“Tissue Model of the Epithelial Mesenchymal Trophic Unit”
BME Design Excellence Award Executive Summary
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Chronic lung diseases such as pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease (COPD) can cause significant damage to the epithelial tissues of the lungs which alters the ECM stiffness, compositions and cell phenotype. Hydrogels that are highly similar to the natural ECM allow for scientists to have an in vitro model that better mimics the complex biological environment of in vivo. No existing cell culture scaffolds accurately model the lung extracellular matrix (ECM) and its changes during cell injury, specifically the following properties in combination: varying mechanical stiffness, porosity, incorporation of collagen and fibroblasts within ECM, and cell adhesive properties. Competing culture methods include 2D and 3D models. Glass 2D culture models struggle to mimic the native lung ECM environment, due to their material stiffness being magnitudes greater than native tissue. 3D models consisting of pure, unmodified ECM (such as Matrigel) have increased batch-to-batch variability and fail to be reproducible in many cases. The material selection for the lung-mimetic hydrogel required consideration of the following criteria: the ability for hydrogel to have similar biochemical properties to that of native ECM (cell adhesion, porosity, and degradation) as well as allowing for tunable mechanical properties to fit that of both normal and fibrotic lung tissue. These specifications guided the selection of Gelatin Methacryloyl (GelMA) which is an engineered gelatin-based material that is produced through the reaction of gelatin with methacrylic anhydride (MA).

A series of GelMA hydrogels were produced. Gelatin Methacryloyl was crosslinked via UV photo-crosslinking, and cooling. Cross linkage and concentration of GelMA were used to control mechanical properties. A 3.6 kPa hydrogel was produced to model “healthy” lung tissue, and a stiffer hydrogel to model “fibrotic” lung tissue with an elastic modulus of around 16.5 kPa was produced. Characterization of the hydrogels’ mechanical properties was done via rheometry. The shear modulus and Poisson’s ratio were used to find the elastic modulus, which quantified the stiffness of the “healthy” and “fibrotic” gels. Statistical analysis determined that the two gel conditions met the desired mechanical property requirements.

The team’s GelMA hydrogels facilitate cell adhesion and viability, as well as accommodate mechanical variations between normal and fibrotic tissues. Moreover, incorporating fibroblast encapsulation and controlling the degradation time could enhance the biomimetic properties of GelMA hydrogels. The GelMA hydrogel design effectively addresses the client’s operational requirements and fulfills their need for a more accurate ECM model. The hydrogels were cultured with human small airway epithelial cells (hSAEpCs) with multiple stiffness trials at 3.6 kPa, 16.5 kPa, and 45 kPa. The hydrogels successfully supported cell adhesion, growth and showed differences in cell shape. The cell adhesion on the hydrogels of 3.6 kPa stiffness was lower than that of higher stiffnesses but over the course of week began to show cell viability and changes in cell shape. These variations in cell behavior between each different hydrogel stiffness can be further studied by conducting cell viability assays and tracking cell expression markers in the epithelial cells that are sensitive to mechanical environment. The cell adhesion and viability seen in the prototype hydrogels show that the GelMA hydrogel design enables cell culturing to be conducted on a surface that mimics the native lung ECM environment, fulfilling the client’s goals.