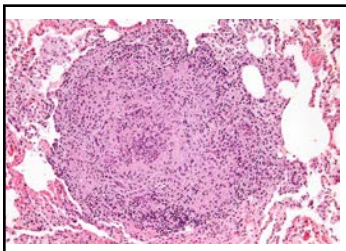
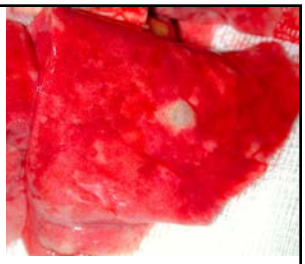
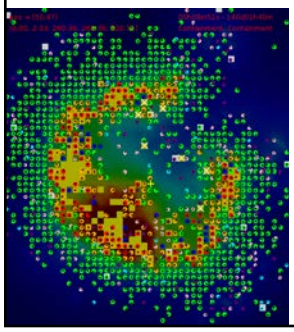




a Multi-scale systems biology approach toward tuberculosis infection interventions



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Co-Director, Center for Systems Biology

1

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My Amazing group at UM

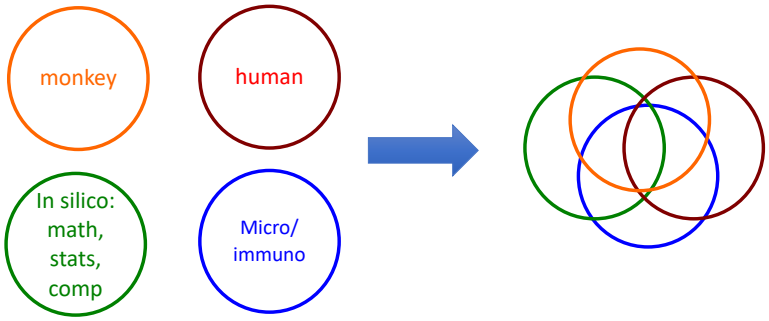
Past lab members: Elsje Pienaar, PhD Purdue
Simeone Marino, PhD UM

***Generous funding from the NIH, B&M Gates**

2

What is a *systems biology* approach?

Integration of data from multiple model systems to understand a complex biological problem and address open questions

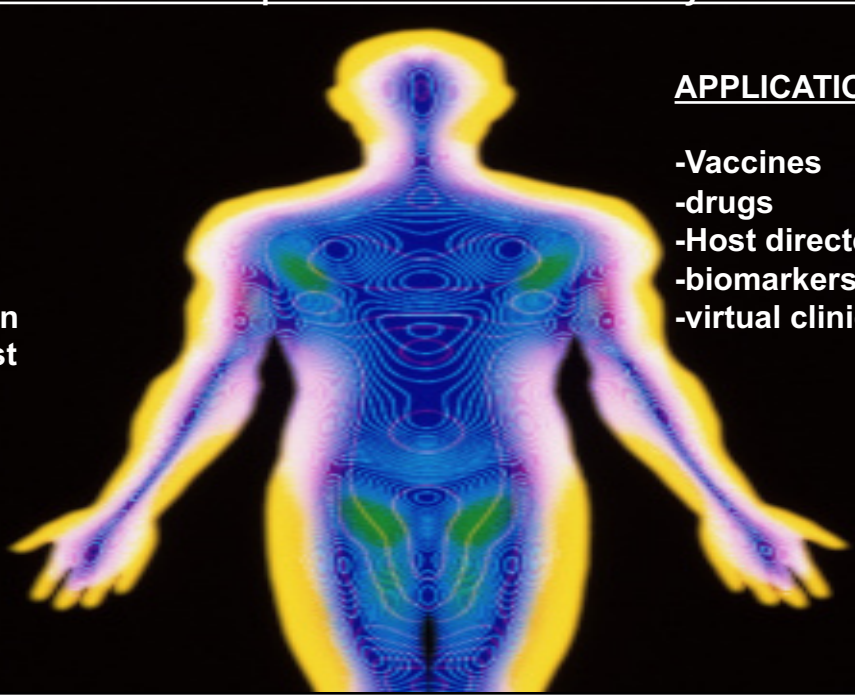


3

Building a virtual human: personalized medicine via systems biology

SCALES

Molecular
Cellular
Tissue
Organ
Multi-organ
Whole host



APPLICATIONS

-Vaccines
-drugs
-Host directed therapies
-biomarkers
-virtual clinical trials

4

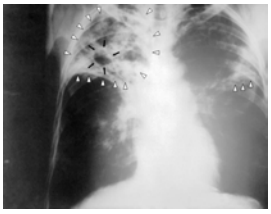
Frontier: Emergent vs Re-emergent diseases

