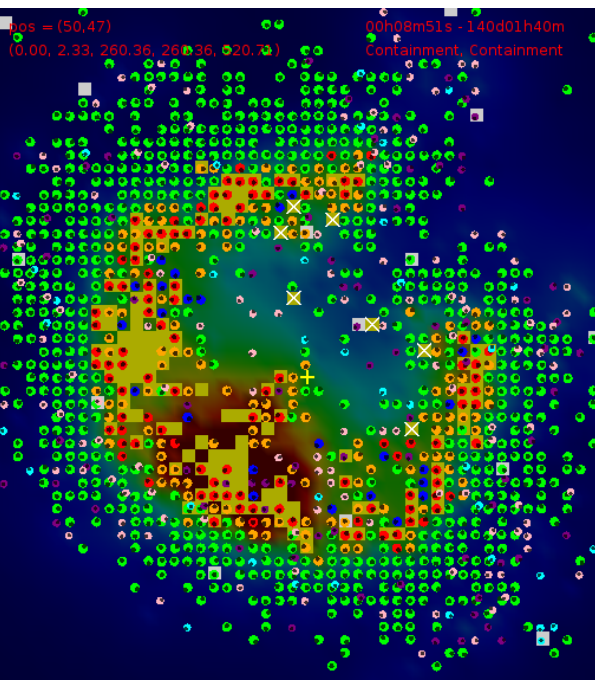


Immunology of TB: insights from *in vivo* models and implications for prevention



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With
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Lymph node

Dendritic cell (DC)

DC responds to pathogen signals and migrates to draining lymph nodes

Mtb

Macrophage

Infection of macrophages and chemokine/cytokine (TNF) production



+TNF

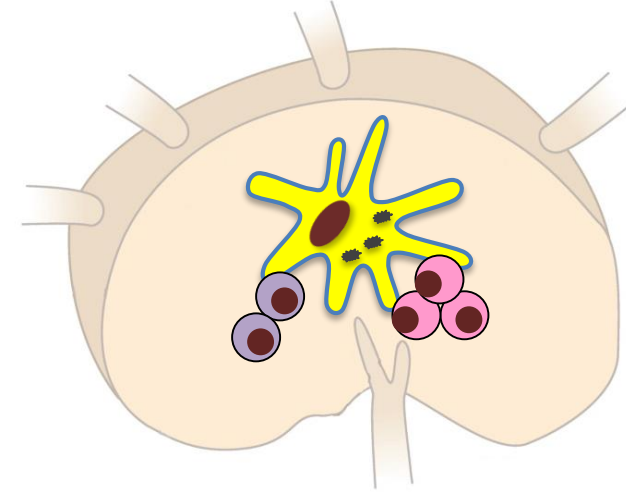
Activation of MΦ

Killing of Infected MΦ

TNF

apoptosis

Granuloma formation in the lung



Naive T cells are primed, proliferate and become effector T cells

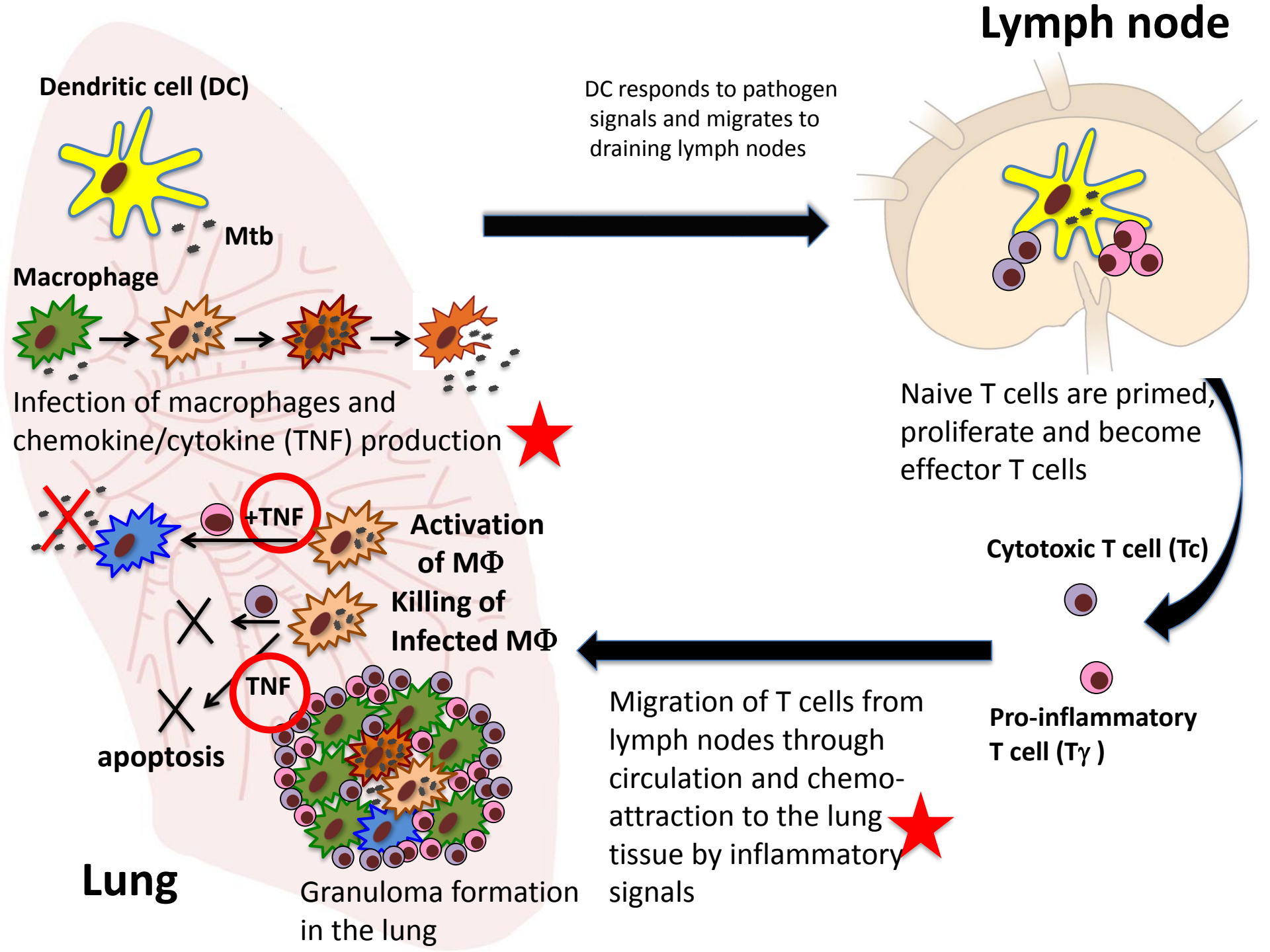
Cytotoxic T cell (T_c)

Pro-inflammatory T cell (T_γ)

Migration of T cells from lymph nodes through circulation and chemoattraction to the lung tissue by inflammatory signals



Lung



A photograph of a brown monkey sitting on a patch of green grass. The monkey is facing right and has a small, light-colored object in its mouth. The background is a light-colored, sandy or dirt surface.

