**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](mailto:NIBIBimag@mail.nih.gov)*) by* ***January 8th, 2018***

**PI(s) of MSM U01: Dartois, Flynn, Kirschner (contact), Linderman**

**Institution(s): Univ. Michigan, Rutgers Univ., Univ. Pittsburgh**

**MSM U01 Grant Number: 5U01HL131072**

**Title of Grant:** **Multi-scale systems pharmacology approach to TB therapy**

**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)

This MSM project integrates computational and biological models that bridge multiple length and time scales with the overall goal of identifying improved antibiotic regimens for TB treatment. Aspects of our project that address the challenges include:

* Unique collaboration of experimentalists and computational modelers in immunology, pharmacology, mathematics and engineering to address a central problem in TB. (challenge #1)
* Our predictive multi-scale model (MSM) bridges multiple physiological spatial and time scales and is aimed at narrowing the design space for antibiotic treatment. Our systems pharmacology approach will for the first time integrate (a) immune and infection processes that occur at multiple scales to produce several granuloma types, (b) bacterial dynamics, including development of resistance and role of the local environment, and (c) antibiotic PK-PD, including penetration into different regions of granulomas, to predict therapy efficacy. Novel heterogeneous agent-based model (ABM) grid will be implemented to capture dissemination of bacteria to airways leading to cavity formation - a major problem in TB patients. (challenges # 5, 15)
* Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) imaging to capture antibiotic penetration into rabbit, NHP and human granulomas. These samples are spatially data-rich but temporally data-poor, and use of our MSM, along with a novel geographical information systems (GIS) approach to compare images with our *in silico* outcomes for validation, will serve to integrate information enabling realistic and predictive modeling. (challenge #3)
* Novel PET imaging measures of inflammation that correlate with disease status (model validation) (challenge #9)
* Model-driven data collection: PK-PD and resistance data will enable model building and calibration. (challenge #6)
* Novel optimization algorithm approach using high performance computing to identify optimal antibiotic regimens at a single granuloma level. (challenge #8)
* Virtual clinical trials using high performance computing to predict population-level treatment outcomes. (challenges #7, 8)
* Incorporation of uncertainty and sensitivity quantification to identify critical mechanisms that influence drug distribution, resistance development, and treatment efficacy with outcome measures bridging different scales. (challenge #10)
* Predicted “Virtual clinical trial best performer” antibiotic regimen will be tested in NHPs against the standard regimen, i.e. we will make model predictions that drive experimentalists toward systematic testing and validation*.* (challenge #6)

The detailed mechanistic and physically-based analysis of infection and antibiotic therapy in TB we propose here has never before been attempted. Our goal is to create a MSM with explicit predictive capability regarding antibiotic combinations and regimens, providing a fundamental infrastructure for antibiotic evaluation for TB, a model-poor field. Our interdisciplinary approach will shift current practice, changing an empirical approach based primarily on mouse data to a predictive computational approach, enabling rapid identification of candidate antibiotic regimens out of thousands of possibilities for further testing.

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

In previous MSM-funded work, we applied a machine learning approach to predict biomarkers (Marino, Gideon, Gong, Mankad, McCrone, Lin, Linderman, Flynn, Kirschner, [**Computational and Empirical Studies Predict Mycobacterium tuberculosis-Specific T Cells as a Biomarker for Infection Outcome**](http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1004804), PLoS Computational Biology, 2016, DOI: [10.1371/journal.pcbi.1004804](http://dx.doi.org/10.1371/journal.pcbi.1004804), PMID: [27065304](http://www.ncbi.nlm.nih.gov/pubmed?term=27065304)). It is not a focus of the currently funded work.

