New insights into lung resident immunity to *Mycobacterium tuberculosis*

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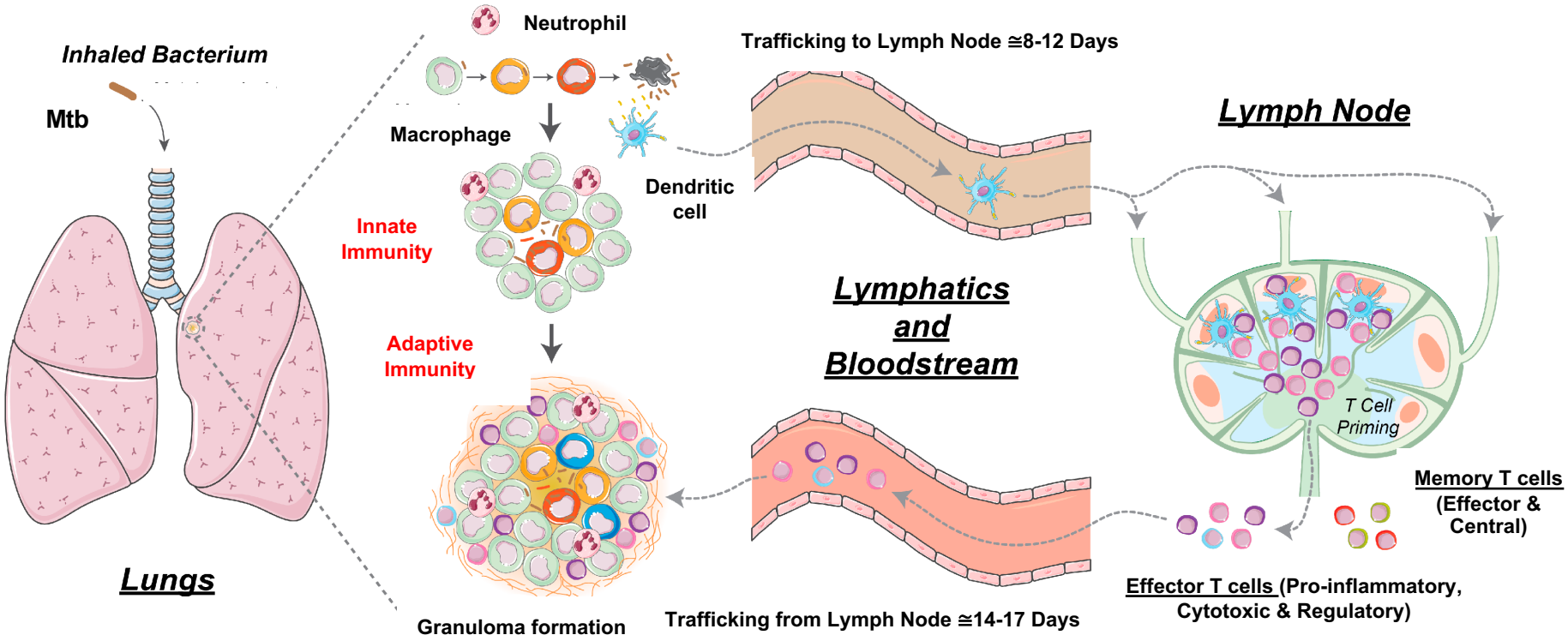
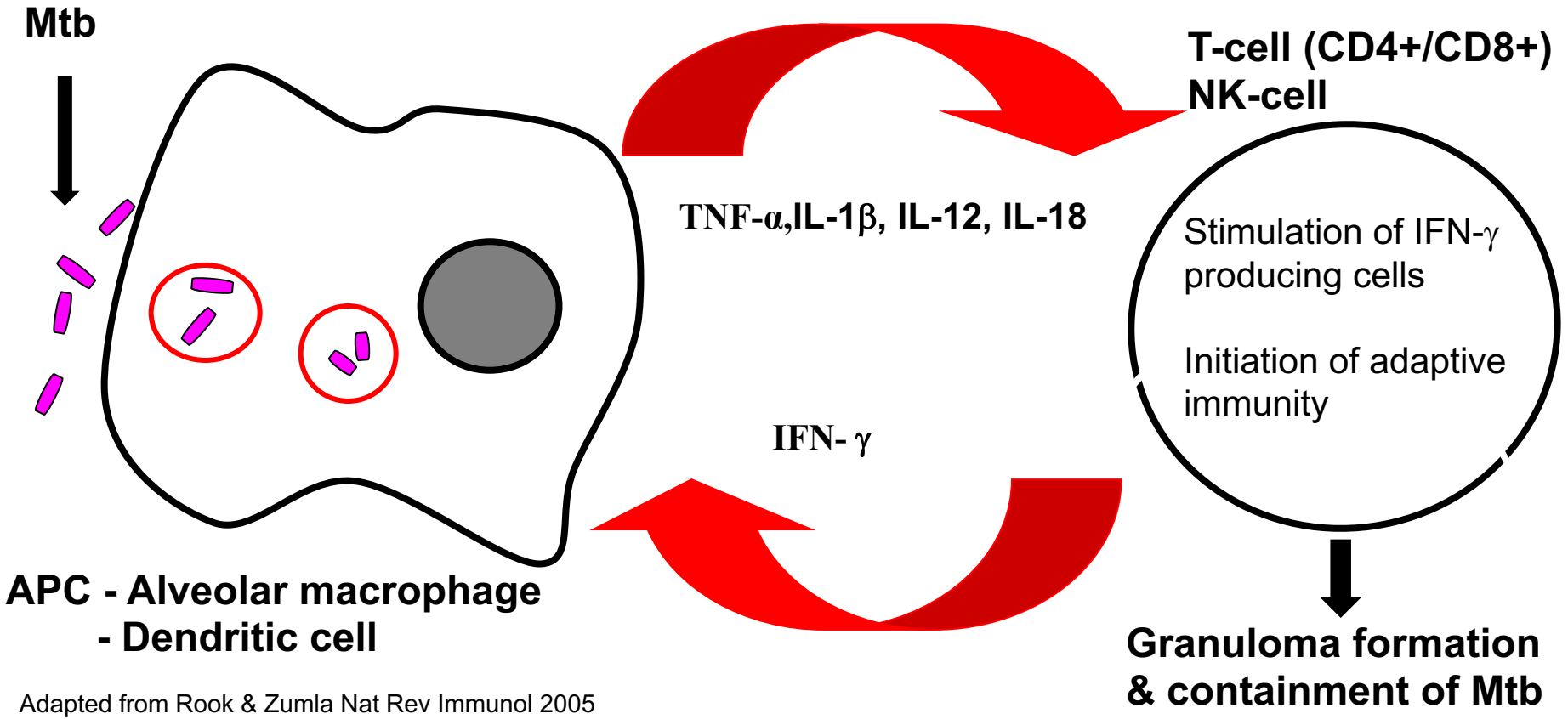
13th June 2023; Recognition and Control of Mtb infected Cells: From Basics to the Clinic

