Recognizing the problem:

Is poor T cell recognition of infected cells a barrier to protective immunity?

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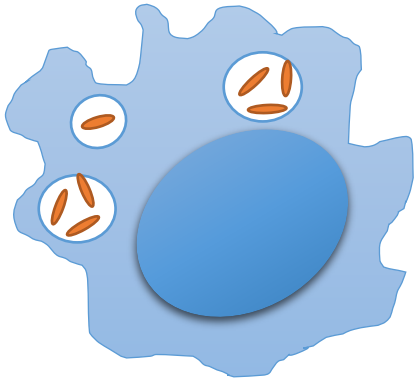
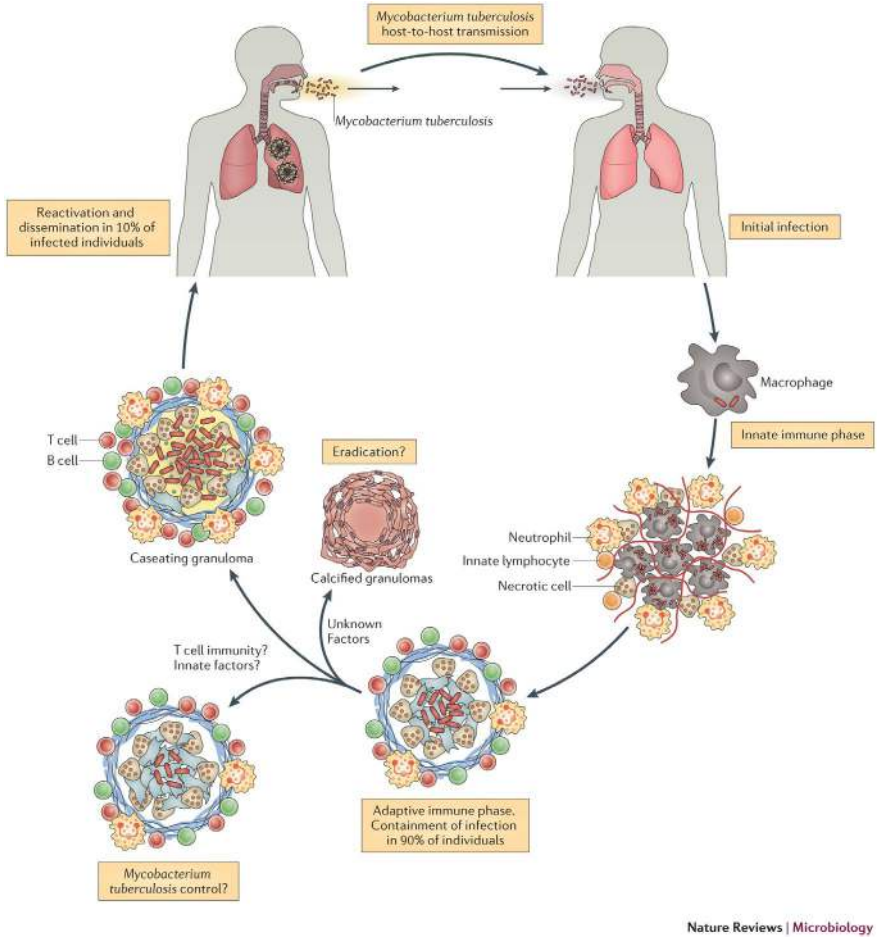
Immune evasion as a microbial pathogenesis strategy

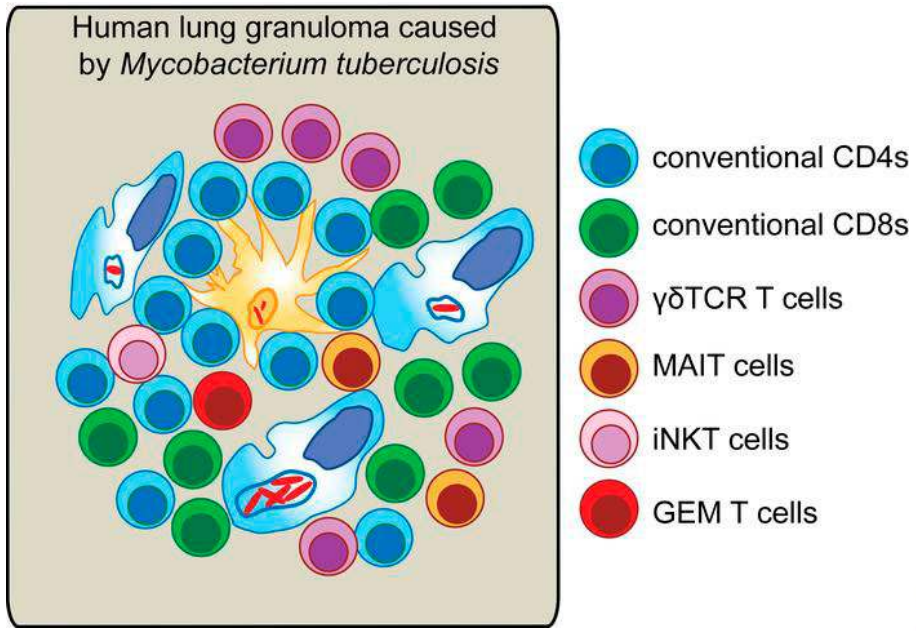


- An intracellular “lifestyle” helps microbes to evade “humoral” immunity
- Intracellular microbes inhibit or avoid intrinsic antimicrobial pathways
- Successful pathogens also evade or tolerate cell-mediated immunity