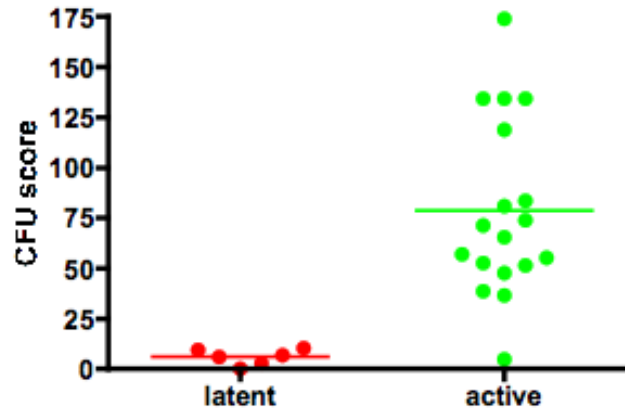
+ *M. tb*
Erdman
10 cfu
via bronchoscope

2-6 weeks

Tuberculin Skin Test +
Other immunologic tests +

6-8 months

No signs of disease
CXR negative by 2 months
Mycobacterial culture
negative after 2 months
Clinical signs--none

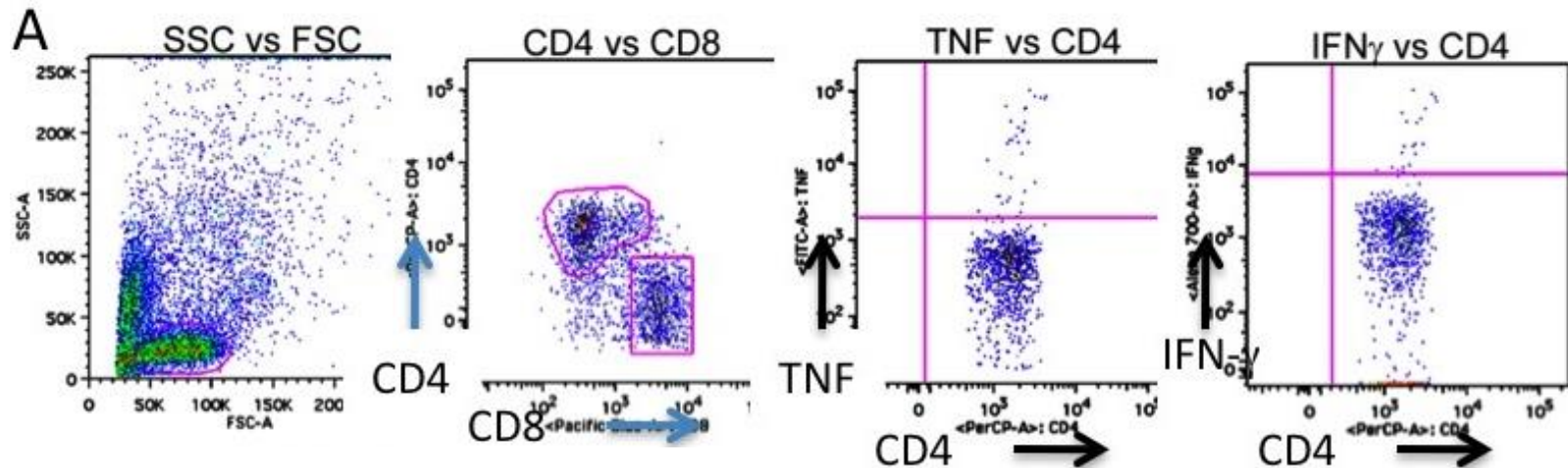


- Positive Chest x-ray
- Mycobacterial culture
 - + GA or BAL culture
- Clinical signs
 - weight loss,
 - appetite loss
 - cough

Quantitative Cellular Data

For calibration and validation of models

- From granulomas at necropsy:
- Obtain data on cell types, cytokines, chemokines
- Across different granulomas at a specific time point



- Flow cytometry,
- Intracellular cytokine staining
- boolean gating,
- SPICE analysis

Spatial Data

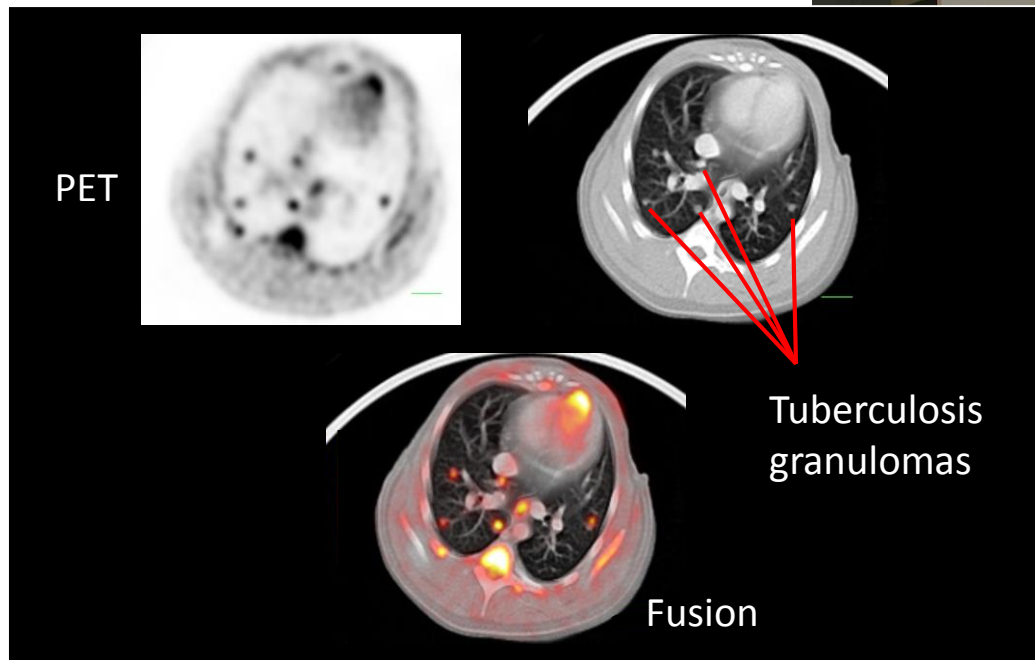
PET/CT: Imaging modality for serial tracking of lesions and disease

CT: structural map of lesions in organs

PET: functional map of lesions in organs



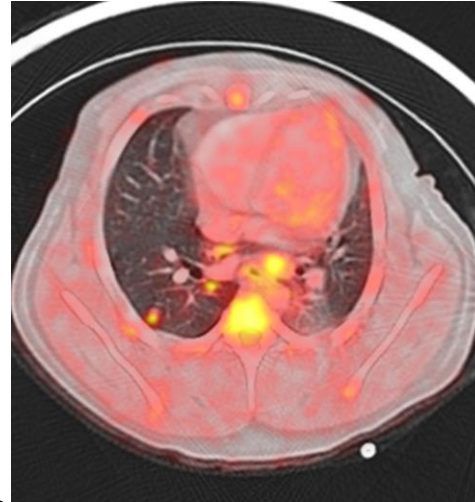
**BSL3 imaging suite
Regional Biocontainment
Lab (RBL), Flynn Lab
University of Pittsburgh**



18F-FDG PET/CT imaging

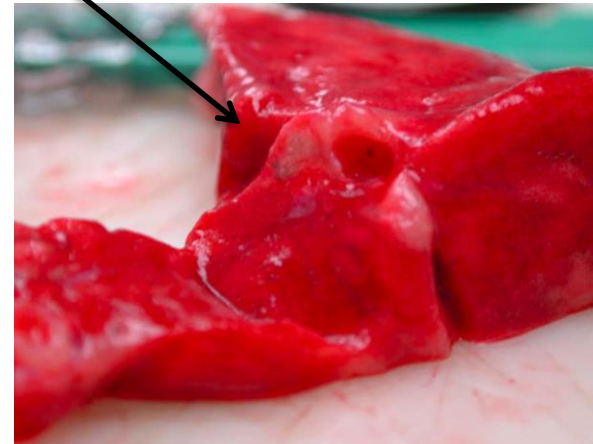
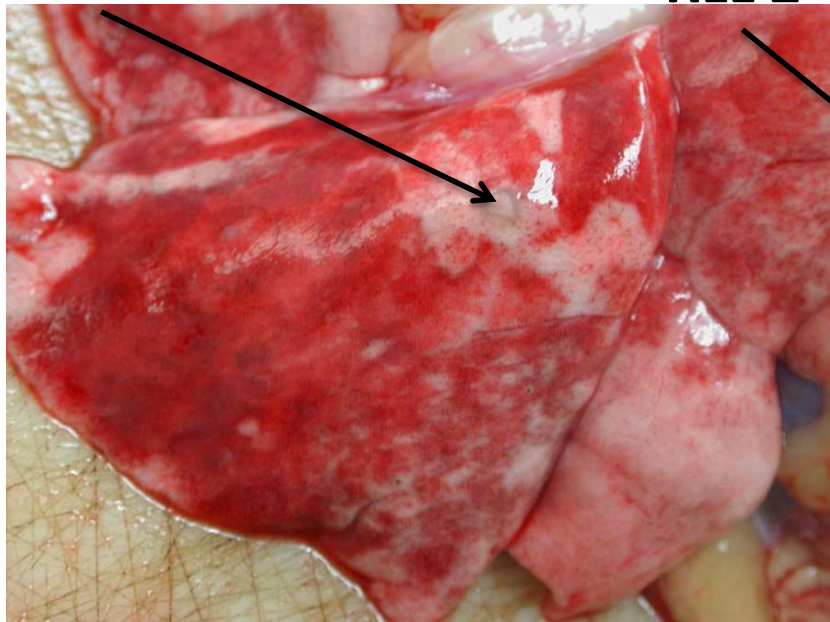
Spatiotemporal Data

