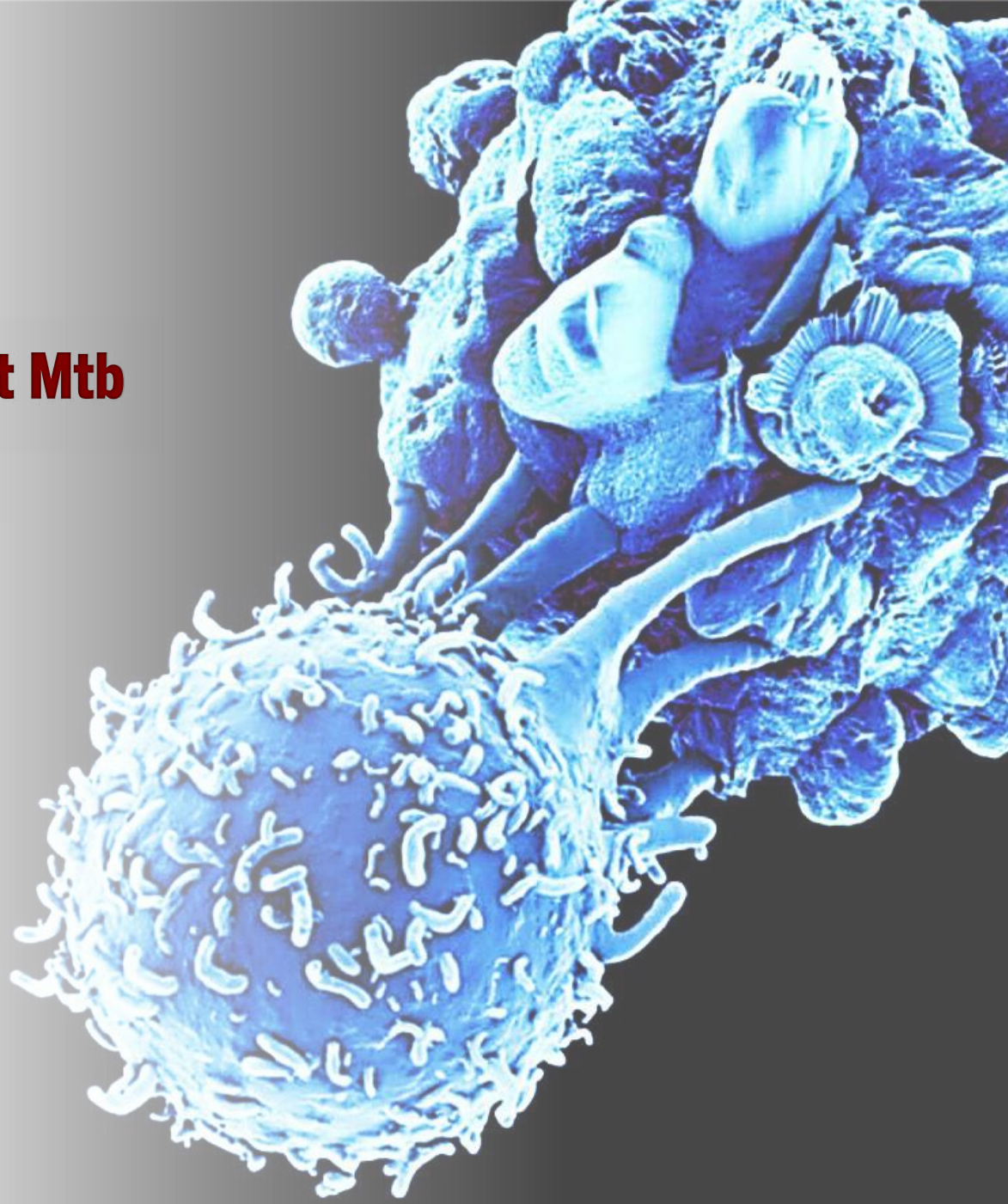
7TH GLOBAL FORUM ON TB VACCINES | 8-10 October 2024 Rio de Janeiro, Brazil

Driving innovation from discovery to access

Macro meets T
SLAMF1 promotes protective immunity against Mtb through macrophage- T cell interaction



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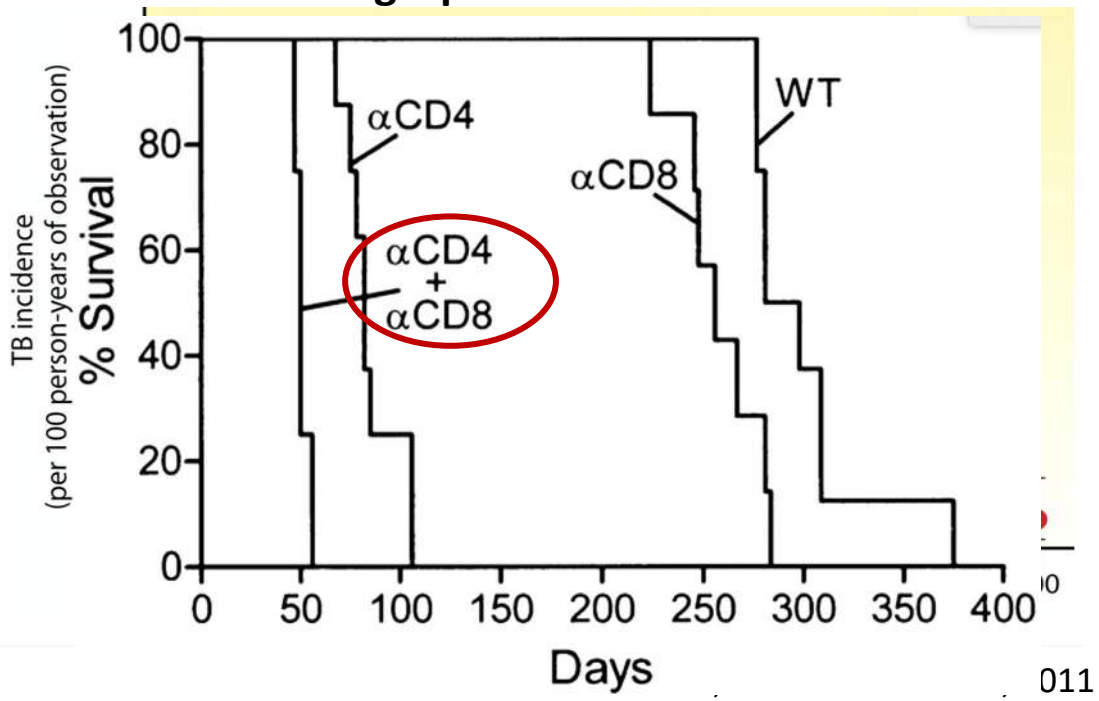
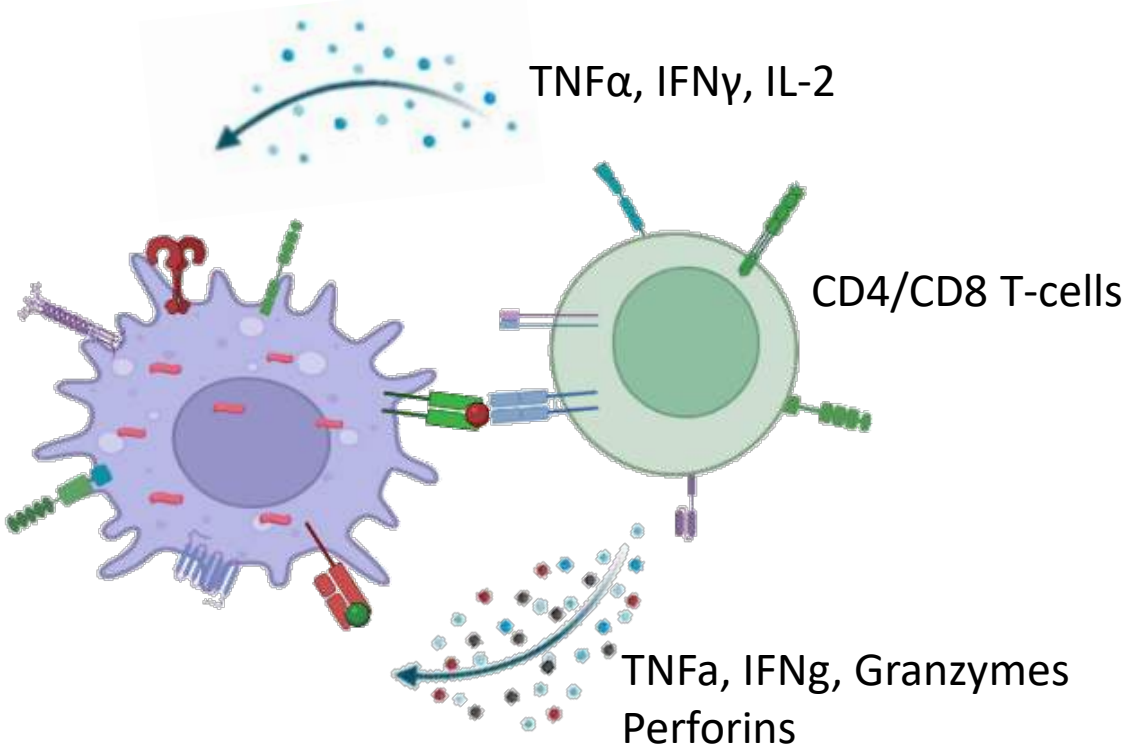
School of Medicine