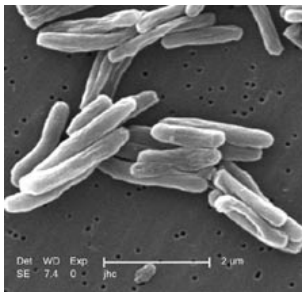
- ***Emerging diseases*** are those that were previously unknown to have afflicted humans
  - like AIDS, Ebola, SARS ← *These are viral driven*
- ***Reemerging diseases*** **a**re familiar scourges whose incidence is rising, or whose geographical range was expanding
  - Cholera or Tuberculosis ← *These are bacterial driven*
  - *Malaria* ← *Parasite driven*

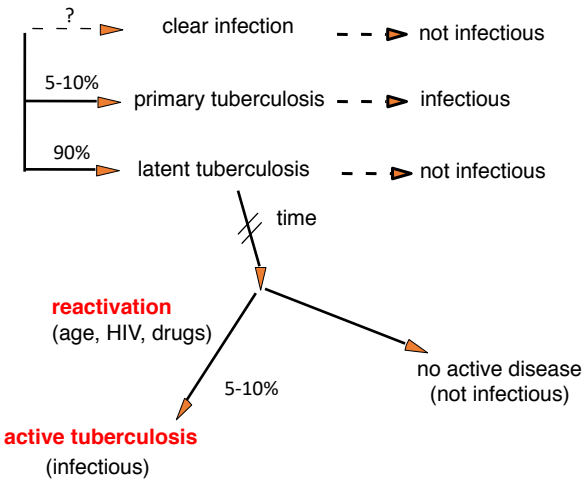
5

Tuberculosis (TB):

Infectious disease caused by *Mycobacterium tuberculosis* (Mtb).
One–third of the world's population is infected with Mtb, and new infections occur at a rate of one per second.
3 people die every minute, i.e. ~1.5 million deaths/year.







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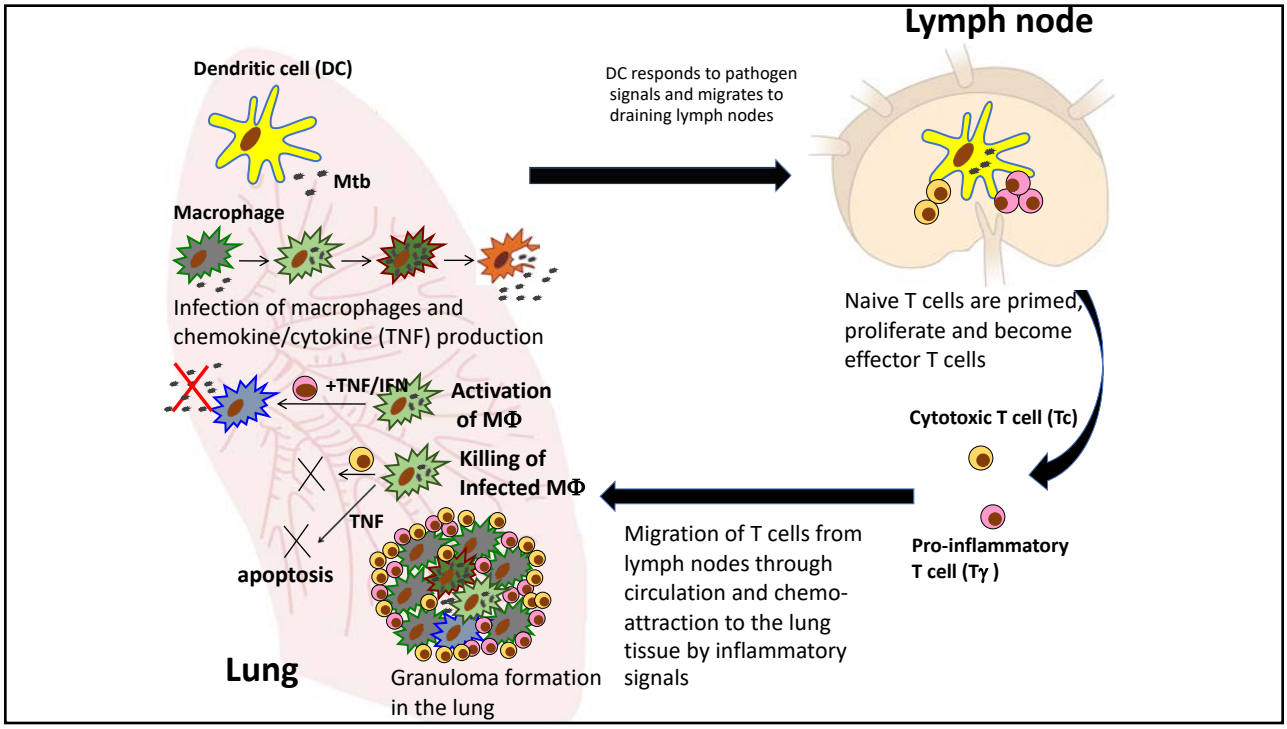

