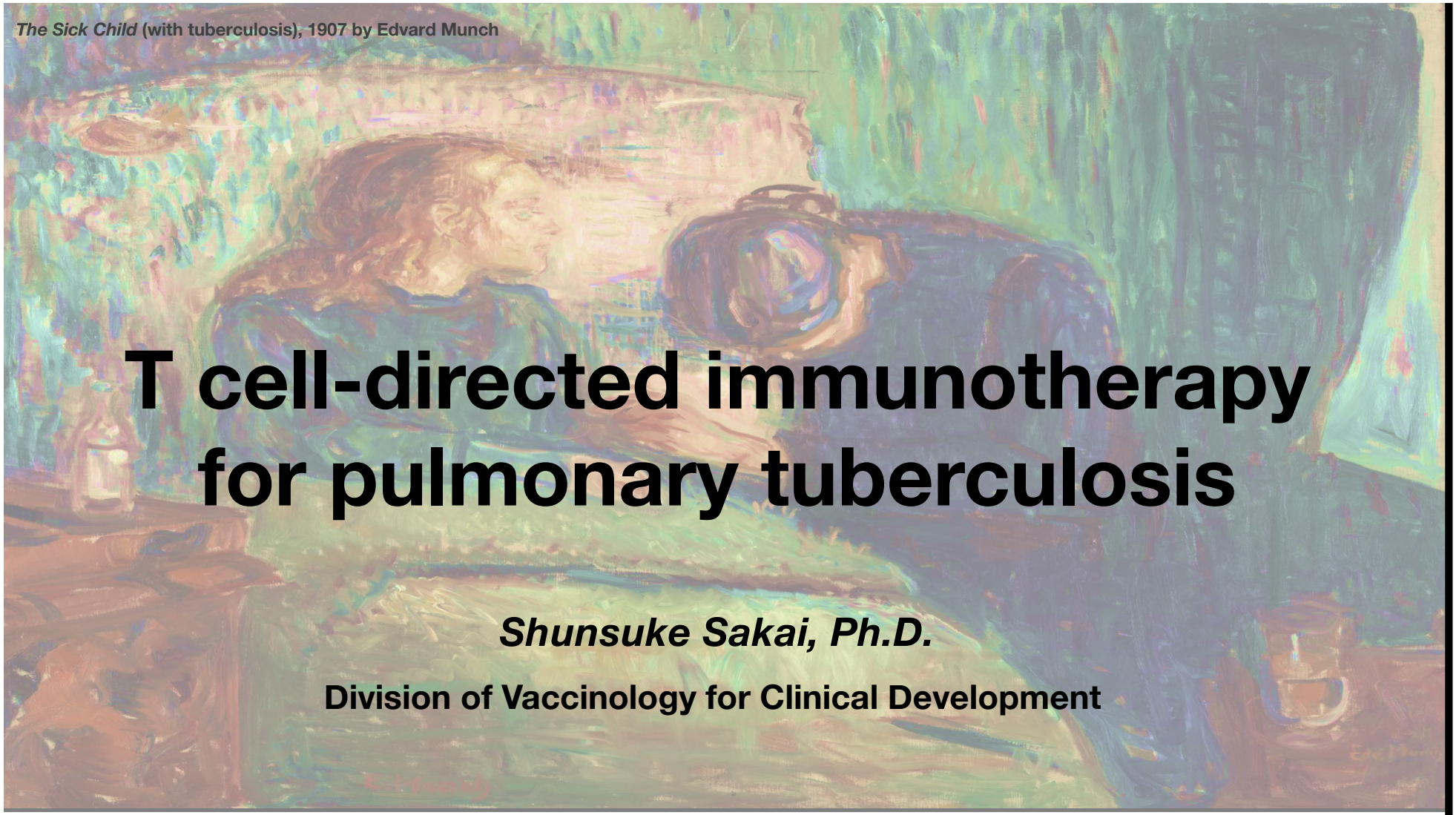

The Sick Child (with tuberculosis), 1907 by Edvard Munch

T cell-directed immunotherapy for pulmonary tuberculosis

Shunsuke Sakai, Ph.D.

