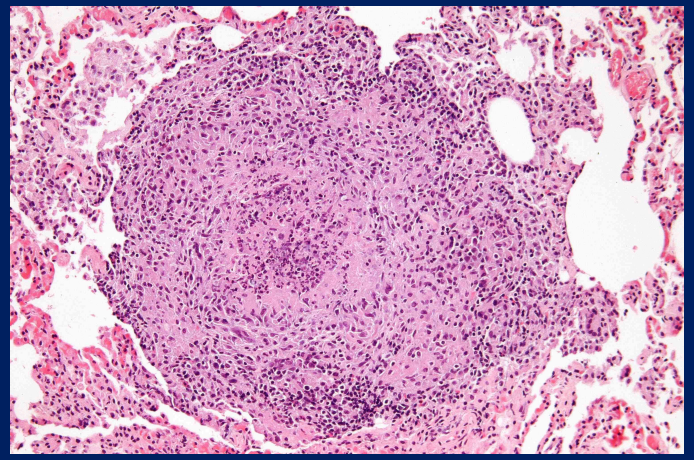
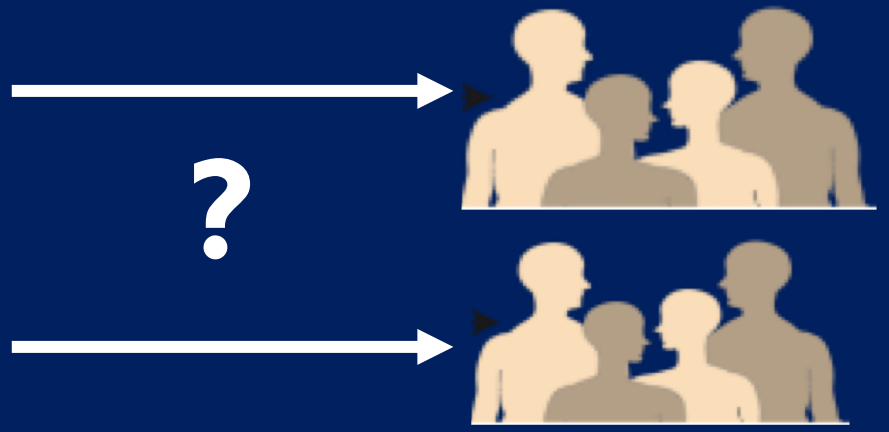
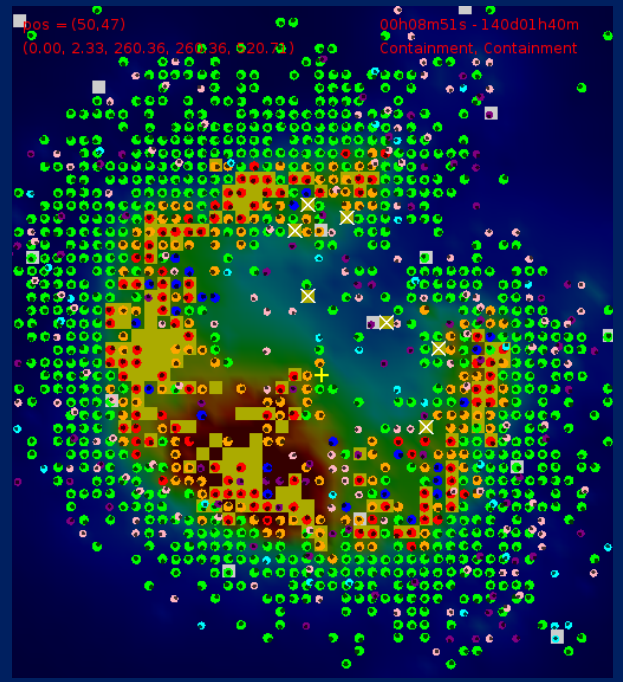