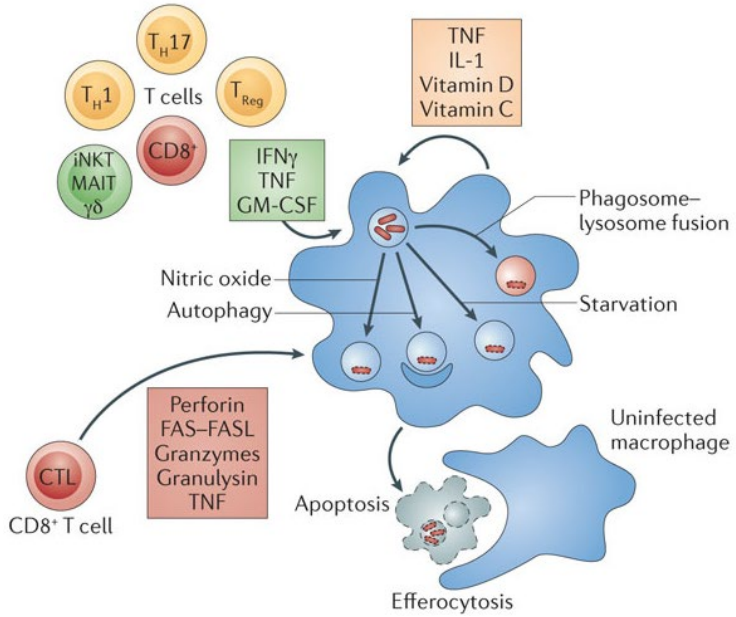


Ultimately, disease is required for transmission

The T cell response to Mtb is complex

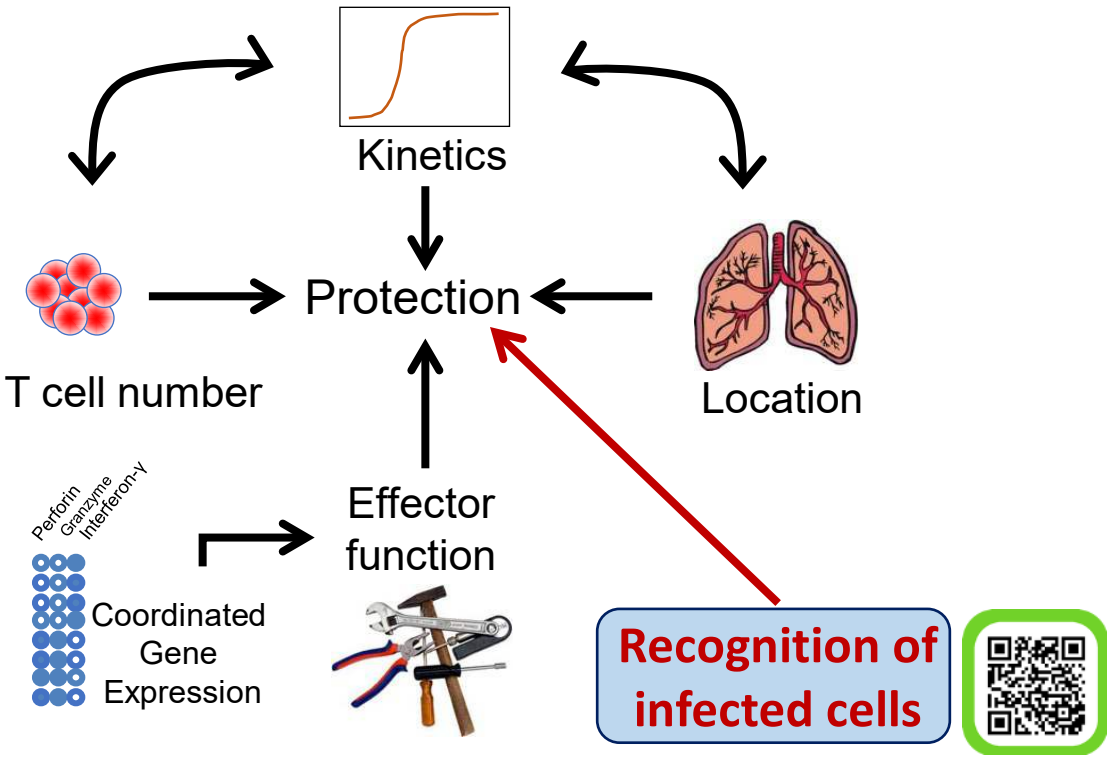


- The T cell response is diverse
- Many different intracellular compartments are surveilled
- Diverse antigens are presented to T cells
- T cells stimulate different effector pathways



Despite protective host response, Mtb survives, persists, and is transmitted

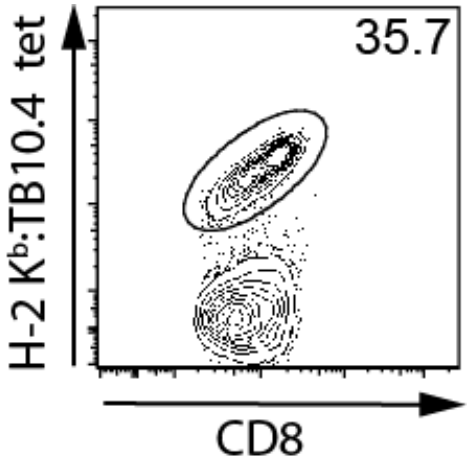
Hypothesis: Mtb avoids T cell recognition