Division of Vaccinology for Clinical Development

Japan Initiative for World-leading Vaccine Research and Development Centers

AMED

SCARDA

November 6, 2025

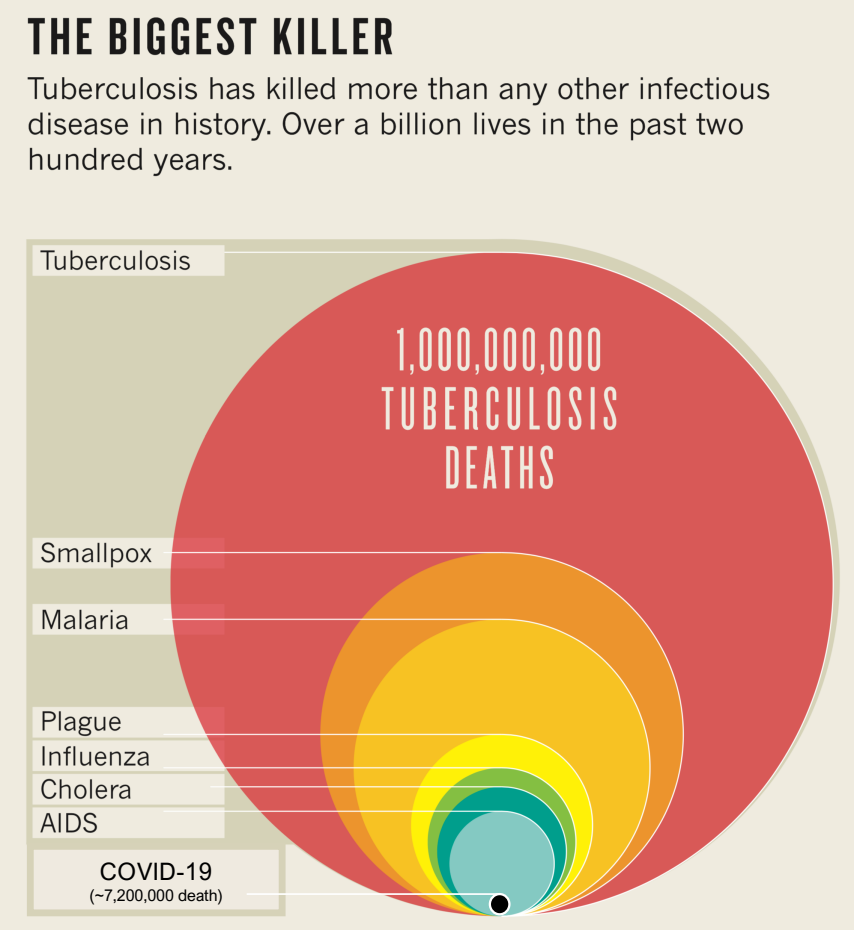
IVReD Research Seminar

IVReD 北海道大学ワクチン研究開発拠点

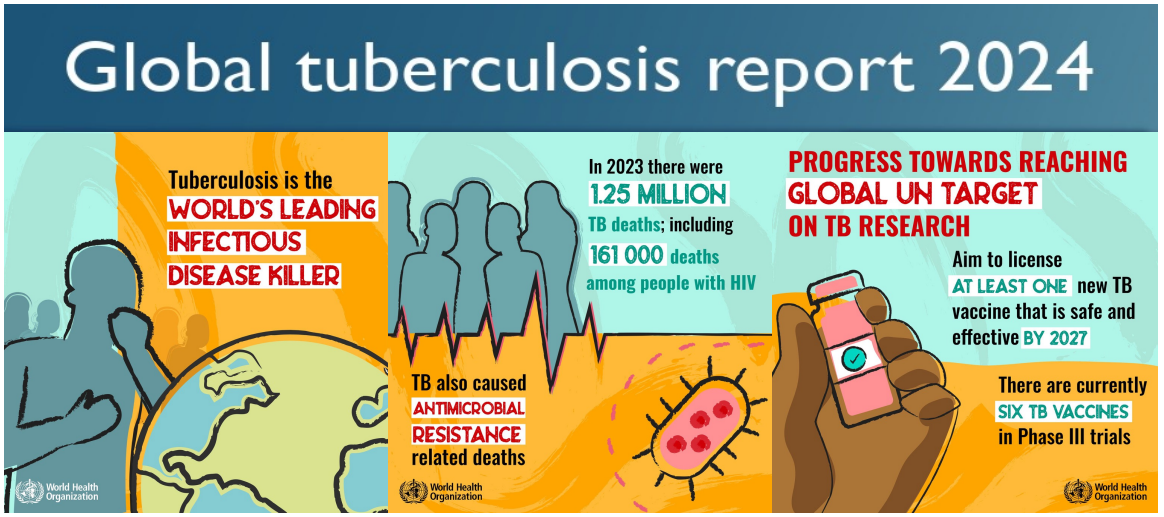
INSTITUTE FOR VACCINE RESEARCH AND DEVELOPMENT

