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Engineered Distal Lung Constructs (EDLC) for High Throughput Drug Discovery and Toxicity Screening *in vitro*

Background: Lung diseases encompassing both neonatal (pulmonary hypoplasia, bronchopulmonary dysplasia), and acquired (e.g. emphysema, chronic obstructive lung disease (COPD) and lung cancer) are well-documented major health problems. For example, preterm delivery with resultant pulmonary hypoplasia is a major problem in obstetrics and accounts for more than 70% of perinatal mortality. In 2004, 12.5% of births in the United States were preterm with 8.1% being low birth weight. These children are born with pulmonary hypoplasia or poor lung development, which causes significant morbidity and mortality.

There is a significant need and unmet demand, especially in the pharmaceutical industry, for novel cell-based 3- dimensional models of healthy and diseased functional lung tissue. These "engineered distal lung equivalents" (EDLC) would allow for reliable preclinical screening of treatment modalities in the process of drug discovery. Current cell-based models of "distal lung" are either simple 2-dimensional cultures of alveolar epithelial cells or lung explant cultures. These models inherently fail morphologically and functionally to mimic the complexity of the alveolar/capillary interface reminiscent of the true distal airway. The availability of high-fidelity complex preclinical models would substantially accelerate the pace of translating effective treatments of lung disease from discovery at the bench to implementation at the bedside.

Technology Innovation: The basis of this translational project is technology that we have developed in our laboratory focusing on our unique approach for generating vascularized pulmonary constructs *in vitro*. An IP disclosure has been filed with Drexel University's Office of Technology Transfer. These engineered constructs morphologically and functionally mimic the 3-D architecture of the alveolar/capillary interface of the distal lung. Operationally, we termed our model "Engineered Distal Lung Constructs" (EDLC). These EDLC can be utilized for designing and testing novel therapies such as drugs or cell-based therapies for neonatal pulmonary diseases. In addition, unique to our concept, these EDLC can also mimic various acquired pulmonary disease states, such as COPD, emphysema, lung cancer, pulmonary hypertension, or infection (such as the H5N1 avian flu virus).

Proposed Study: The purpose of this grant proposal to the Coulter foundation is to explore the feasibility and usefulness of EDLCs as high fidelity pharmacologic test-beds for various disease states of the lung. Our deliverable will be a "medical device" as a platform technology, i.e. arrays of tissue-engineered miniature distal lung constructs, which will be packaged and sold in a multi-well format. Researchers in the pharmaceutical industry will be able to utilize these EDLCs to identify potentially therapeutic drugs/technology and perform necessary toxicity screening. As a proof-of-concept, we propose to establish a viral infectivity model and evaluate the efficacy of two established antiviral drugs, Oseltamivir (Tamiflu) and Zanamivir, to ameliorate or revert avian bird flu induced morphological and/or functional damage to the model lung tissues.