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Tuberculosis is multi-scale in nature

Population scale

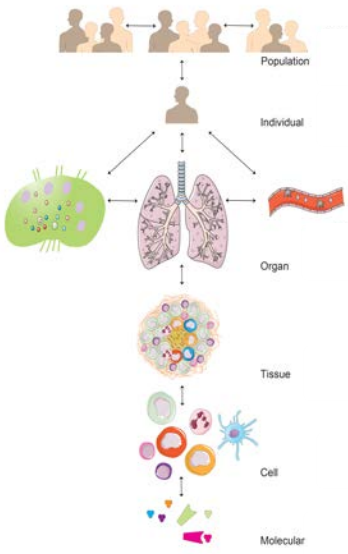
Whole host

Major organs

Granuloma (tissue)

Cellular scale

Molecular scale



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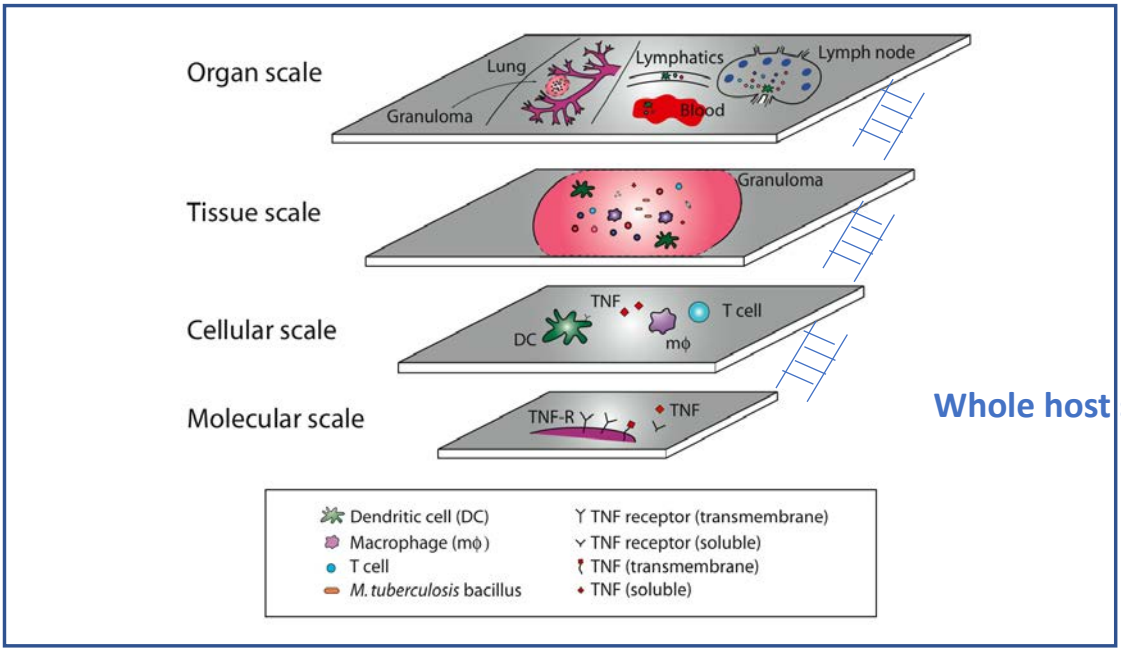
Granulomas are a result of multi-scale dynamics in both space & time



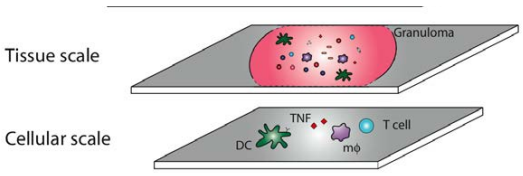
Whole host scale

9

GranSim

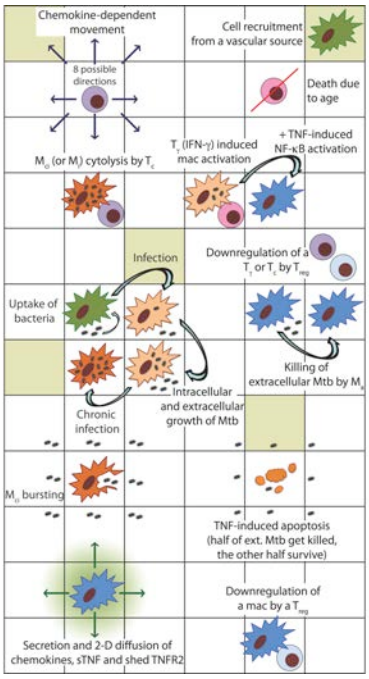
Cellular/tissue scale Model--

An agent-base hybrid **model** that captures discrete cellular dynamics via a set of well-described interactions between immune cells and Mtb leading to tissue scale outcomes