HOKKAIDO UNIVERSITY

Tuberculosis (TB) remains a leading contributor to global infectious disease morbidity and mortality



Adopted from Poulson (2013) *Nature*

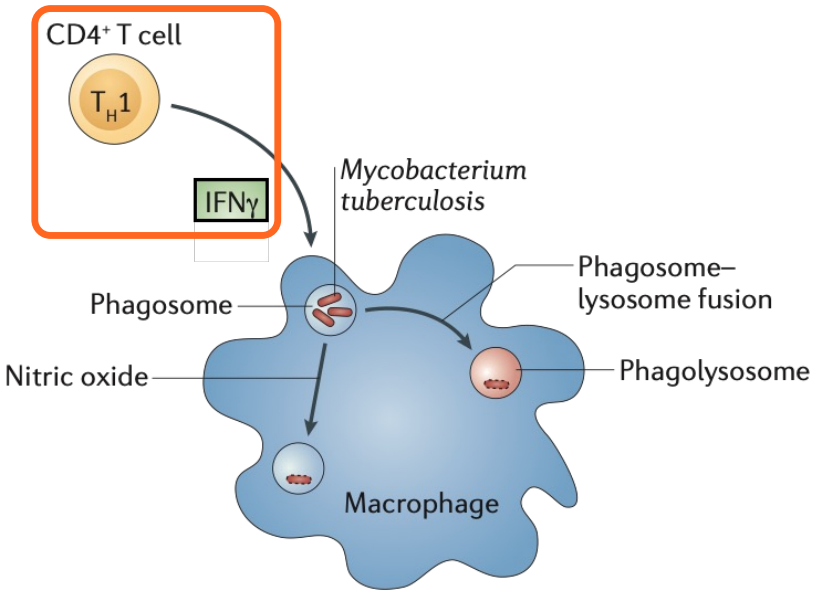


Novel prophylactics and therapeutics are needed

- ➤ **EFFECTIVE VACCINES**
- ➤ **ANTIBIOTICS**
- ➤ **HOST-DIRECTED THERAPIES**
  (targeting host immunity rather than pathogens)

IVReD

T cell immunity is necessary to control of *M. tuberculosis* but unable to eradicate the chronic infection

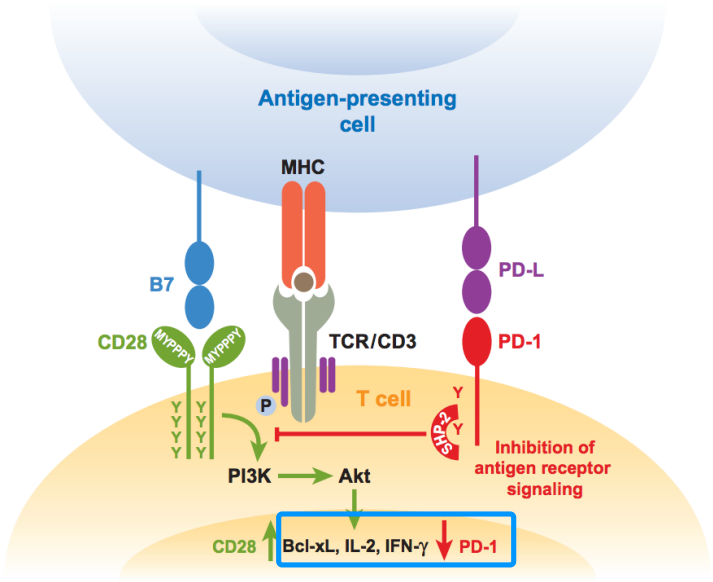


Nunes-Alves et al. (2014) *Nat Rev Micro.*

Can we manipulate T cell functions to enhance control of *M. tuberculosis* (*Mtb*) infection?

