4D Bioprinting Smart And Nanomaterials For Complex Tissue Regeneration

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Pillar I: 3D Bioprinting

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

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...

• Self-assembly DNA based nanotubes
• Core-shell nanospheres
• Nanocrystalline hydroxyapatites
• Graphene nanoplatelets
NEW FRONTIER:

4D BIOPRINTING
The printed constructs are able to change and mutate *over time*.

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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


Anisotropic Smart Structure Design for 4D Transformation

Various Structure Design

Solvent Triggered 4D Transformation

Reverse shape change effect

I: 4D transformation
(Immersed in ethanol)

II: 4D transformation
(Immersed in water)
Temperature Sensitive 4D Printing

Shape memory effect

<table>
<thead>
<tr>
<th>Original shape</th>
<th>Temporary -18°C, 0s</th>
<th>-18°C, 10min</th>
<th>37°C, 0s</th>
<th>37°C, 3s</th>
<th>37°C, 6s</th>
<th>37°C, 10s</th>
<th>37°C, 60s</th>
</tr>
</thead>
</table>

III: 4D transformation

(Thermomechanical-programming)
4D Printing Nanomaterials

Graphene

Soybean oil epoxidized acrylate

Graphene bioink

3D laser printer

Smart scaffold
The Effect of Graphene on 4D Printing

Mimic Flying Bird

Under UV
4D Printed NIR Sensitive Structures

Other Noteworthy 4D printing Nanomaterial Research

Ferromagnetic particles as magnetothermal fillers in 4D actuators

Carbon Nanoparticles as electrothermal fillers in 4D actuators

Iron oxide nanoparticles as magnetothermal fillers in 4D stents

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

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

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

Magnetothermal recovery of the 4D actuators

Electrothermal recovery of the 4D construct

Magnetothermal recovery of the 4D stent

Printing ferromagnetic domains for untethered fast-transforming soft materials


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

Application II: 4D Smart Cardiac Patch for Heart Repair

Myocardial infarction

Cardiac tissue patch
- Cell delivery
- Mechanical supporting
- Biophysical integration

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.

**In Vivo Heart Implantation:**
Myocardial Infarct Mice for 4 months

Cardiac troponin I (red) / VWF (green)

Human CD31 (red) / DAPI

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

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**
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Questions?