****Leads to "emergent behavior"**

*Segovia-Juarez et al J. Theor Biol. 2004
* Ray *et al*, J. Immunol. 2009



2mm x 2mm Lung tissue

Vascular sources

-Immune cells
T and Mp

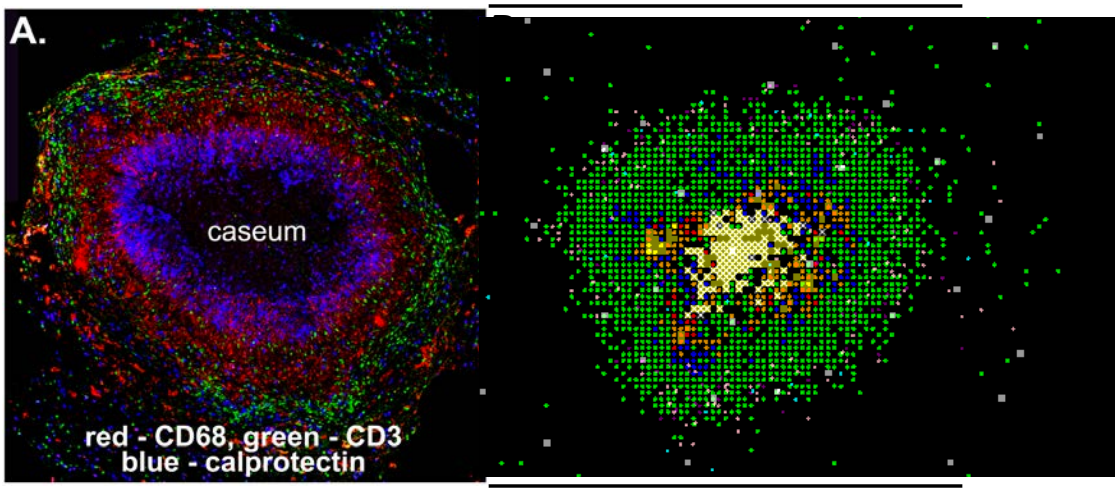
-Bacteria

-Cytokines

-chemokines

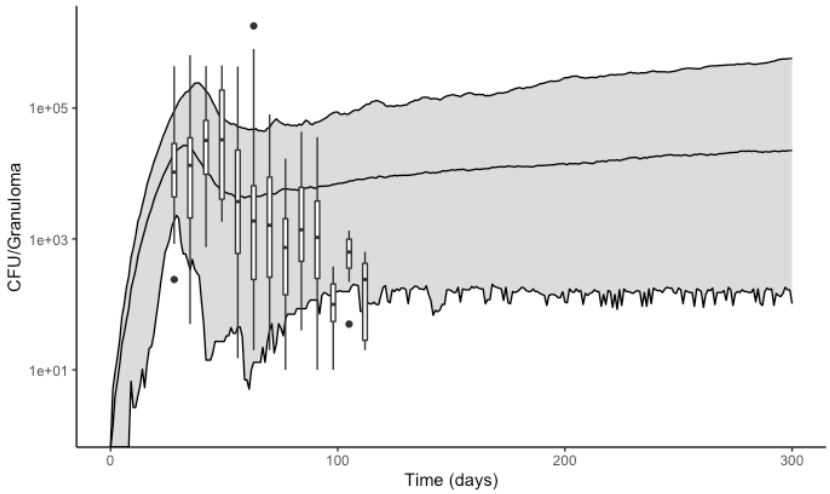
10

Experimental & computer-generated granulomas



11

GranSim match to 600 granulomas from NHPs



Louis R. Joslyn*, et al, Temporal and spatial analyses of TB granulomas to predict long-term outcomes (in press for) 2020
Marissa Renardy etal Global sensitivity analysis of biological multi-scale models, Curr Opin Biomed Eng. 2019 Sep; 11: 109-116 , Volume 11, DOI: 10.1016/j.cobme.2019.09.012, PMID: 32864523, PMCID: 7450543

12

Frontier: TREATMENT ---Standard TB therapy

6-9 months of up to four antibiotics

1. isoniazid (INH)
2. rifampin (RIF)
3. ethambutol (EMB)
4. pyrazinamide (PZA)

HRZE
~95% effective for drug-sensitive TB

Treatment shortcomings

*Too long *Poor adherence
*Side-effects *Drug resistance

*Granulomas are heterogeneous
*Patients are heterogeneous

Many other antibiotics in development/trials

13

13

What's the best antibiotic regimen?

