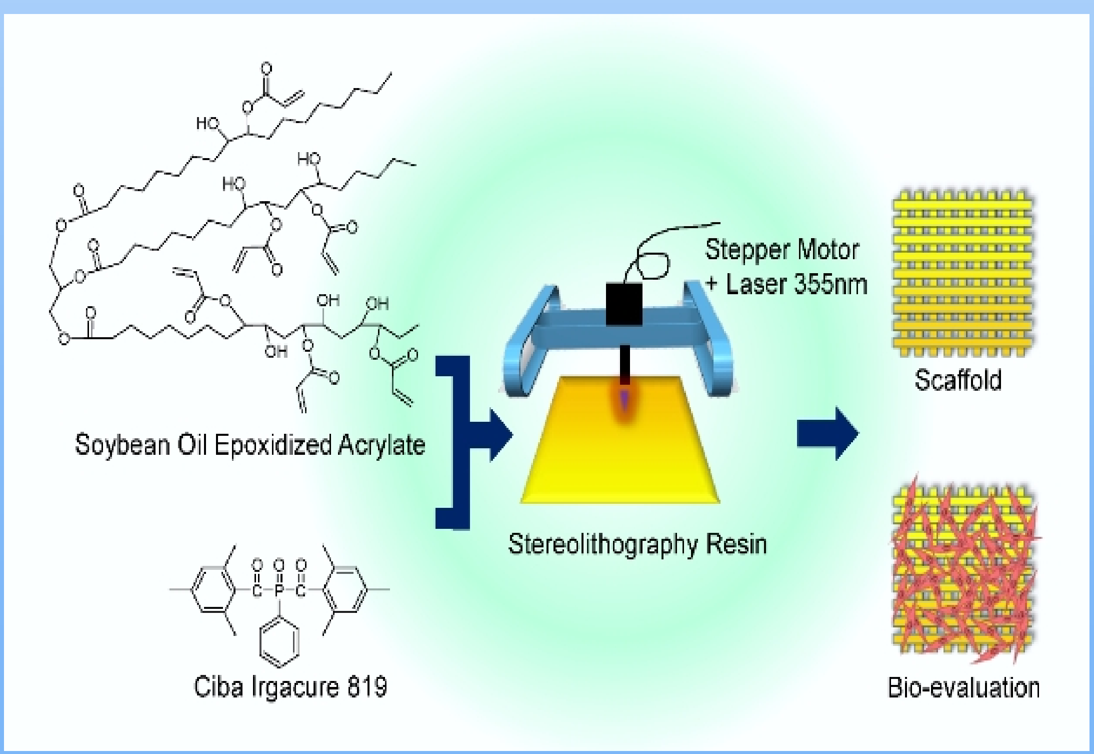
Stimuli and Mechanism
Temperature, Chemicals, Light, Magnetism and etc.

Application
Biomedical and Healthcare, Soft Robotics, Aerospace, Fashion and Wearable Technology and etc.

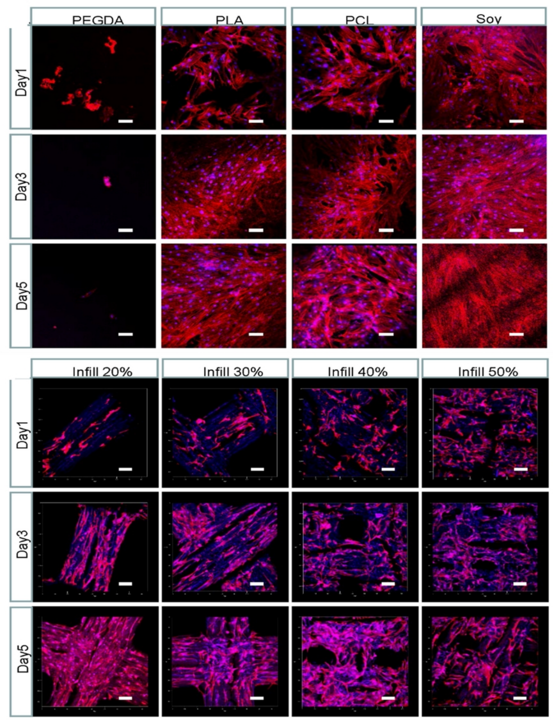


Novel Natural Smart Materials for 4D Bioprinting

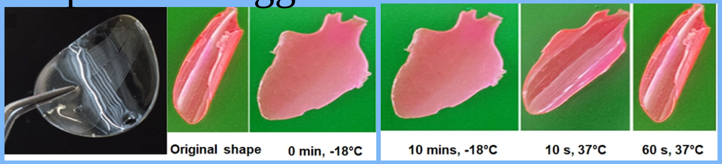
- **Synthesize novel smart natural biomaterials (plant oil) for 4D bioprinting complex tissues**