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

1. *Applying optimization algorithms to tuberculosis antibiotic treatment regimens.* Tuberculosis (TB) requires treatment with multiple antibiotics taken over at least 6 months. This long treatment often results in poor patient-adherence, which can lead to the emergence of multi-drug resistant TB. New antibiotic treatment strategies are sorely needed. New antibiotics are being developed or repurposed to treat TB, but as there are numerous potential antibiotics, dosing sizes and potential schedules, the regimen design space for new treatments is too large to search exhaustively. In this work, we propose a method that combines an agent-based multi-scale model capturing TB granuloma formation with algorithms for mathematical optimization to identify optimal TB treatment regimens. We define two different single-antibiotic treatments to compare the efficiency and accuracy in predicting optimal treatment regimens of two optimization algorithms: genetic algorithms (GA) and surrogate-assisted optimization through radial basis function (RBF) networks. We also illustrate the use of RBF networks to optimize double-antibiotic treatments.We found that while GAs can locate optimal treatment regimens more accurately, RBF networks provide a more practical strategy to TB treatment optimization with fewer simulations, and successfully estimated optimal double-antibiotic treatment regimens. Our results indicate surrogate-assisted optimization can locate optimal TB treatment regimens from a larger set of antibiotics, doses and schedules, and could be applied to solve optimization problems in other areas of research using systems biology approaches. Our findings have important implications for the treatment of diseases like TB that have lengthy protocols or for any disease that requires multiple drugs.
2. *Comparing efficacies of fluoroquinolones in TB granulomas using a multi-scale systems pharmacology approach.* Granulomas are complex lung lesions that are the hallmark of TB. Understanding antibiotic dynamics within lung granulomas will be vital to improving and shortening the long course of TB treatment. Three fluoroquinolones (FQs) are commonly prescribed as part of multi-drug resistant TB therapy: moxifloxacin (MXF), levofloxacin (LVX) or gatifloxacin (GFX). To date, insufficient data are available to support selection of one FQ over another, or to show that these drugs are clinically equivalent. To predict the efficacy of MXF,LVX and GFX at a single granuloma level, we integrate computational modeling with experimental datasets into a single mechanistic framework, *GranSim. GranSim* is a hybrid agent-based computational model that simulates granuloma formation and function, FQ plasma and tissue pharmacokinetics and pharmacodynamics and is based on extensive in vitro and in vivo data. We treat in silico granulomas with recommended daily doses of each FQ and compare efficacy by multiple metrics: bacterial load, sterilization rates, early bactericidal activity and efficacy under non-compliance and treatment interruption. *GranSim* reproduces in vivo plasma pharmacokinetics, spatial and temporal tissue pharmacokinetics and in vitro pharmacodynamics of these FQs. We predict that MXF kills intracellular bacteria more quickly than LVX and GFX due in part to a higher cellular accumulation ratio. We also show that all three FQs struggle to sterilize non-replicating bacteria residing in caseum. This is due to modest drug concentrations inside caseum and high inhibitory concentrations for this bacterial subpopulation. MXF and LVX have higher granuloma sterilization rates compared to GFX; and MXF performs better in a simulated non-compliance or treatment interruption scenario. We conclude that MXF has a small but potentially clinically significant advantage over LVX, as well as LVX over GFX. We illustrate how a systems pharmacology approach combining experimental and computational methods can guide antibiotic selection for TB.
3. *Emergence and selection of isoniazid and rifampin resistance in TB granulomas.* TB remains a global public health challenge, and the number of drug-resistant cases is increasing world-wide. Resistance against isoniazid (INH), rifampicin (RIF), or both (multi-drug resistant TB, MDR-TB) is of particular concern, since INH and RIF form part of the standard 4-drug regimen for active TB disease. While it is widely accepted that suboptimal treatment leads to resistance, it remains unclear how host immune responses and antibiotic dynamics within granulomas (sites of infection) affect emergence and selection of drug-resistant bacteria. We take a systems pharmacology approach to explore resistance dynamics within granulomas. We integrate spatio-temporal host immunity and bacterial, INH and RIF dynamics into our computational framework, *GranSim*. In this work, we expand *GranSim* to allow simulated bacteria to acquire resistance to INH and RIF, including fitness costs and compensatory mutations. We use *GranSim* to simulate resistance emergence in the absence of treatment, as well as resistance selection during treatment with INH and/or RIF. There are four main findings. First, in the absence of treatment, the percentage of granulomas containing resistant bacteria mirrors the non-monotonic bacterial dynamics within granulomas. Second, drug-resistant bacteria are less frequently found in non-replicating states in the caseum as compared to drug-sensitive bacteria. Third, due to pharmacokinetic and pharmacodynamics differences between INH and RIF, pre-existing INH-resistant bacteria have a stronger influence on treatment outcomes than RIF-resistant bacteria. Finally, under combination therapy with INH and RIF, only a few MDR bacteria are able to significantly affect treatment outcomes, and all drug-susceptible bacteria are eliminated within ~20 days of starting treatment, leaving only drug-resistant bacteria. Taken together, these results indicate that resistant bacteria emerge prior to treatment, and the existence of a few drug-resistant bacteria present at the start of treatment can disrupt efficacy. Overall, our approach allows exploration of resistance at bacterial, granuloma, host and population scales. These methods can be applied toward optimizing treatment regimen design to minimize resistance selection for new and existing anti-TB antibiotics.
4. *Predicting the role of pro- and anti-inflammatory cytokines on granuloma function.* Developing new therapies requires a better understanding of the complex host immune response to infection, including dissecting the processes leading to formation of granulomas, the dense cellular lesions associated with TB. In this work, we pair experimental and computational modeling studies to explore cytokine regulation in the context of TB. We use our next-generation hybrid multi-scale model of granuloma formation (*GranSim*) to capture molecular, cellular, and tissue scale dynamics of granuloma formation. We identify TGF-β1 as a major inhibitor of cytotoxic T-cell effector function in granulomas. Deletion of TGF-β1 from the system results in improved bacterial clearance and lesion sterilization. We also identify a novel dichotomous regulation of cytotoxic T cells and macrophages by TGF-β1 and IL-10, respectively. These findings suggest that increasing cytotoxic T-cell effector functions may increase bacterial clearance in granulomas, and highlight potential new therapeutic targets for treating TB. Using immunotherapeutic approaches together with antibiotics has the highest chance of improving treatment and provides a new route to success.