Macrophage-T cell interactions vital for controlling TB



Mogues T et al, *J Exp Med,* 2001

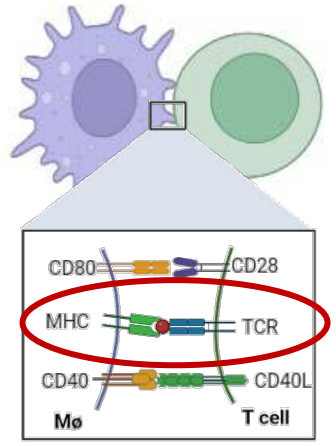


Anti-mycobacterial responses

- phagosome maturation
- ROS, RNI
- Inflammatory responses
- Apoptosis
- Antigen presentation

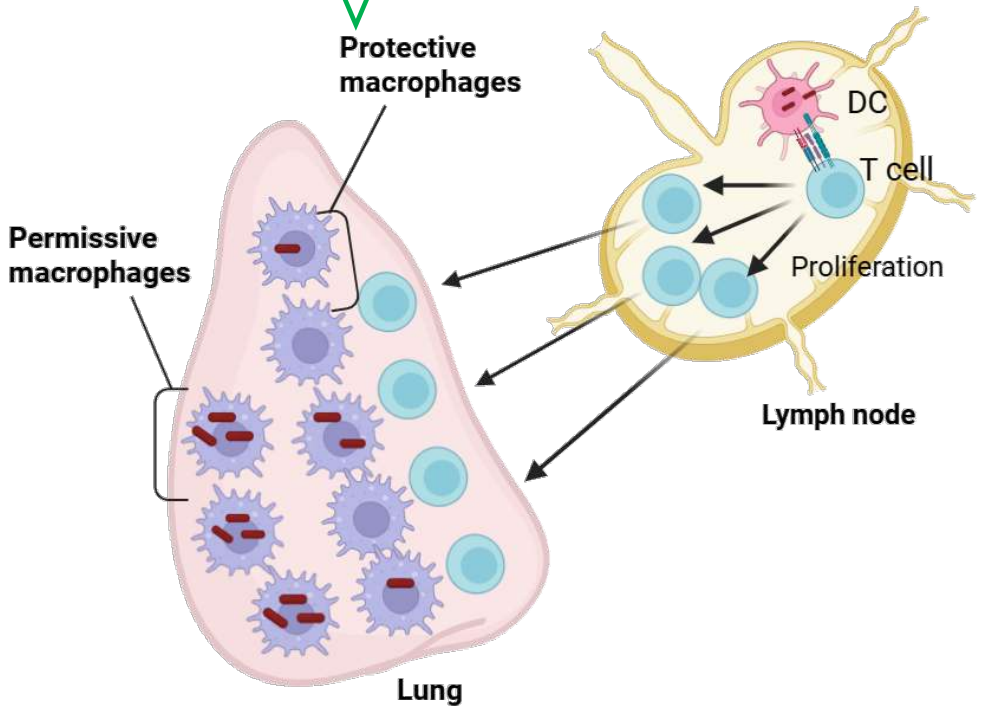
Restrict bacterial growth
Kill bacteria.

Mtb control depends on interaction of infected macrophages with T cells

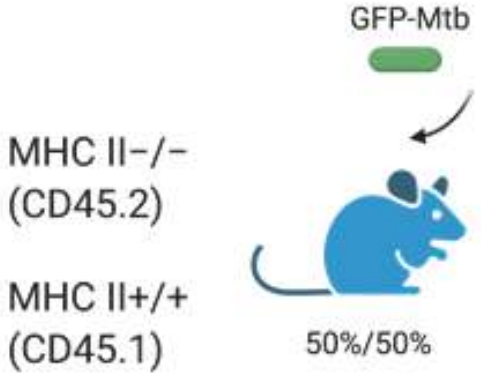


- No interaction with T cells
- Promote Mtb growth

- Direct interaction with T cells
- Restrict Mtb growth



MHCII BM chimera

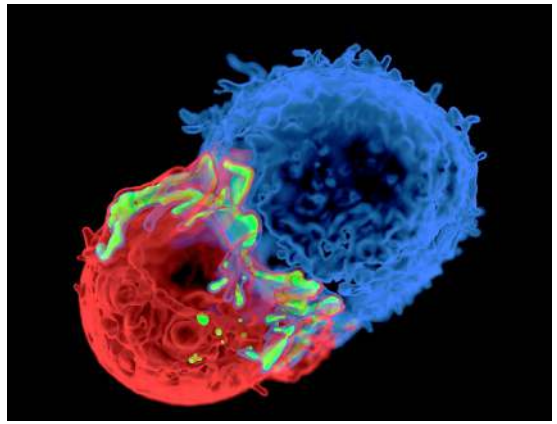


Srivastava S *et.al* (2013) *J. Immunology*

Cognate interaction between Macrophages and T cells is crucial to contain TB

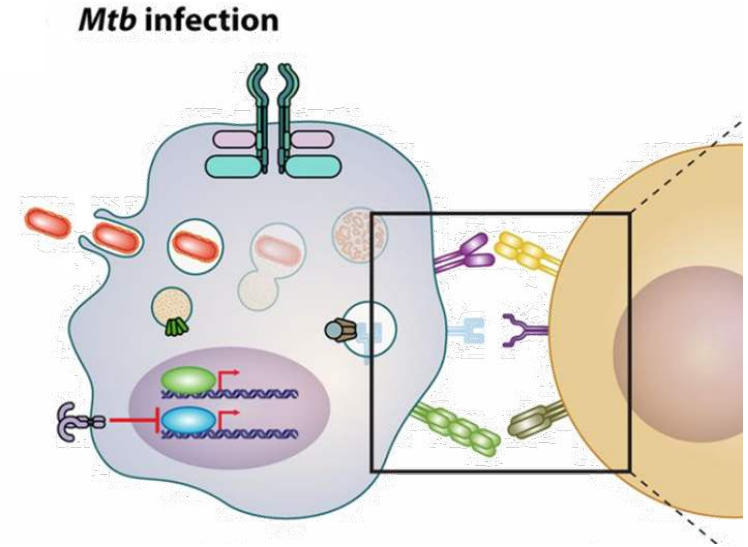
Unanswered questions

Direct interaction= Mtb control



James JR and Vale RD, 2012, *Nature*, 487:64-69

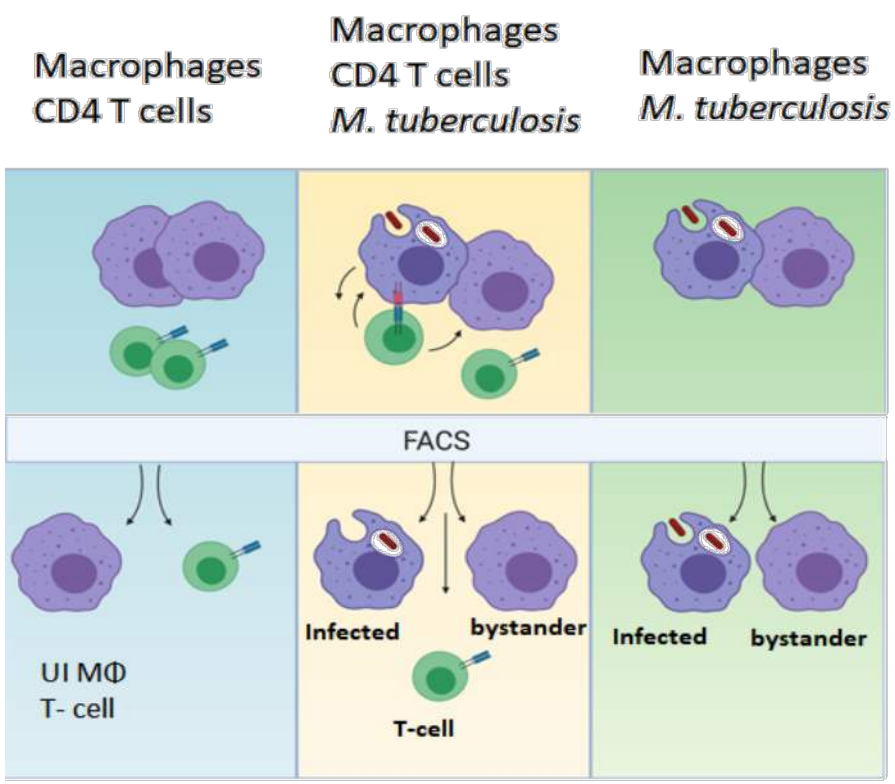
How does “direct” contact mediate protection?

