Building multi-level models of therapeutic response in the lungs

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Model Credibility Plan

Lightning Presentation

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Study goal:

For Cystic Fibrosis, create in silico models to predict organ (lung) level therapeutic response based on response in nasal cell cultures.

Currently enrolling subjects to inform models:

Collecting cell level physiology/response data from nasal cells

Collecting organ level physiology/response from imaging studies, sweat chloride measurements, and pulmonary function tests.

First half of subjects informs model. Second half validates model.

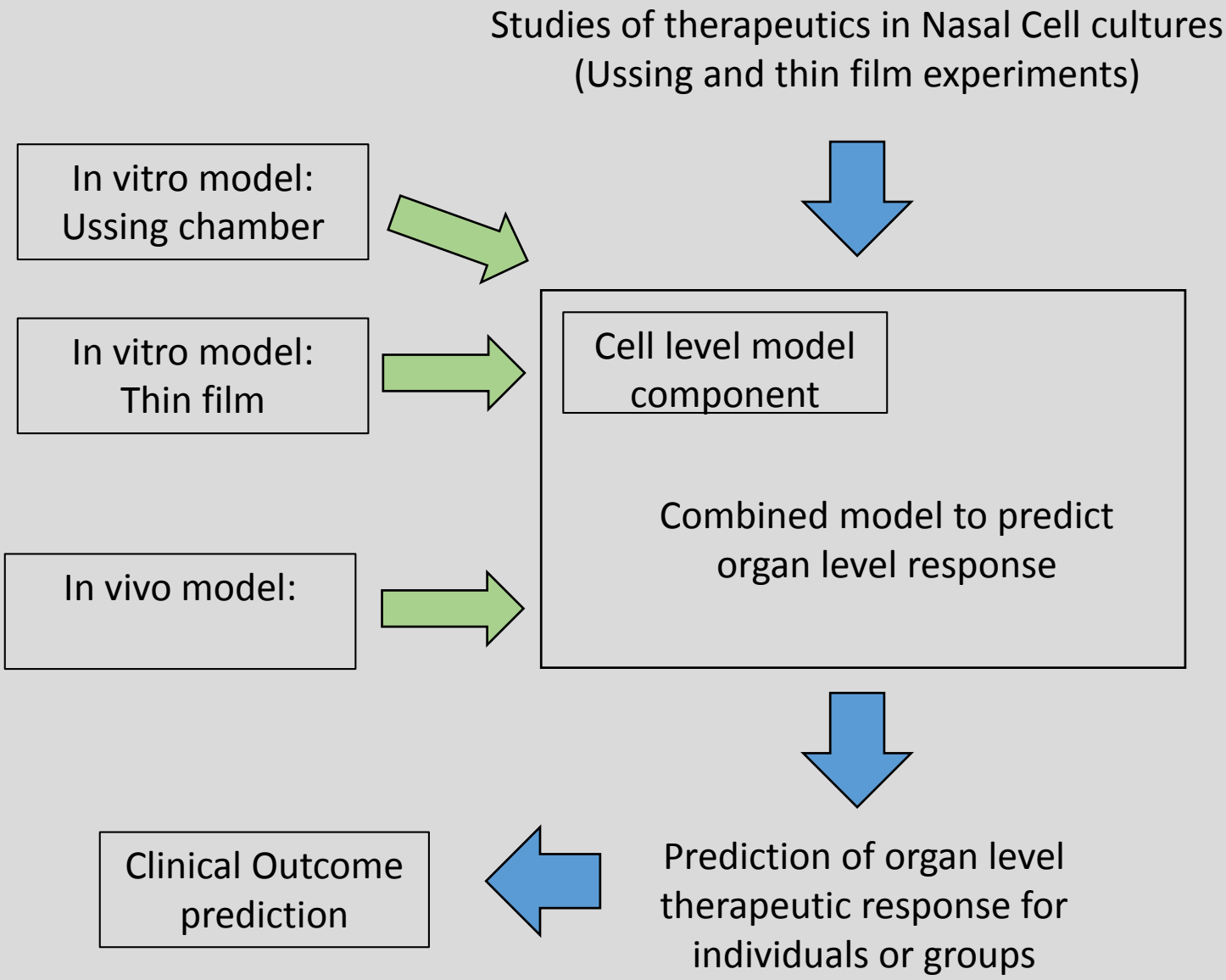
Enrollment:

group	Enrolled as of 3/2018	Planned total enrollment
CF patients	11	30
Single mutation carrier parents of CF patient	6	16
Healthy controls	12	16

Funding start 9/2016, First enrollment 1/23/17

Clinicaltrials.gov NCT02947126

Measurements and information flow for final model:



Model Credibility: Timeline and Milestones

- Existing, ready for review
  - organ-scale submodel (Markovetz *et al.*, PLoS One, 2014)
  - prospective validation will be conducted through our award

- In development (Lung 2017-18; nasal 2018-19)
  - cell-scale electrophysiologically-based submodel of human lung epithelia
  - extension to human nasal epithelia
  - extensibility of structure across populations (non-CF, carriers, CF patients)

- Planned (2019-2020)
  - integrated model, using nasal epithelial data to understand lung dynamics
  - development of model-based for treatment design

Model Credibility: Ideal Third-Party Evaluation Team

1. **systems engineering**, including experience constructing nonlinear dynamical models of physical systems using experimental data
2. **epithelial disease basic science**, ideally with cystic fibrosis and/or the lung, with a focus that may range from intracellular response to cell-scale regulation to systems-level (or organ-level) monitoring and disease progression
3. **clinical training**, with experience in pharmacologically-guided treatment of disease; it would be advantageous, but not necessary, to have lung disease/CF experience
4. **regulatory/industrial pharmacology/translational experience**, with a history of using mathematical models in concert with disease treatment

Cell-to-Macroscale, Clinical and Translational issues, Model and Data Sharing, and potentially the Theoretical and Computational Methods Working Groups

Python/Pyomo and C++ are our primary tools