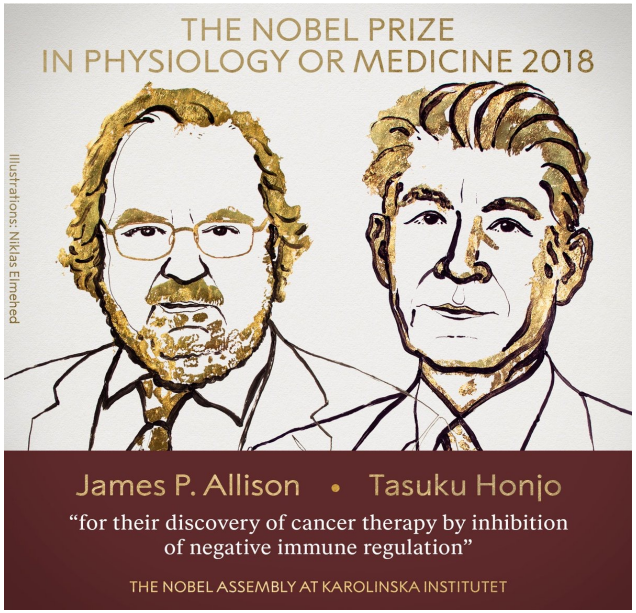
IVReD

Blockade of the PD-1 immune checkpoint pathway to enhance T cell immunity to cancer



Keir et al. (2014) *Ann Rev Immunol.*

- discovered in 1992 by Prof. Honjo and colleagues in Kyoto University, Japan.
- inhibits T cell activation by interacting with its ligands (PD-L1 or PD-L2).
- a major role in regulating "T-cell exhaustion" in cancer and chronic infection.



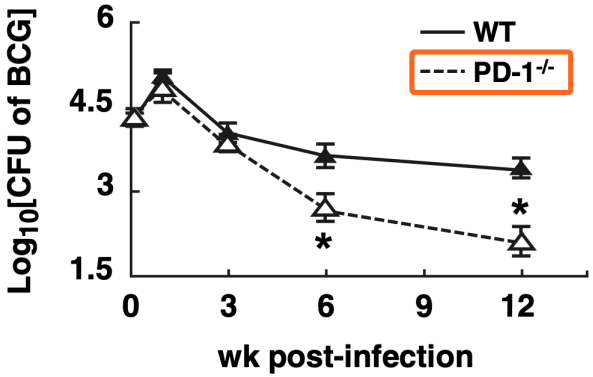
IVReD

PD-1 deficiency exacerbates tuberculosis in mice

PD-1–PD-L1 pathway impairs T_h1 immune response in the late stage of infection with *Mycobacterium bovis* bacillus Calmette–Guérin

Shunsuke Sakai[1], Ikuo Kawamura[1], Taku Okazaki[2], Kohsuke Tsuchiya[1], Ryousuke Uchiyama[3] and Masao Mitsuyama[1]