The challenge: Matching lesions from scan to lesions at necropsy



RLL 1

RLL 2



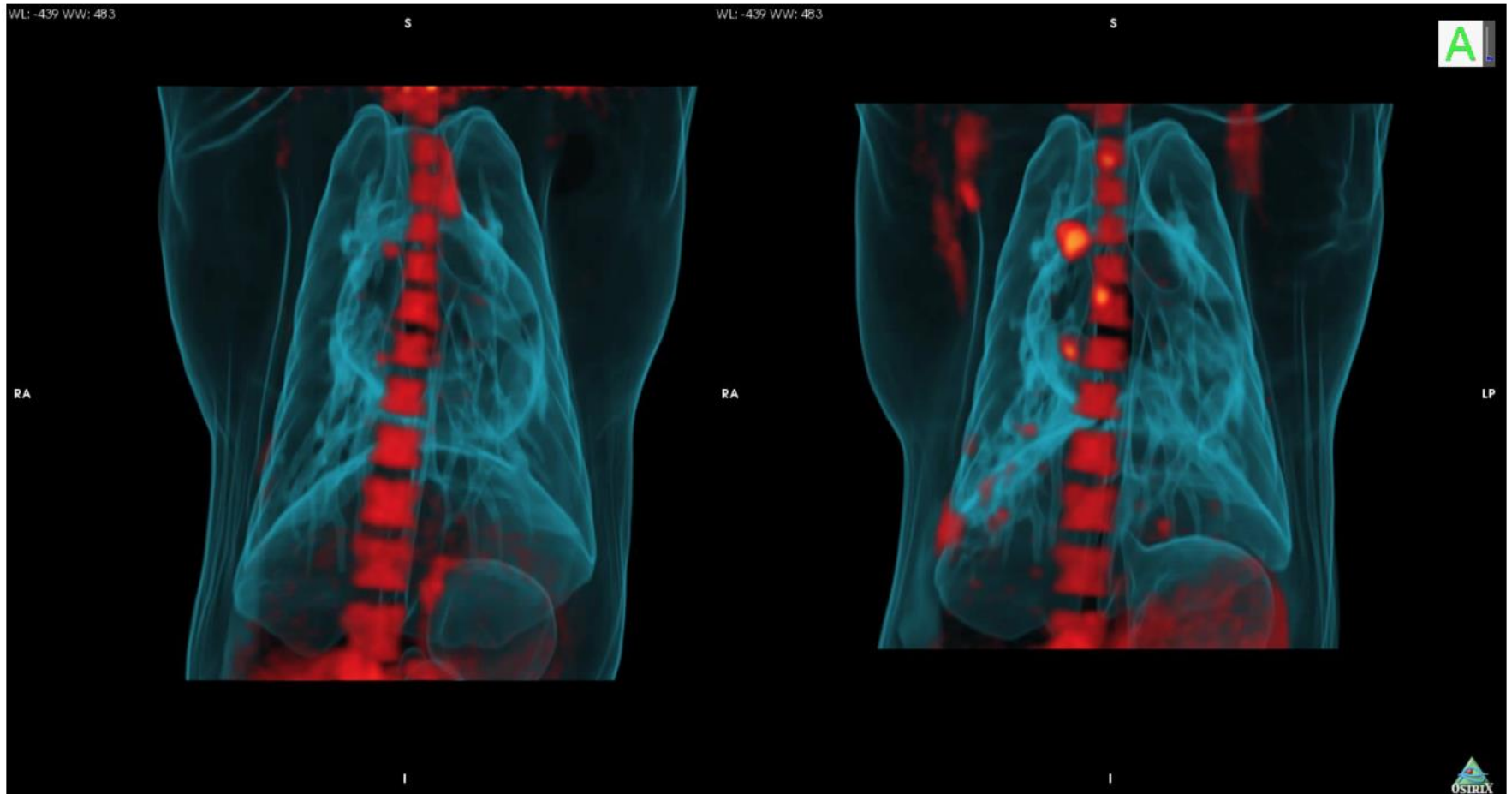
	SUV max	size	CFU
RLL 1	4.6	2.7 mm	7000
RLL 2	3.4	1.7 mm	1333