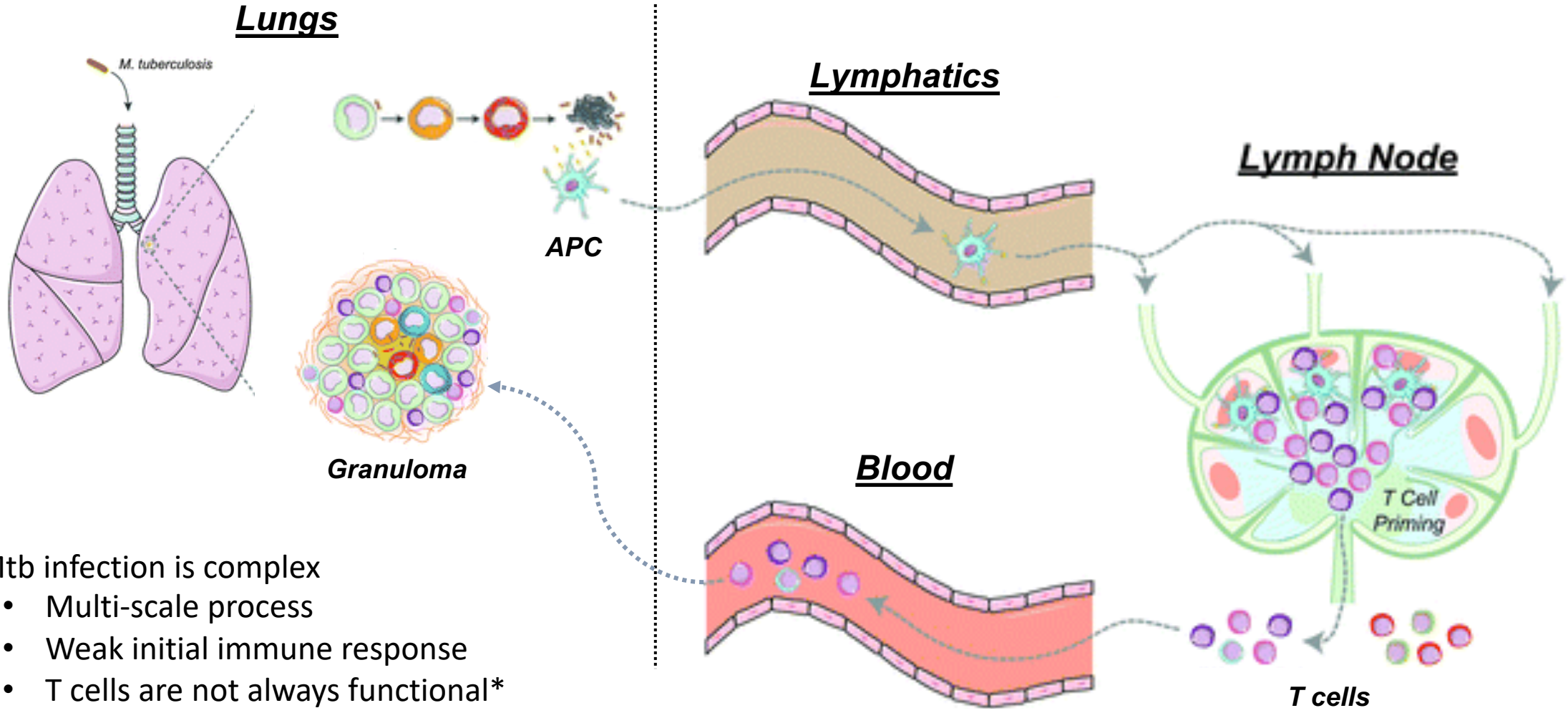
Integrating H56 preclinical and clinical data to translate results from primates to humans using math modeling

Louis Joslyn
Dept of Bioinformatics

With
Dr. Denise Kirschner and Dr. Jennifer Linderman



Immune response to Mtb is delayed



- Mtb infection is complex
  - Multi-scale process
  - Weak initial immune response
  - T cells are not always functional*

*Gideon et al. Plos Pathogen 2015

Linderman et al. 2015 Integrative Bio

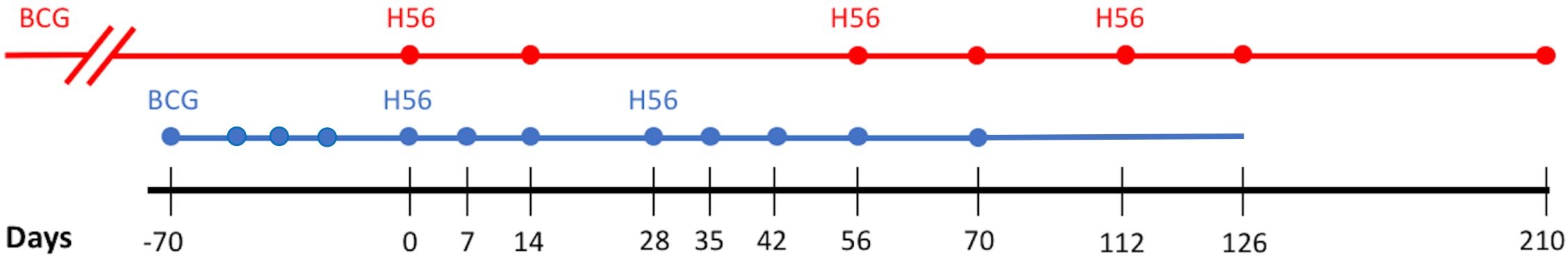
The search for an effective vaccine

Vaccines:

- Bacillus Calmette-Guerin (BCG)
  - Currently given world-wide except Australia, USA, and some European countries
  - Intradermal route of administration
  - Variable efficacy in adults (0-80%)
- H56
  - Subunit vaccine: ESAT6+Ag85B+Rv2660c
  - Ag85B antigen secreted by BCG