Overview of the immune response to Mtb



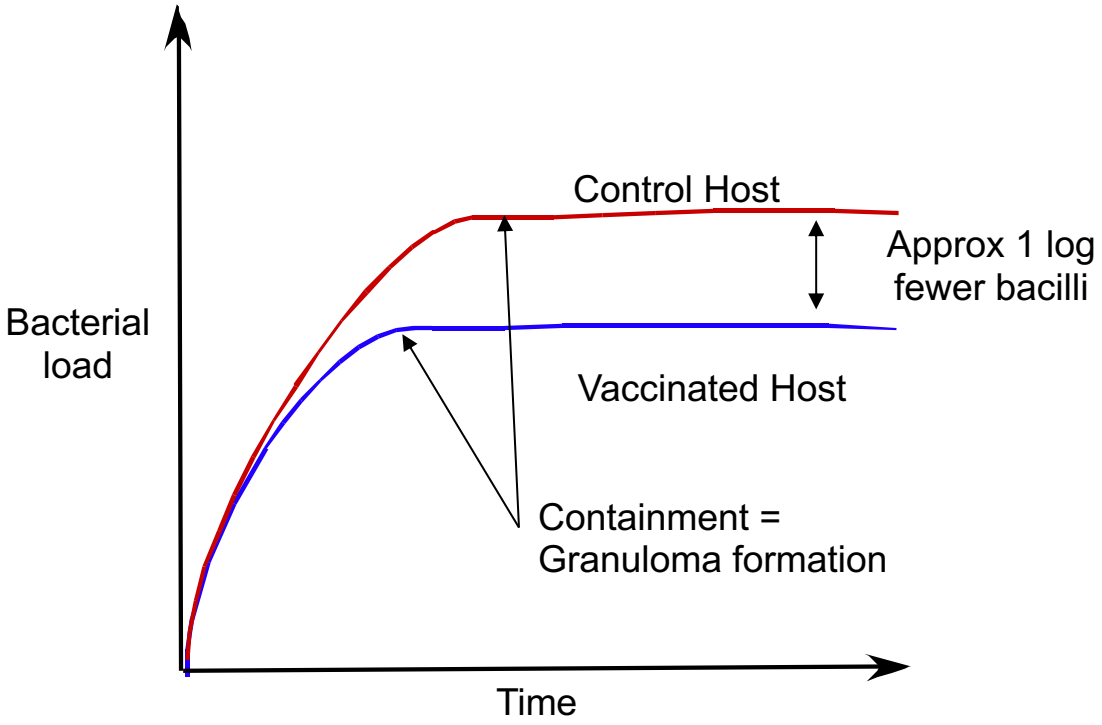
Marino S & Kirschner DE, Computation (Basel) 2017