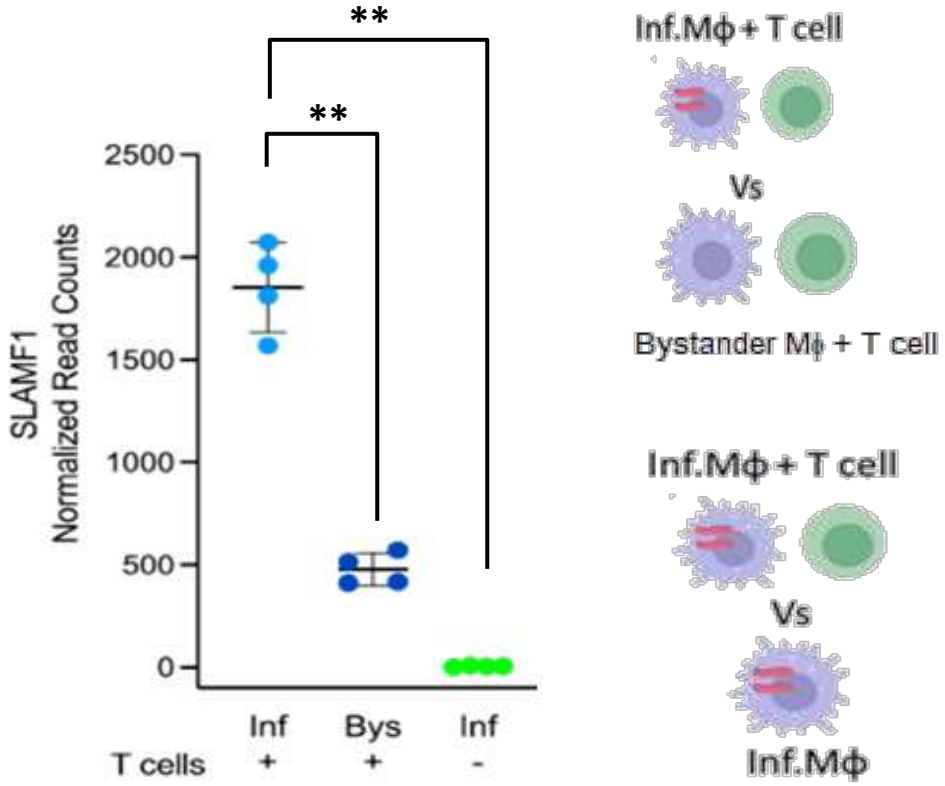


Ankley L *et.al,* 2020, *Infect Immun,*88(7): e00916-19

How to determine infected macrophage had contact with CD4 T cell during infection?

Differences in the macrophages that “directly” see a T cell compared to bystanders?





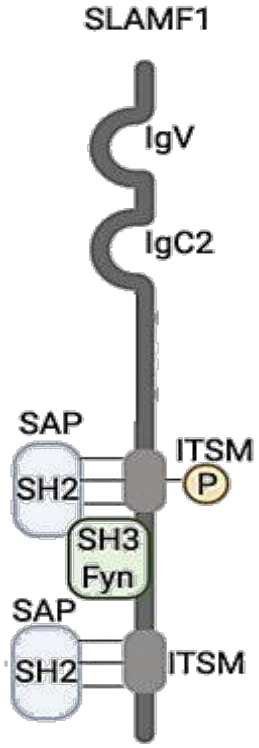
SLAMF1

- most highly induced cell surface molecule
- Regulated by infection and the presence of T cells

Cynthia-Porter Celhay
Gideon E. Watsa

**p<0.01, Brown Forsythe and Welch ANOVA test

Signalling Lymphocytic Activation Molecule Family member 1 (SLAMF1)



- Immunoglobulin like structure
- Homophilic receptor
- Present on macrophages, monocytes, lymphocytes, DCs
- **Microbial sensor**

Functions

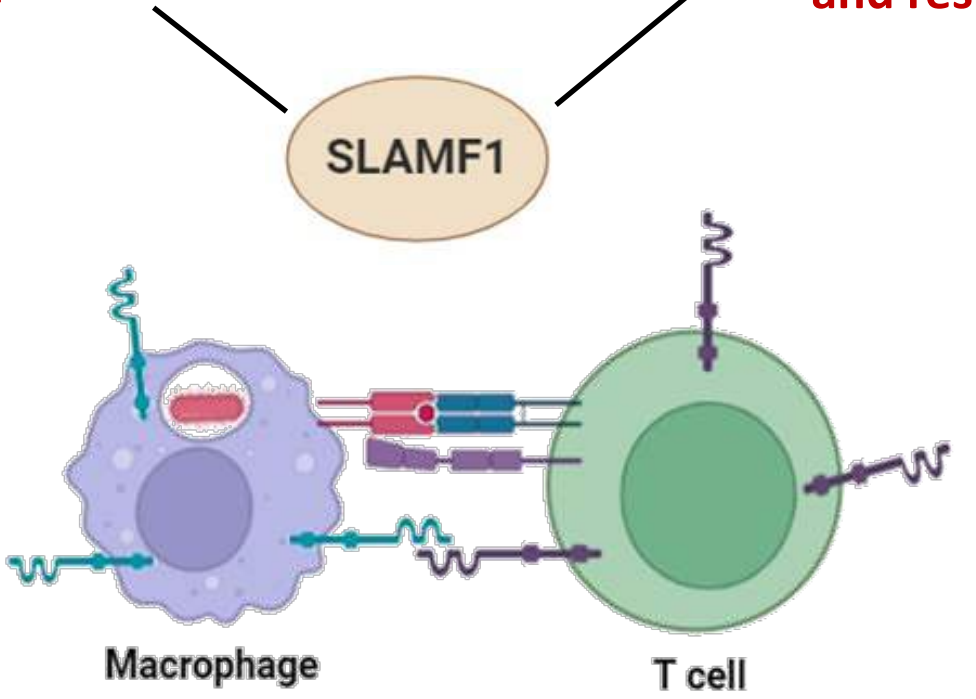
- Phagocytosis
- ROS production
- Bacterial killing
- Co-stimulatory molecule
- Autophagy
- Cytokine production

Hypothesis

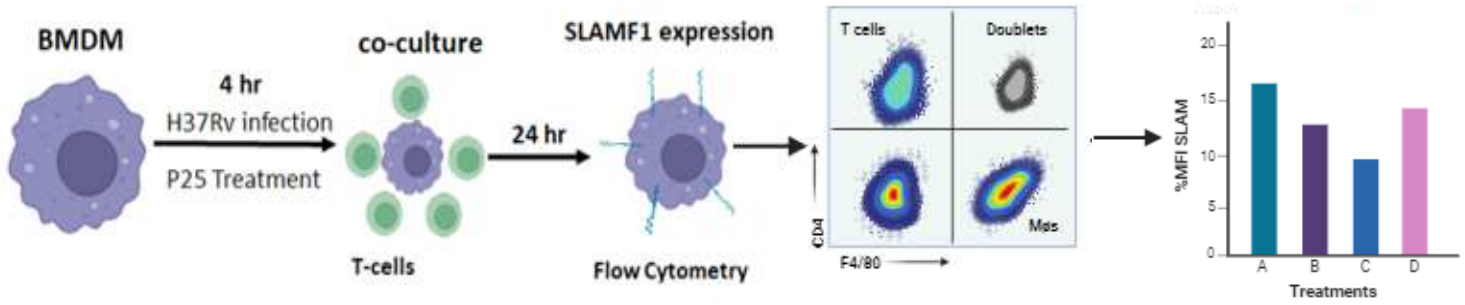
SLAMF1 modulates macrophage-T cell interaction and promotes protective immune responses during Mtb infection

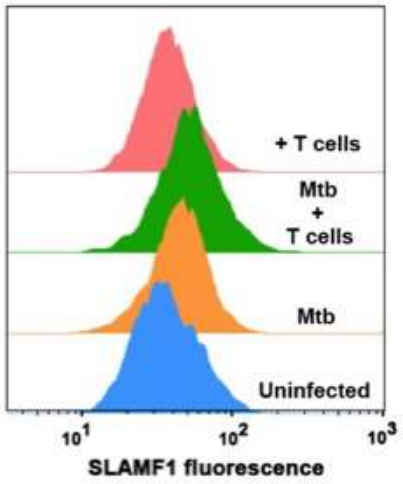
SLAMF1 marker for Macrophage- T cell interaction

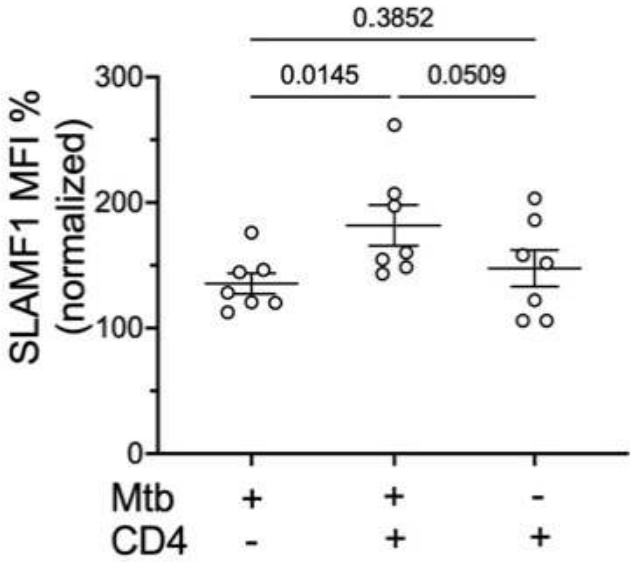
SLAMF1 promotes immune responses and restrict Mtb growth