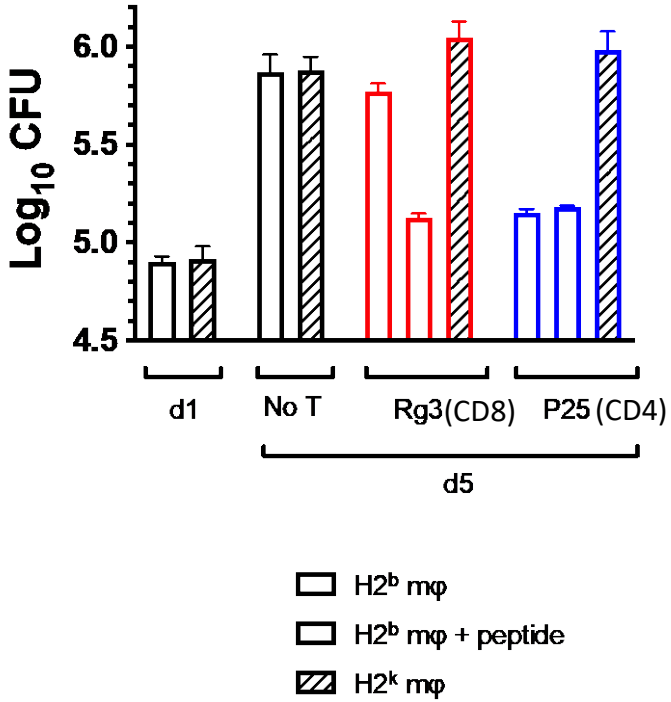


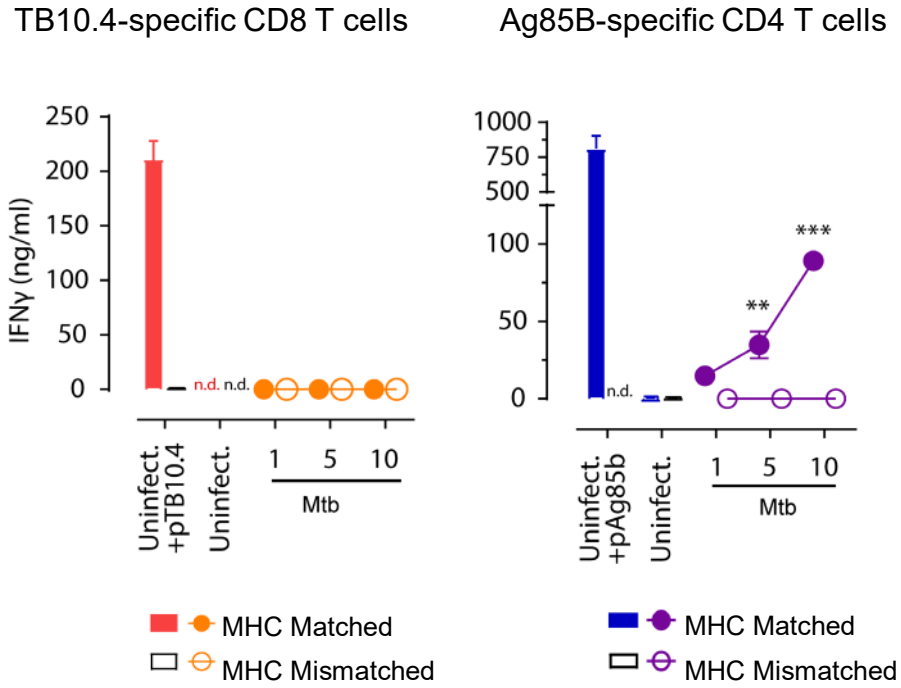
Implications for vaccines

- Evasion of T cell immunity may pose a roadblock to vaccine development
- Infected macrophages containing single bacteria may be difficult for T cells to recognize
- Vaccines may elicit functional T cells; however, they fail because Mtb-infected macrophages are inefficient APC.
- Identifying antigens that are presented by infected cells may be an effective way to select vaccine targets

Mtb elicits an immunodominant CD8 T cell response that doesn't recognize infected macrophages



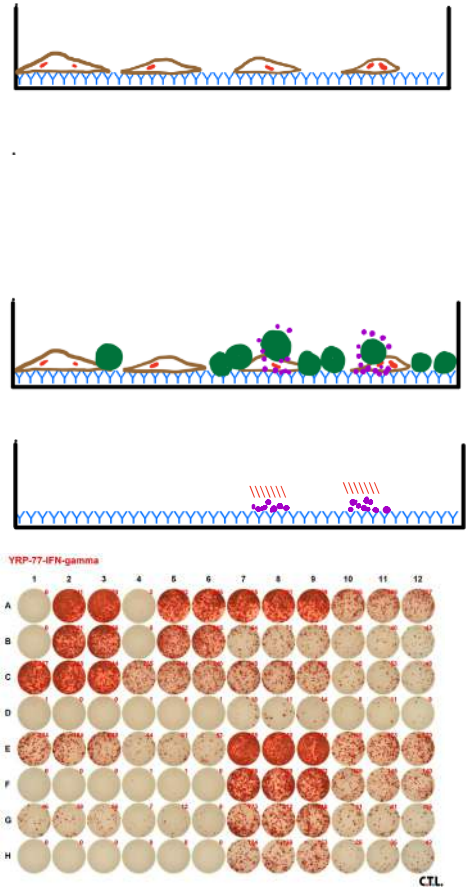


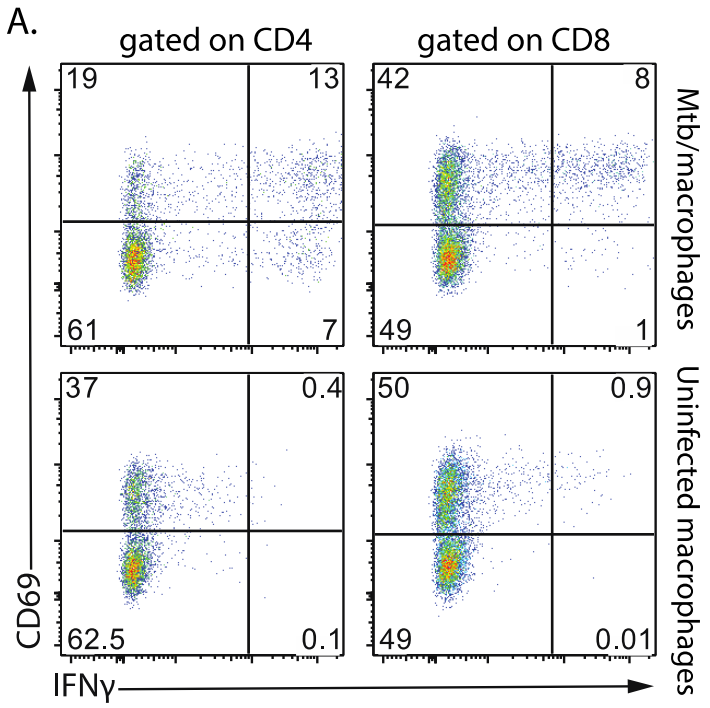


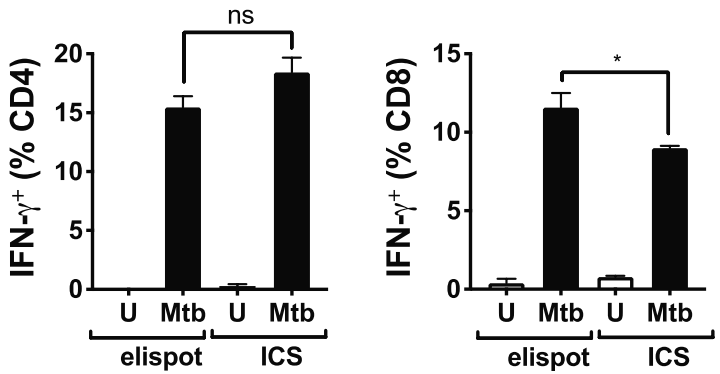
Jason Yang et al, PLoS Pathogens (2018)

How many T cells recognize Mtb-infected macrophages?