Excellent stem cell proliferation



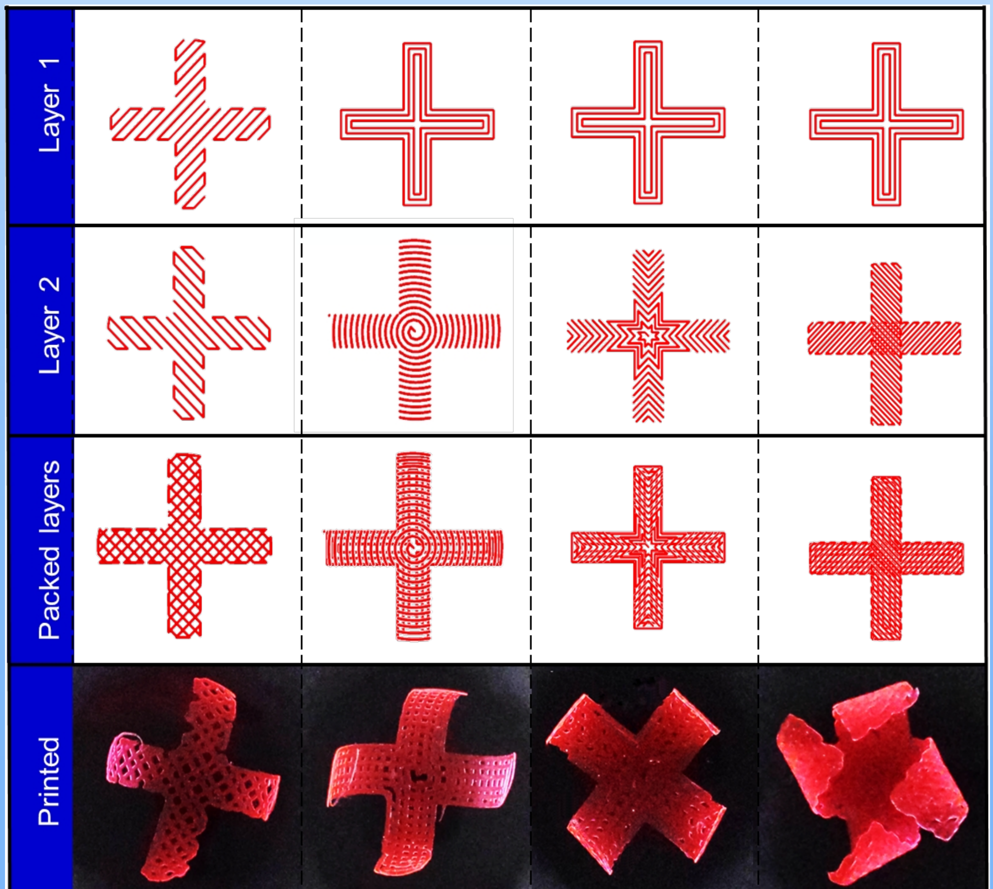
Temperature triggered 4D transformation

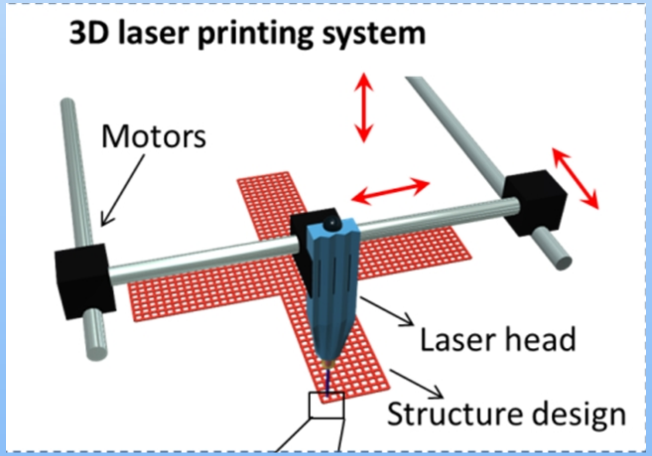


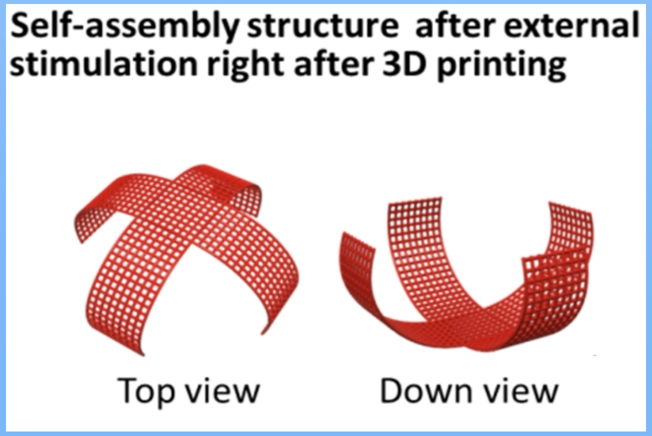
S. Miao, W. Zhu, N. Castro, J.S. Leng and L. Zhang. *Tissue Engineering Part C*, 22(10): 952–963 (2016). **Cover image of the Oct issue.*
S. Miao, W. Zhu, N. Castro, M. Nowicki, H. Cui, X. Zhou, J.P Fisher, and L. Zhang. *Scientific Reports*, 6:27226 (2016).
S. Miao, H. Cui, M. Nowicki, et al. *Biofabrication*, 10(3):035007, (2018).

Anisotropic Smart Structure Design for 4D Transformation

Various Structure Design



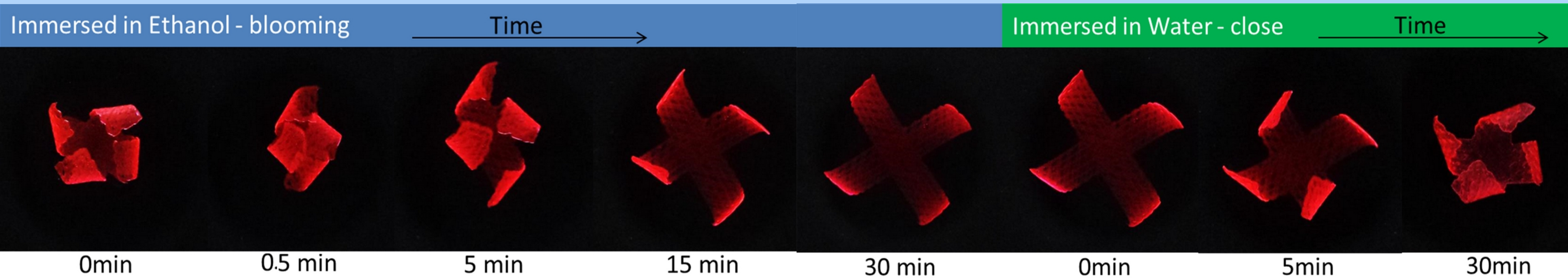


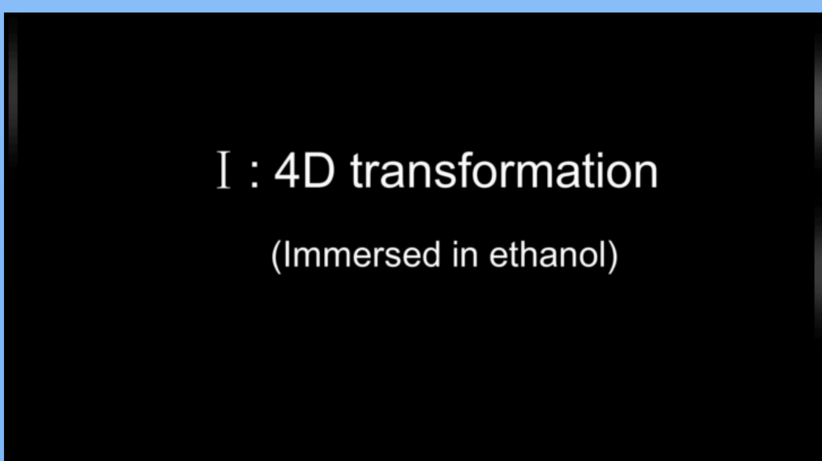


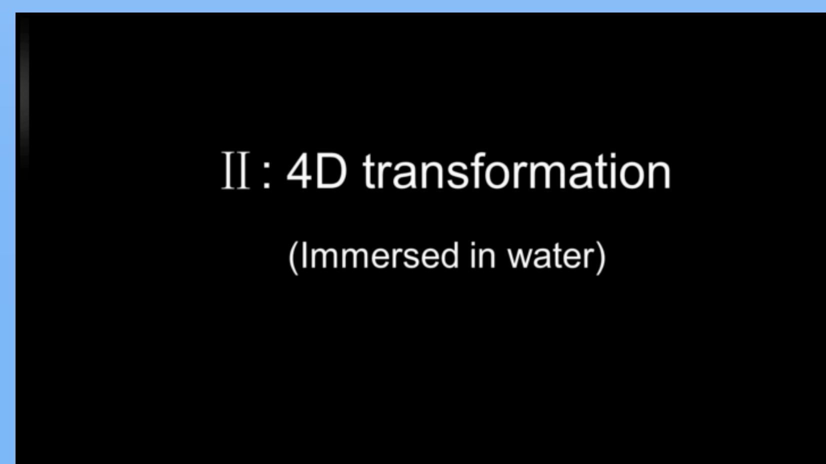
S. Miao, et al. Stereolithographic 4D bioprinting of multi-responsive architectures for neural engineering, *Advanced Biosystems*, 2(9): 1800101, (2018). **Cover image*