Regimen design space (RDS)

Treatment segments (M)	2
Number of drugs (c)	10
Drugs per segment (n)	4
Dose (D, mg/kg)	5
Frequency (F, week^{-1})	7

Number of possible regimens:

$$RDS = \left(\binom{c}{n}(D \times F)^n\right)^M = 9.9 \times 10^{16}$$

Cicchese *et al.* CMBE (2017)

- Too many options to test
  - Clinically or computationally

↓

- Optimization problem
  - Best x to minimize or maximize some objective function(s)

14

14

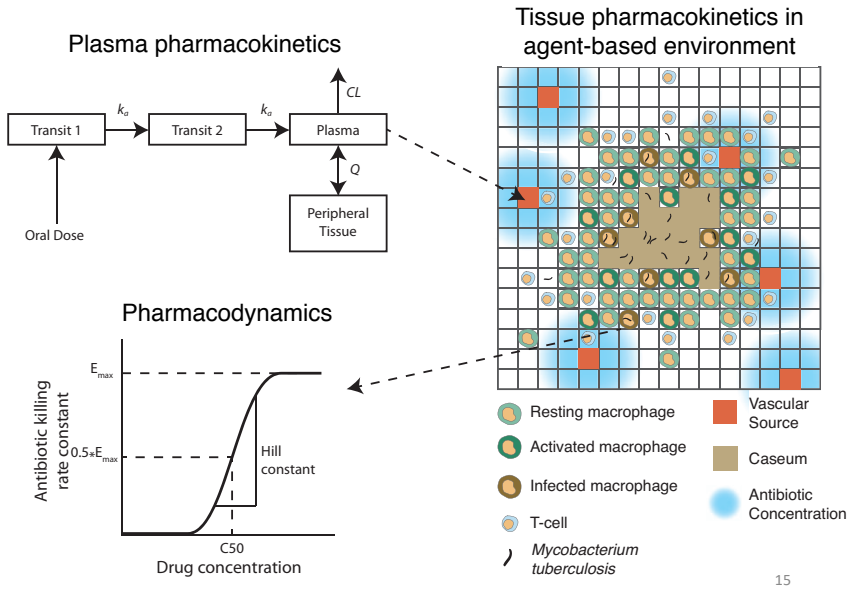
Pharmacokinetics/pharmacodynamics in a single granuloma

Tissue pharmacokinetics includes
- Vascular permeability
- Diffusion
- Binding to environment
- Partitioning into cells

Pharmacodynamics
- Assuming antibiotics are indifferent
- Combined effect is equal to maximum of the individuals

$$k = E_{max}\frac{C^h}{C^h + {C_{50}}^h}$$

Kjellsson *et al. AAC* (2015)
Pienaar *et al. JTB* (2015)
Cicchese *et al. Front. Pharm.* (2020)



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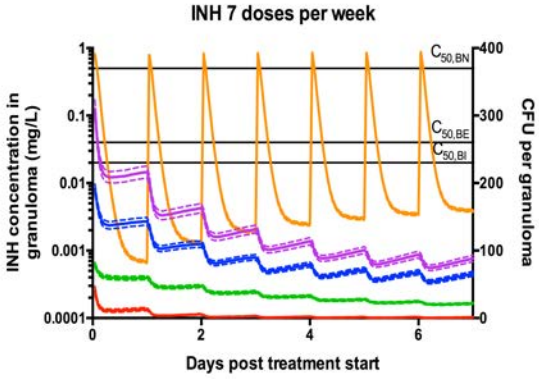
15

2. Predicting granuloma antibiotic exposure



Concentration oscillates between above and below effective concentrations

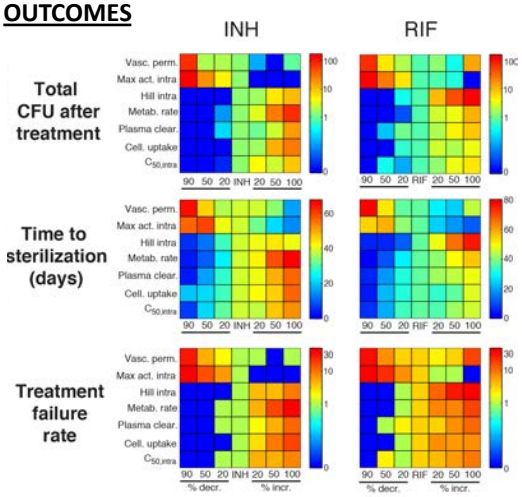
Pienaar *et al. BMC Sys. Bio.* (2015)

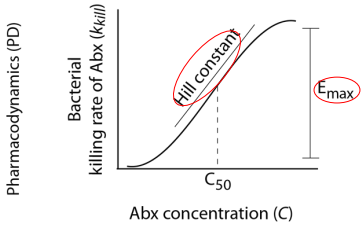
Orange trace – INH concentration over time
Purple trace – Total bacteria over time

16

Can we predict what can improve existing drugs?
i.e. which PK and PD properties are good targets for modification?