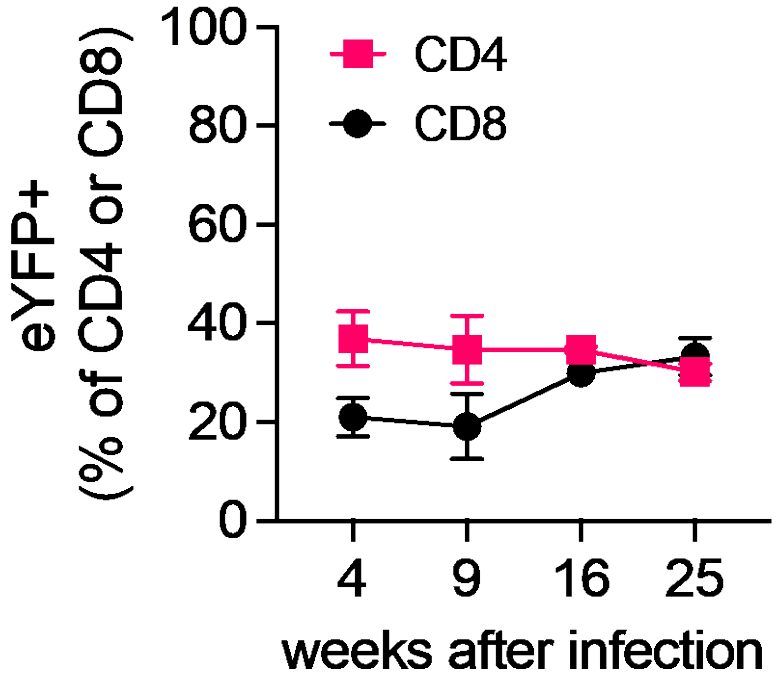
Mtb-infected macrophage elispot

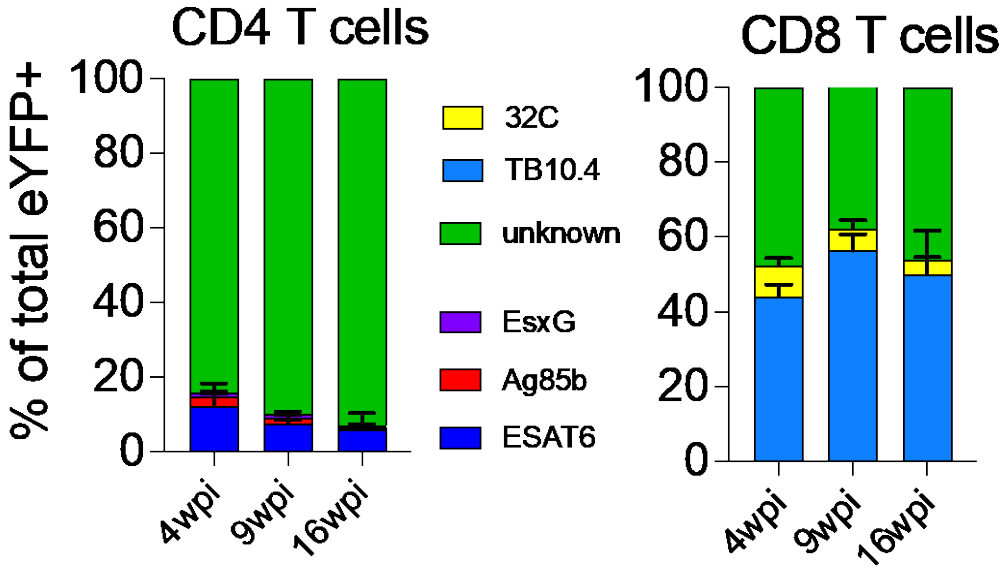






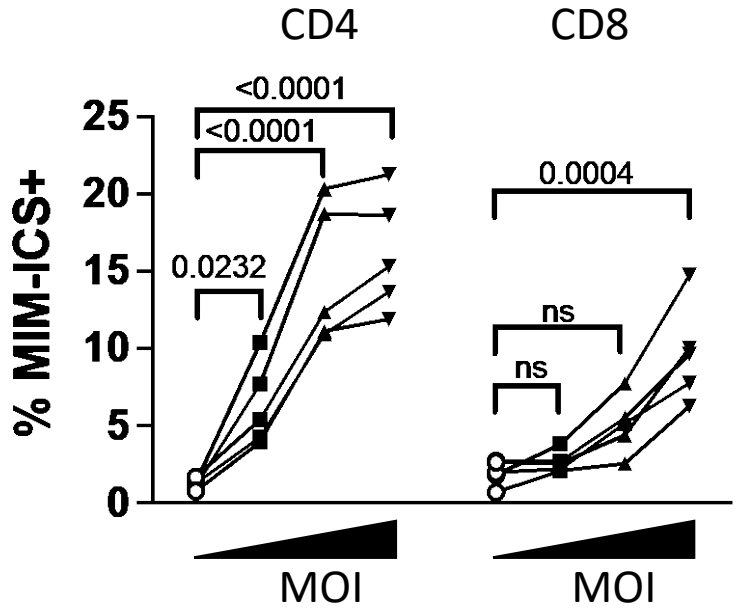
T cell activation in vivo during Mtb infection





