**Modelling the Airway Epithelium to Facilitate Cystic Fibrosis Drug Development**

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Cystic fibrosis (CF) is a life-shortening diseased caused by mutations of the Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR). Dysfunction of the associated anion channel, also called CFTR, results in osmotic gradients that favor dehydration of the airway surface liquid (ASL) layer. CF lung disease is associated with airway mucus dehydration and accumulation, chronic infection and inflammation, and respiratory failure. We have developed organ scale models of mucus clearance and ASL absorption, informed by nuclear imaging studies of particle and small-molecule probe clearance from the lungs of CF patients and healthy controls, including tests of therapeutic response (Markovetz et al, PLOS One 2014).

More recently we have developed cell-scale models that allow for exploration of electrophysiological dynamics in Human Bronchial Epithelial (HBE) cell cultures. HBE cultures are derived from airways removed at the time of lung transplant. CF HBEs demonstrate the ion and liquid transport defects associated with CF lung disease. One of our cell-scale models describes the cell’s ion-transport and volume regulation under conditions simulating those of an Ussing Chamber (UC) experiment− the most commonly used tool for epithelial functional characterization, drug screening, and other electrophysiological studies. The model is designed around a cellular compartment interfacing two source/sinks representing the apical and basolateral fluid volumes in an UC. It utilizes a set of differential algebraic equations (DAE) that relate changes in electrolyte concentrations, membrane potentials, and liquid transport as functions of time and satisfy the electrical constraints of the system. The model was informed with data obtained from UC experiments on fully differentiated, primary CF HBE. The model was constructed in Pyomo (a Python package), and parameters for cellular volume regulation, ionic fluxes, and channel permeabilities were estimated using IPOPT (a nonlinear interior point solver). This approach allows for simultaneous parameter fit and solution of the electronically constrained DAE system. Parameters for modeling HBE electrophysiology were obtained from published literature (Garcia, *et al*, Biophys. J., 2013; Falkenberg, *et al*, Biophys. J., 2010). The model returns predicted trajectories for key transport mechanisms within the cell, and provides insight into membrane pathway activities that is not experimentally accessible without significantly disturbing the cell monolayer. Next steps include further development of cell-level models pertinent to physiological (“thin-film” ASL) conditions.

Clinical studies are under way to link the cell and organ level models. CF and control subjects perform nuclear imaging scans and other measures of lung and epithelial physiology. They also provide nasal epithelial cells for culturing. Human nasal epithelial (HNE) cell cultures demonstrate similar function to HBE cultures. Matched physiological data at the organ and cell levels will facilitate development of a single composite model, which may allow us to predict organ-level therapeutic response from cell-culture studies.