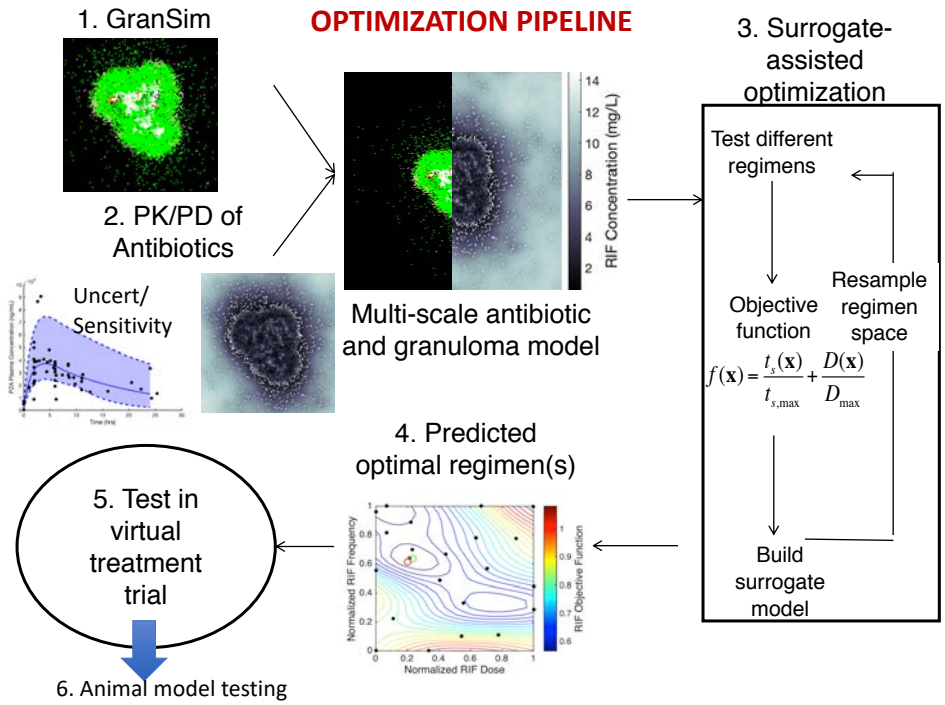
OUTCOMES





We use sensitivity and uncertainty analysis to determine this, Marino et al. JTB 2018

17



18

Frontier: Vaccines: Modeling and Tuberculosis

- Attenuated live vaccine with BCG (Bacille Calmette-Guerin strain)
- Given in most of the world (not in USA or UK)
- Low to very low efficacy with waning protection over time (0-80%)
- Vaccine invalidates PPD skin test which works very well
- IGRA test -interferon gamma release assay-mixed response to BCG vaccinated

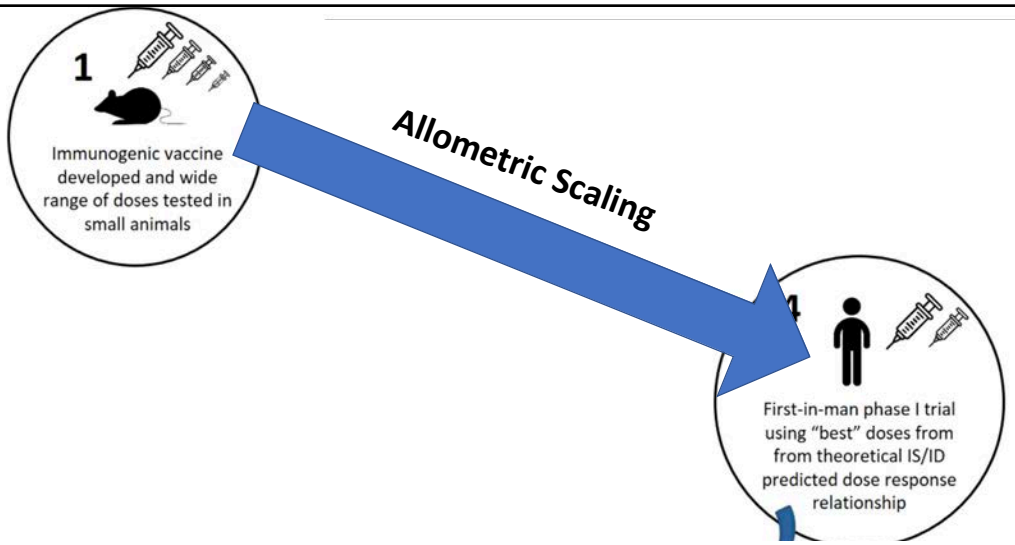
19

Vaccine datasets through a systems biology lens

- Human studies go into Phase 1 after mouse studies
- NHP are also being used to study vaccine efficacy
- Can modeling help decipher differences in vaccine responses between species and predict better or even optimal dosing?
- **immunostimulation/immunodynamic (IS/ID) modeling**