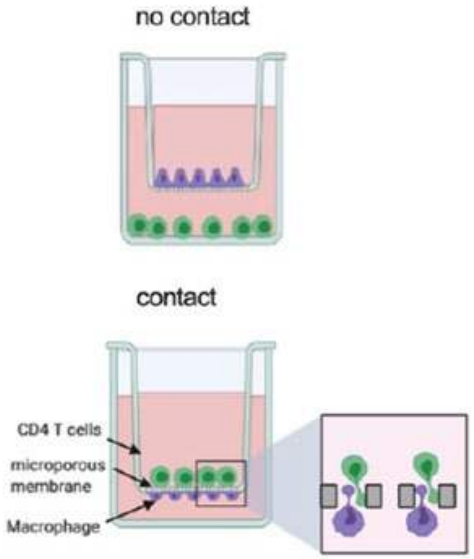


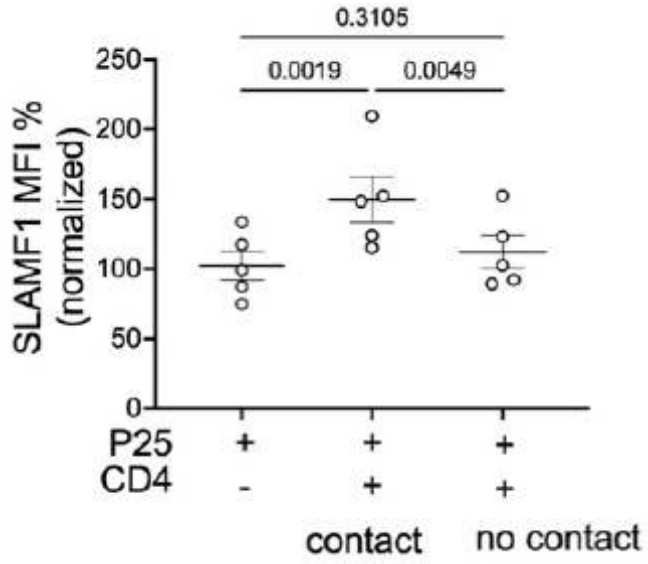
SLAMF1 is induced in macrophages in the presence of T cells upon Mtb infection









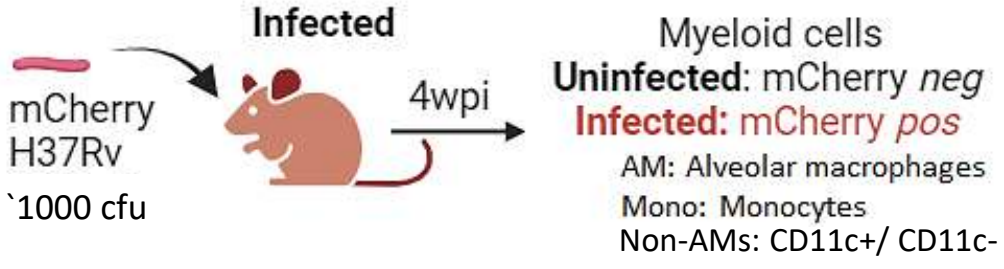


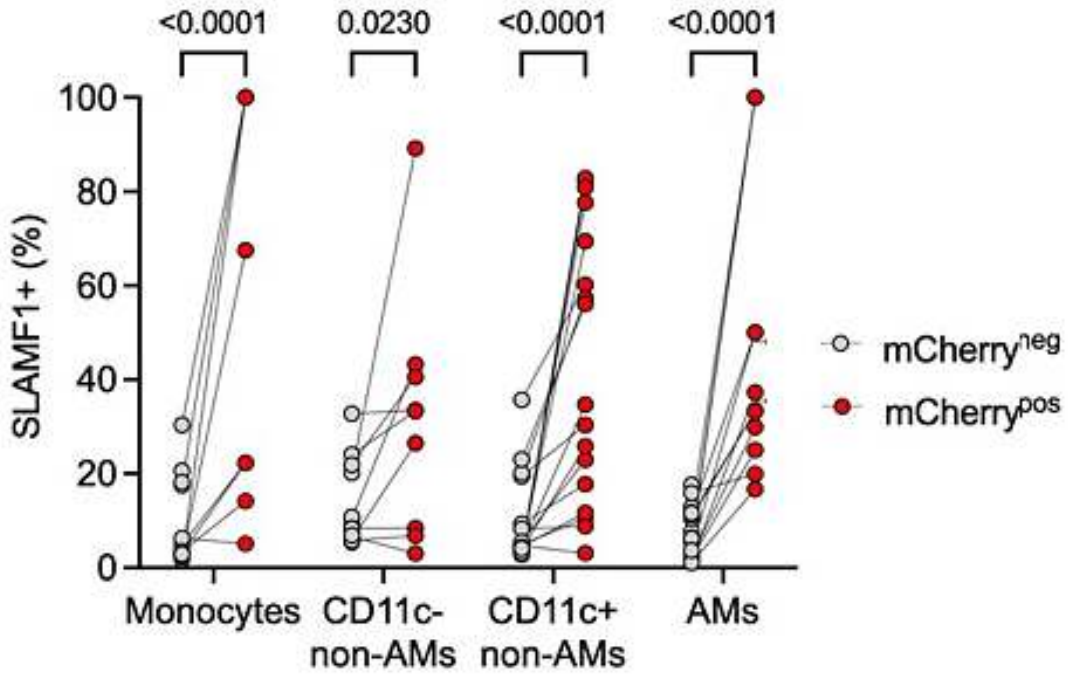
Direct contact between macrophage and T cells is required for SLAMF1 expression