Spatial Quantification Data

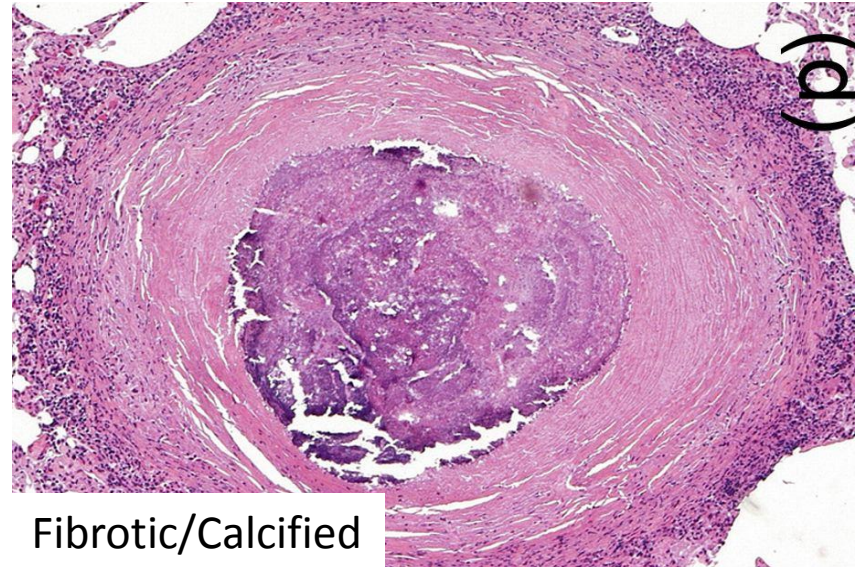
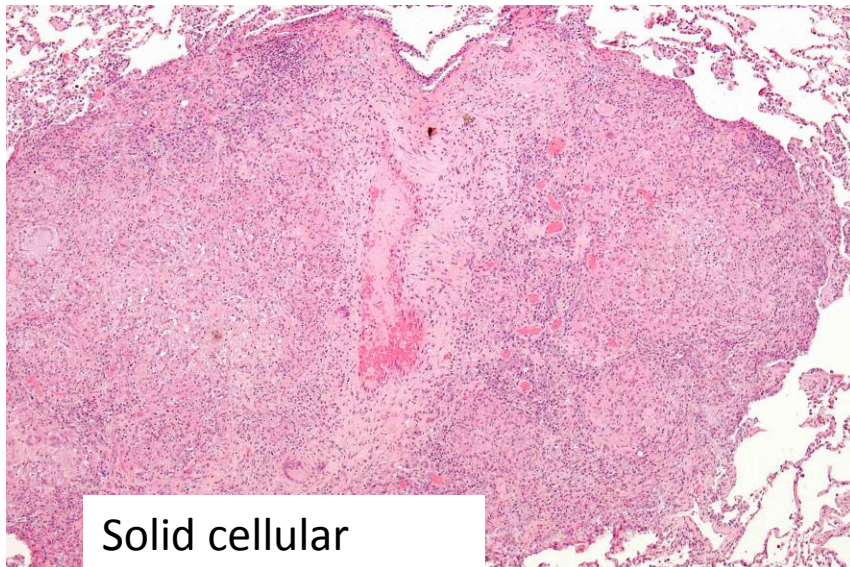
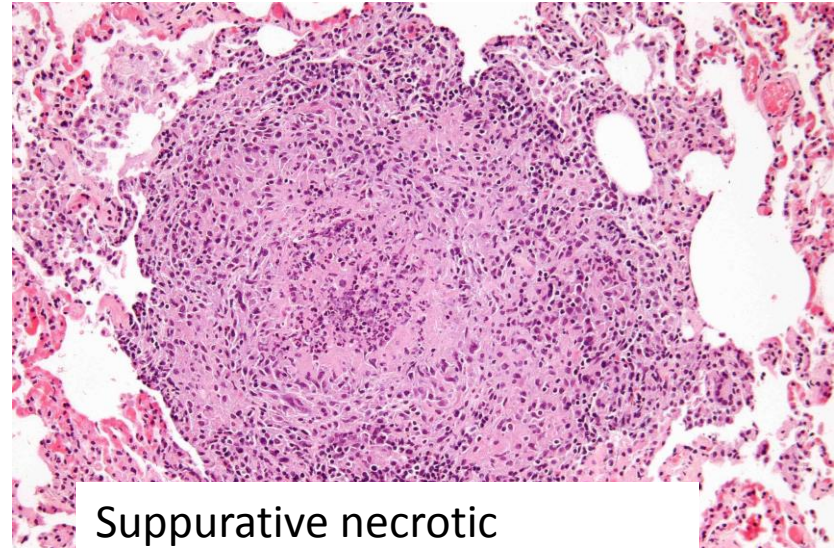
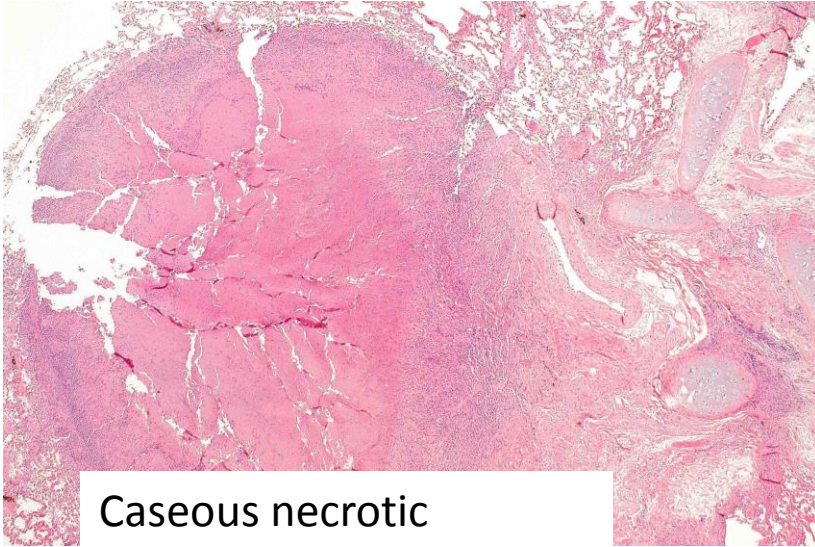
Reactivation of latent infection by anti-TNF

Baseline (Latent)

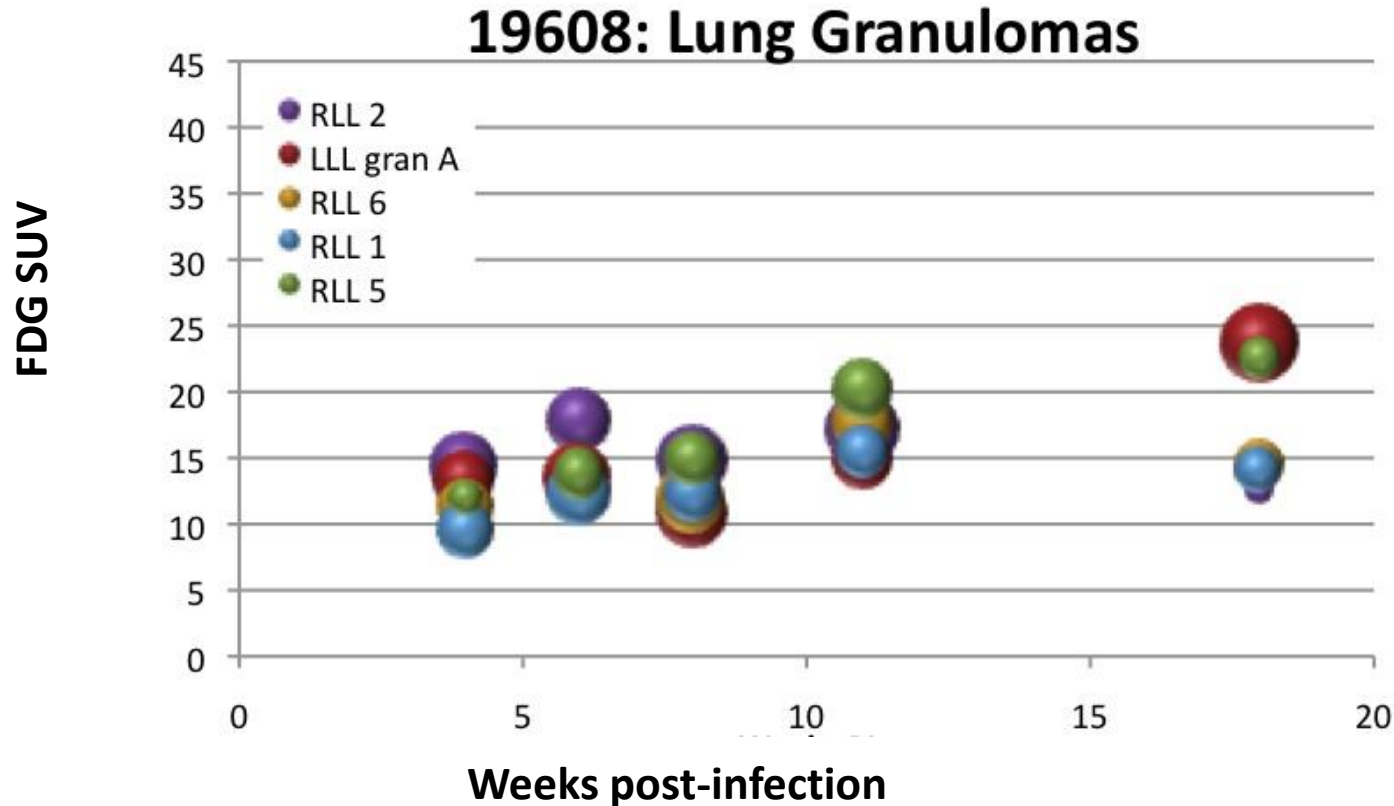
2 months anti-TNF



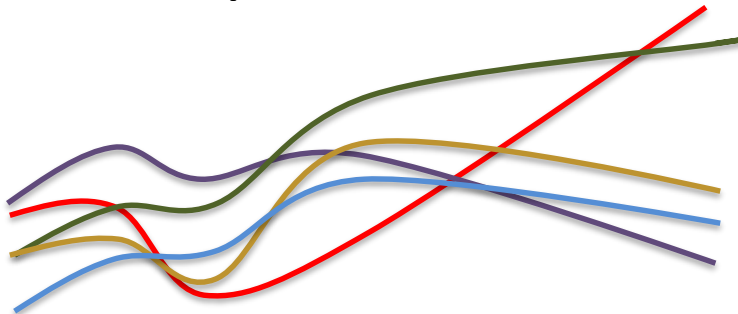
How do we understand the spectrum of granulomas observed in primates?