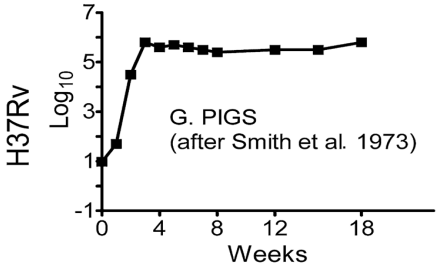
Classical paradigm of host lung immune response to Mtb

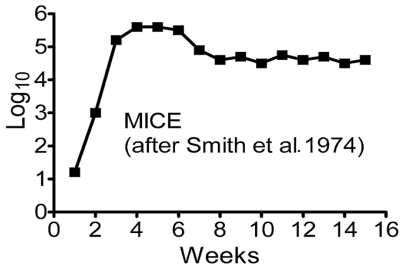


Adapted from Rook & Zumla Nat Rev Immunol 2005

Delayed onset of adaptive immunity following Mtb infection



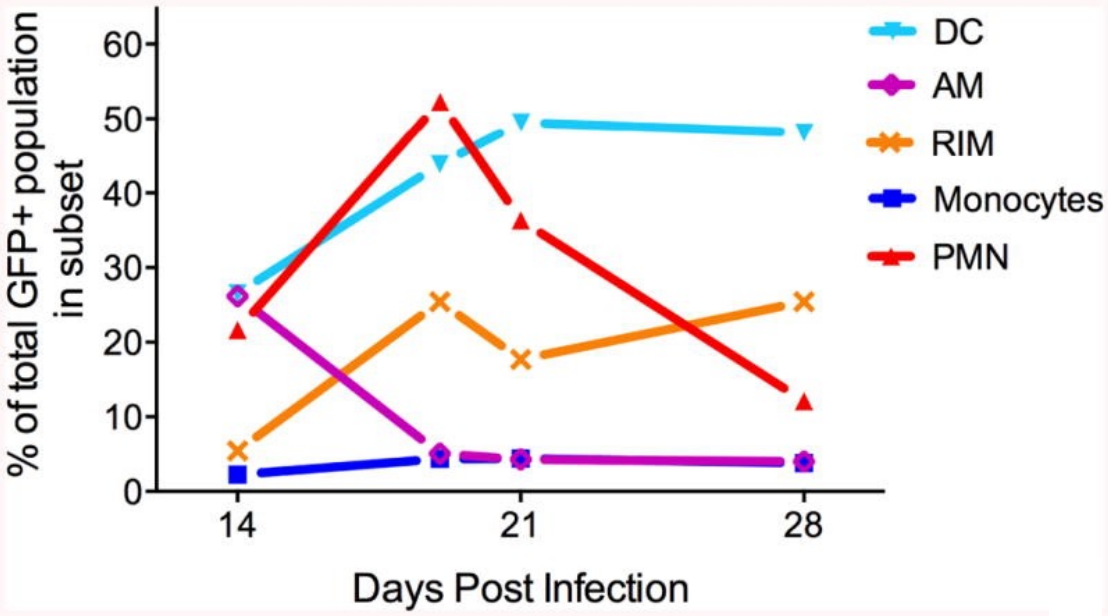


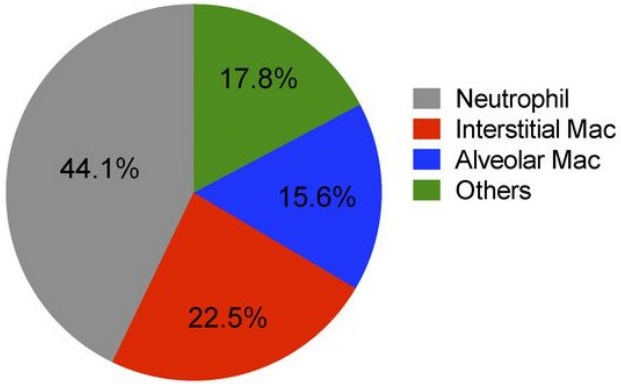


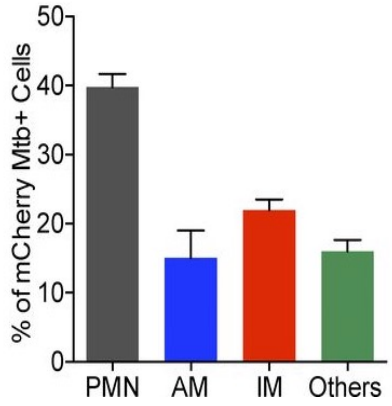
Progression of *Mtb* infection in all animal models follows the same basic pattern: Rapid expansion followed by immune-controlled "stasis".