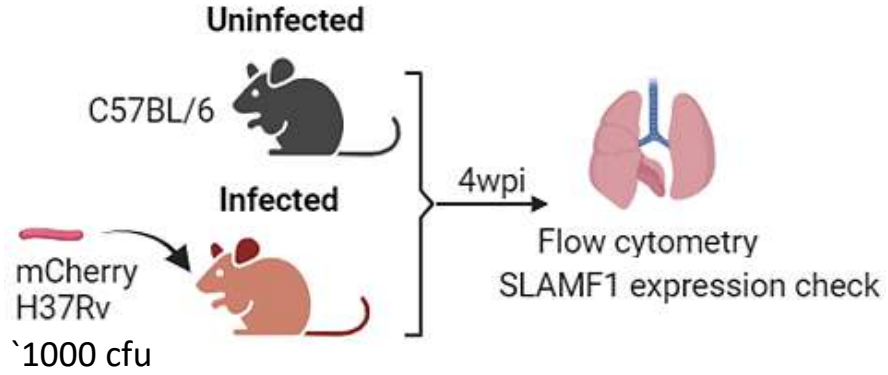
One-way ANOVA

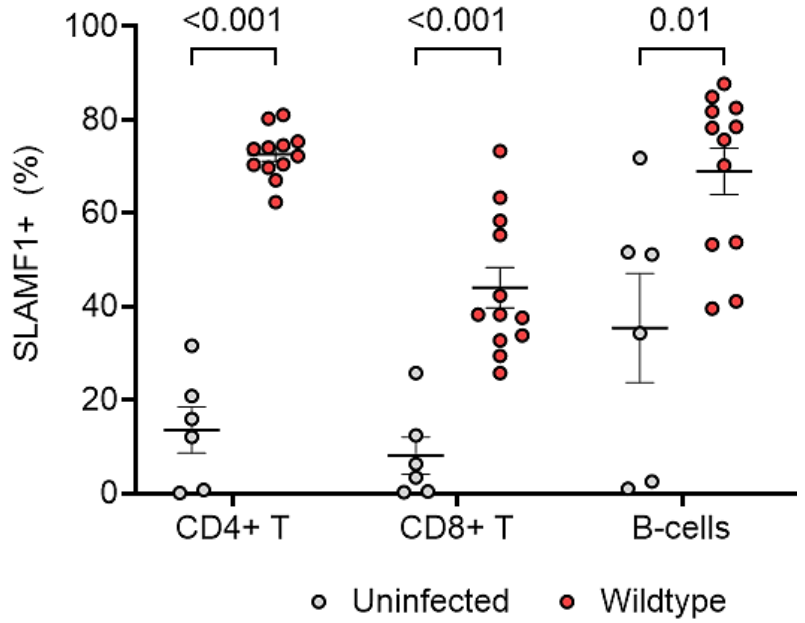
Two-way ANOVA

SLAMF1 is induced in the lung myeloid and lymphoid cells from Mtb-infected mouse







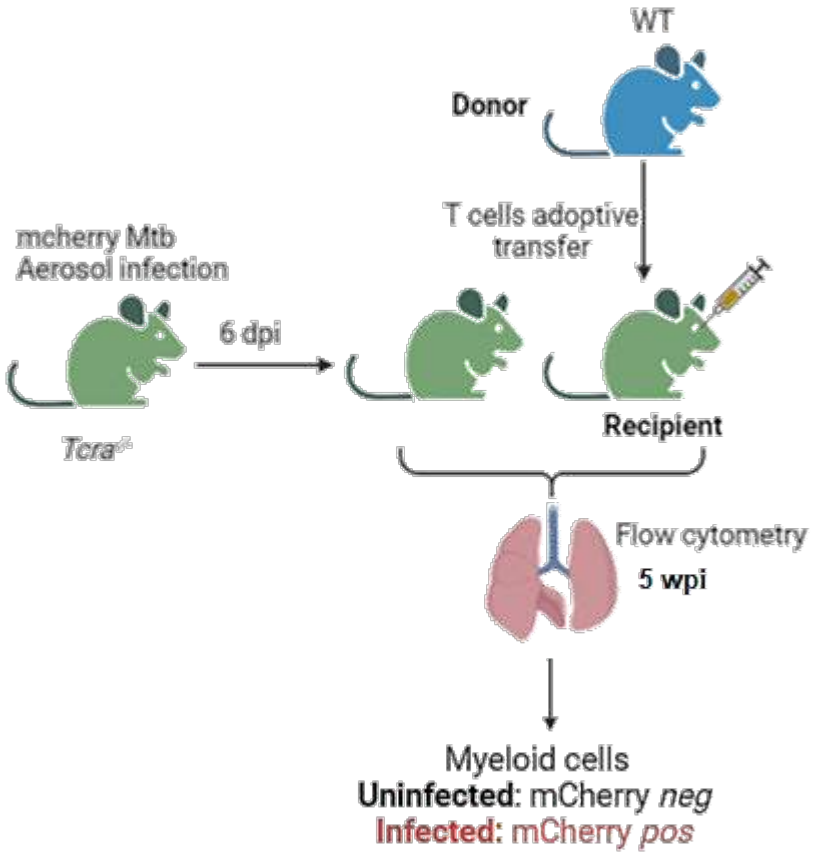


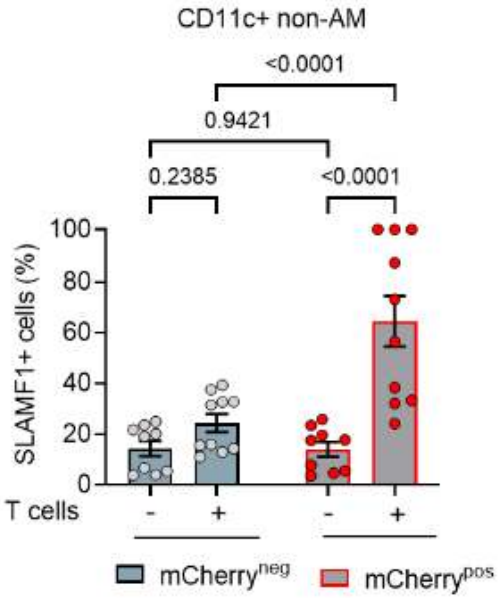
Mtb infection increases SLAMF1 expression on immune cells in mice

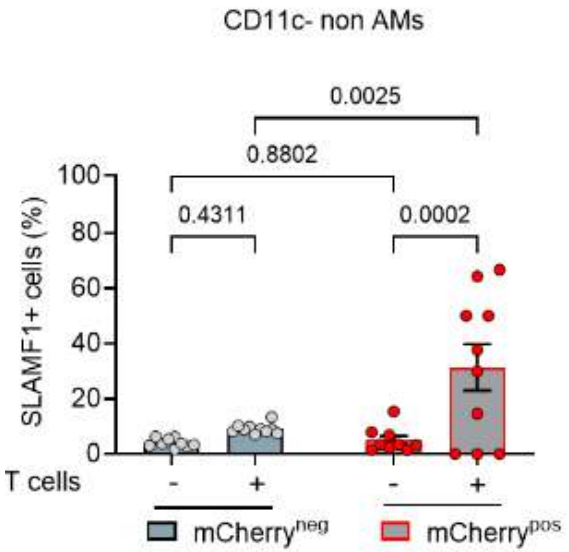
Multiple Mann-Whitney *t* tests

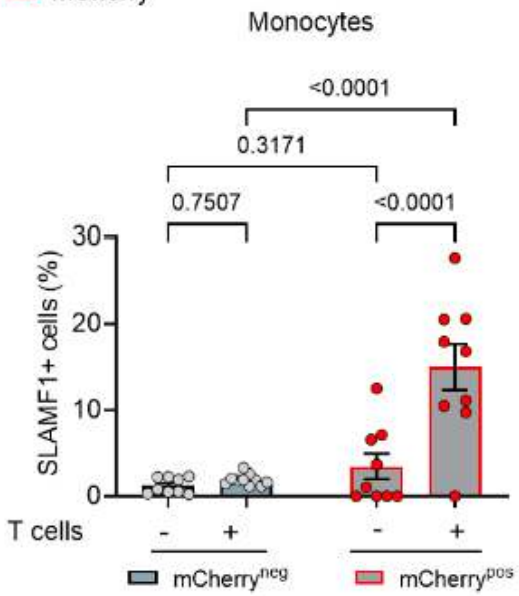
Two-way ANOVA

T-cells are required for SLAMF1 expression









Tcrα$^{-/-}$ = no T cells

Tcrα$^{-/-}$ + WT/T= received WT splenic T cells

Two-way ANOVA

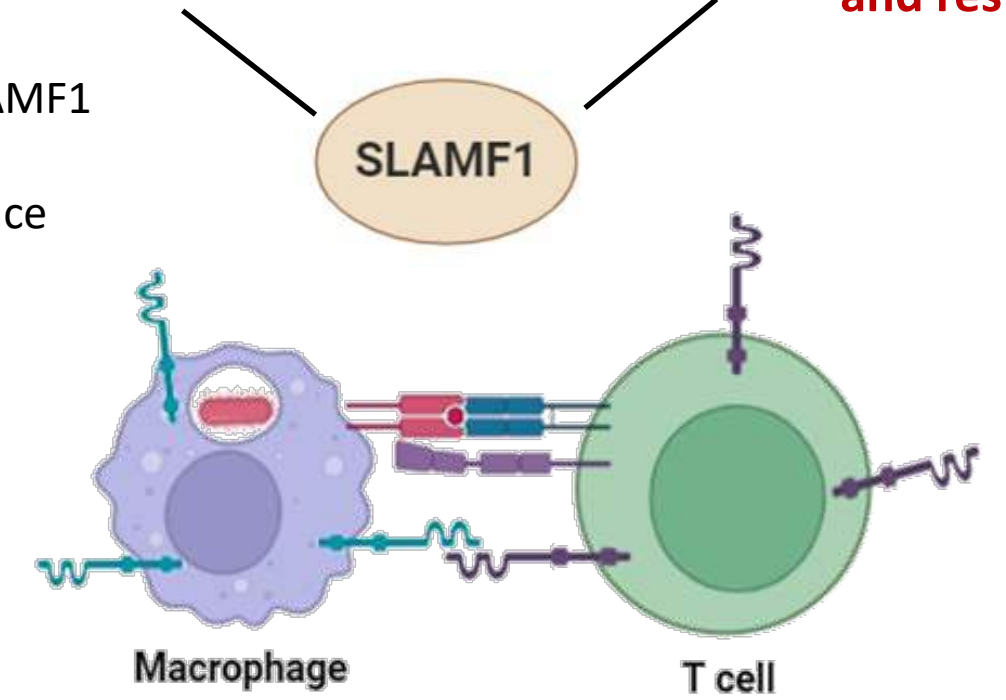
Hypothesis

SLAMF1 modulates macrophage-T cell interaction and promotes protective immune responses during Mtb infection

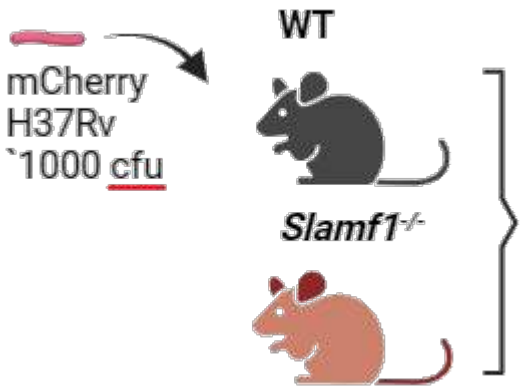
SLAMF1 marker for Macrophage- T cell interaction

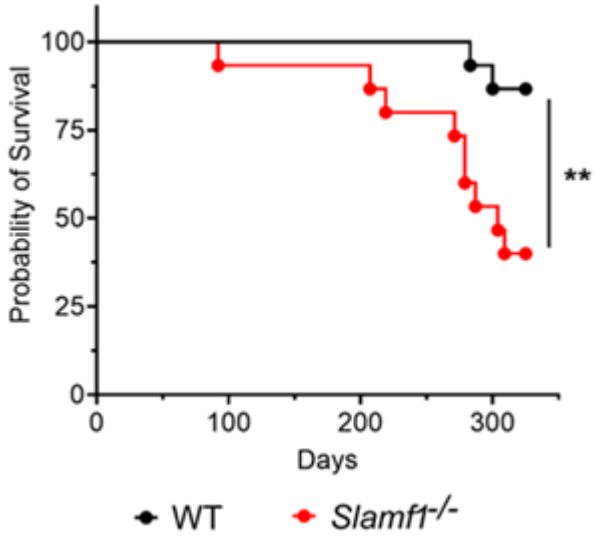
- Mtb infection induces SLAMF1 expression
- T-cells are needed to induce SLAMF1 expression

