**2018 IMAG Futures Meeting – Moving Forward with the MSM Consortium (March 21-22, 2018)**

*Pre-Meeting Abstract Submission Form*

*\*Please submit to the NIBIB IMAG mailbox (*NIBIBimag@mail.nih.gov*) by* ***January 8th, 2018***

*\*Save your abstract as “MSM PI Last Name \_ 2018 IMAG Futures Pre-Meeting Abstract”*

**PI(s) of MSM U01: Timothy E. Corcoran and Robert S. Parker**

**Institution(s): University of Pittsburgh**

**MSM U01 Grant Number:** 1UO1 HL131046-01

**Title of Grant:** Building Multilevel Models of Therapeutic Response in the Lungs

**Abstract**

Which MSM challenges are you addressing from the IMAG 2009 Report and how?

<https://www.imagwiki.nibib.nih.gov/content/2009-imag-futures-report-challenges>

(indicate which challenge (#) you’re addressing)

*You may insert images by copying and pasting below*

(**11) Mechanistic multiscale models that bridge to the population level to capture more clinical and biological realism for the population**.A key contribution of our proposed work is to bridge Cystic Fibrosis (CF) associated cell-level ion channel malfunction to the individual and population functional assessment of mucociliary clearance (MCC) from the whole lung. At the cell scale, we have human nasal epithelial cell cultures collected from healthy donors, parents of CF patients, and CF patients. The model employs differential-algebraic equations to capture ion transport, fluid trafficking, and electrophysiology to match experimental Ussing chamber assessments for the various patient groups, both individually and as a population. At the organ scale, we have previously constructed lumped-parameter ODE models to capture the MCC and fluid trafficking response of individuals and the patient population during a functional imaging studies.

**(18) Predictive multiscale models to improve clinical workflow, standard operating procedures, patient-specific modeling for diagnosis and therapy planning.** Using patient-specific models at the systems, and ultimately, cell scale(s), it becomes possible to conduct *in silico* assessments of possible treatment strategies to promote mucus clearance. An example of a present therapy is inhaled hypertonic saline, which is not very durable. Our multi-scale models, calibrated against inhaled normal and hyperosmotic saline, can be used to design an inhalation protocol to target normal hydration levels for CF patients, based on models calibrated to individual patients. Furthermore, we are testing the model with other hyperosmotic therapies (e.g., inhaled mannitol) to assess durability of action and decrease the burden of repeated treatments.

Are you using machine learning and or causal inference methods and how?

*You may insert images by copying and pasting below*

 We are not presently using machine learning methods as part of this project. Other projects in the Parker lab are employing logistic regression, clustering methods (hierarchical, KNN), and other data-driven approaches with large data sets to identify subpopulation phenotypes and endotypes by grouping patients according to measurable blood or clinical biomarkers.

Please briefly describe significant MSM achievements made (or expected).

*You may insert images by copying and pasting below*

 We have enrolled 24 subjects (11 controls, 8 CF, and 5 CF parents). These subjects have all had nasal cells collected for culturing and performed a series of lung physiology studies, including our imaging-based assessments of MCC and small molecule absorption (ABS). This data will be used to inform our models. We continue to evolve our generalized, compartment-based model of epithelial cell physiology based on Ussing chamber conditions (a well-defined experimental case) and are now transitioning to the use of a thin-film conditions (more difficult to define but more physiologically relevant). We continue to refine our organ level model to improve both quality of fit to experimental (human imaging) data and the ability to link model parameters to the underlying biology We have also performed a series of experiments comparing the physiology of human nasal epithelial (HNE) and bronchial epithelial (HBE) cell cultures. HBEs have received more use as a disease model in CF and directly illustrate conditions in the lungs but are generally not as accessible as HNEs.

Please suggest any new MSM challenges that should be addressed by the MSM Consortium moving forward.

*You may insert images by copying and pasting below*

 We have categorized our cell-to-organ-to-organism-to-population work under item (11) from the 2009 IMAG report. It may be more appropriate to make a new challenge heading to span the full range with models grounded in experimental data that capture as much mechanistic understanding as possible at the various scales. The mechanism component, when grounded in observations, would aid linkage across scales by helping direct how smaller-scale models might fit into higher-level models either parametrically or spatially. Models would need to explicitly address the spatiotemporal nature of organ function, while also being tied to a functional/clinical readout that could differentiate healthy and diseased individuals (perhaps also allowing endo/phenotyping of the diseased population into subpopulations based on model-captured differences).

What expertise are on your team (e.g. engineering, math, statistics, computer science, clinical, industry) and who?

*Please list as “Expertise – Name, email”*

Clinical Imaging/engineering - Timothy E. Corcoran, corcorante@upmc.edu; Engineering / mathematics - Robert S. Parker, rparker@pitt.edu; Cell electrophysiology - Carol Bertrand, cbertra@pitt.edu; Cell physiology and CF Clinical - Michael J. Myerburg - myerburgm@upmc.edu, and Joseph M. Pilewski -pilewskijm@upmc.edu

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