North & Jung. Ann Rev. Immunol. 2004

Time course and distribution of Mtb by lung cell subsets



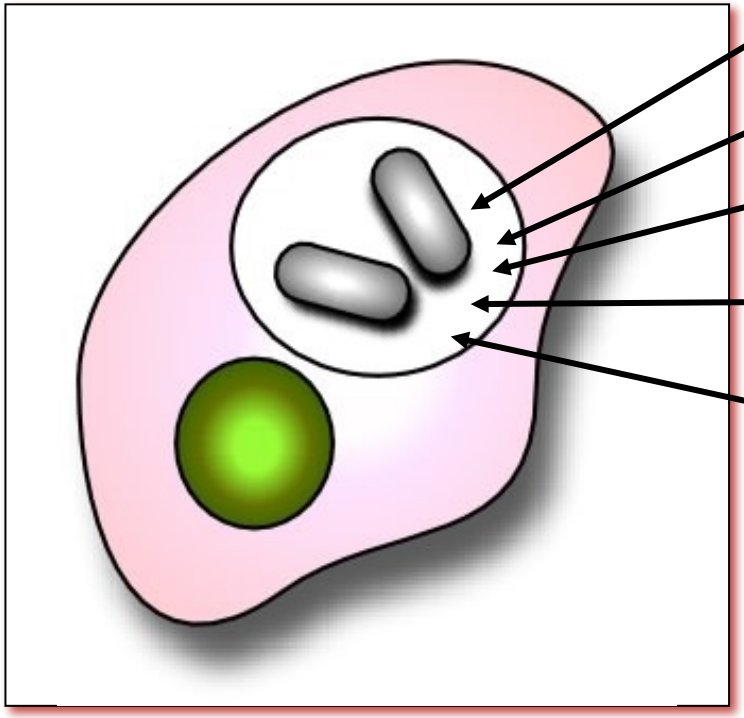




***M. tuberculosis* infection triggers recruitment of interstitial macrophages to the infected lung**

Srivastava S et al., Immunol Rev 2014; Huang L et al., J Exp Med 2018

Alveolar phagocytes are critical in early immune responses to Mtb



Nutritional shift

Production of ROIs

Production of RNIs

Acidification of the phagosome

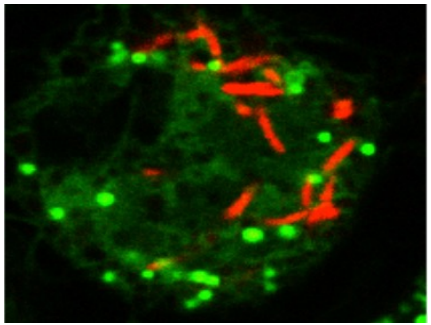
Acquisition of lysosomal hydrolases, i.e.
- proteinases
- lipases
- glucosidases
- nucleotidases

Environmental pressures active within the phagocyte.

Current paradigm of macrophage control of Mtb

Controller Cells

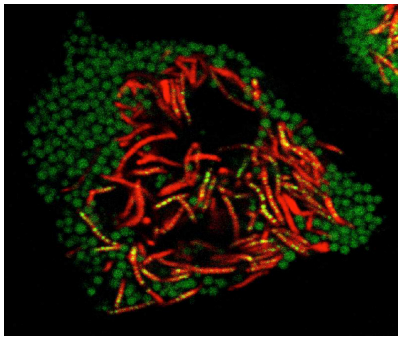
- Th1 activated macrophages
- Product of IFN-g exposure
- Good at controlling Mtb *in vitro* and *in vivo* (in mice)
- Efficacy revealed in loss of function studies (KO mice)