SLAMF1 promotes immune responses and restrict Mtb growth

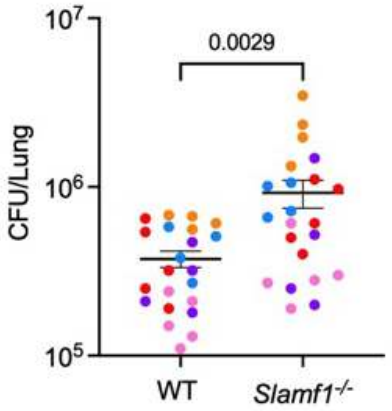


SLAMF1 confers protection against TB in mice





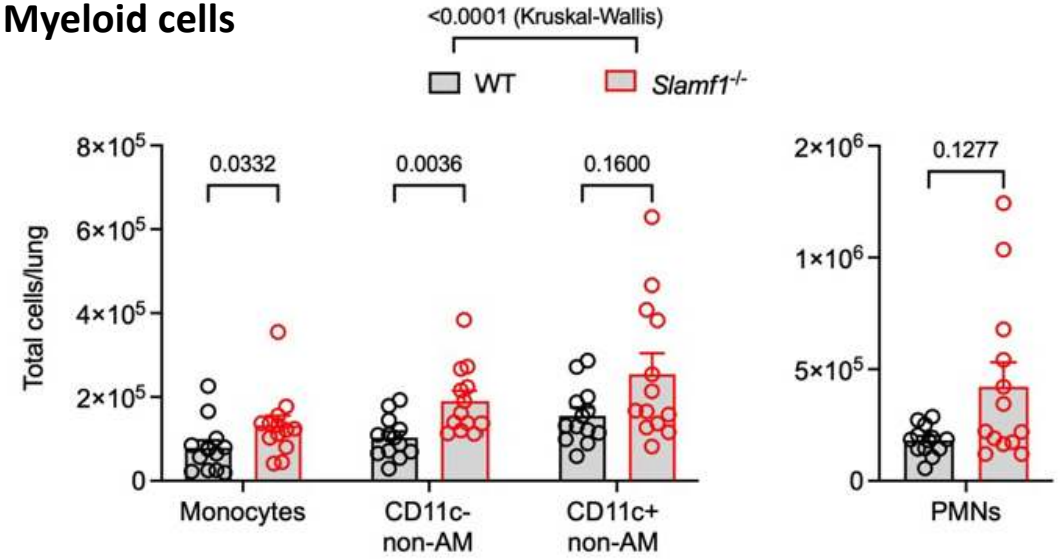
28 dpi



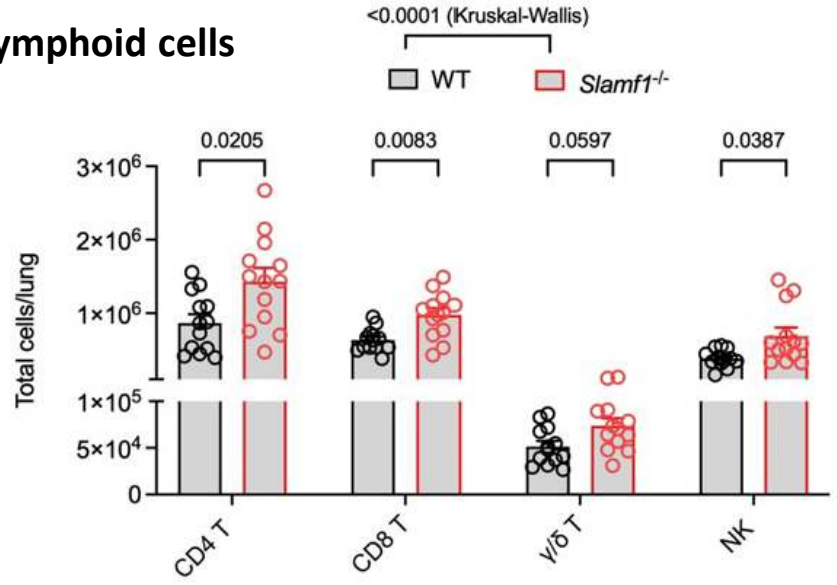
In the absence of SLAMF1

- Low survival
- High bacterial burden
- Higher immune cell infiltration

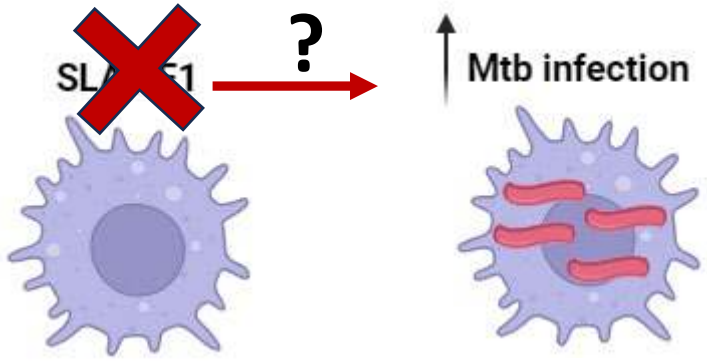
Myeloid cells

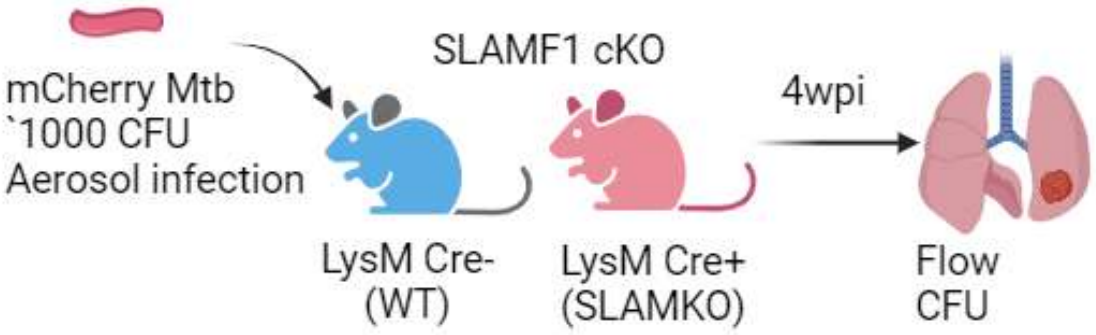


Lymphoid cells

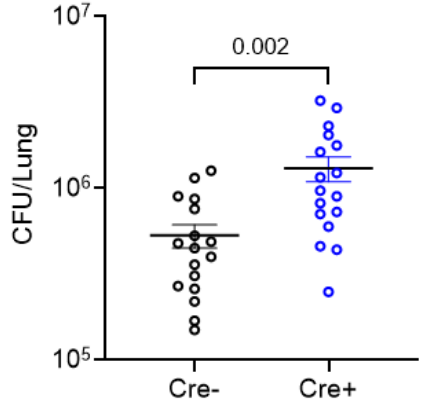


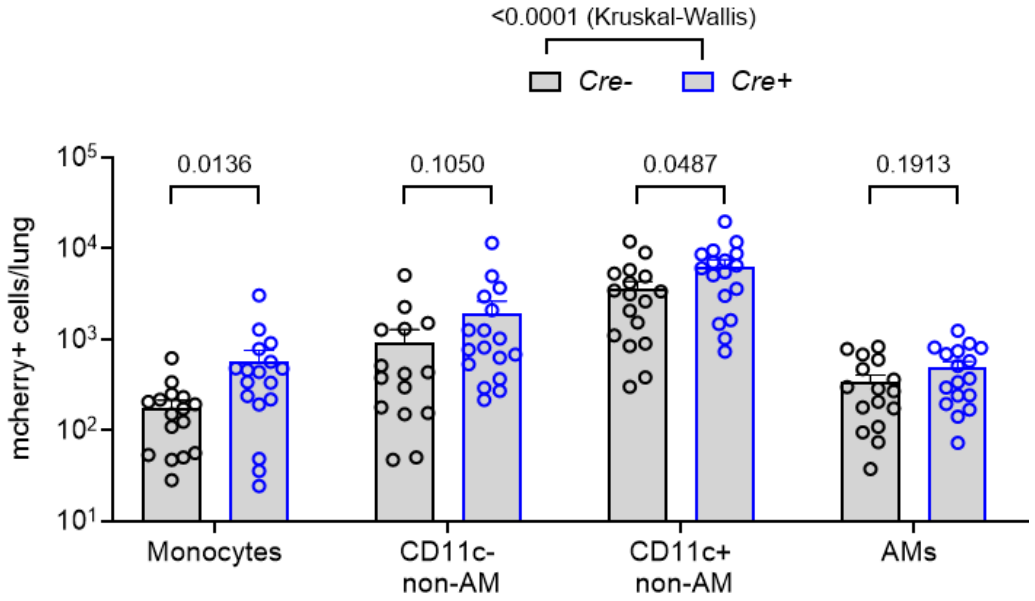
SLAMF1 restricts Mtb burden in macrophages