**Published and submitted work to date on this project:**

Kirschner D, Pienaar E, Marino S, Linderman JJ. A review of computational and mathematical modeling contributions to our understanding of Mycobacterium tuberculosis within-host infection and treatment. Current Opinion in Systems Biology 3:170-185. <http://dx.doi.org/10.1016/j.coisb.2017.05.014>. 2017.

Warsinske HC, DiFazio RM, Linderman JJ, Flynn JL, Kirschner DE.Identifying mechanisms driving formation of granuloma-associated fibrosis during Mycobacterium tuberculosis infection. J. Theor. Biology 429: 1-17. 2017.

Pienaar E, Sarathy J, Prideaux B, Dietzold J, Dartois V, Kirschner DE, Linderman JJ. Comparing efficacies of moxifloxacin, levofloxacin and gatifloxacin in tuberculosis granulomas using a multi-scale systems pharmacology approach. PLoS Computational Biology 13(8): e1005650. 2017. <https://doi.org/10.1371/journal.pcbi.1005650>.

Cicchese J, Pienaar E, Kirschner DE, Linderman JJ. Applying optimization algorithms to tuberculosis antibiotic treatment regimens. Cellular and Molecular Bioengineering 10: 523. 2017. https://doi.org/10.1007/s12195-017-0507-6.

Warsinske HC, Pienaar E, Linderman JJ, Mattila JT, Kirschner DE.. Deletion of TGF-β1 Increases Bacterial Clearance by Cytotoxic T Cells in a Tuberculosis Granuloma Model. Frontiers in Immunology 8:1843, 2017, DOI: [10.3389/fimmu.2017.01843](https://doi.org/10.3389/fimmu.2017.01843)

Marino S, Kirschner DE, A multicompartment hybrid computational model predicts key roles for dendritic cells in TB Infection, Academic Editors: Gennady Bocharov, Olga Solovyova and Vitaly Volpert, Computation 2016, 4, 39, DOI: [10.3390/computation4040039](http://dx.doi.org/10.3390/computation4040039), PMID: [28989808](http://www.ncbi.nlm.nih.gov/pubmed?term=28989808).

Pienaar E, Linderman JJ, Kirschner DE. Emergence and selection of isoniazid and rifampin resistance in tuberculosis granulomas. Submitted for publication, 2017.

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

Some of our group has been funded by the MSM mechanism since the origin of the program. We wonder if there is a better way to archive for tutorial purposes or to communicate findings and approaches, i.e. to share the collective expertise of MSM-funded researchers with the next generation of researchers. While there are many wonderful examples of models in published works from the community, and some attempt at a central repository of models, there is little in the way of a higher-level introduction to the field. This could be accomplished via a book and/or summer schools.

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

PI -Dartois – pharmacology, imaging. (dartoiva@njms.rutgers.edu)

PI -Flynn – immunology, primates, microbiology. (joanne@pitt.edu)

PI -Kirschner – mathematics, computation, modeling. (kirschne@umich.edu)

PI -Linderman – engineering, computation, modeling. ([linderma@umich.edu](mailto:linderma@umich.edu))

Consultant-Russ Butler- spatial geography and GIS (russ.butler@adu.edu)