Solvent Triggered 4D Transformation

Reverse shape change effect

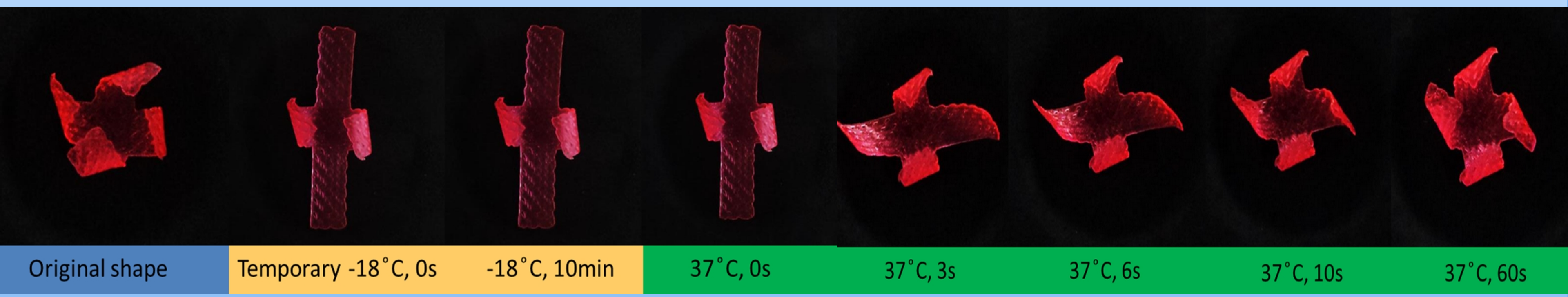


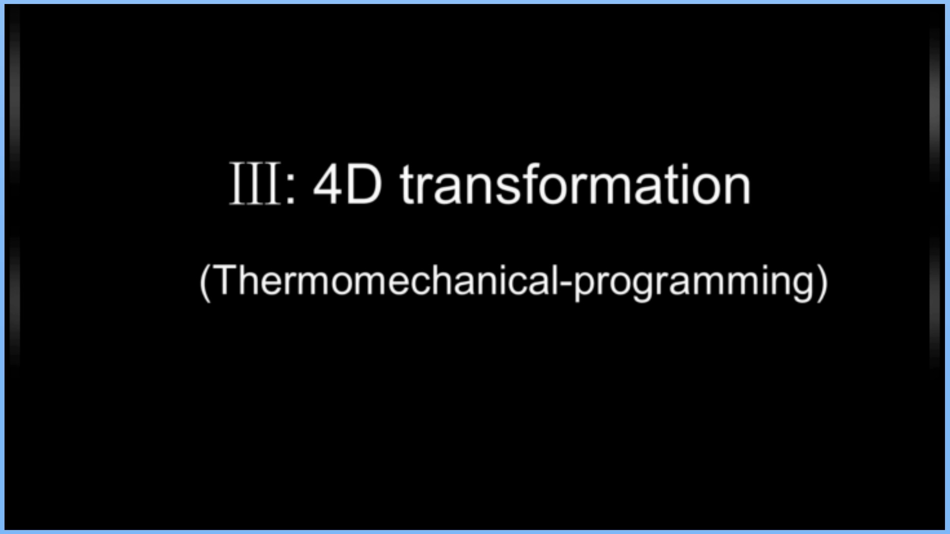




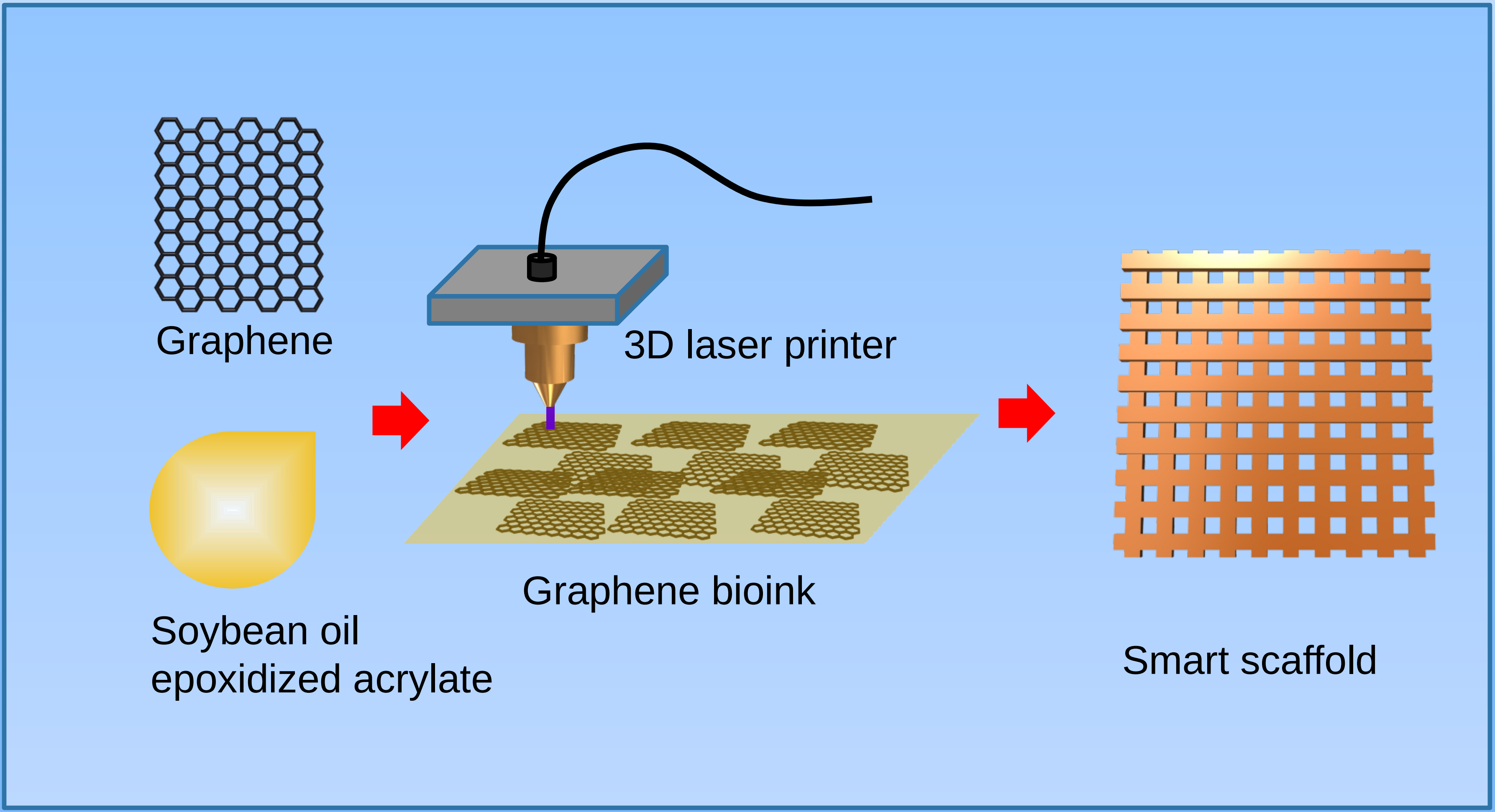
Temperature Sensitive 4D Printing

Shape memory effect

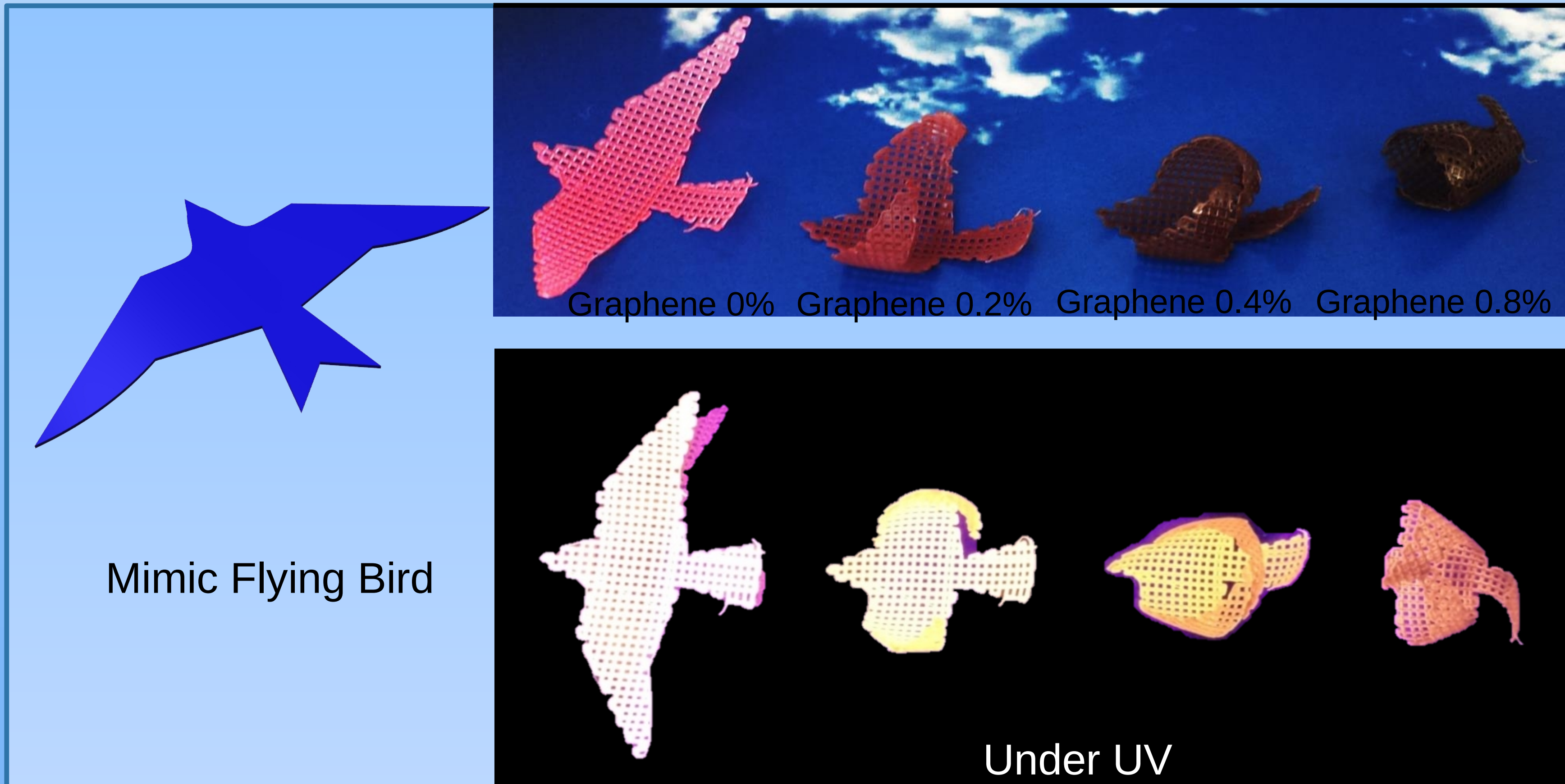




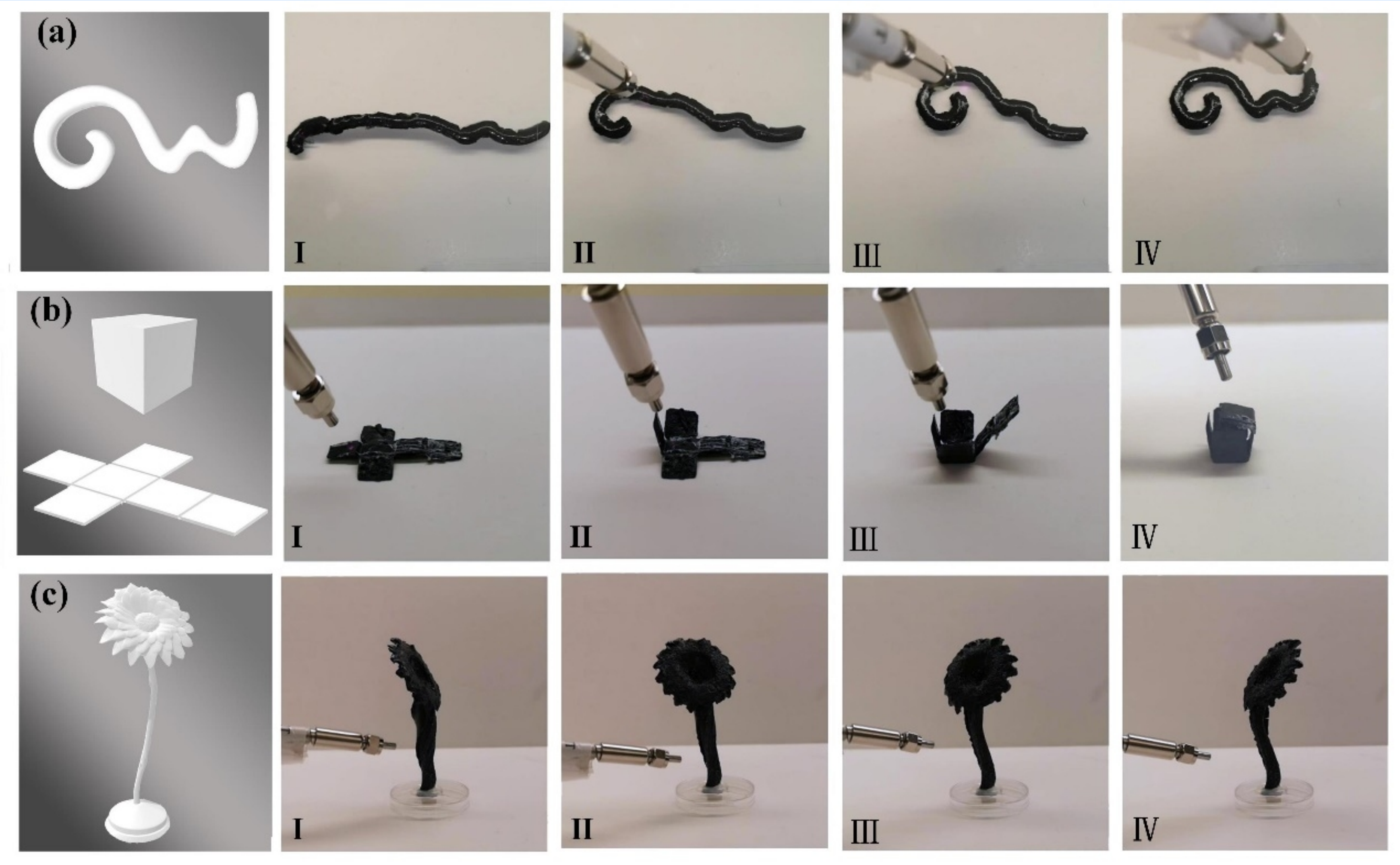
4D Printing Nanomaterials



The Effect of Graphene on 4D Printing

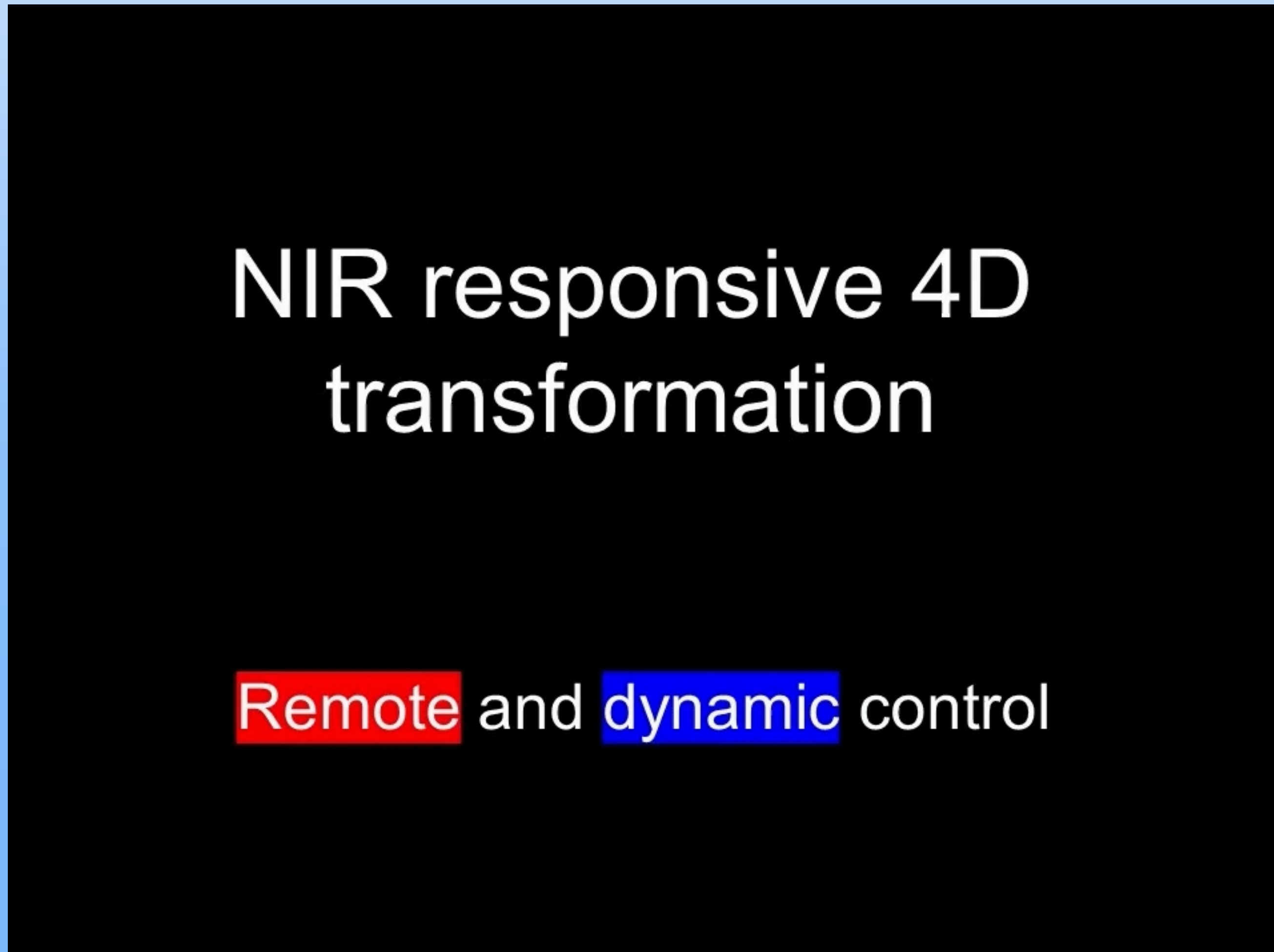


4D Printed NIR Sensitive Structures



Y. Wang, H. Cui, et al., ACS Applied Materials & Interfaces, 13(11):12746–12758 (2021)