- Vaccine efficacy assessed by immune correlates of Th1

Permissive Cells

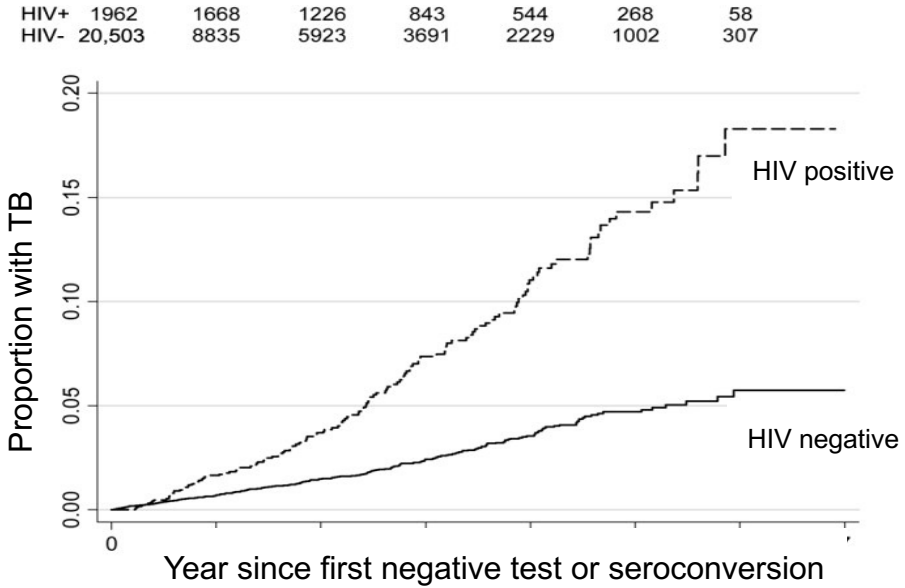
- M2 macrophages or another cell type?
- Exposure to IL-10/IL-4 or TGF-b?
- Permissive for bacterial expansion *in vitro* and *in vivo*?
- We have minimal data on bacterial permissiveness as an immune function



- We also need bacterial correlates of permissiveness +/- immune correlates.

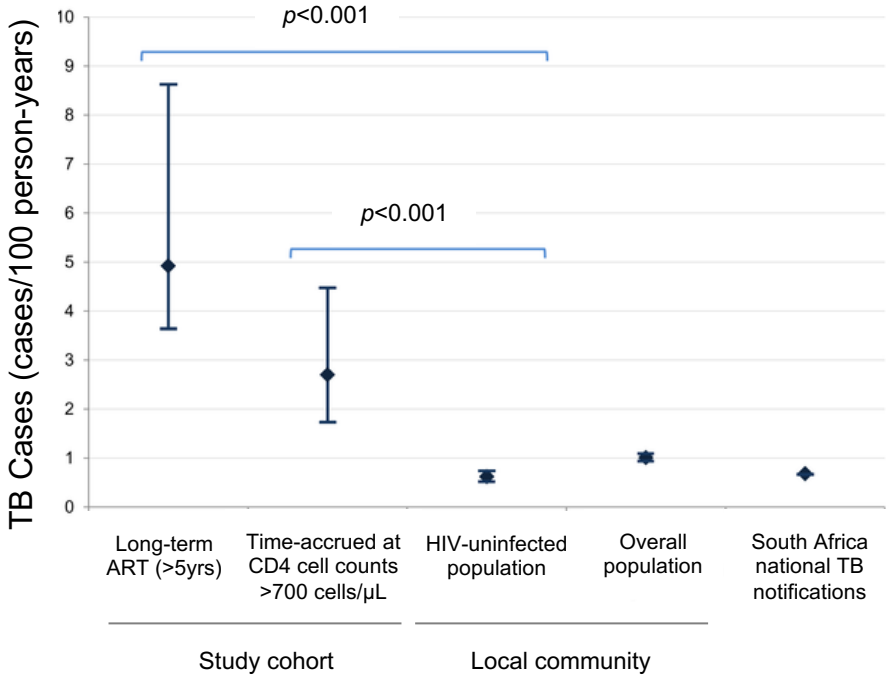
Using HIV infection to understand immunity to *M. tuberculosis* in the human lung

HIV infection increases the risk of developing TB disease



Sonnenberg et al., *J Infect Dis* 2005

Cumulative hazard estimate of pulmonary TB incidence, by HIV status among South African gold miners (Pre-ART)

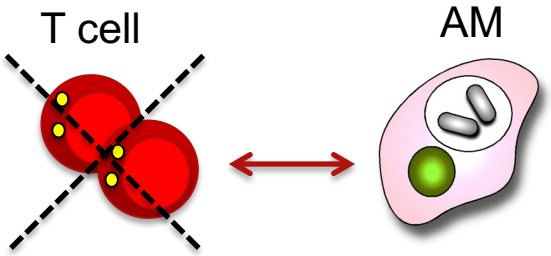


TB incidence rates during 8 years of follow-up of an ART cohort in South Africa: comparison with rates in the community

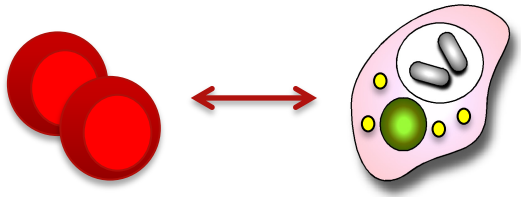
Gupta et al., PLoS One 2012

Potential mechanisms for increased risk of TB disease in HIV-infected people

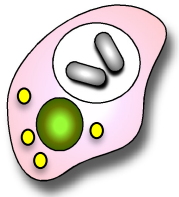
HIV infection of alveolar CD4⁺ T-cells:
Loss of immune surveillance



