One-step 3D Differentiation of Cardiac Cells from Adult Human iPS Cells

Auburn University is seeking a licensee or development partner for a rapid method of differentiating cardiac cells from human iPS cells directly in 3D.

Overview: Engineered cardiac tissues are useful in medical applications, drug screens, and research. In the U.S. alone, the regenerative cardiac tissue market is expected to top $20 billion by 2019. Generating cardiac tissue from induced pluripotent stem cells (iPS cells) provides the ability to study human cardiac physiology and drug responses in culture, and the potential to create cardiac cells for clinical therapies. These cardiac tissues also avoid ethical concerns involving the use of embryonic stem cells. Current methods produce tissue that includes only some of the features found in mature cardiac tissue in animals. In addition, tools and reagents for these methods are expensive and culturing can be time-consuming. A faster, simpler method for growing and differentiating human iPS cells directly in a 3D environment has been devised that also generates high quality, cardiac tissue that includes more mature features found *in vivo*.

Advantages:

- **COST EFFECTIVE** — Faster and less expensive with up to 2X better cell survival
- **HIGH QUALITY** — Forms mature cardiac structures not observed in other approaches
- **LONG-LIVED** — Contractile function maintainable for over one year
- **SCALABLE** — Compatible with bioprinting and high throughput encapsulation

Description: Current state-of-the-art human iPS cell differentiation into contracting cardiomyocytes (CMs) follows either a 2D sheet approach or employs 3D cell aggregates (embryoid bodies). Both of these techniques require cells to be dissociated for downstream applications, resulting in multiple cell handling steps that disrupt cell-cell interactions and structures and result in high levels of cell death. This method cultures and differentiates human iPS cells into cardiomyocytes directly in materials of a particular stiffness, without 2D culturing or differentiating prior to 3D hydrogel encapsulation. No external electrochemical stimuli are required. Cardiomyocytes generated by this method retain their contractile function for months and have observable aligned sarcomeres, Z-bands, H-bands, and t-tubules. Sarcomeric α-actinin, Cx43, and Nkx2.5 have been detected throughout the entire tissue (Panels c & d on page 2) and better mimic tissue features found *in vivo*. This method can be used for more rapid, cost effective production of 3D cardiomyocyte structures for drug screening, engineered cardiac tissue formation, or other uses.

Status:

- Reproducibly demonstrated using human iPS cells
- Subject of US Patents 9,587,221, 10,301,597 and a pending application (20190284534)
- Microfluidic encapsulation device allows for high throughput production (20190105279)
- Available for licensing and development via funded research or a joint venture

See page two for additional details about the differentiation method

Inventors:

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References:

Biomaterials, 83: 383-395, 2016 (Link)

ACS Biomater. Sci. Eng., 3 (8): 1499–1509, 2017 (Link)

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Early Stage — *Prototype* — *Pilot* — *Market Ready*

One-step 3D Differentiation of Cardiac Cells from Adult Human iPS Cells (Cont'd)

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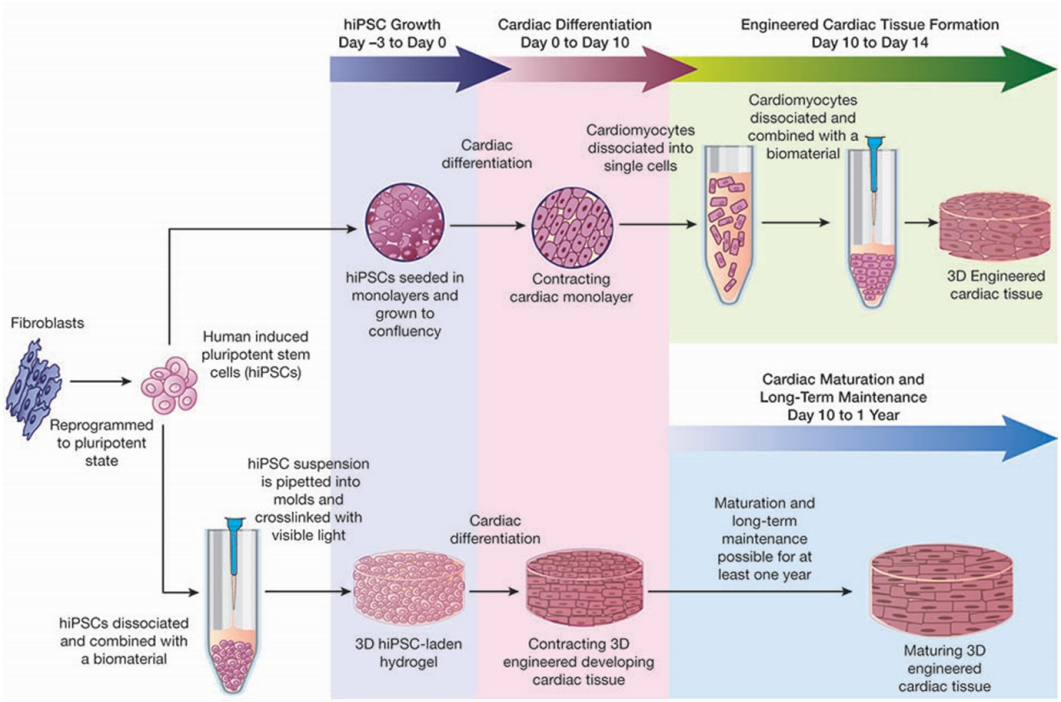
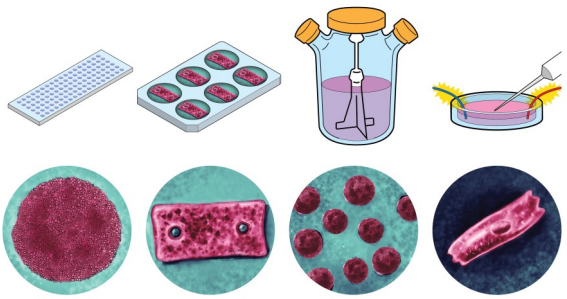
Applications:

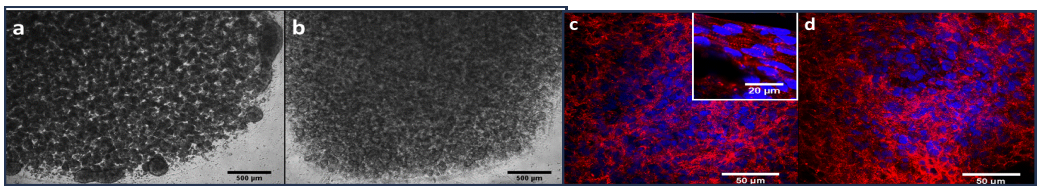
- Bioprinting
- Microislands
- Macrotissues
- Spheroids
- Drug screens
- Toxicity screens
- Patch clamp analysis
- Tissue engineering

Comparison of traditional differentiation (top) vs the one step method (bottom) starting with fibroblast-derived induced pluripotent stem cells





One-step method is compatible with multiple applications (left). Hydrogel materials facilitate direct formation of cardiac tissues with a range of tested geometries, from printable micro-islands to macro tissues to spheroids for cell production in scalable culture systems. Single cells for automated patch clamp analysis can be readily obtained following standard cardiac tissue dissociation protocols.



PEG-fibrinogen hydrogels enable iPS cell culture and differentiation in 3D. PEG-fb encapsulated clump (a) and single (b) human iPS cells. Immunostaining showing sarcomeric α-actinin (red) throughout the tissue in clump (c) and single (d) human iPS cells. Cell nuclei are shown in blue.

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