Research Thrusts and Testbeds

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## Technology Tasks and Flows Between TAs

<table>
<thead>
<tr>
<th>THRUST AREA 1</th>
<th>TECHNIQUE</th>
<th>MATERIALS</th>
<th>STRUCTURES</th>
<th>FEATURE</th>
<th>PURPOSE</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atomic Calligraphy</td>
<td>Au, Ag, Ni, Al, etc.</td>
<td></td>
<td>&lt;50 nm</td>
<td>High resolution patterns of metal that template organic/cellular assembly</td>
<td>BU</td>
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<tr>
<td></td>
<td>OVJP</td>
<td>C60, fluorescent, PEG OTS, HMDS, PEGDA, dPMT, pluronic, thiols, other organic, linear &amp; cyclic RGD</td>
<td></td>
<td>&lt; 2 µm</td>
<td>Functional coatings to create attachment points for cells</td>
<td>UM</td>
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<thead>
<tr>
<th>THRUST AREA 2</th>
<th>TECHNIQUE</th>
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<tbody>
<tr>
<td></td>
<td>Nanoscribe</td>
<td>PEG, PEO, PMMA, etc.</td>
<td></td>
<td>&lt;1 µm</td>
<td>3D nanoscale structures to act as scaffolds for cells and sensors/actuators</td>
<td>BU</td>
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<tr>
<td></td>
<td>AC + OVJP +Scaffolds</td>
<td></td>
<td></td>
<td>&lt; 50 nm</td>
<td>Patterned 3D structures with focal attachments that direct cell binding, motion and function</td>
<td>BU</td>
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<tr>
<th>THRUST AREA 3</th>
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<tbody>
<tr>
<td></td>
<td>Tissue Assembly</td>
<td></td>
<td></td>
<td>&lt; 50 nm</td>
<td>Complex surfaces and 3D scaffolds for cell binding/proliferation-multiscale, hierarchical, dynamic, embedded sensing</td>
<td>BU</td>
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<tr>
<th>THRUST AREA 4</th>
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<th>PURPOSE</th>
<th>WHO</th>
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<td></td>
<td>Imaging &amp; Actuation</td>
<td>fluorescent proteins, quantum dots</td>
<td></td>
<td>&lt; 1 µm</td>
<td>Deep 3D tissue imaging, fluorescent tagging, optogenetic actuation of tissue</td>
<td>BU</td>
</tr>
</tbody>
</table>
Functional Syncytium of Heart Muscle

- Mechanically and electrically coupled cardiomyocytes
- Aligned muscle units
- Interwoven microvessels
- Soft extracellular matrix (ECM) scaffolding supports architecture
CELL-MET Test beds

Cardiomyocytes
- Patterened adhesion proteins
- 3D printed scaffold
- Nucleus
- Integrated sensors
- Cardiomyocytes

Instrumented Cardiac Sheet
- Sensor/Actuator

Cardiac Microbundle
- Flexible post

Vascularized Cardiac Patch
- Angio port
- Sensor/Actuator
- Sensor/Actuator
Pre-ERC: Cardiac cell structure and function are controlled by materials
1) Patterning cell shape drives cell differentiation, alignment, and mechanics;
2) Scaffold stiffness regulates sarcomere maturation and force generation;
3) Focal adhesion distribution regulates sarcomere alignment and architecture
ERC Goals

1) Nanoscale control over cell adhesion will enable control over cell shape, sarcomere architecture, and cardiac function (TA1)

2) Controlling scaffold mechanics via both materials and architecture will allow control over cardiomyocyte mechanics (TA2)

3) Embedded sensors and actuators will allow real-time modulation of cell environment and assessment of cell function (TA2, TA4)

Approach

- Control the organization and alignment of cardiomyocytes (TA3), using metamaterials (TA2) and nanoscale adhesive patches (TA1)

- Use actuators (TA1 and TA4) to apply optical and electrical signals, mechanical loads, and structural changes to stimulate the tissue

- Use of feedback loop controls to provide adaptive responses between cells/tissues and their environmental signals

- Iteration based on performance and structural metrics
ERC Goals

1) Spatial control over mechanical environment will enable more complex alignments (TA2)

2) Specified nanoscale structure and adhesion will enable cell alignment/position control (TA1/2)

3) Embedded conduits will enable sensors and actuators (TA2, TA4)

Hinson et al., Science 2015
Cardiac Sheet

**Approach**

- Control the organization and alignment of cardiomyocytes, as with microbundles, but extended to larger sheets (TA1, TA2, TA3)
- Use actuators to apply electrical signals, mechanical loads, and structural changes to stimulate the tissue (TA1, TA2, TA3, TA4)
- Use embedded sensors and optical approaches to monitor cardiac function, including electrical potential, oxygen levels, pH, material strains, force (TA1, TA2, TA4)
- Use of feedback loop controls to provide adaptive responses between cells/tissues and their environmental signals (TA3, TA4)
Approach

- Control the organization vasculature and registration with aligned cardiomyocytes; Integration with microfluidic controls to perfuse tissue ex vivo (TA1, TA2, TA3)

- Use embedded sensors and optical approaches to monitor both vascular and cardiac function, including electrical potential, oxygen levels, pH, material strains, force (TA1, TA2, TA4)

- Use of feedback loop controls to provide adaptive responses between cells/tissues and their environmental signals (TA3, TA4)
Vascularized Patch

ERC Goals

1) Channels branched and tapered down to 3 µm diameter will match scales of vessels in tissues (TA2, TA3)

2) Introduction of embedded sensors and actuators will allow monitoring and manipulation of the engineered tissue (TA1, TA4)
Integrated Test Beds

A. Cardiac microbundle

B. Instrumented cardiac sheet

C. Vascularized cardiac patch
The Approach

Adhesive nanopatterns (TA1)
3D fabrication (TA2)
Cell Engineering (TA3)
Deep 3D (TA4)

System level test bed:
• 3D Organs-on-Chip
• Structured Implants
Provide a foundation for synthetic tissue manufacturing

- Understanding the *rules* that govern multicellular organization, how cells $\rightarrow$ tissues
- Establishing the *technologies* to control tissue assembly
- Engineering human tissues as *models for research* (e.g., heart-on-chip)
- Engineering human tissues as *therapeutics for transplant*
Two strategies for heart disease

Sarcomere Proteins (TTN, MYH7, MYBPC3, TNNT2, TPM1)
Lamin A/C
RNA-binding motif protein 20
Transcriptional Regulators
Z-disc Proteins
Intermediate Filaments
Dystrophin/Glycoproteins
ATP-binding Cassette
Heat Shock Proteins
Presenilin
αB Crystallin

Sarcomere Proteins (MYH7, MYBPC3, TNNT2, TPM1)
Lysosome-associated Membrane Protein-2
γ-2 subunit AMP-dependent Protein Kinase
Desmin
Trans-Thyretin
Alpha acid glucosidase
Alpha-D galactosidase
Myozenin-2
Actinin

HEART FAILURE:
~5 million Americans
500,000 new cases/year
Annual costs = $17.8 billion
Prognosis: 75% Die within 8 Years
Patients with dilated cardiomyopathy

Hinson et al., Science 2015
Questions