Alveolar macrophages (AMs) co-infected with HIV & Mtb:
Impaired phagocyte function & loss of immune recognition

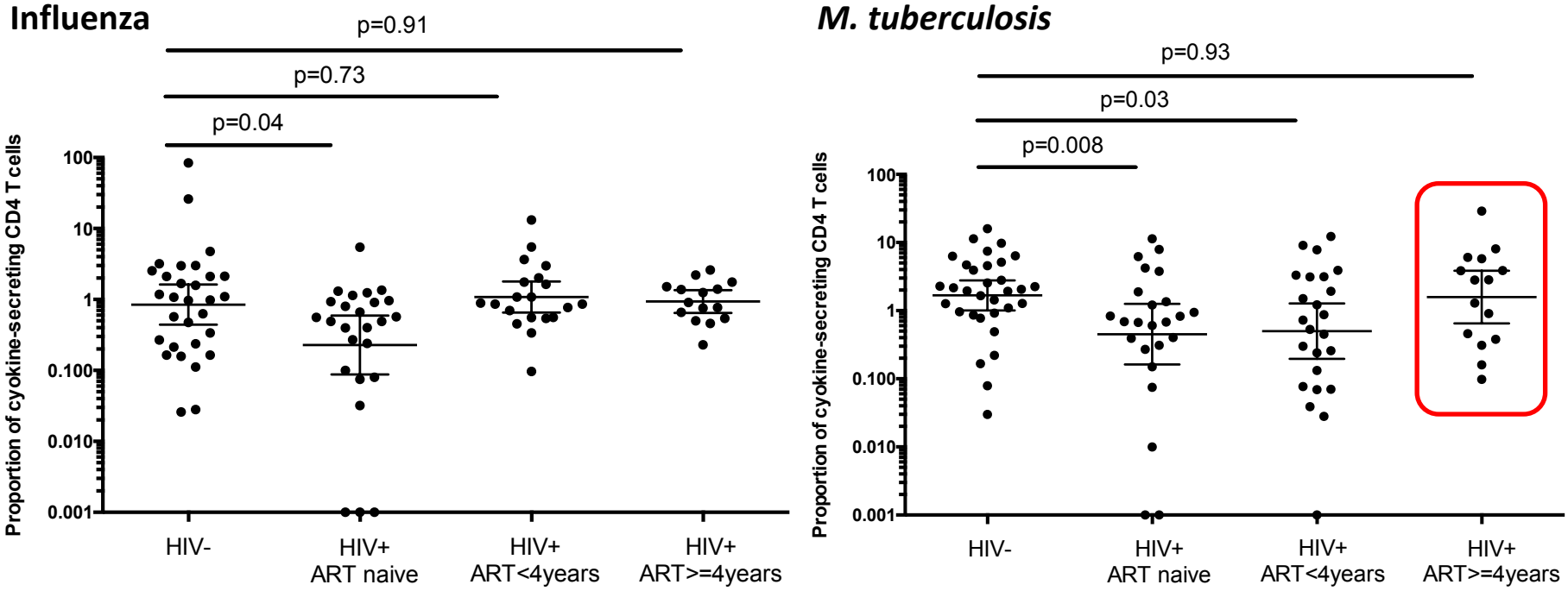


Alveolar macrophages co-infected with HIV & Mtb:
Increased permissiveness for Mtb



Altered airway immune microenvironment

HIV-associated impairment and ART-mediated recovery of alveolar pathogen-specific immune responses

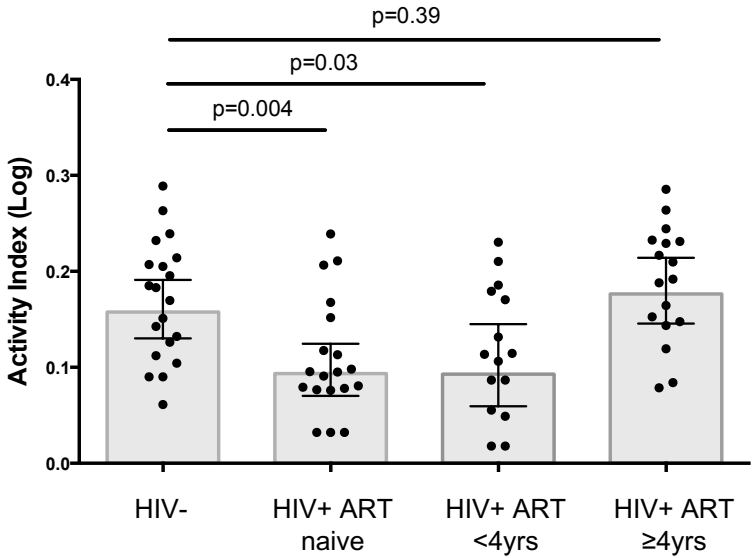


Delayed and incomplete recovery of *M. tuberculosis*-specific CD4+ T cell numbers and function in HIV-infected adults on long term ART