Light Sensitive 4D Printing

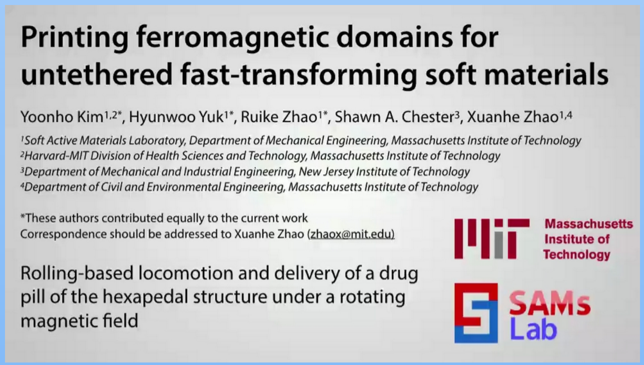


H. Cui, S. Miao, T. Esworthy, S. Lee, X. Zhou, S.Y. Hann, T.J. Webster, B. Harris, and L.G. Zhang. A novel near-infrared light responsive 4D printed nanoarchitecture with dynamically and remotely controllable transformation. *Nano Research*, 12(6): 1381–1388 (2019)

Other Noteworthy 4D printing Nanomaterial Research

Ferromagnetic particles as magnetothermal fillers in 4D actuators

Magnetothermal recovery of the 4D actuators



Printing ferromagnetic domains for untethered fast-transforming soft materials

Yoonho Kim[1,2*], Hyunwoo Yuk[1*], Ruike Zhao[1*], Shawn A. Chester[3], Xuanhe Zhao[1,4]

[1]Soft Active Materials Laboratory, Department of Mechanical Engineering, Massachusetts Institute of Technology
[2]Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology
[3]Department of Mechanical and Industrial Engineering, New Jersey Institute of Technology
[4]Department of Civil and Environmental Engineering, Massachusetts Institute of Technology