Every granuloma is an island

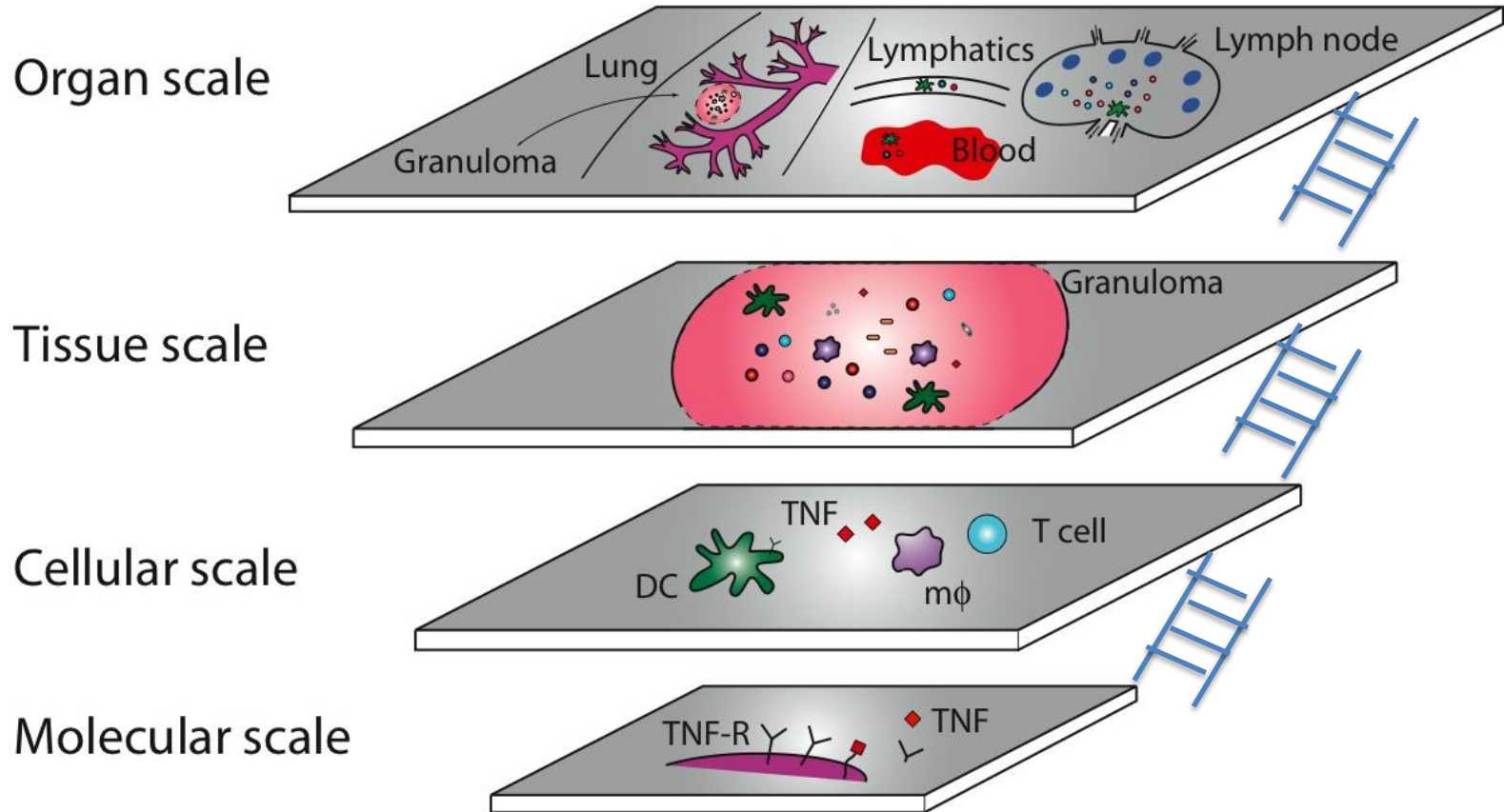


Lin, Philana Ling, et al. *Nature medicine* 20.1 (2014): 75-79.



Understanding each granuloma individually can help distinguish infection outcomes

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



- ★ Dendritic cell (DC)
- ✱ Macrophage (mφ)
- T cell
- *M. tuberculosis* bacillus

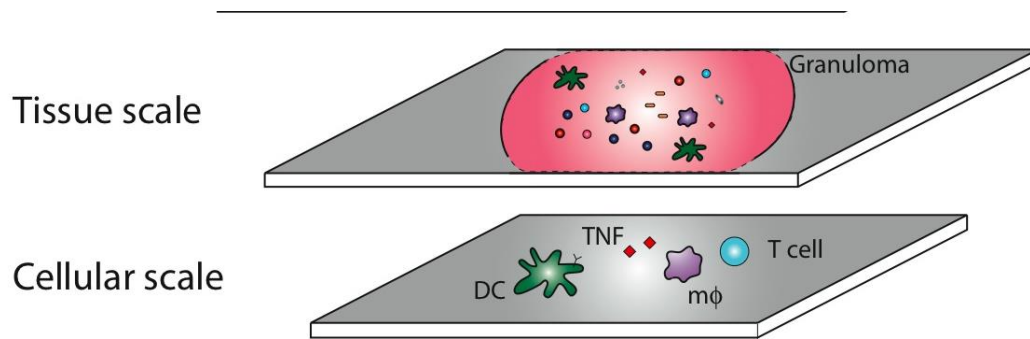
- Y TNF receptor (transmembrane)
- ∨ TNF receptor (soluble)
- ⌋ TNF (transmembrane)
- ◆ TNF (soluble)

GranSim-our approach to modeling
the immune response to TB

GranSim

Cellular/tissue scale Model--

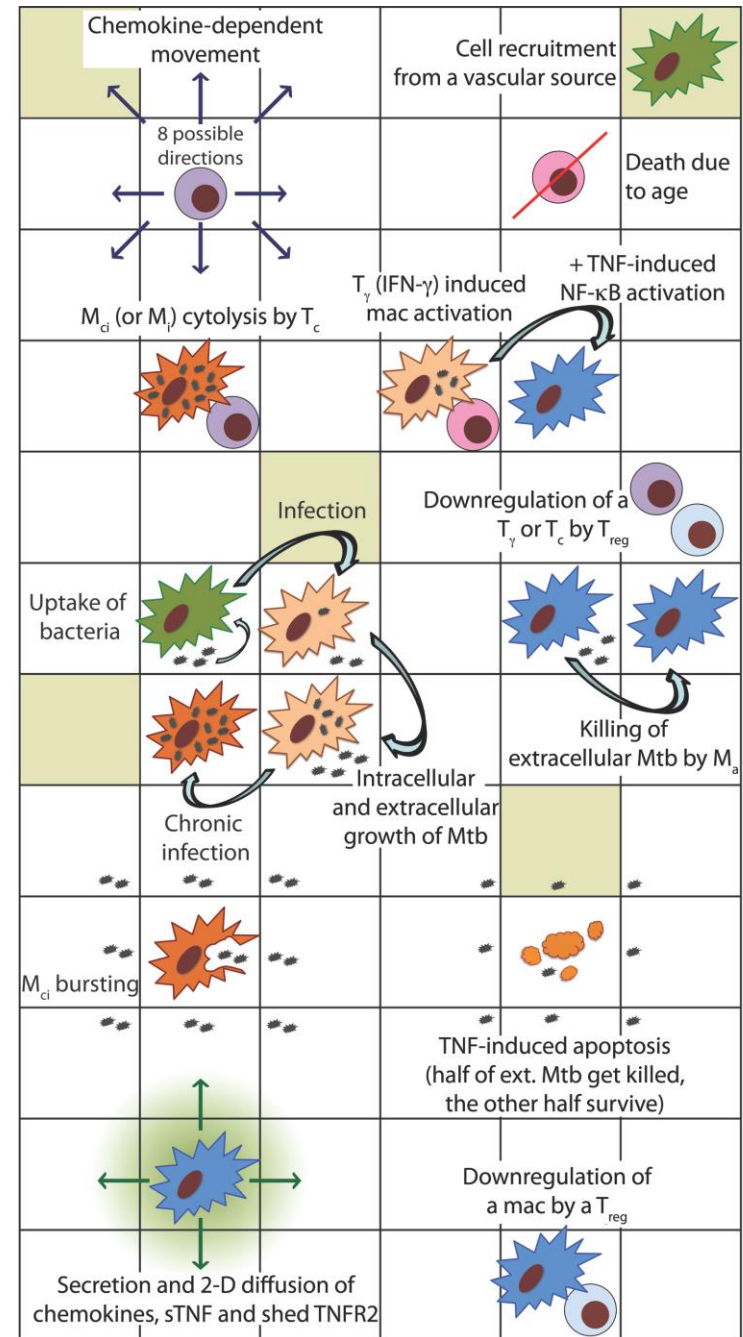
A stochastic **model** that captures discrete cellular dynamics via a set of well-described interactions between immune cells and Mtb leading to tissue scale outcomes



