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Well-defined Bioinspired Multidimensional Culture Systems For Studying Cellular Responses To Injury And Pathogens

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Changes in the microenvironment of cells that occur with injury, including maladaptive extracellular matrix (ECM) remodeling, are thought to contribute to the initiation of disease. For example, repeated injuries to the lung epithelium are hypothesized to initiate a maladaptive cascade of immune cell and fibroblast activation, where the persistent activation of fibroblasts contributes to excess deposition and crosslinking of collagen, stiffening of tissue, and ultimately organ dysfunction and death. Engineered culture systems provide great opportunities for studying these complex processes for improved mechanistic understanding and establishing improved treatment strategies.

We have established synthetic extracellular matrices (ECMs) for the creation of multi-dimensional culture systems that allow us to probe the response of lung cells (e.g., epithelial cells, fibroblasts, immune cells) to ‘injury’ to the ECM, triggered by the application light or other stimuli. To allow real-time monitoring of cell responses to injury, we have established human reporter cell lines for dynamically probing changes in cell phenotype in response to these microenvironment changes. We are utilizing these systems to probe mechanisms and potential interventions to prevent the initiation and progression of maladaptive wound healing after injury and thereby the disease processes that follow. We are translating our 3D culture models into a high-throughput format utilizing a bioprinter for accessible mechanistic studies, including examination of host-pathogen interactions, and to enable screening of drug and agent effects. Further, we are adapting our approaches for the creation of other relevant 3D culture models for probing responses to pathogens and agents at the ‘front lines’ of the human body, with 3D bioprinted skin models in addition to lung models.

These innovative approaches contribute to and advance microphysiological system tools relevant to studying chemical and biological agents in the Department of Defense Chemical, Biological, Radiological and Nuclear Defense realm. Additionally, these models are amenable to a variety of downstream analysis methods, providing more pathways for incorporating high-throughput data compilation. Through collaboration with the U.S. Army DEVCOM Chemical Biological Center, we are applying and refining these systems to better model and understand the effects of agents that may be threats to the warfighter.

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