Ginsberg et al. 2016 Tuberculosis
Andersen et al. 2005 Nature Reviews Microbiology
TB Alliance Mission 2016
Leung et al. 2018 TB updates - Respirology
Global Tuberculosis Report 2017 20th edition, World Health Organization

BCG and H56 NHP & human data



Legend:

Humans (QFT-)

Non-human Primates (NHPs)

Blood Draws (Dots):

- Isolate T cell by phenotype and lineage
- Antigen-specific T cell response isolated and collected

Dose Amounts

- Human: 50 µg
- NHP: 50 µg
- 0.1 mL BCG

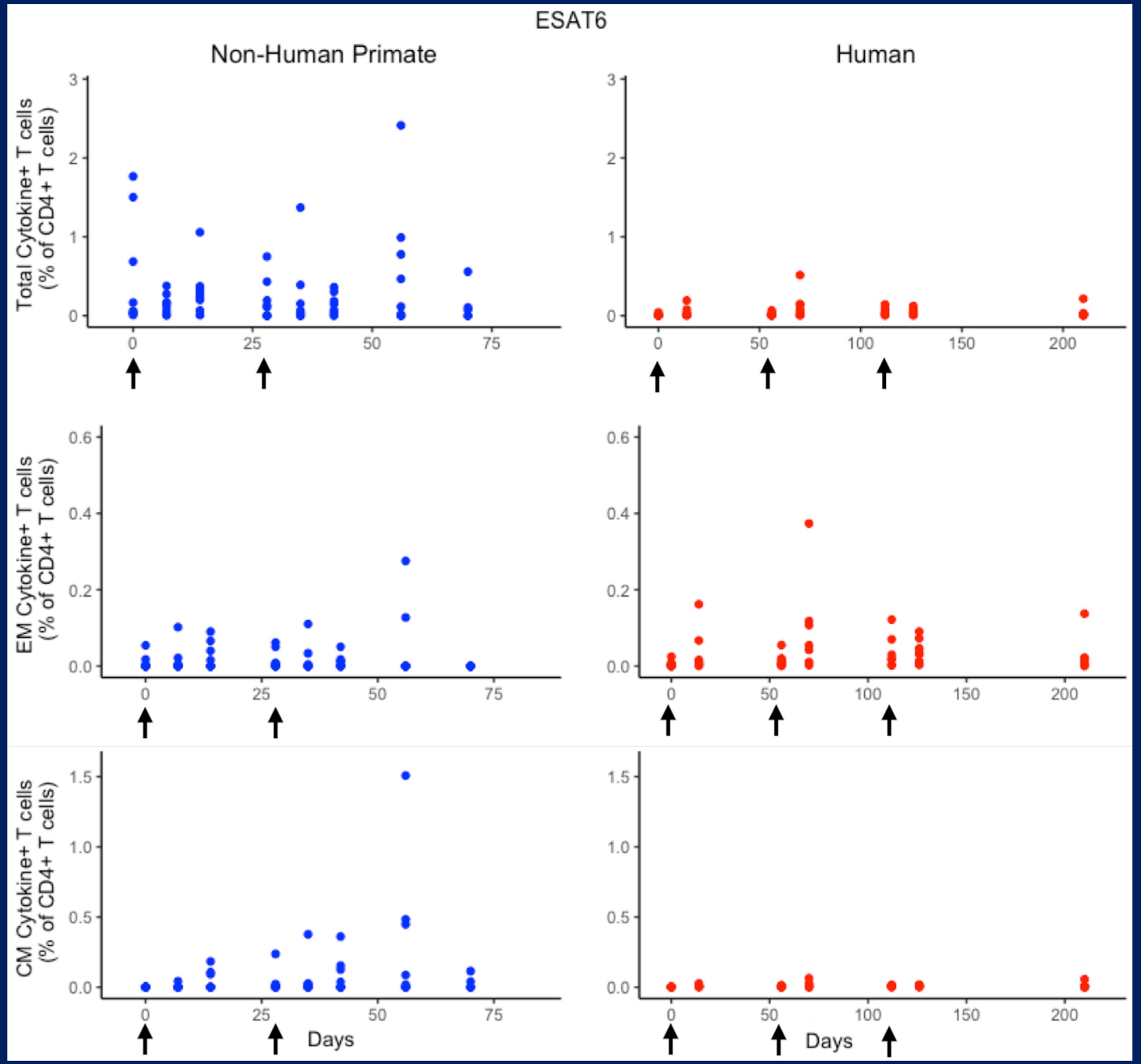
Joslyn et al. 2018 Frontiers in Micro

Luabeya et al. 2015

Preclinical & clinical H56 response data

Difference in ESAT6 Response:

- NHP response highly variable
- Effector Memory response is similar

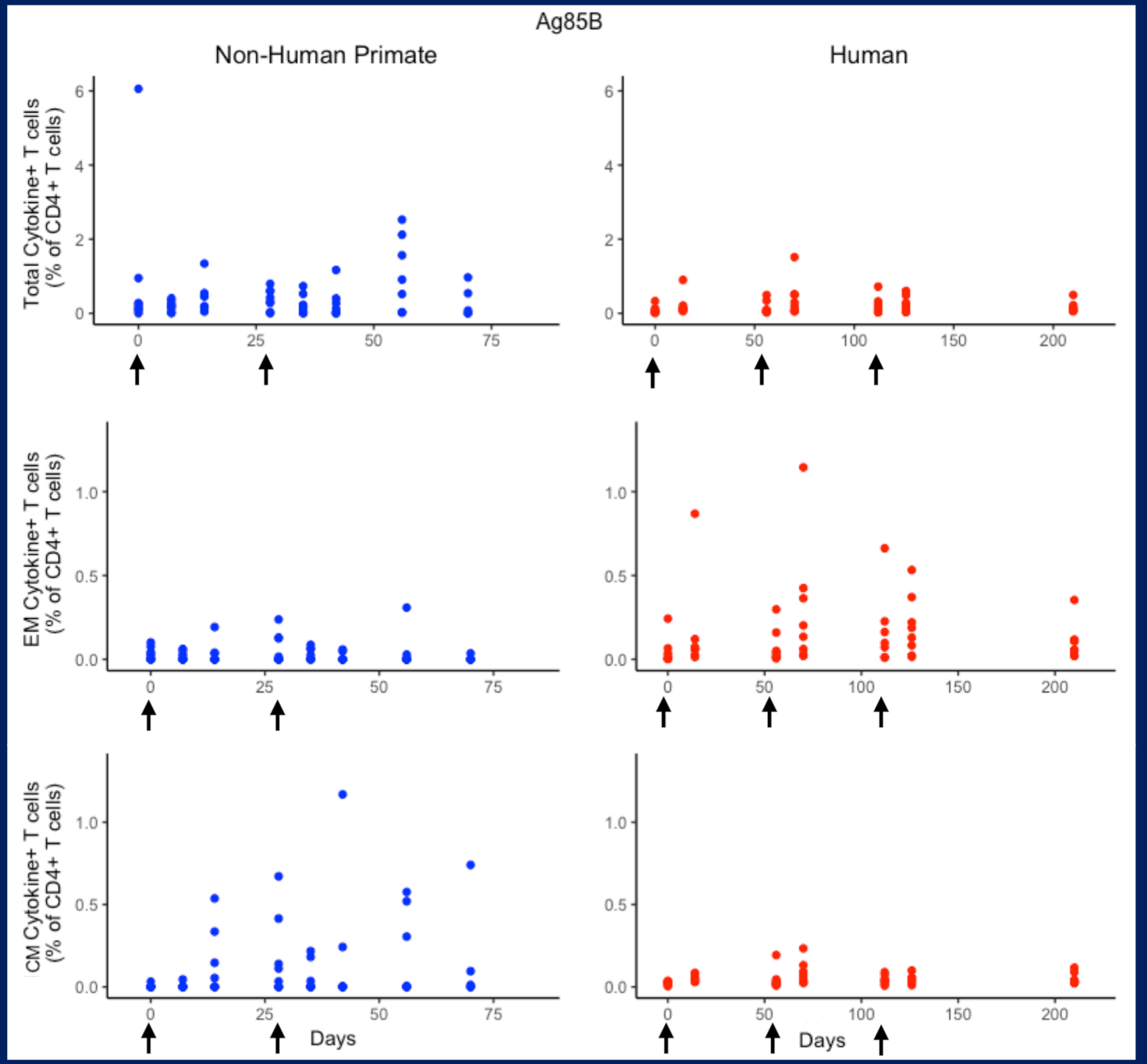


Joslyn et al. 2018 Frontiers in Micro

Preclinical & clinical H56 response data

<u>Difference in Ag85B Response:</u>

- NHP response even more variable
- Effector Memory response remains similar



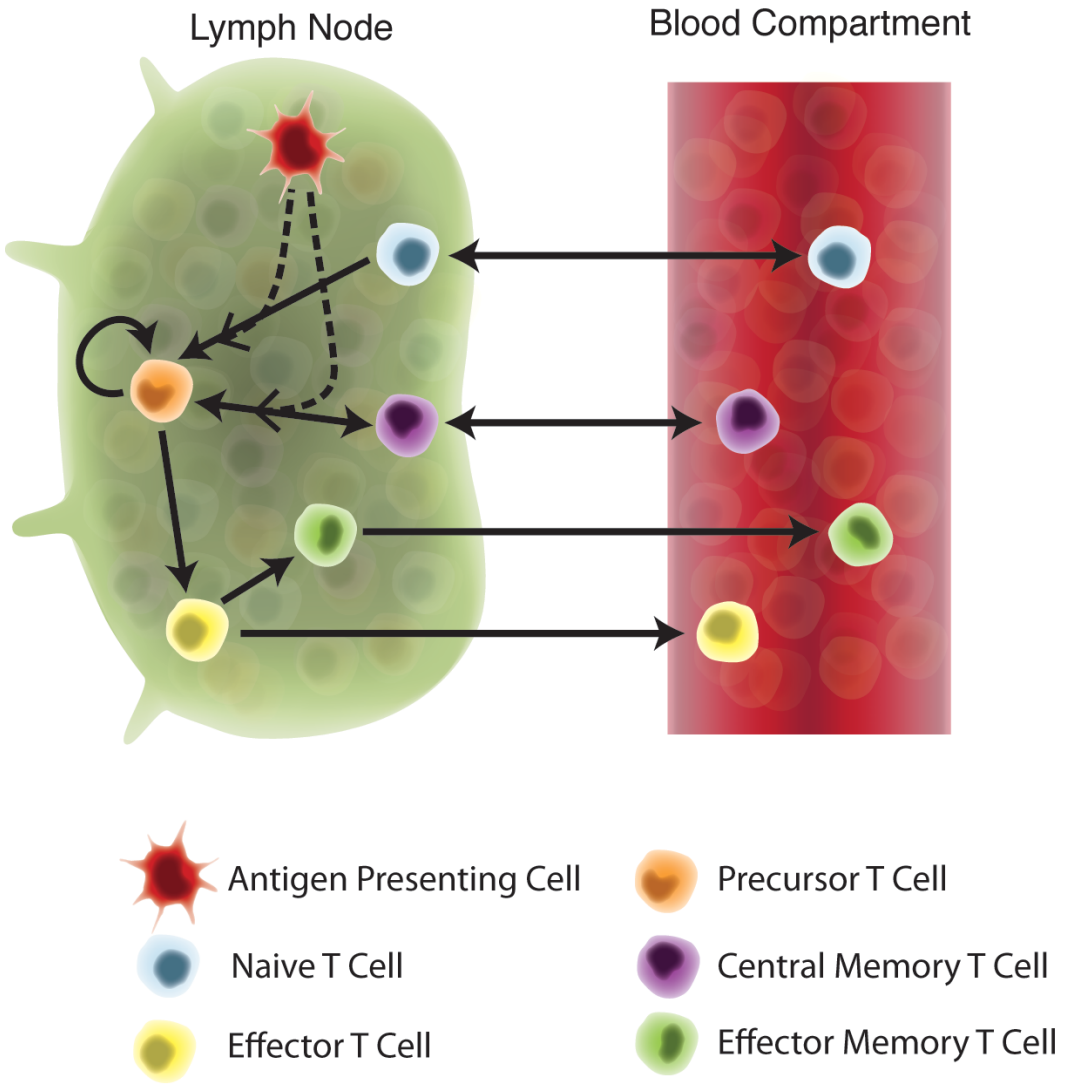
Joslyn et al. 2018 Frontiers in Micro

Goals for published and current work

- Provide a mathematical framework to evaluate the response of a vaccine within host
- Can we use modeling of H56 as a case study to evaluate similarities/differences in NHP and human response?
- Can we evaluate the impact of prior BCG vaccination on H56 immunogenicity in blood and lymph nodes?
- (Current Work) Can we evaluate efficacy of H56 as a pre- and post-exposure vaccine?

Creating a pre-infection vaccine model

- Two Compartment ODE model
  - 31 Ordinary Differential Equations across the blood and LN representing:
    - APCs
    - CD4 specific, nonspecific T cells
    - CD8 specific, nonspecific T cells
  - Parameter values estimated from data
    - can vary all parameters
    - can vary all initial conditions