LysM Cre+: SLAMF1 deleted in monocytes, macrophages

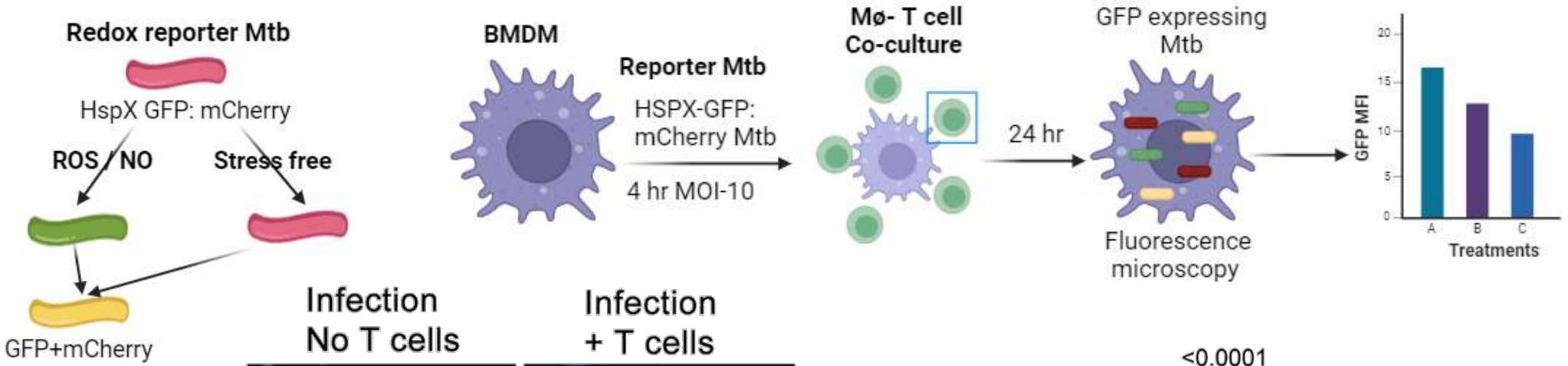


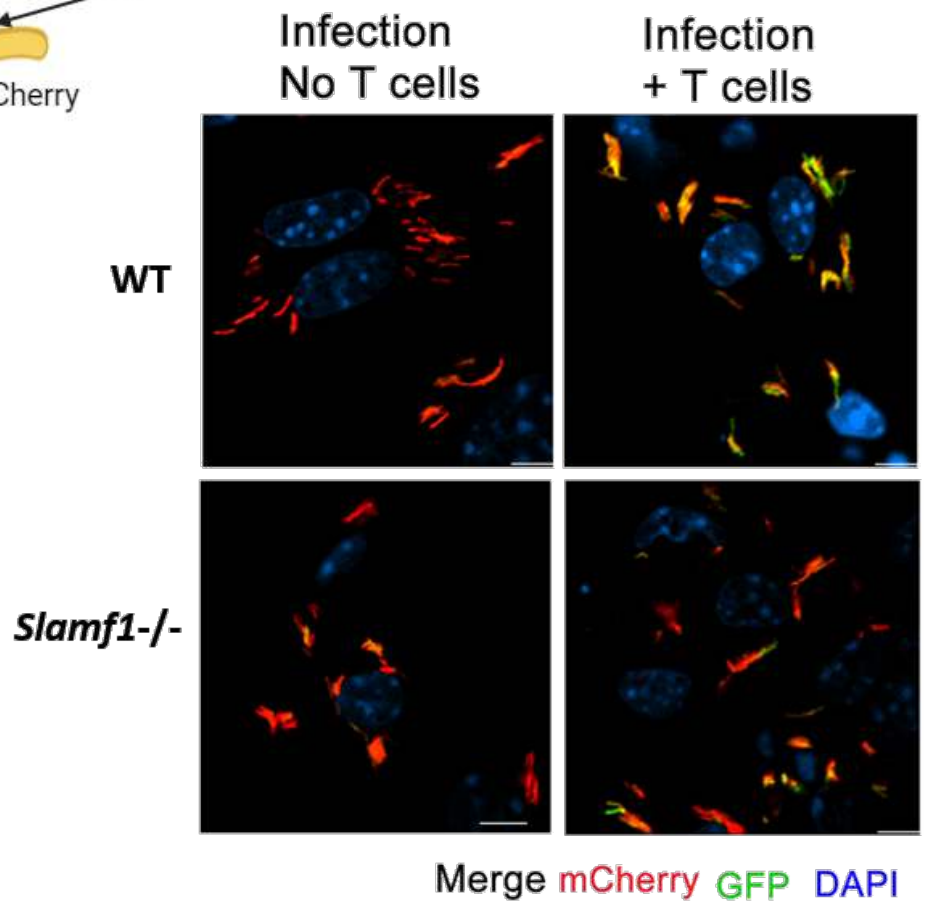


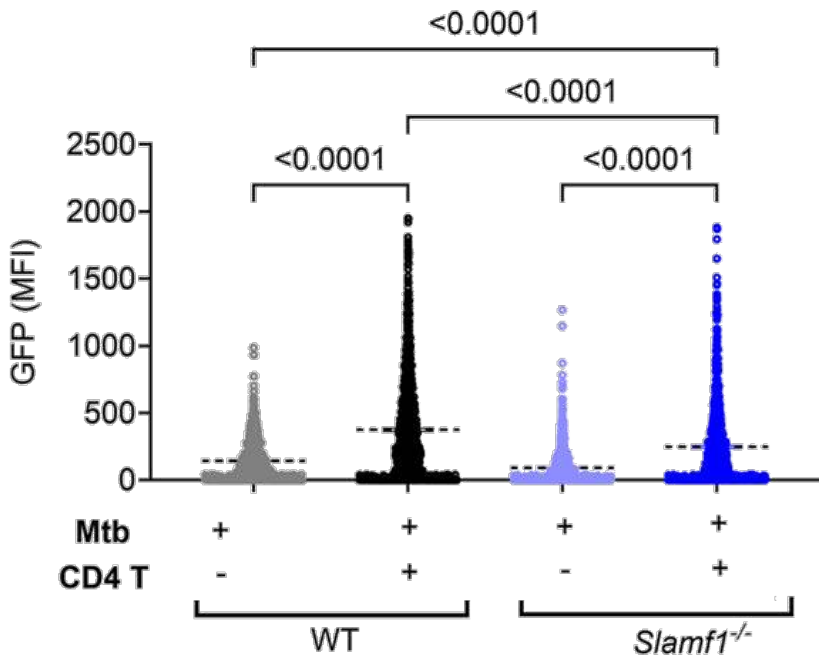
SLAMF1 expression in macrophages is crucial to restrict Mtb growth