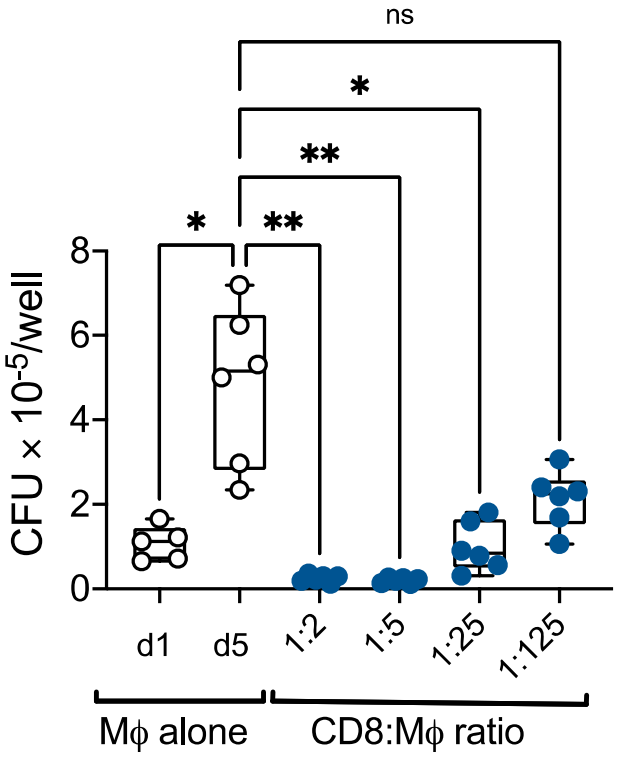
Tomoyo Shinkawa et al, unpublished data

Polyclonal CD8 T cells recognize heavily infected macrophages

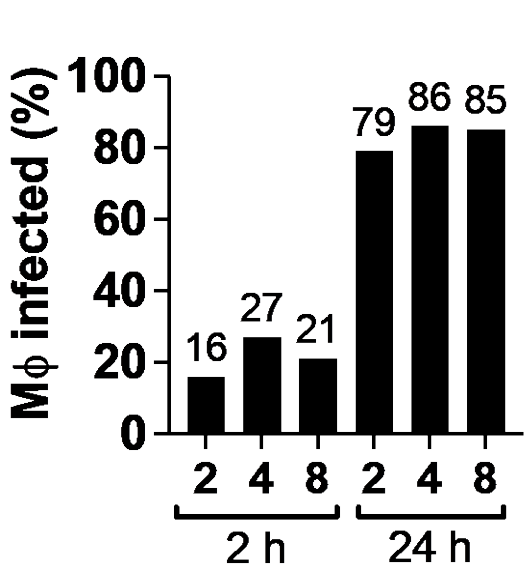


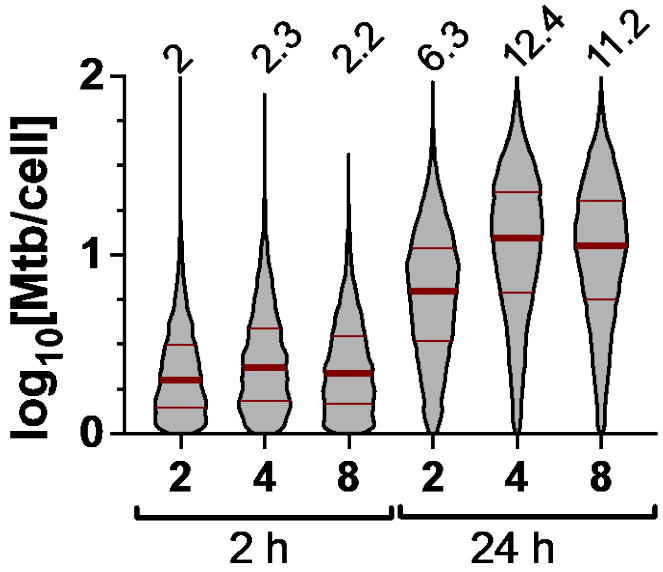
Antigens

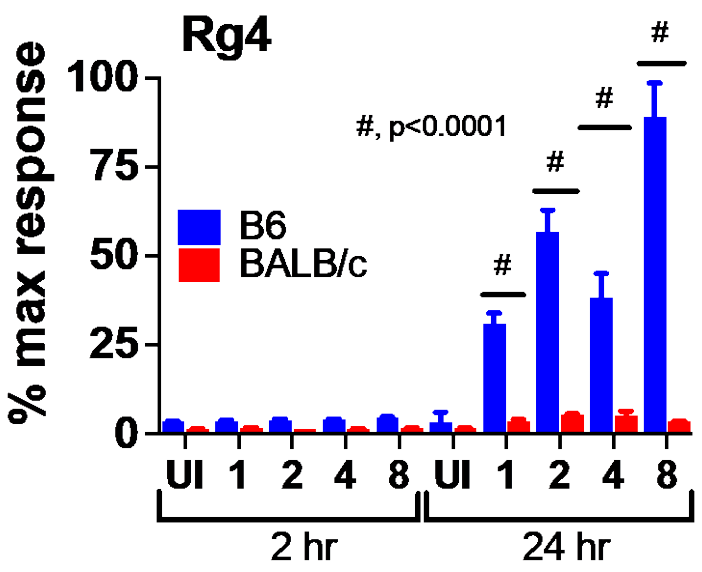
Erdmann infected mice
H37Rv infected macrophages



TB10.4-specific CD8 T cells recognize heavily infected macrophages







High intracellular burden after aerosol Mtb infection

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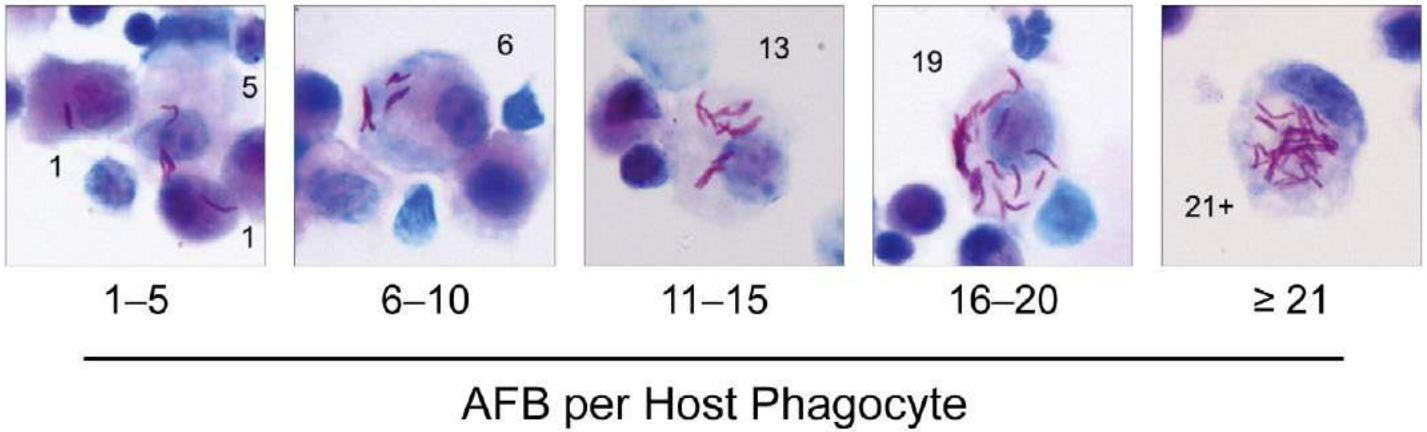
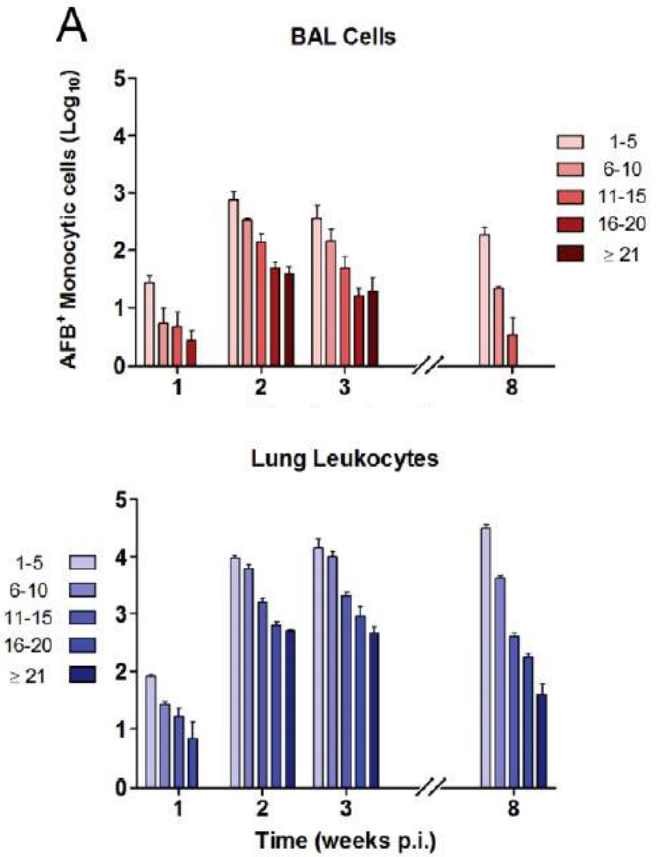
PLOS | PATHOGENS

Intracellular Bacillary Burden Reflects a Burst Size for *Mycobacterium tuberculosis* In Vivo