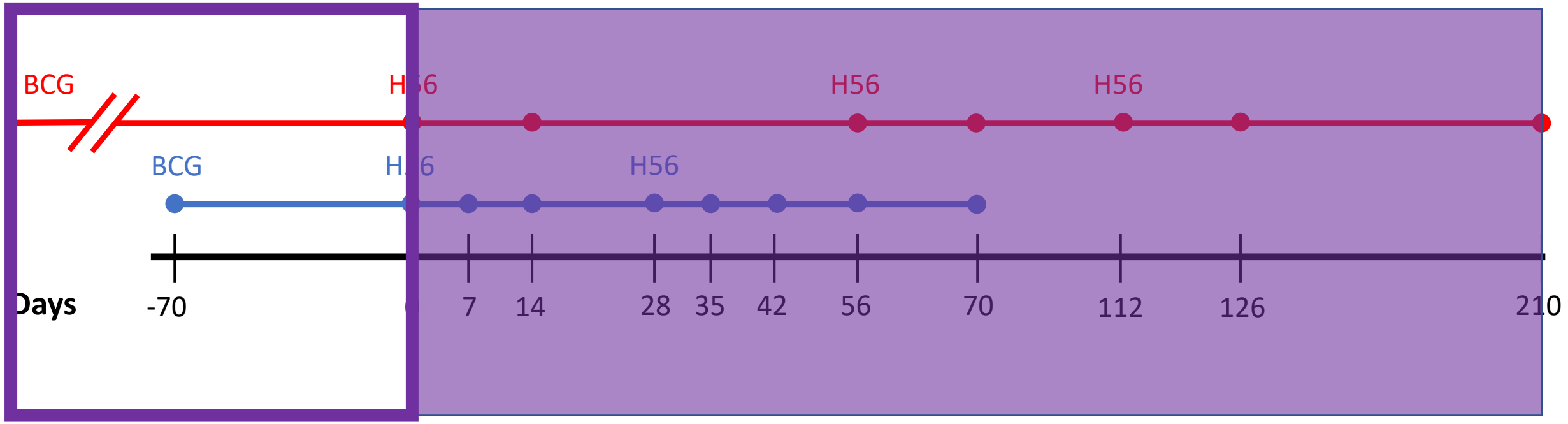
Marino et al. 2016 PLOS Comp Bio
Marino et al. 2016 Computation

Joslyn et al. 2018 Frontiers in Micro

Capturing vaccination time points

Varied Initial Conditions

Introduced APCs



Model Predictions

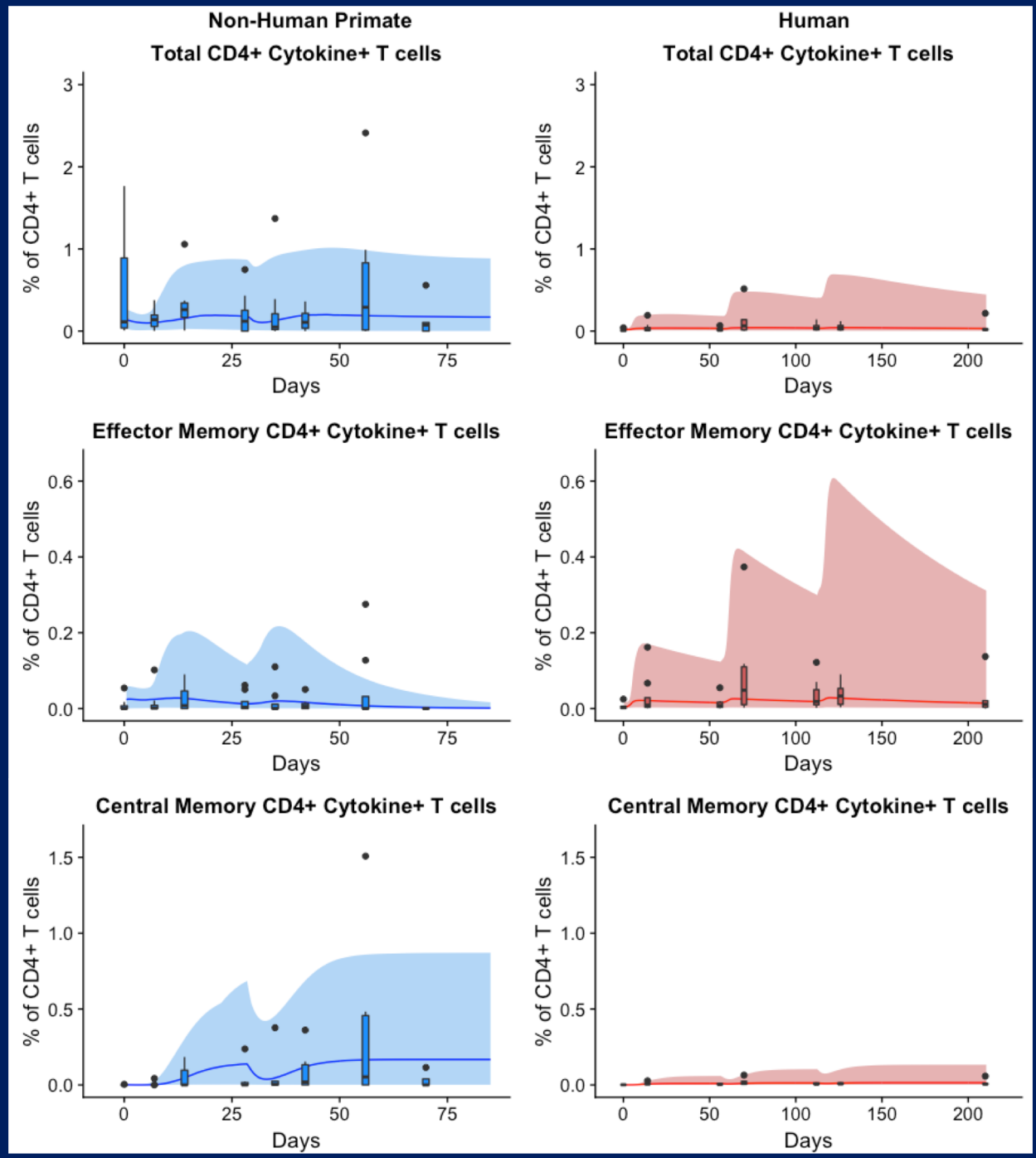
What was important in the NHP and human response?

