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A multi-scale model to predict outcomes of immunomodulation and drug therapy during tuberculosis.

This document contains three abstracts for IMAG 2014 MSM Consortium meeting. The titles have already been entered at the website, but we were not able to enter the full information that is included here.

Tuneable resolution as a systems biology approach for multi-scale, multi-compartment computational models

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The use of multi-scale mathematical and computational models to study complex biological processes is becoming increasingly productive. Multi-scale models span a range of spatial and/or temporal scales and can encompass multi-compartment (e.g. multi-organ) models. Modeling advances are enabling virtual experiments to explore and answer questions that are problematic to address in the wet-lab. Wet-lab experimental technologies now allow scientists to observe, measure, record, and analyze experiments focusing on different system aspects at a variety of biological scales. We need the technical ability to mirror that same flexibility in virtual experiments using multi-scale models. Here we present a new approach, tuneable resolution, which can begin providing that flexibility. Tuneable resolution involves fine- or coarse-graining existing multi-scale models at the user's discretion, allowing adjustment of the level of resolution specific to a question, an experiment, or a scale of interest. Tuneable resolution expands options for revising and validating mechanistic multi-scale models, can extend the longevity of multi-scale models, and may increase computational efficiency. The tuneable resolution approach can be applied to many model types, including differential equation, agent-based, and hybrid models. We demonstrate our tuneable resolution ideas with examples relevant to infectious disease modeling, illustrating key principles at work.

High pre-treatment bacterial burden and sub-optimal antibiotic concentrations within granulomas result in treatment failure in TB

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While active tuberculosis (TB) is treatable, factors such as long treatment regimens, HIV co-infection, treatment failure, relapse and drug-resistance prevent its global elimination. Part of the difficulty in developing optimal drugs and regimens is our lack of understanding of antibiotic dynamics at the site of infection, i.e. lung granulomas. To help address these issues, we develop a computational model of granuloma formation and function that includes plasma pharmacokinetics, lung tissue pharmacokinetics and pharmacodynamics for two first line anti-TB antibiotics and is calibrated to data from animal models of TB. We use the model to study treatment dynamics and outcomes. The model predicts that antibiotic concentrations remain below effective concentrations for the majority of dosing intervals inside granulomas, leading to bacterial growth between doses, contributing to the long treatment periods required. Also, antibiotic concentration gradients form within granulomas, with lower concentrations toward the center. Bacterial subpopulations shift from mostly intracellular to mostly extracellular; however, located in areas non-permissive for replication during treatment, presenting a changing target population over time. Intermittent regimens (twice/thrice weekly dosing) have longer predicted times to clearance and fewer sterilized granulomas compared with daily regimens. The model predicts that changes in antibiotic plasma clearance rates and intracellular activity can most significantly improve treatment outcomes and should be considered when designing new drugs. On a per granuloma basis, pre-treatment infection severity (including bacterial burden, host cell activation and host cell death) is predictive of treatment outcome. Finally, we use the computational model to propose ways to optimize current regimens.

Identifying key mechanisms in fibroblast disregulation using a systems biology approach

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Pulmonary fibrosis, stiffening and scarring of the lung tissue, is a symptom of interstitial lung disease with no available treatments and poor prognosis for patients. It occurs when disregulation of the proliferative and remodeling phases of the wound healing process result in uncontrolled proliferation and activation of fibroblasts, excessive extracellular matrix deposition (ECM), and detrimental tissue remodeling. The molecular mechanisms underlying this disregulation are poorly understood providing an untapped pool of potential therapeutic targets. TGFβ is known to be an important factor in fibroblast activation while Pge2 has been shown to counteract TGFβ in the context; however the mechanistic details of this relationship have not been characterized. Using a multi-scale systems biology approach we are able to predict mechanisms responsible for disregulated fibroblast behavior and propose potential therapeutic targets. We have created a hybrid multi-scale model with a focus at the molecular level on the role of TGFβ receptor ligand signaling dynamics and downstream signaling events in fibroblast activation, and at the cellular level on fibroblast and epithelial cell co-regulation. Our model allows us to evaluate real-time molecular events in the context of a fibroblast/epithelial cell co-culture. With this tool we derive mechanisms driving pathogenic fibroblast behavior across the cellular and molecular scales. The use of statistical uncertainty and sensitivity analysis enables us to identify key factors in fibroblast regulation and predict potential therapeutic targets for pulmonary fibrosis.