Sophie J. Rhodes, et al Journal of Theoretical Biology 465 (2019) 51–55

20



Sophie J. Rhodes, et al Journal of Theoretical Biology 465 (2019) 51–55

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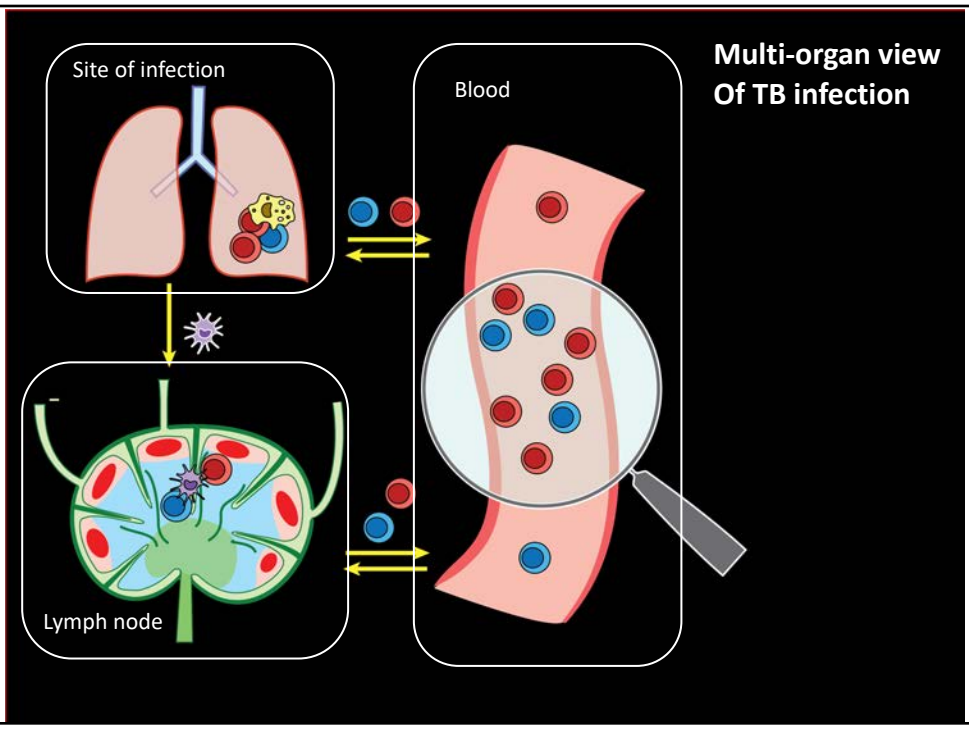
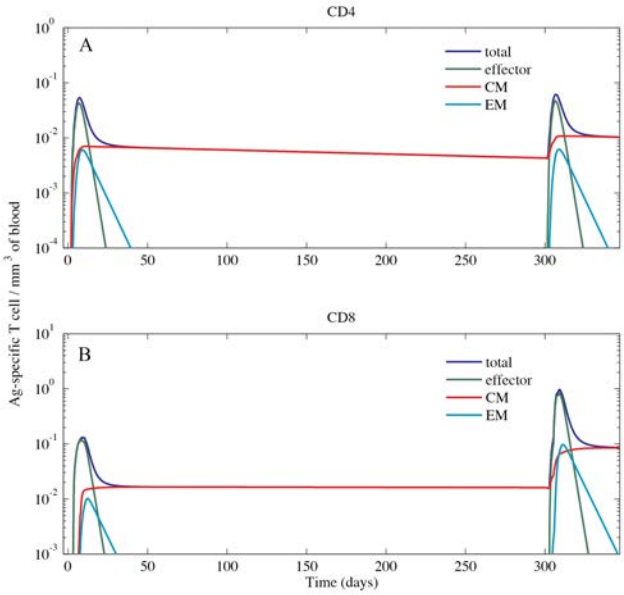