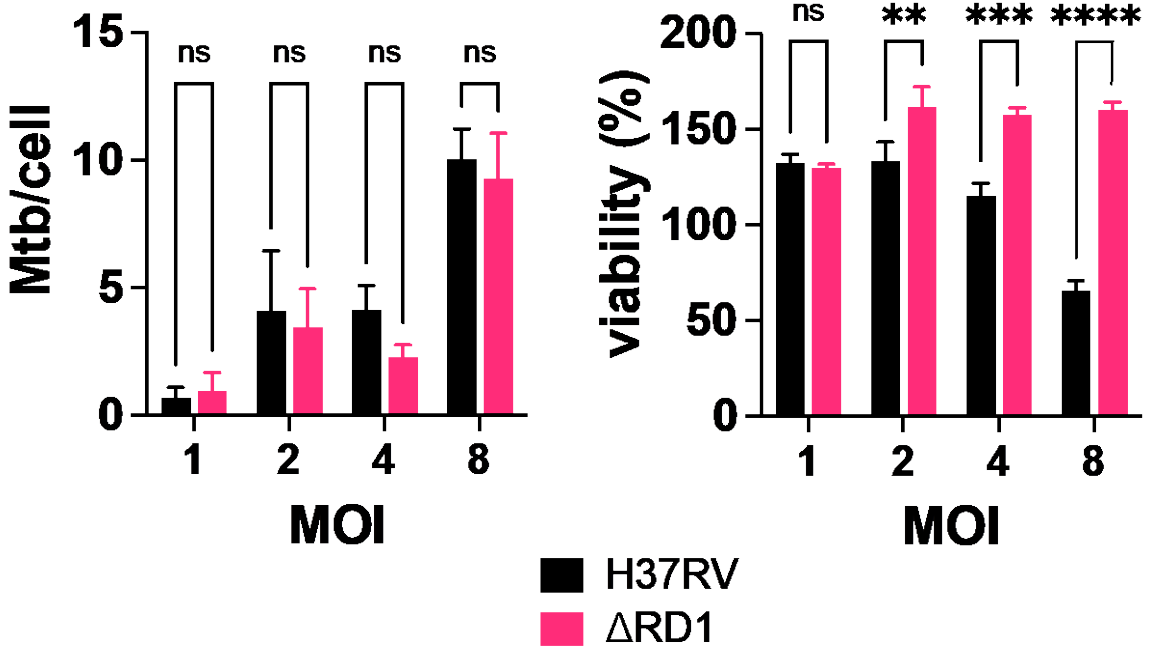
Teresa Repasy[1], Jinhee Lee[1], Simeone Marino[2], Nuria Martinez[1], Denise E. Kirschner[2], Gregory Hendricks[3], Stephen Baker[4], Andrew A. Wilson[5], Darrell N. Kotton[5], Hardy Kornfeld[1]*

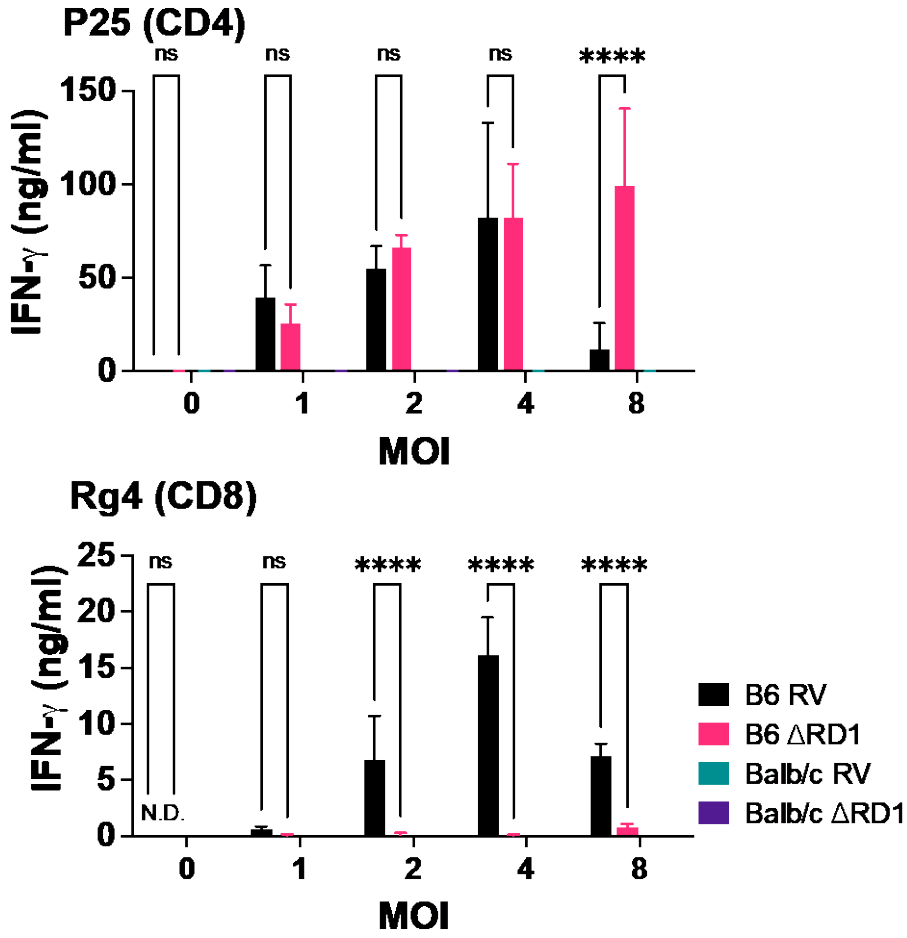




Repasy et al, PLoS Pathogens (2013)

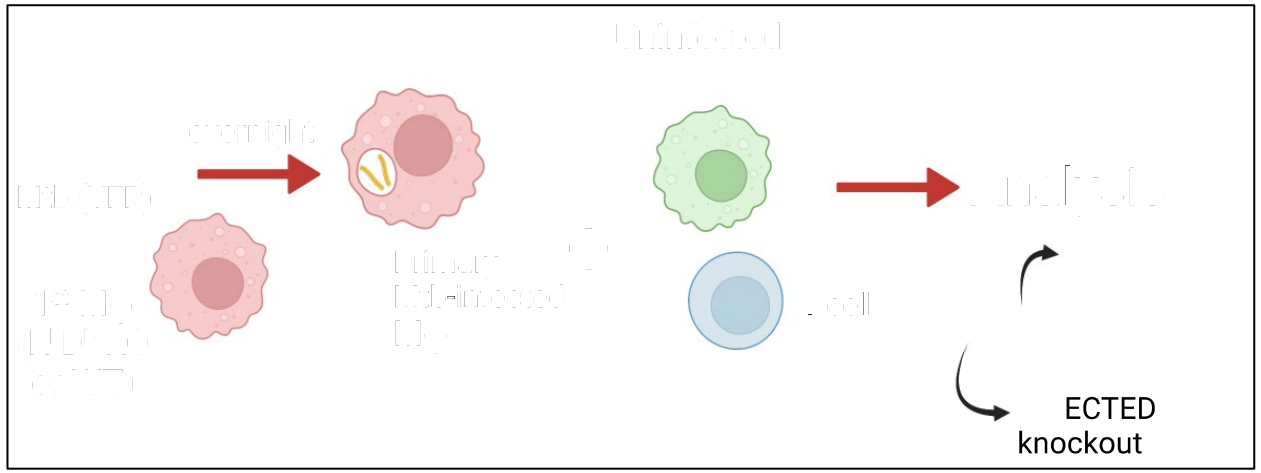
The ESX1 type VII secretion system leads to cell death and is required for antigen presentation to CD8 T cells