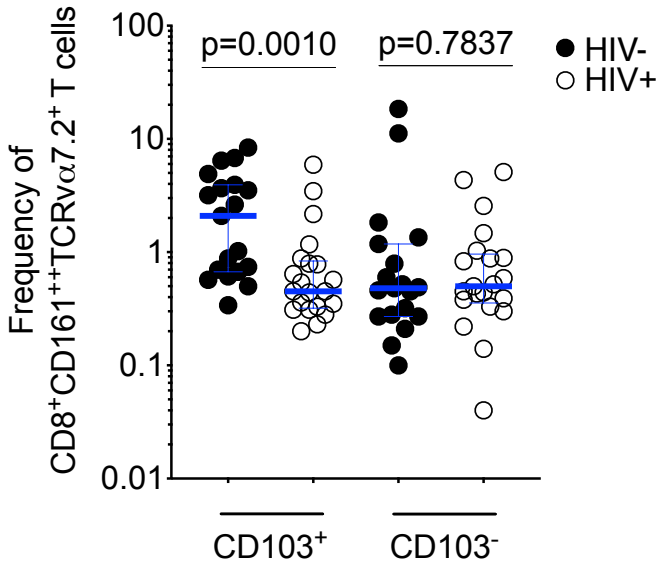
Jambo *et al., Am J Respir Crit Care Med* 2014

HIV-associated impairment of airway innate effector cells

A. **Alveolar macrophage (AM) proteolytic function**



B. **Frequency of airway MAIT cells**



Impaired AM phagosome function pre-ART and delayed recovery on ART.

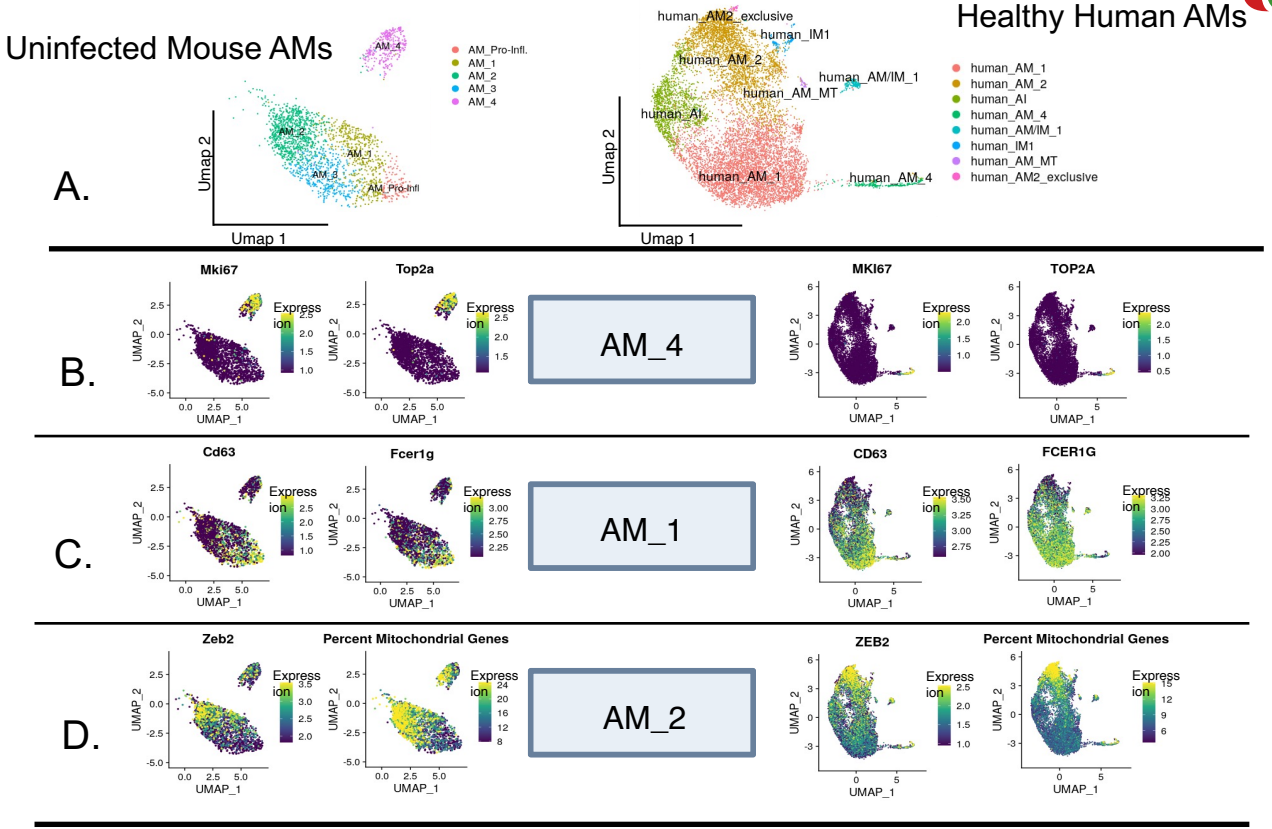
HIV-associated depletion of MAIT cells in the airway targets the resident population.