22

Memory T cells induce enhanced immunity in recall challenge



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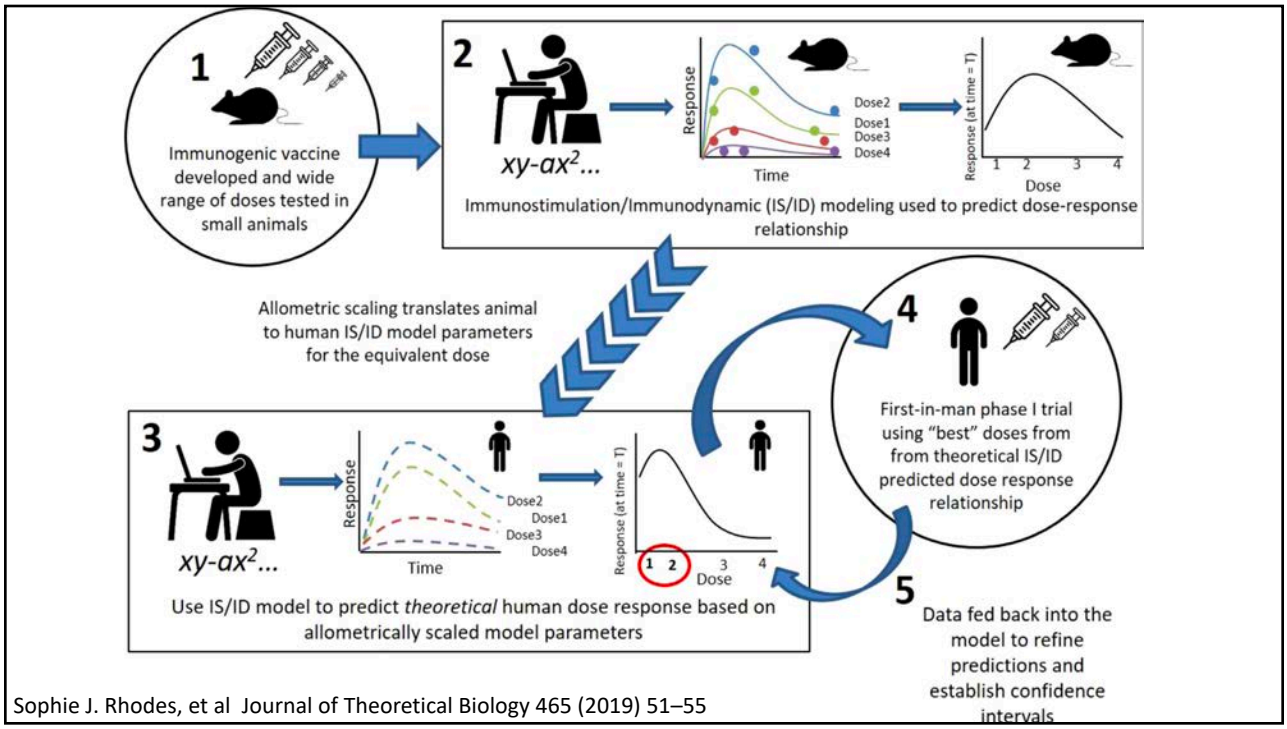

Sophie J. Rhodes, et al Journal of Theoretical Biology 465 (2019) 51–55

24

Modeling can distinguish mechanisms behind animal model outputs from human outputs (sensitivity analysis)

TABLE 3 | Significant PRCCs for Ag85B immune response outcomes.

Ag85B	Central memory	Effector	Effector memory
NHP	central memory reactivation rate; Likelihood of differentiation; precursor proliferation and differentiation into central memory cells; APC and precursor death rates	Likelihood of differentiation; precursor proliferation and differentiation into effector cells; effector, APC, and precursor death rates	precursor proliferation and differentiation into effector cells; APC and precursor death rates
Human	Likelihood of proliferation; precursor proliferation and differentiation into central memory; central memory recruitment rate; APC and precursor death rates	Likelihood of proliferation and differentiation; naïve T cell recruitment; precursor proliferation and differentiation to effector; effector differentiation to effector memory; effector Lymph efflux; effector, APC, and precursor death rates	Likelihood of proliferation; precursor Proliferation; effector memory, APC, and precursor death rates

One row represents humans, the other represents NHPs. Columns list the 3 model outcomes of interest–Ag85B-specific central memory, effector and effector memory T cell phenotypes. These outcomes were selected for analysis because the model was calibrated to their dataspace. Each table cell contains a general description of significant (i.e., $p < 10^{-3}$) parameters with respect to outputs of the model.

Louis R. Joslyn et al, **Mathematical Studies to Determine the Influence of BCG Timing on H56 Vaccine Outcomes**
Frontiers in Microbiology, 17 August 2018

25

Tools we have developed or specialized to study multi-scale mathematical and computational models

- Mechanistic, multi-scale hybrid models- containing stochastic and probabilistic factors
- Uncertainty and Sensitivity Analysis quantification tools
- Model Calibration Tools
- Tuneable resolution tools- coarse and fine grain
- Parameter identifiability tools
- Optimization tools
- Machine learning on datasets combined with synthetic datasets

malthus.micro.med.umich.edu

26

Summary

- Mechanistic models are key to identifying key processes driving outcomes
- Prevention efforts for endemic diseases as important as for emergent diseases
- Within host modeling can aid significantly in identifying
  - vaccine targets, drug regimen optimization, drug development, drug targets
- Virtual clinical trials can speed time and save cost prior to human clinical trials
- Modeling can link within host infection dynamics to blood readouts- the most sampled compartment
  - This can also aid in biomarker discovery
- Modeling can distinguish differences between animal and human studies so they can be accounted for when translating data
- Collaborations **necessary** between experimental, clinical and computational/mathematical scientists and grant support to foster (barrier)
- *co-morbities* are extremely important to consider (heart disease USA,HIV Africa) (barrier)
- Need to fund access to high throughput computing (barrier)

27