Unpaired *t* test- : ns > 0.05, *P≤0.05, **P≤0.01

ROS production in macrophages is abrogated in the absence of SLAMF1



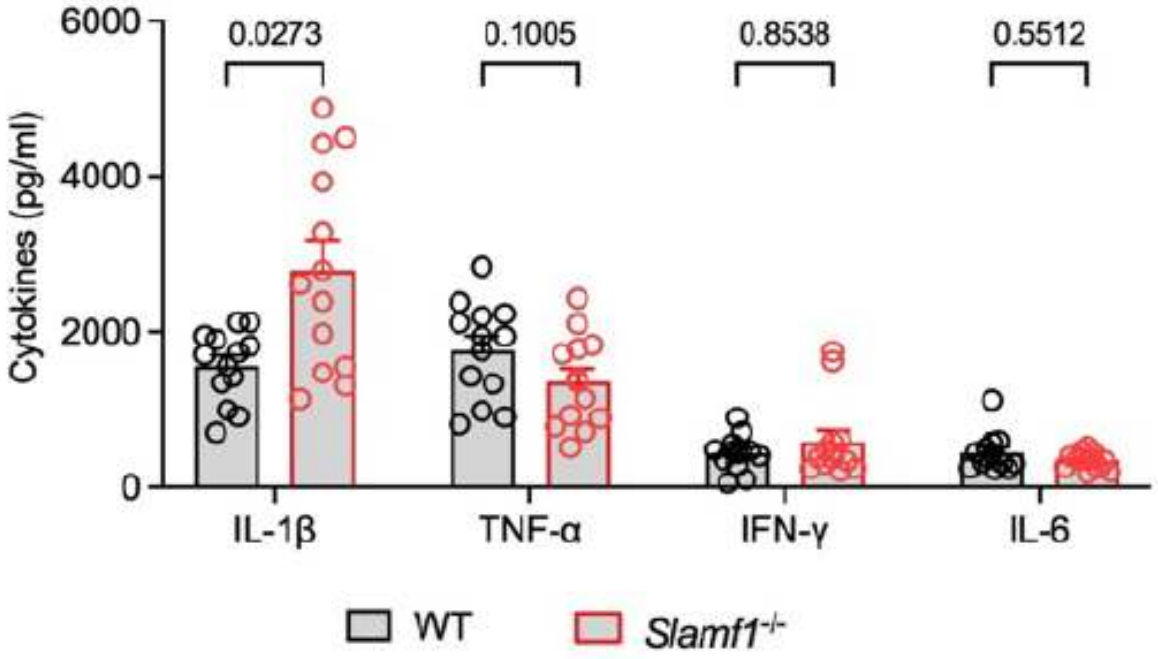


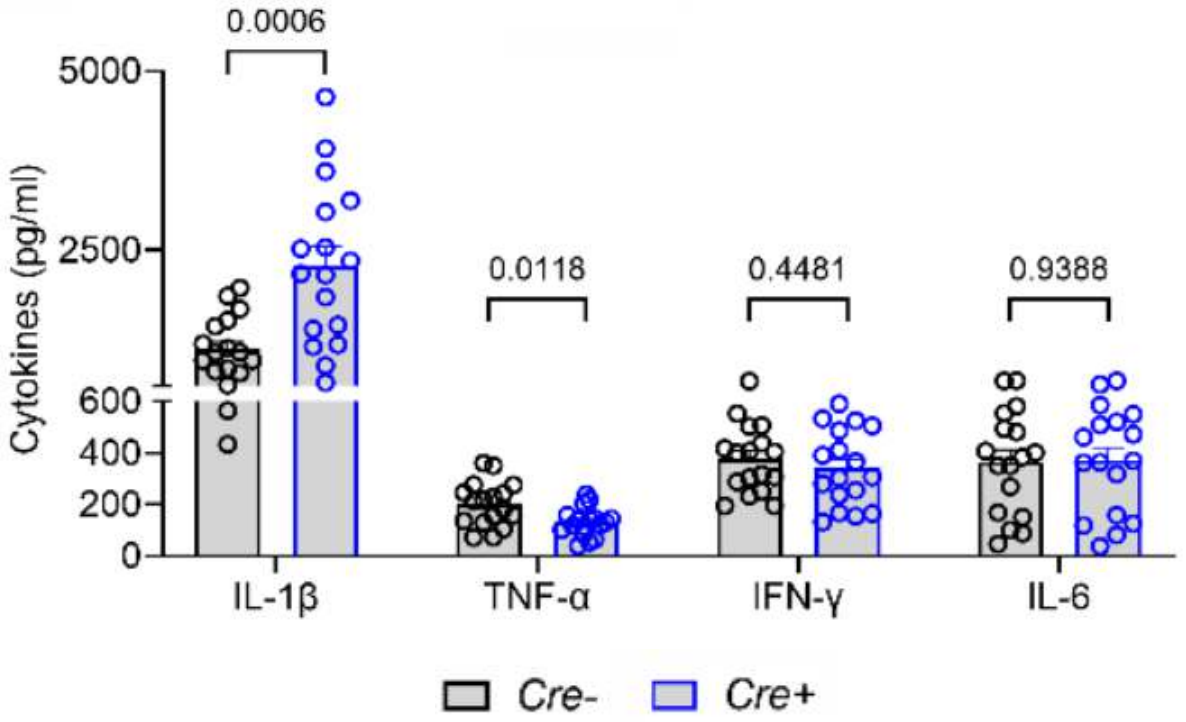


SLAMF1 modulated NO/ROS production in macrophages

One-way ANOVA- Tukey multiple comparisons test

Dysregulated cytokine production in the absence of SLAMF1 in mice





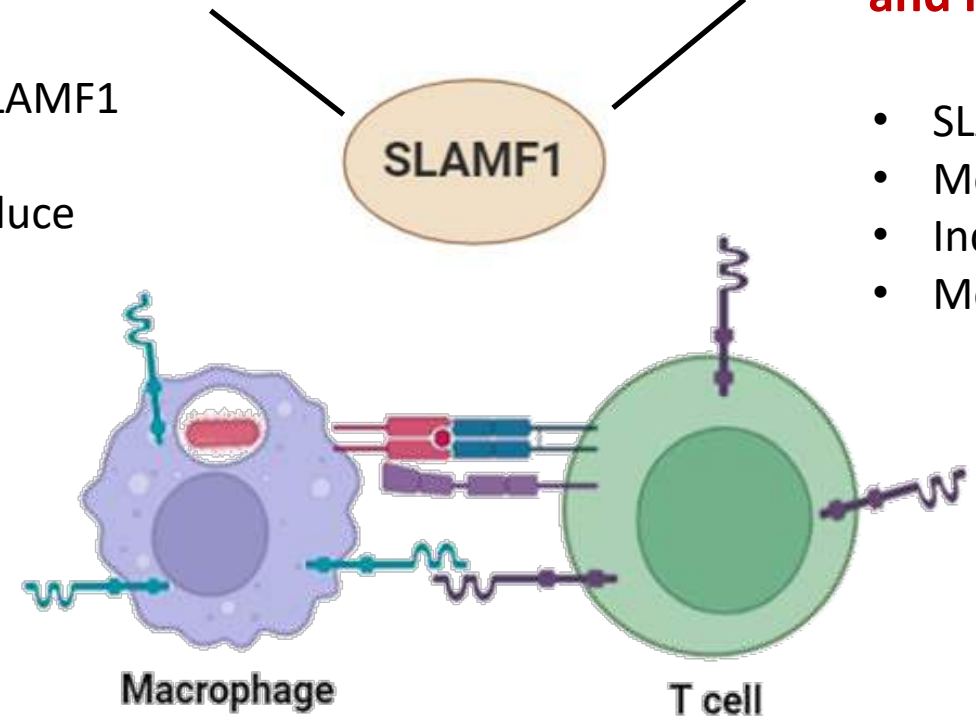
↑IL-1β ↓TNF-α = INF-γ and IL-6

Hypothesis

SLAMF1 modulates macrophage-T cell interaction and promotes protective immune responses during Mtb infection

SLAMF1 marker for Macrophage- T cell interaction

- Mtb infection induces SLAMF1 expression
- T-cells are needed to induce SLAMF1 expression

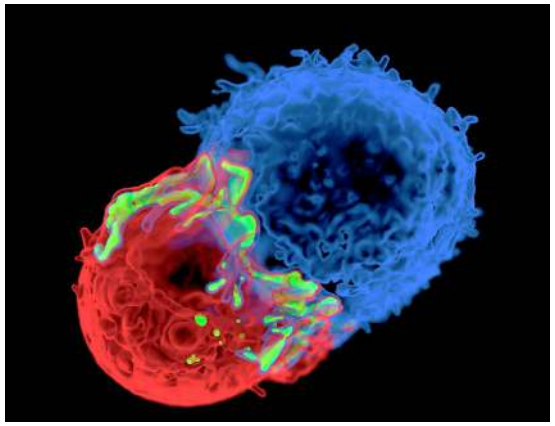


SLAMF1 promote immune responses and restrict Mtb growth

- SLAMF1 restricts Mtb growth in lungs
- Modulates immune cells infiltration
- Induces NO/Hypoxic stress on Mtb
- Modulate cytokine production

Unanswered questions

Direct interaction= Mtb control



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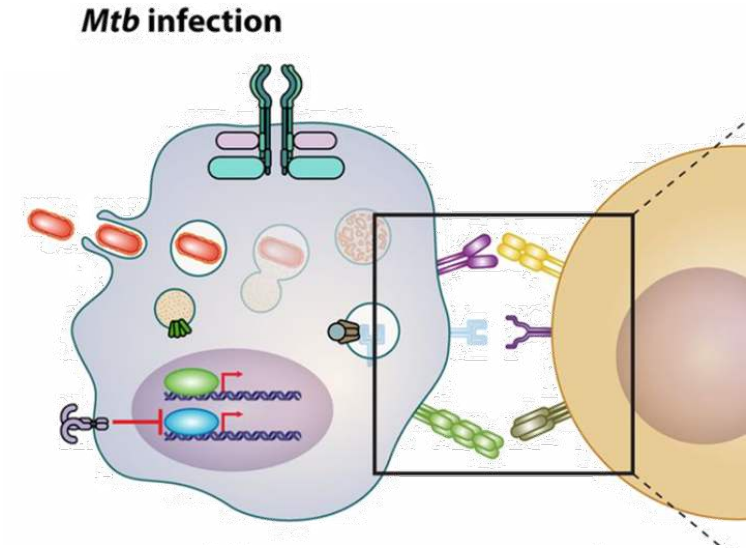

Ankley L *et.al,* 2020, *Infect Immun,*88(7): e00916-19

How does "direct" contact mediate protection?

SLAMF1

Host directed therapies or vaccines promoting SLAMF1 expression on immune cells might help in controlling TB infection

How to determine cognate interaction between infected macrophage and CD4 T cell occured?

Acknowledgements

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Research Scientist
1963-2023

Current lab members

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Sharvath Kathi
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School of Medicine

CHiPs
Flow Cytometry & Fluorescence Activated Cell Sorting Core

NIH R21 AI155380

NIH TETRAMER CORE FACILITY

Manuscript under review:

Macrophage-T cell interactions promote SLAMF1 expression for enhanced TB defense

For queries

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