*These authors contributed equally to the current work
Correspondence should be addressed to Xuanhe Zhao (zhaox@mit.edu)

Rolling-based locomotion and delivery of a drug pill of the hexapedal structure under a rotating magnetic field

Massachusetts Institute of Technology

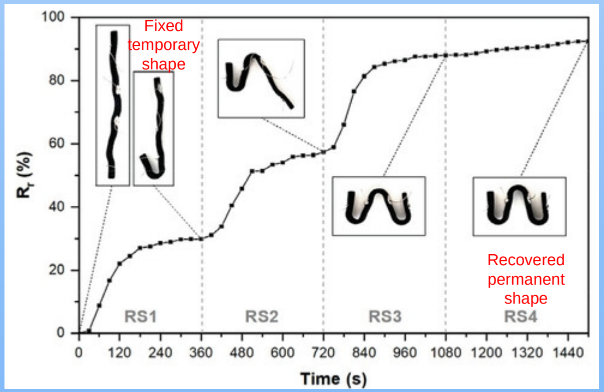
SAMs Lab

4D ink composition:
- SE 1700
- Ecoflex 00-30
- NdFeB particles

Kim, Yoonho, et al. Nature 558.7709 (2018): 274-279.

Carbon Nanoparticles as electrothermal fillers in 4D actuators

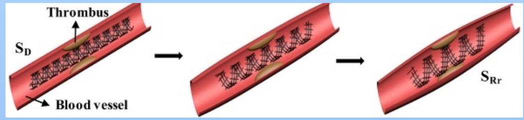
Electrothermal recovery of the 4D construct



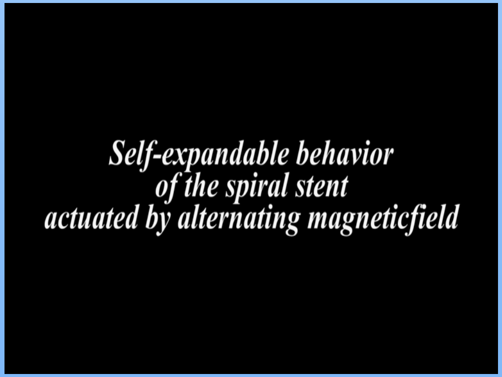
4D ink composition:
- Poly(ethylene glycol) diacrylate
- Poly(hydroxyethyl methacrylate)
- Carbon Nanotubes

Cortés, Alejandro, et al. Advanced Functional Materials 31.50 (2021): 2106774.

Iron oxide nanoparticles as magnetothermal fillers in 4D stents



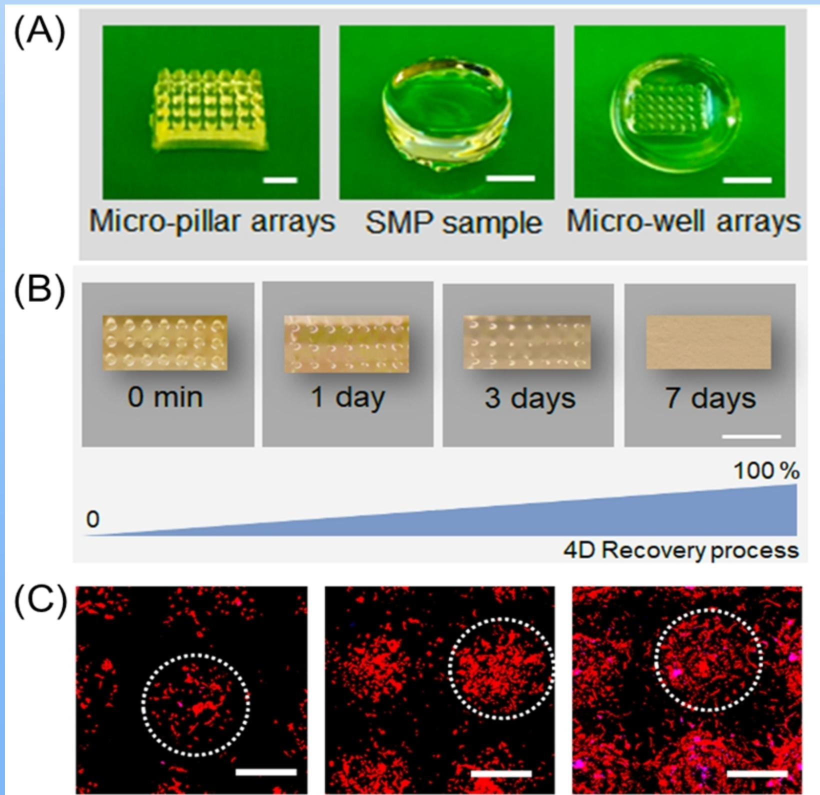
Magnetothermal recovery of the 4D stent

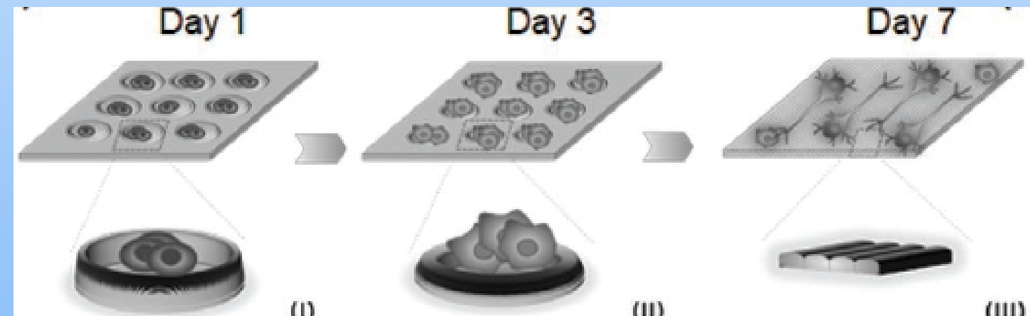


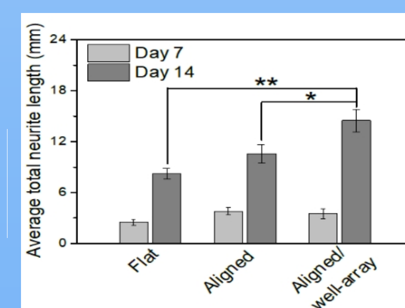
4D ink composition:
- Poly(lactic acid)
- Iron oxide nanoparticles

Wei, Hongqiu, et al. ACS applied materials & interfaces 9.1 (2017): 876-883.