NHP ESAT6 Response:

- Central Memory reactivation
- Precursor Proliferation

Human ESAT6 Response:

- Central Memory recruitment
- Precursor Proliferation



Model Predictions

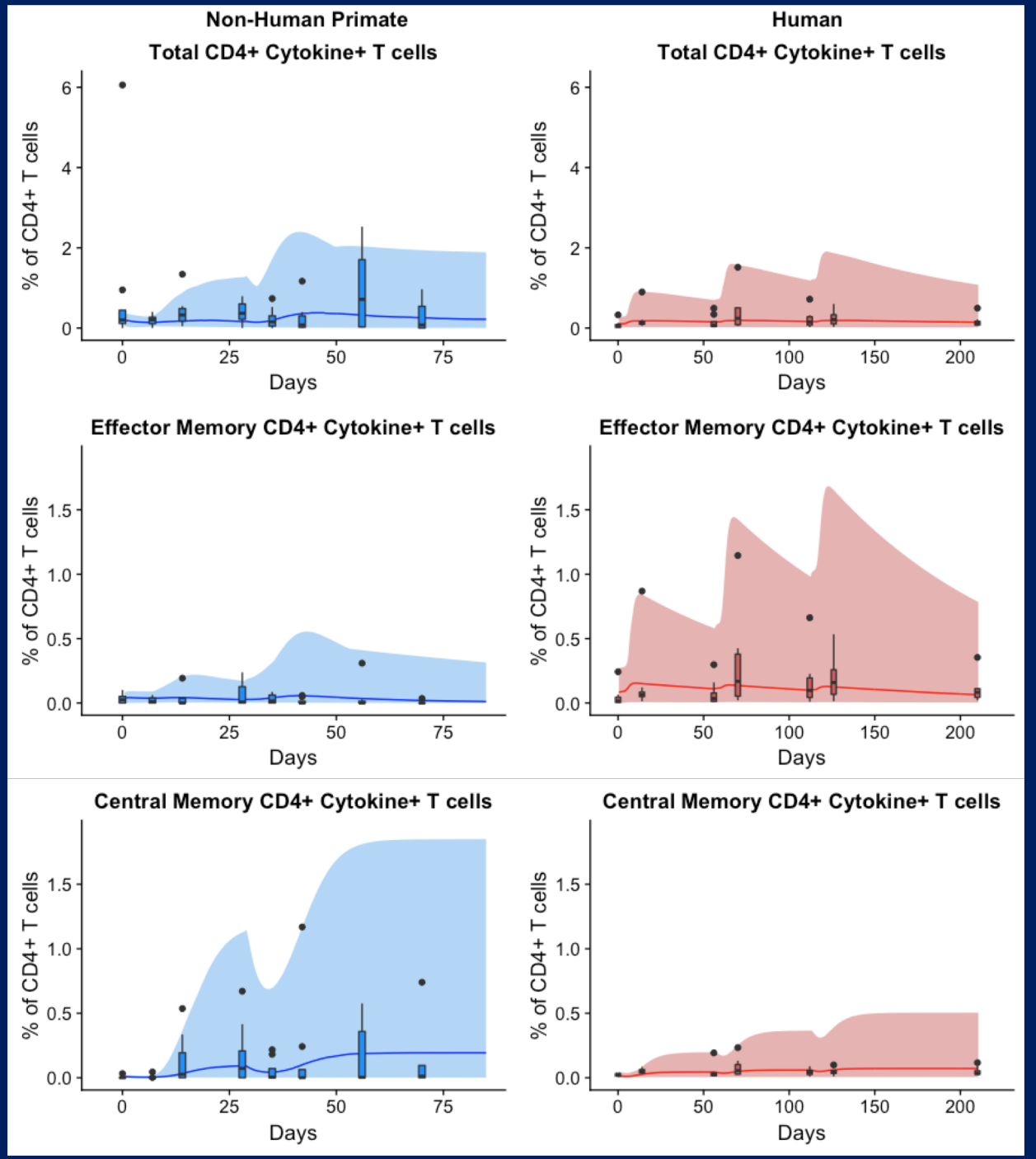
What was important in the NHP and human response?