****Leads to “emergent behavior”**

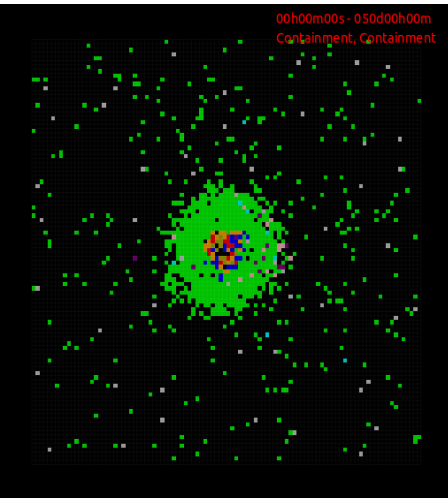
*Segovia-Juarez et al J. Theor Biol. 2004

* Ray *et al*, J. Immunol. 2009

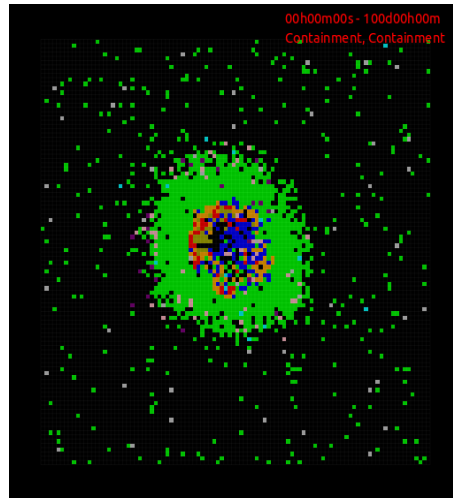


GranSim: granuloma developing over time

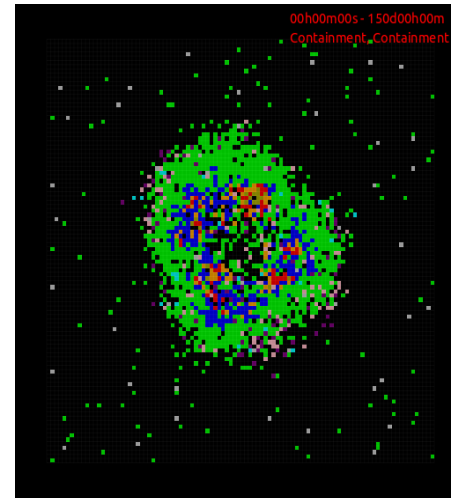
Containment Parameter Set - WT



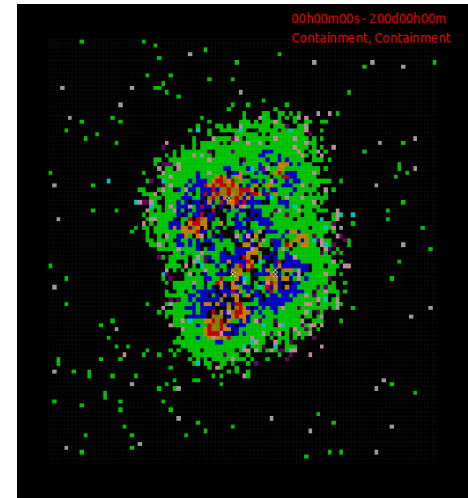
50 days PI



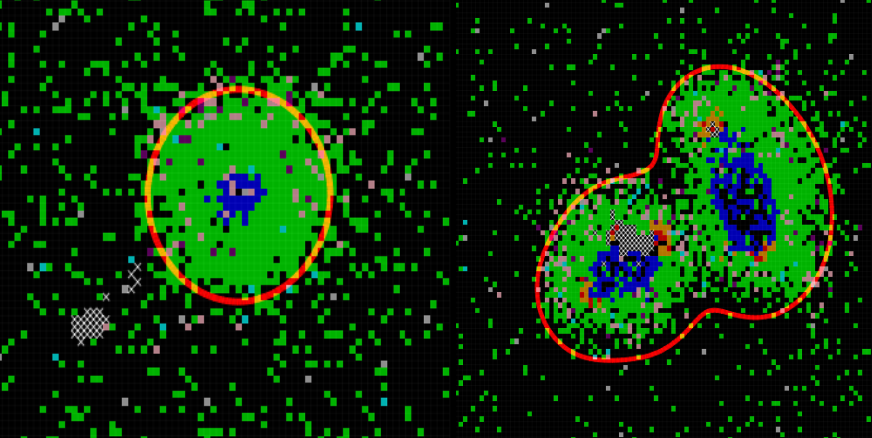
100 days PI



150 days PI

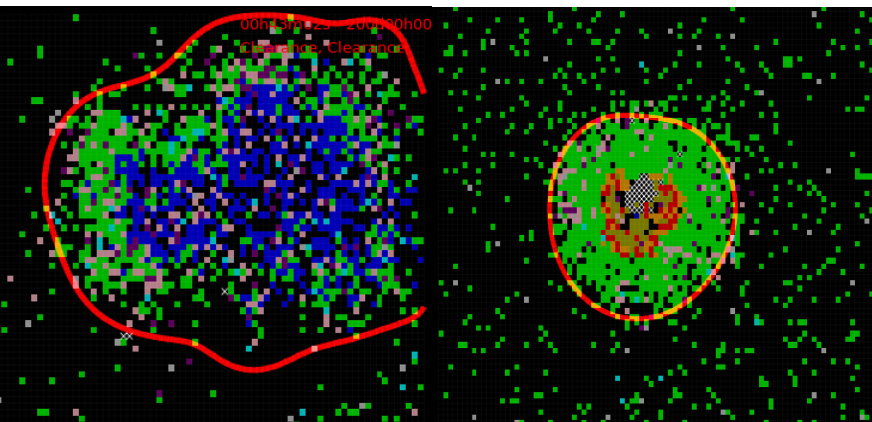


200 days PI



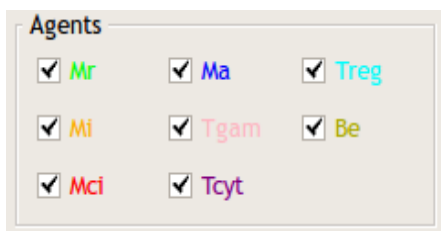
A: Containment

B: Disseminating

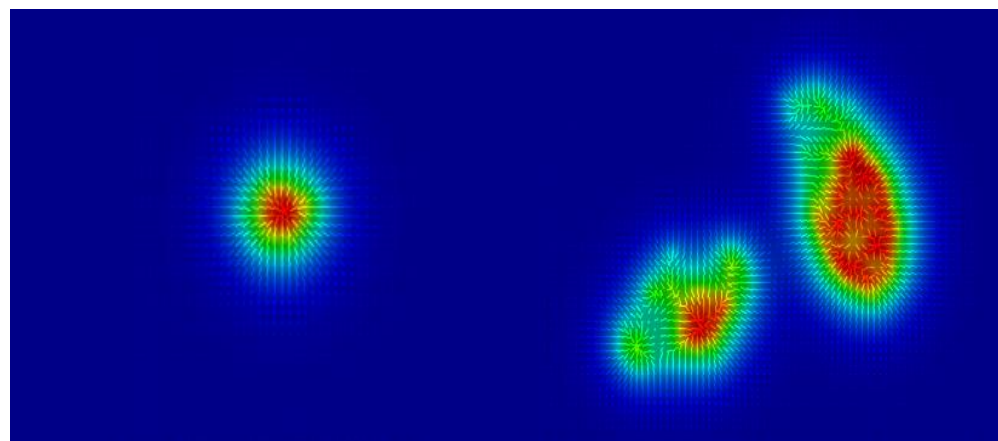


C: Clearance with inflammation

D: uncontrolled growth

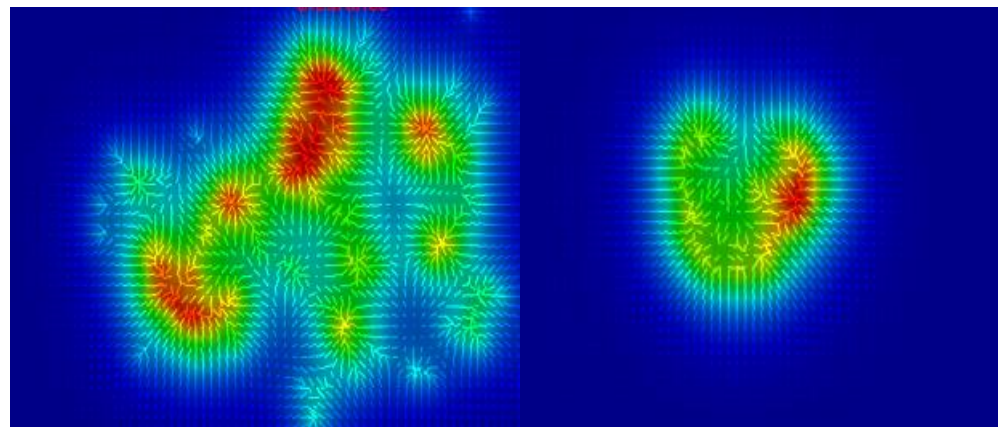