Application I: 4D Printed Self-Morphing Culture Substrate for Improving Neural Stem Cell Functions



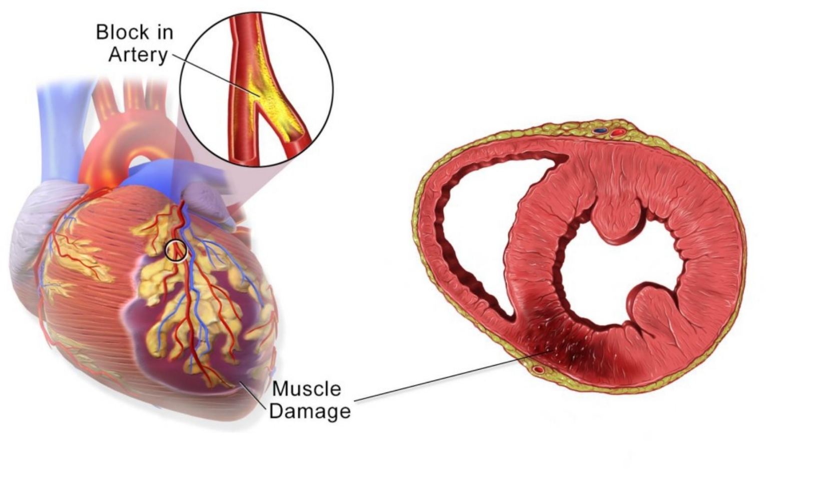


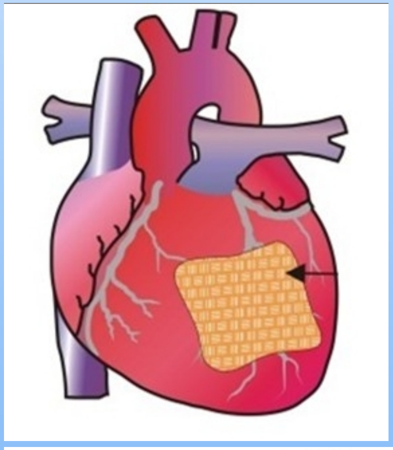


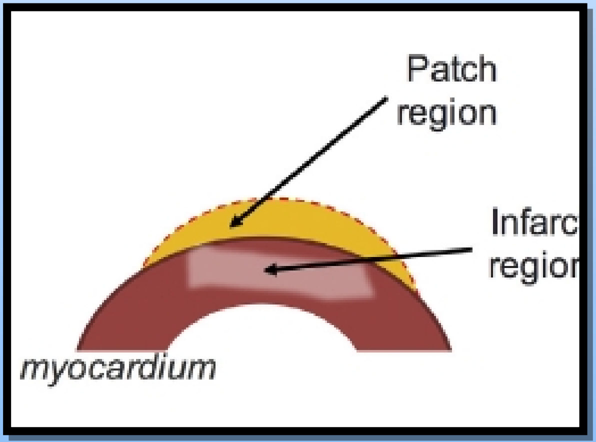
S. Miao et al. 4D Self-morphing Culture Substrate for Modulating Cell Differentiation. *Advanced Science*, 7:1902403 (2020)

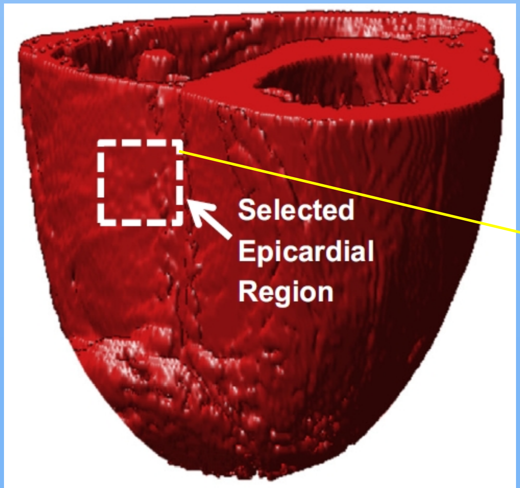
Application II: 4D Smart Cardiac Patch for Heart Repair

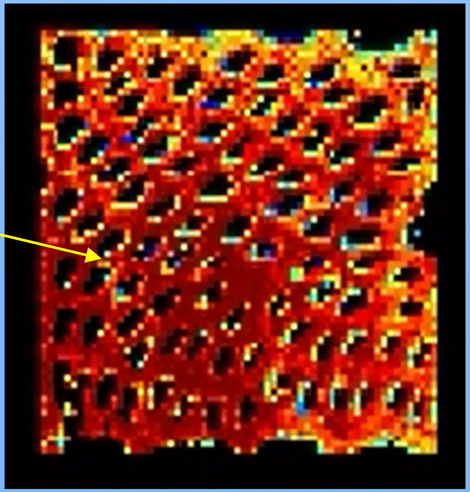
Myocardial infarction











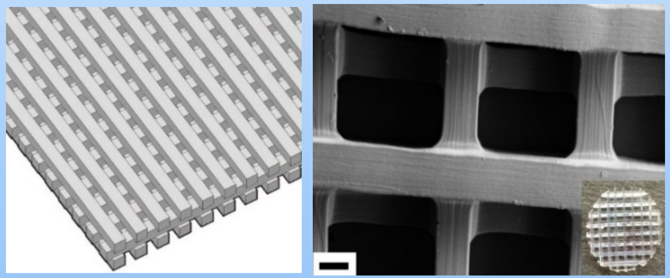
Cardiac tissue patch

- Cell delivery
- Mechanical supporting
- Biophysical integration

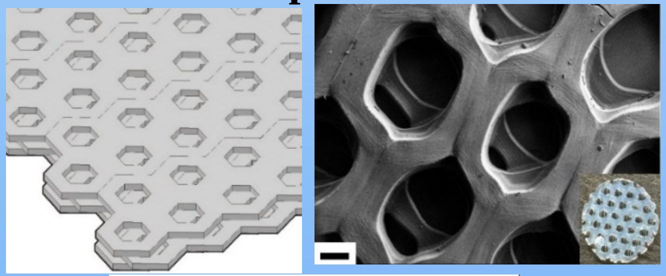
Bian W, et. al. Biomaterials. 2014;35(12):3819.
J. Jang et al. Biomaterials 112 (2017) 264.

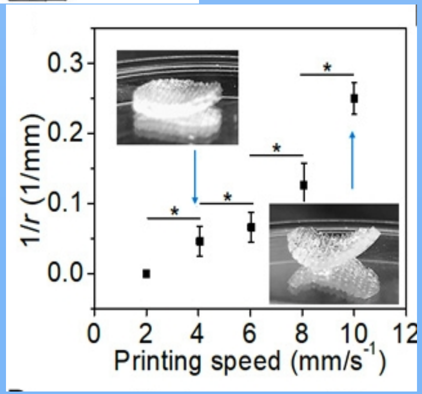
Cardiac Patch: Structural Design and 7 Days of Dynamic Cell Co-Culture

