Cardiac Flow Cell for Monitoring Damage of Three Dimensional Tissues Under Stress

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Electrospinning (ES) is a fabrication technique for producing fibrous polymeric materials with nanoscale features and high surface areas. Electrospun fibers exhibit high surface-area-to-volume ratios, tunable porosity, and mechanical properties that can mimic the extracellular matrix (ECM), making them ideal candidates for biomedical applications. One of the most promising uses of electrospun fibers is in the development of cell scaffolds, where their structural and biochemical similarity to native ECM provides an optimal environment for cell adhesion, proliferation, and differentiation.

Traditional tissue research involves growing cells in a flask (*Figure 1A*) containing media and a treated surface under physiological conditions (37 °C, 5 % CO_2). The treated surface is meant to promote cell adhesion and tissue growth in a monolayer along the bottom of the flask (*Figure 1B*). To remove cells from a flask for testing, the cells must be lifted and separated into individual cells (using a trypsin-EDTA solution). As opposed to monolayer growth, several products such as Matrigel® from Corning® enable cells to grow within a gelatin matrix in three dimensions that mimic the extracellular matrix and provide an environment that better mimics a living physiological system. In Matrigel®, cells grow into organoid structures (*Figure 2*). In either the case of growing a tissue monolayer or growing cells in a gelatin matrix, cells cannot be transported without disrupting the tissue or organoid structures. Alternatively, we have electrospun crosshatch patterns to mimic the ECM onto nylon supports that can be moved for testing. In our method, we used polycaprolactone (PCL) for the ECM and moved the scaffold to a sterile well plate for tissue growth. Under physiological conditions, cardiac muscle and endothelial cells were seeded into the matrix in supplemented vascular media and growth was monitored by light (*Figure 3A*) and confocal microscopy (*Figure 3B*).

Using our mobile 3D cardiac tissue samples, we were able to place tissue grown on nylon support samples into a flow cell system constructed primarily of polypropylene block and that is entirely sterilizable. The flow cell has been equipped with time relays, solenoid valves, and peristaltic pumps to provide a pressure waveform based on electrocardiograph (ECG) signals (*Figure 4*). A metabolic assay test has been developed to monitor tissue damage following testing in the flow cell under hypertensive pressures. In this work, our goal is to better mimic real physiological growth, fluid flow, and stresses for the development of therapies and therapeutics that may prevent cardiac tissue damage under hypertensive pressures.

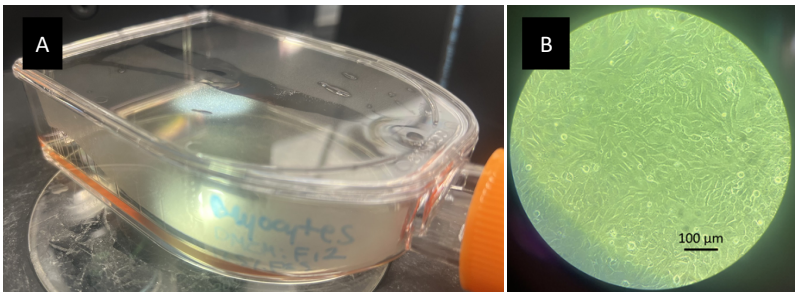

Figure 1. *(A) Cell culture flask containing cell media and cardiac muscle cells. The cells form a confluent tissue along the treated surface at the bottom of the flask (red arrow). (B) Electron micrograph showing an example of a cardiac endothelial tissue monolayer grown in a cell culture flask.*

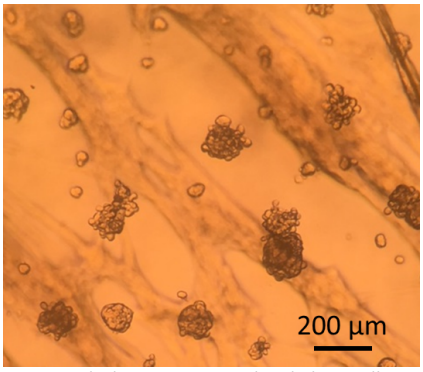

Figure 2. *Light micrograph showing mammalian kidney cells grown in three-dimensional organoid structures in Matrigel®.*

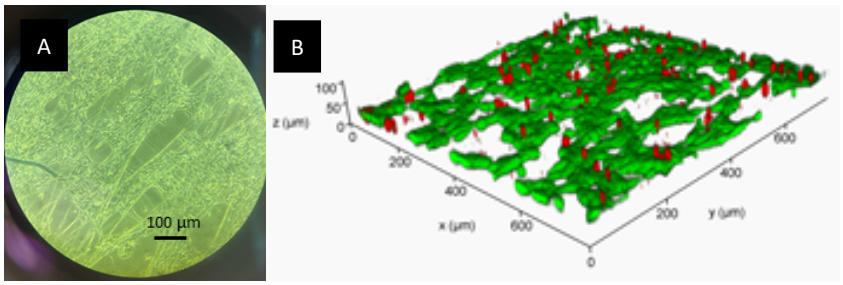

Figure 3. *(A) Light micrograph showing a cardiac myocyte tissue layer growing on a PCL electrospun scaffold. (B) Confocal microscopy map showing 3D growth of the myocyte tissue.*

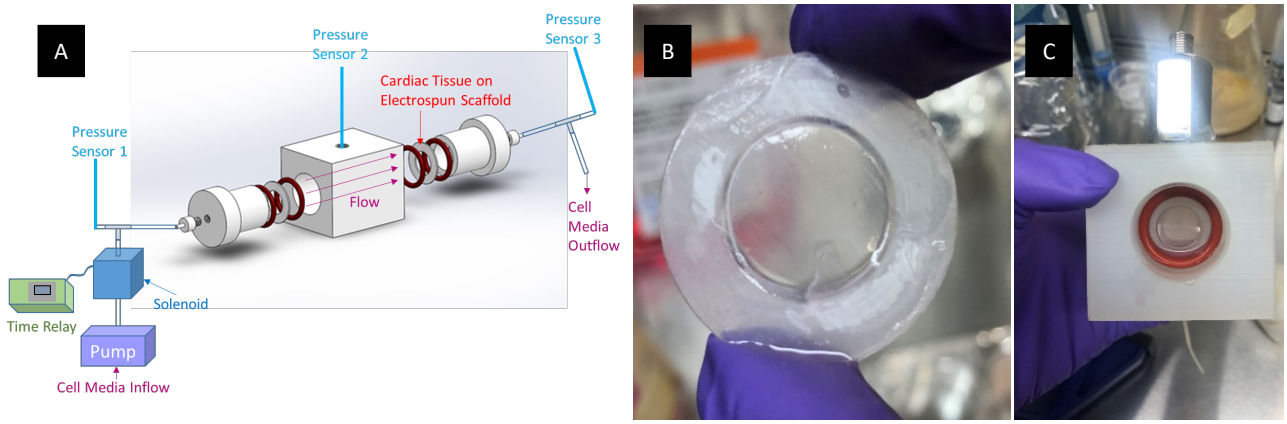

Figure 4. *(A) Depiction of the physiological flow cell modified to provide flow and pressures mimicking ECG signals. (B) Electrospun scaffold being moved to the flow cell for testing. The scaffold was made of electrospun PCL with a 3D mammalian kidney tissue grown onto the scaffold. (C) An image showing the scaffold after being placed into the flow cell for testing.*