Jambo KC *et al., Am J Respir Crit Care Med* 2014

Mvaya L *et al., Frontiers Immunol* 2019

Single cell analysis of alveolar macrophages reveals heterogeneity

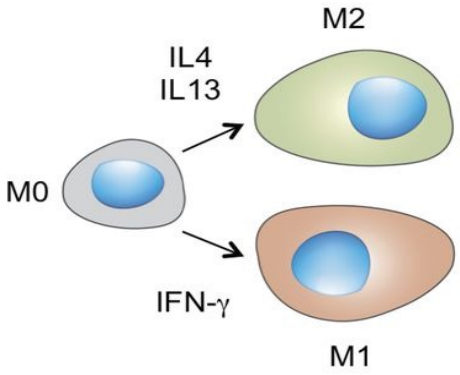
(**A**) Umap plots showing unbiased clustering of AMs in mice and humans. (**B**) Gene expression values for the marker genes (*Top2a* and *Mki67)* of the AM_4 population indicative of cell replication (**C**) Gene expression values for (*Cd63* and *Fcer1g)* of the AM_1 population. (**D**) Gene expression values for *Zeb2,* as well as the percentage of mitochondrial reads of the AM_2 population indicative of OXPHOS metabolism.



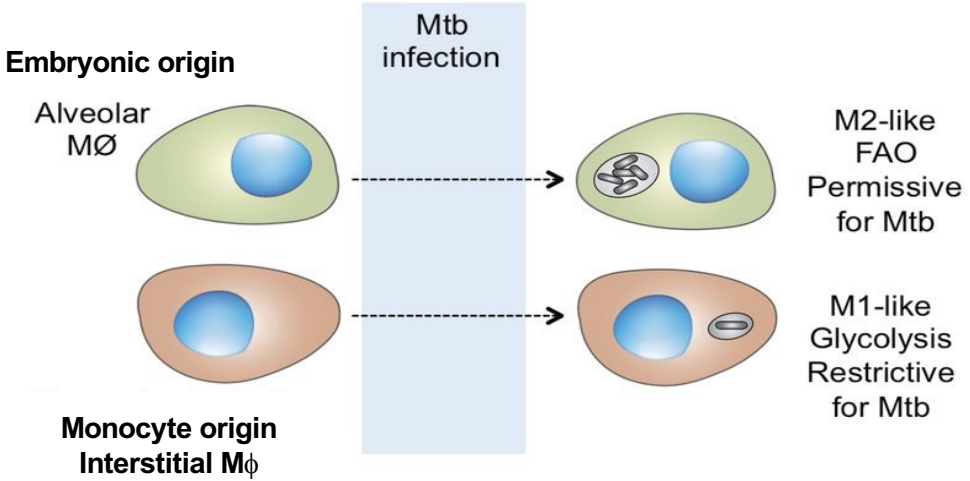
Pisu *et al., J Exp Med* 2021

Growth of Mtb *in vivo* segregates with host macrophage metabolism and ontogeny

Model 1. Re-Programming



Model 2. Pre-Programming



- In the M1/M2 Re-Programming model Mtb growth is regulated by cytokine environment.
- In the Pre-Programming model macrophage metabolism and ontogeny regulate Mtb growth.

Lu Huang et al. J Exp Med 2018

Concluding remarks

1. Immunity to *M. tuberculosis* is complex.

2. Altered lung immune environment may promote/enhance growth & survival of Mtb in permissive AMs and progression to active TB.

3. Exploiting HIV-mediated lung immune impairment may unravel what constitutes protective immunity to TB in humans.

4. Modulation of epigenetic programming of tissue resident macrophage lineages by new TB vaccines/drugs could be a novel strategy to impact Mtb infection, control and persistence in humans.