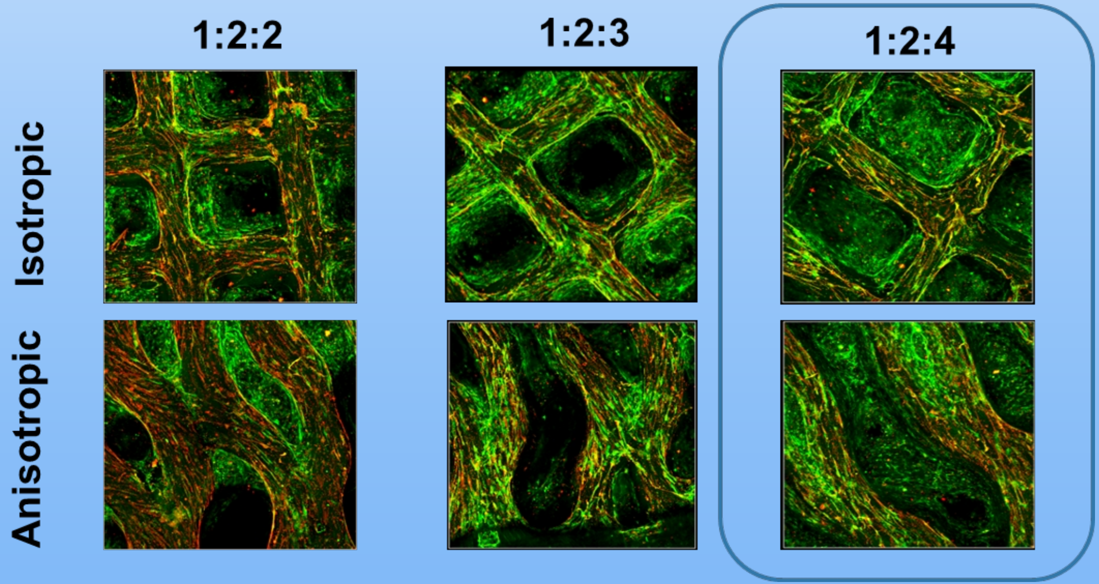
Isotropic Patch



Anisotropic Patch



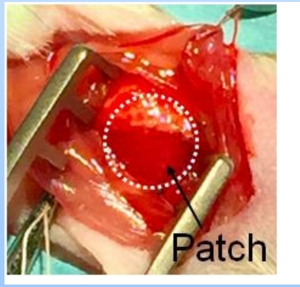




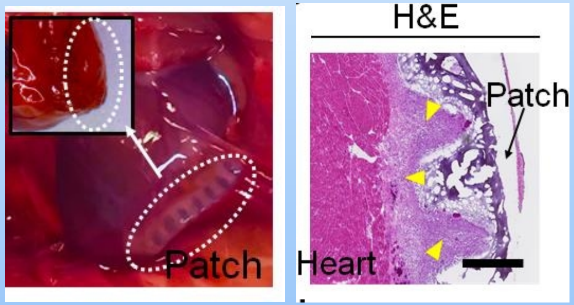
- The above cell images showed 1:2:4 is the best cell ratio for co-culture of MSCs, HUVECs (red) and iPS-cardiomyocyte (green) implantation.

H. Cui, C. Liu, T. Esworthy, et al. 4D Physiologically Adaptable Smart Vascularized Cardiac Patch: a Four-month *in vivo* Study for Myocardial Infarction Treatment. *Science Advances*, 6 (26), eabb5067 (2020).

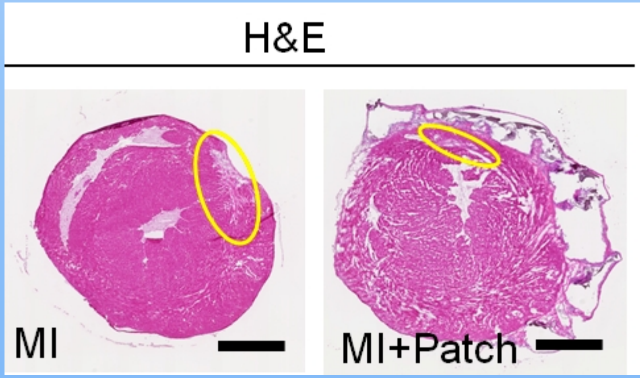
In Vivo Heart Implantation: Myocardial Infarct Mice for 4 months

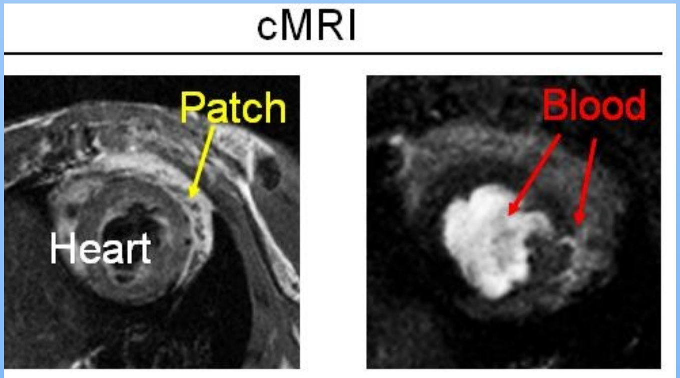


Implantation



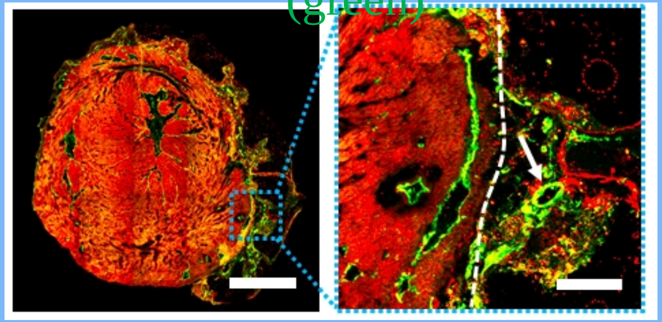
A firm adhesion & cell clusters with a high density



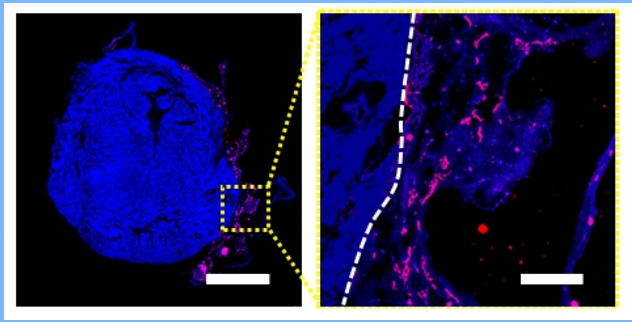


Smaller infarct size & contract and relax with the heartbeat and evident blood perfusion from the heart to the patch

Cardiac troponin I (red) /VwF (green)



Human CD31 (red) /DAPI



Robust survival of cardiomyocytes and vascularization *in vivo*. & a high density of capillaries.

Challenges and Future Directions

- **Smart bioprinting "inks": not biomimetic and bioactive for maximal cell growth and tissue integration**
- **Bioprinting platforms: low resolution, low cell viability and low yield**
- **Human benign stimulus-responsive performance and controllable function**
- **Improving the printed product lifespan, recycle times, multi-responsibility, and preprogrammed cycle capability**
- **"Functional" organs**

Acknowledgements

Students:

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Dr. Shida Miao
Dr. Tarun Agarwal
Timothy Esworthy
Shengbo Guo
Shuaiqi Song

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Dr. Brent Harris	Georgetown University
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Dr. Manfred Boehm	National Heart Lung Blood Institute
Dr. Michael Plesniak	The George Washington University
Dr. Rong Li	The George Washington University
Dr. Michael Keidar	The George Washington University
Dr. Kausik Sarkar	The George Washington University
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Dr. John Fisher	University of Maryland, College Park

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Questions?