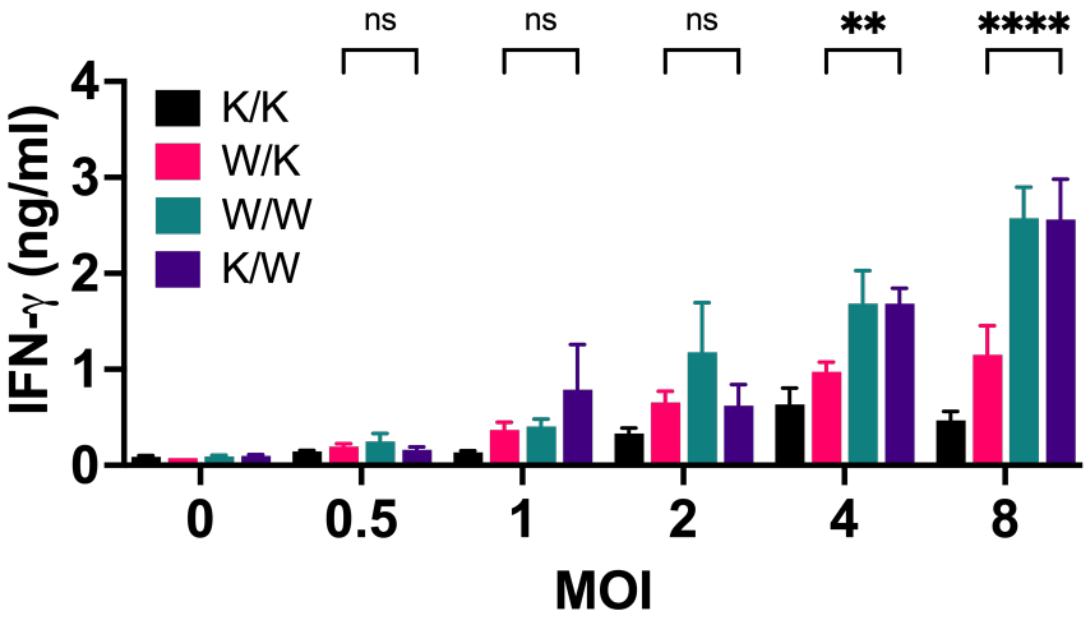




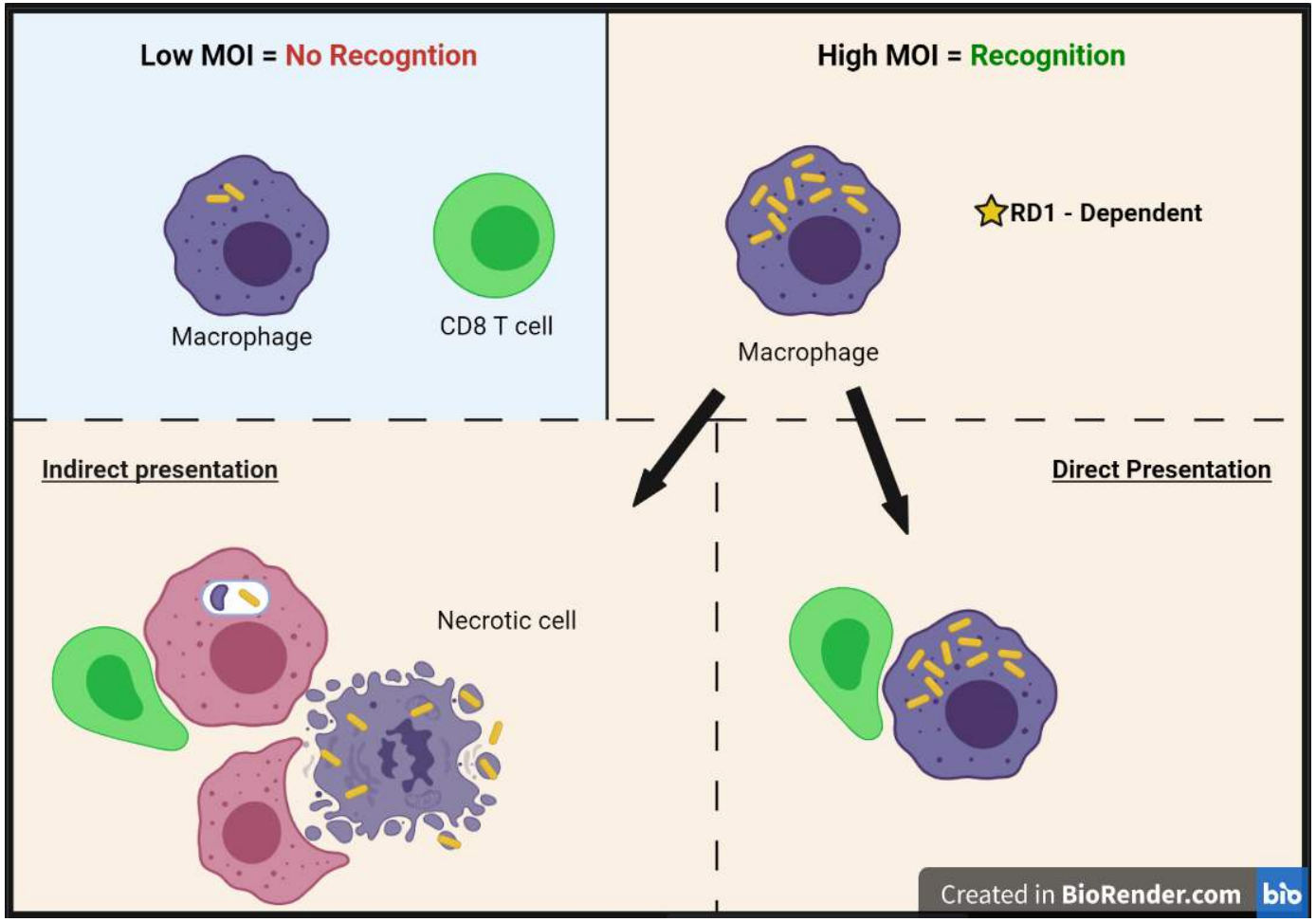
Danny Mott et al, J Immunol (2023)