NHP Ag85B Response:

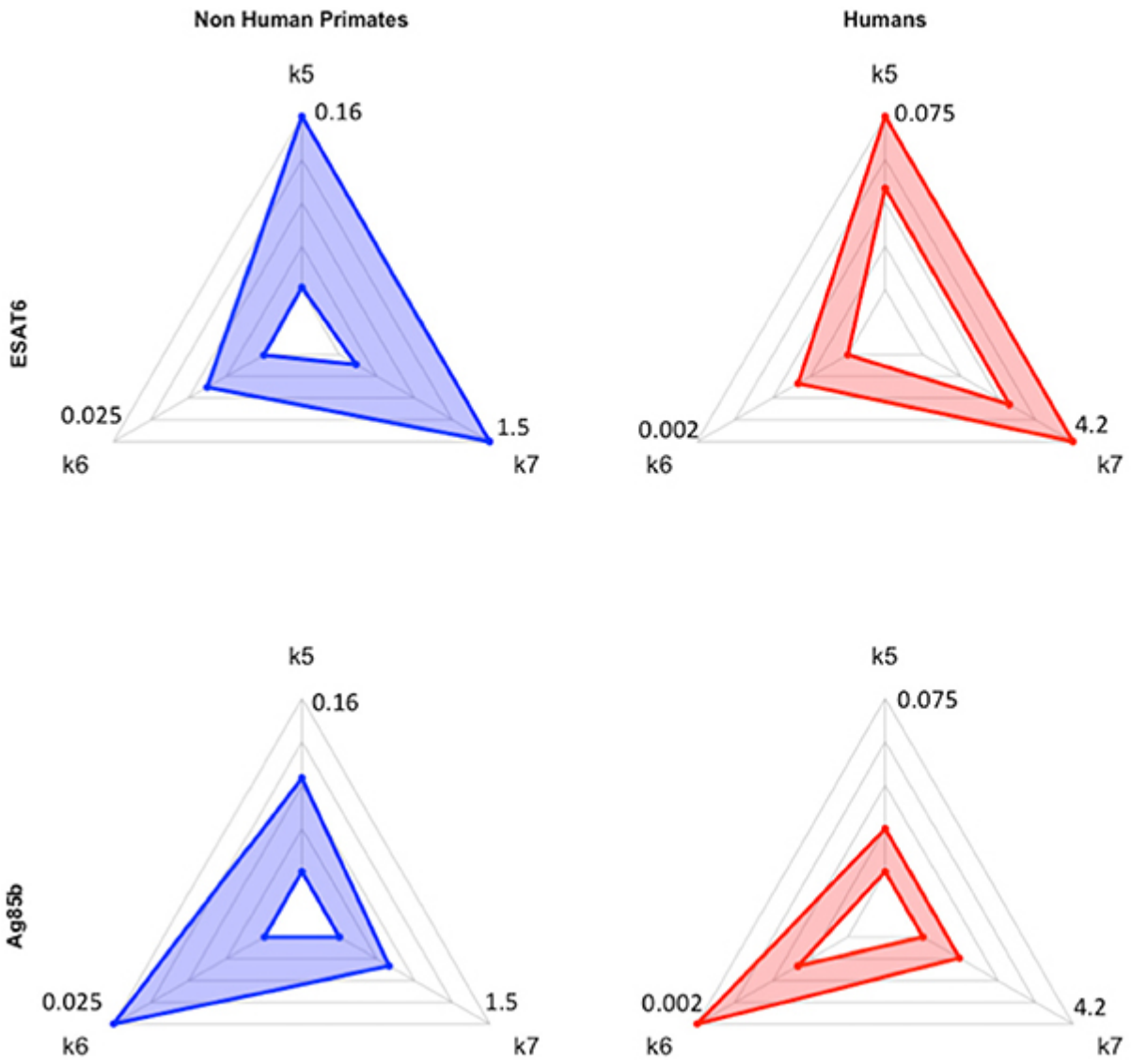
- Initial Conditions in Lymph Node
- Precursor Proliferation

Human Ag85B Response:

- Central Memory recruitment
- Precursor Proliferation
- Likelihood of proliferation



Radar Charts Reveal Impact of Memory on Parameter Space



K5 = Precursor to Effector
K6 = Precursor to CM
K7 = Effector to Effector Memory

Response to ESAT6:

- Humans, NHPs produce a primarily effector and effector memory response

Response to Ag85B:

- Humans, NHPs produce more Central Memory cells than in the ESAT-6 response

Conclusions

- Successfully built a pre-infection vaccination framework using a systems biology approach that integrated NHP and human data.
- Prior BCG vaccination similarly impacts NHPs and humans response to H56 (Radar Charts)
  - but timing is important.
- Can not give BCG years before boost in NHPs
  - Too expensive
  - But this timing is incredibly important, and must be considered.
- Our analysis revealed that the 3rd vaccination dose in humans was not associated with positive changes in memory cells across time.
  - Could have been omitted!

Acknowledgments

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