	Be	Bi
A:	0	10
B:	232	437
C:	0	0
D:	1930	950



A

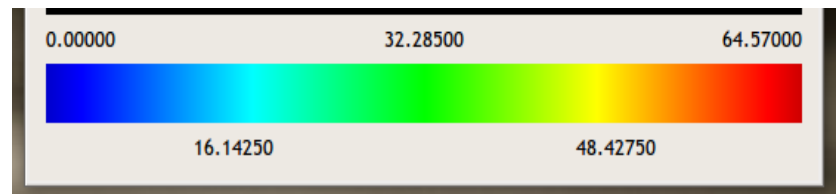
B



C

D

Concentration of TNF scale



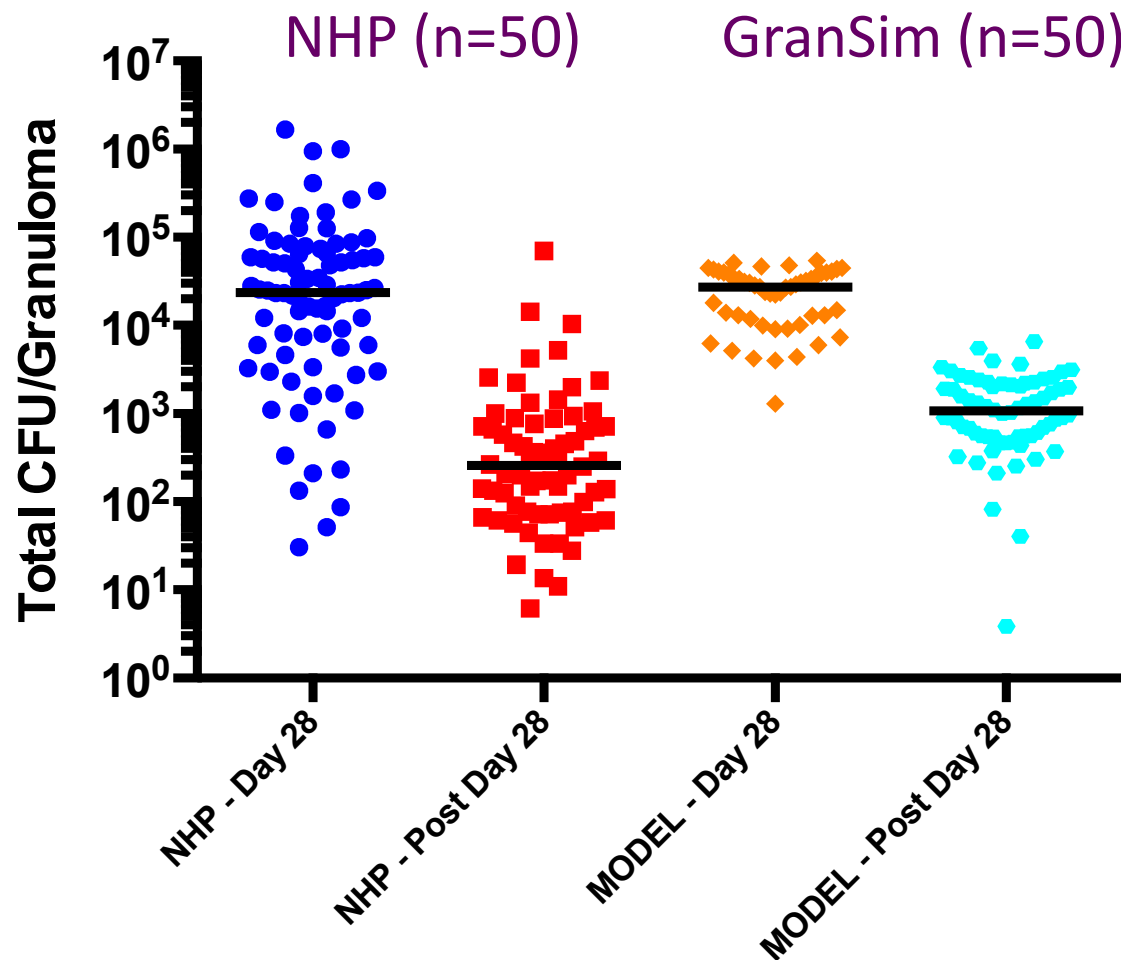
*Gray hashed areas are caseous

Distributions and Gradients of TNF in a granuloma

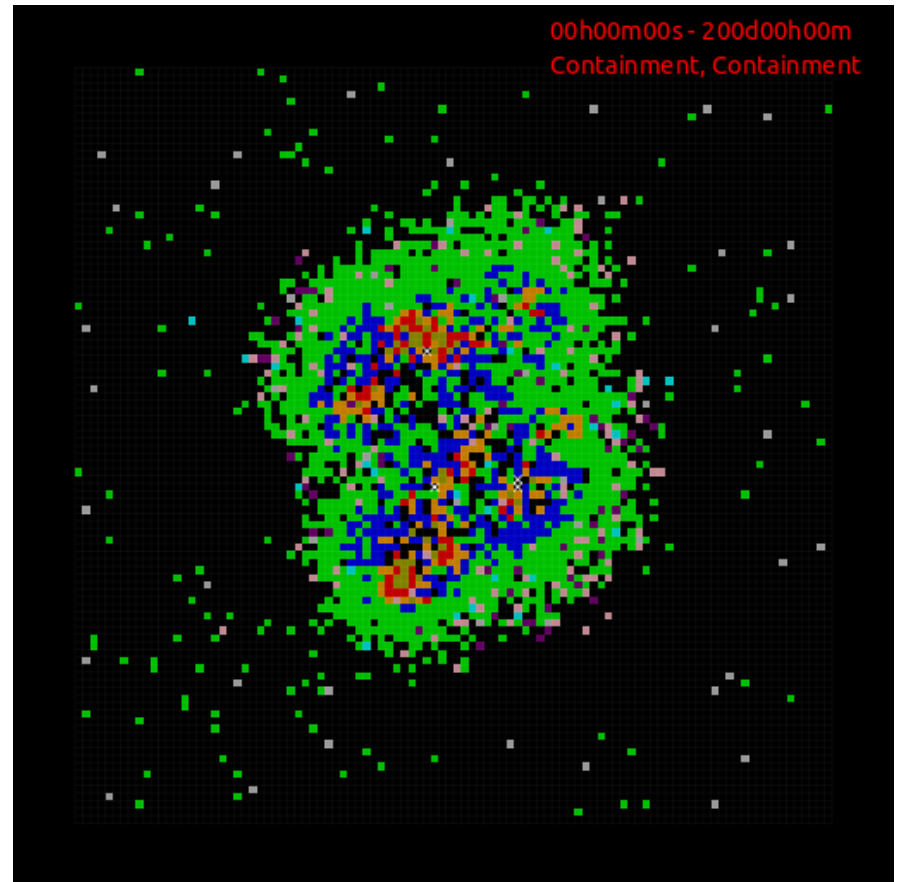
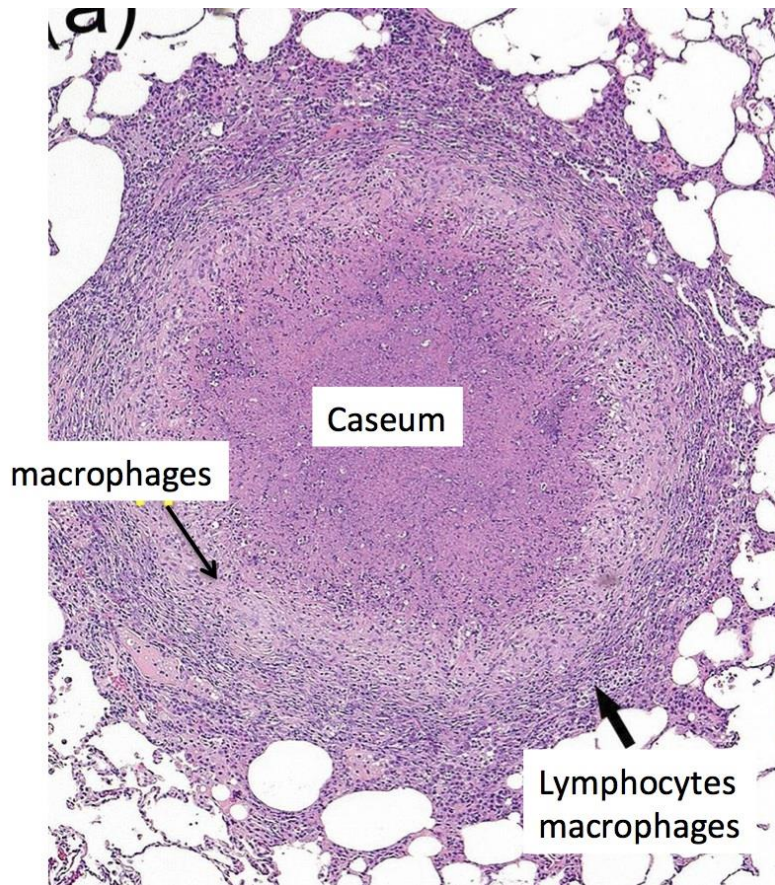
00h00m01s - 00d06h00m
Containment, Containment

600 μm

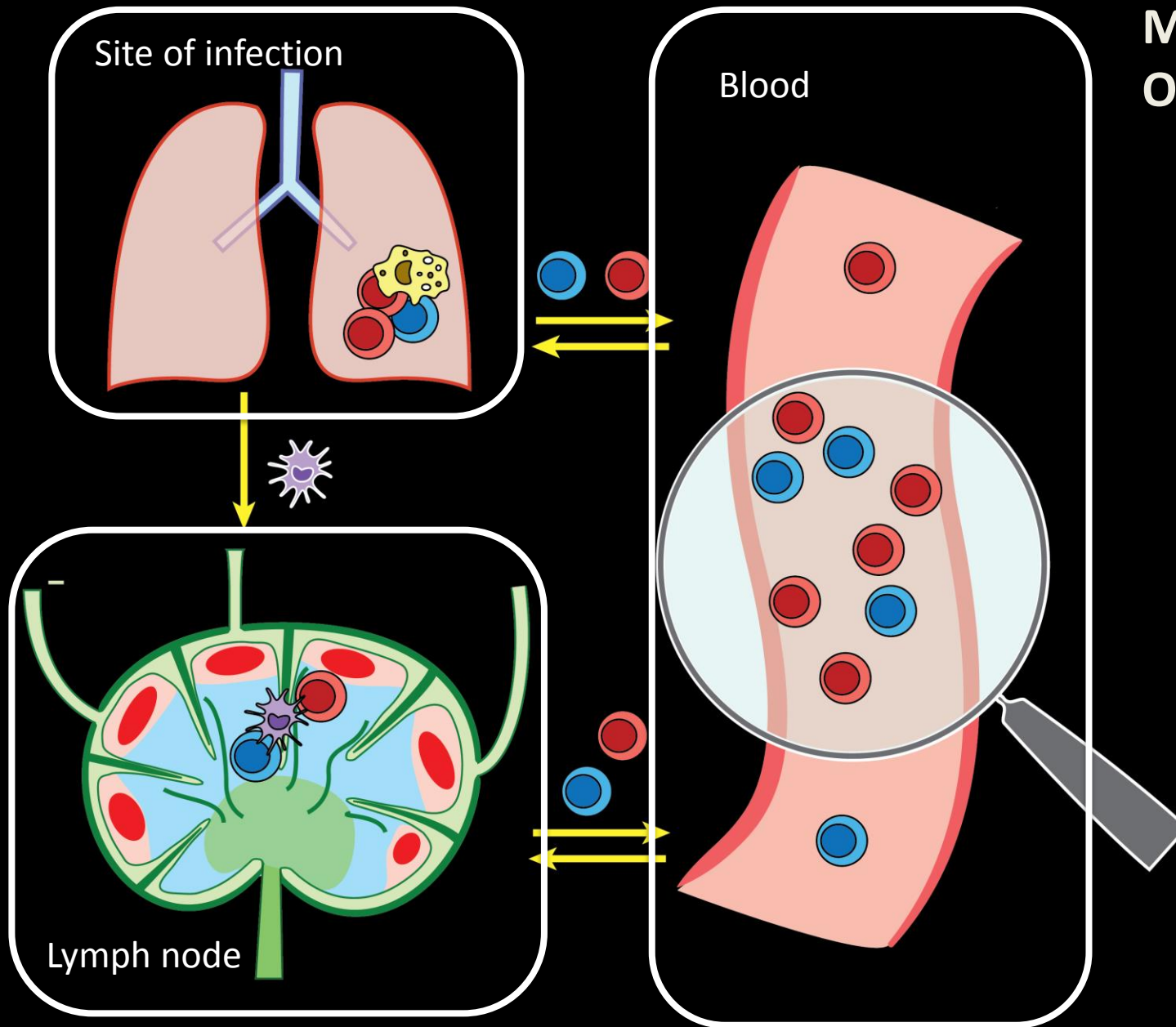
GRANSIM matches quantitative Non-Human Primate CFU data



GRANSIM matches spatial Non-Human Primate data



Multi-organ view Of TB infection



Concluding thoughts:
insights from *in vivo* models and
implications for prevention

- **Pairing experimental and computational:**
 - can be a useful tool for identification of potential therapeutic targets at any biological scale
 - can better fine tune vaccine, drug, and biomarker discovery
 - can accelerate drug or treatment discovery
- ***In vitro* and *in vivo* models can inform our *in silico* models, systems biology approach can streamline experimental protocols or clinical trials**

How can we better integrate data and modeling?

- Systems Biology approach
 - Multiscale
- Development of methods which allow for better use of bioinformatics/sequencing data
- Machine Learning
- Choosing the right model for the right problem

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