TB10.4 is more efficiently presented by bystander macrophages than directly infected macrophages



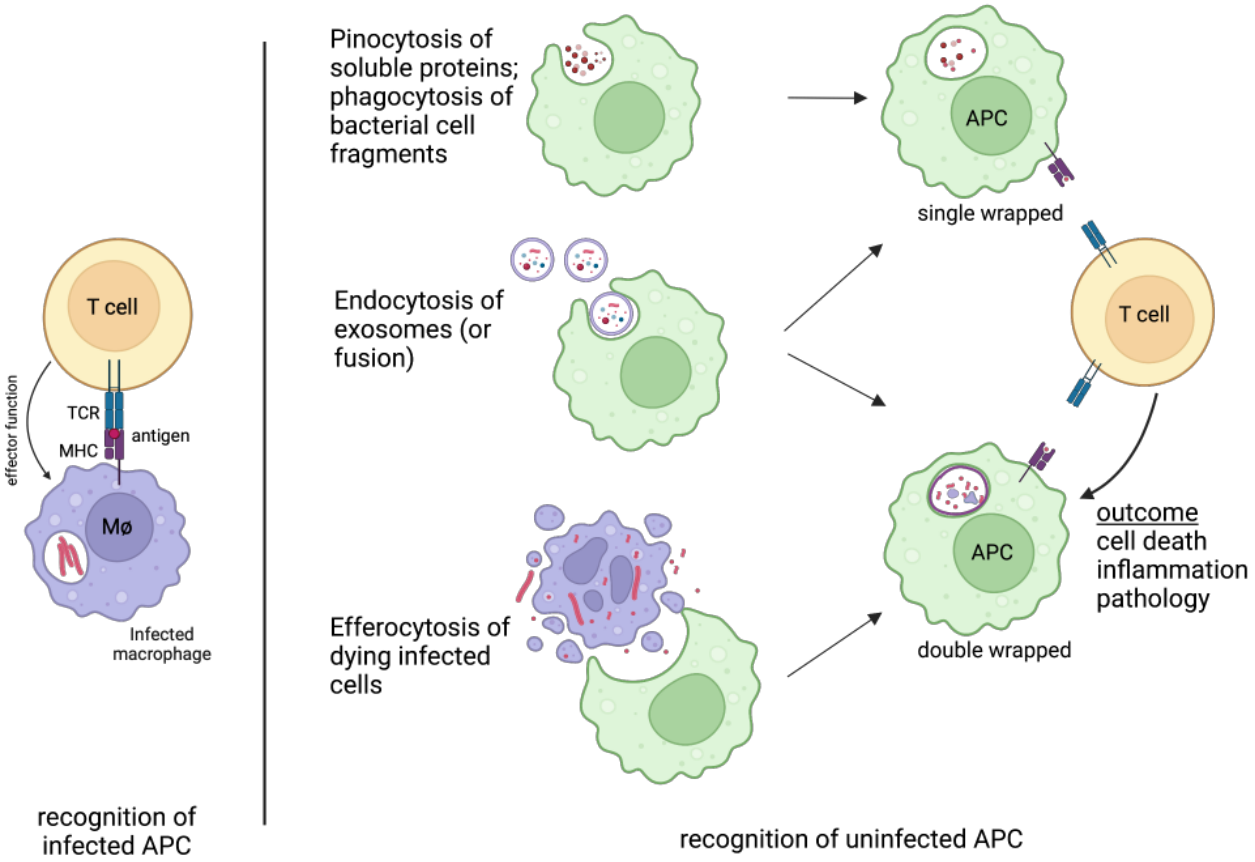


Recognition of heavily infected macrophages by CD8 T cells requires ESX-1



Danny Mott et al, J Immunol (2023)

What are Mtb-specific T cells in the lung recognizing?



1. <u>Direct recognition of infected cells</u>:
- Are certain antigens more likely to be presented by Mtb-infected cells?
- Does this depend on the antigen, the Mtb strain or host genetics (e.g., HLA)?
- Are such antigens the targets of protective T cells?
- Can they be identified and developed into vaccine candidates?
- Could T cell recognition of infected cells serve as a correlate of protective immunity?

2. <u>Presentation of antigens by uninfected bystander cells</u>:
- Is bystander activation of T cells beneficial? Does it contribute to anti-mycobacterial immunity?
- Is bystander activation of T cells detrimental? Does T cell recognition of uninfected cells lead to inflammation, cell death, and exacerbate pathology, which could promote Mtb transmission?
- Does bystander activation distract T cells from focusing on infected cells

3. <u>Why is antigen presentation by Mtb-infected cells suboptimal</u>?
- Is it passive inhibition of recognition (limiting amounts of antigen)?
- Is it active inhibition of antigen presentation?
- Is it inhibition of APC function (costimulation, etc)?

The Behar lab: Immunity to TB

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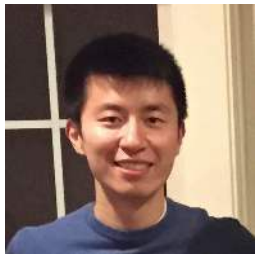
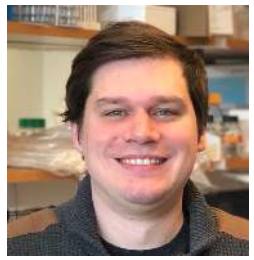
Matt Booty

Dr. Christina Baer



Jason Yang

Yash Patankar



Dan Mott

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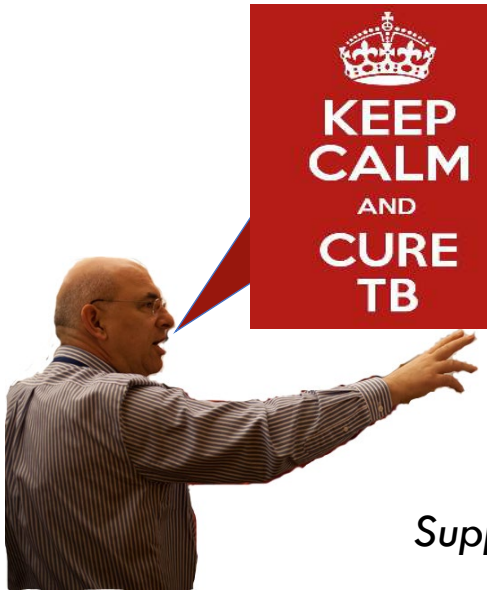

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--Ralph Waldo Emerson

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