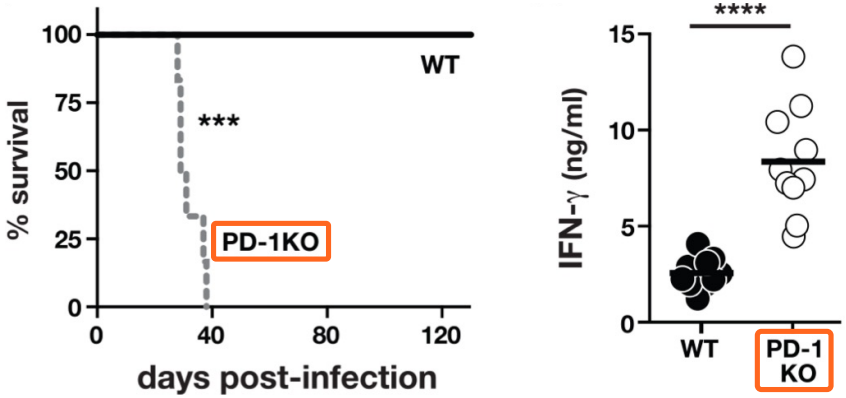
(2010) international immunology



CD4 T Cell-Derived IFN-γ Plays a Minimal Role in Control of Pulmonary *Mycobacterium tuberculosis* Infection and Must Be Actively Repressed by PD-1 to Prevent Lethal Disease

Shunsuke Sakai[1], Keith D. Kauffman[1], Michelle A. Sallin[1], Arlene H. Sharpe[2], Howard A. Young[3], Vitaly V. Ganusov[4], Daniel L. Barber[1]*

(2016) PLOS | PATHOGENS



IVReD

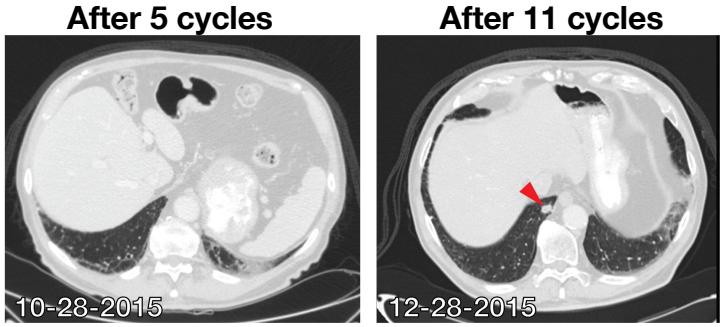
TB after PD-1 blockade for Merkel cell carcinoma

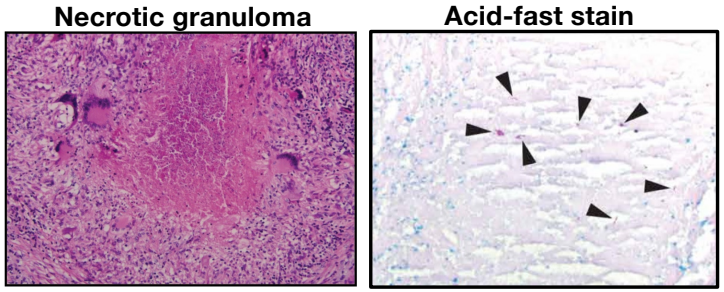
Tuberculosis following PD-1 blockade for cancer immunotherapy

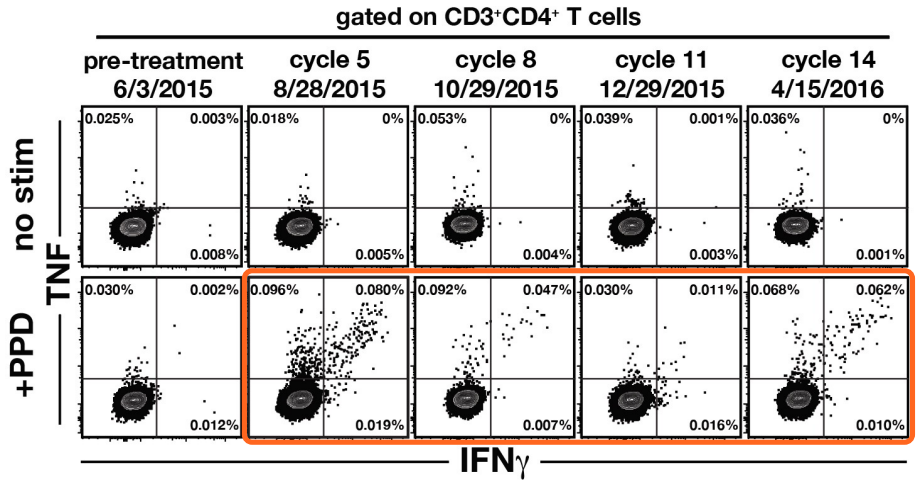
Daniel L. Barber[1]*, Shunsuke Sakai[1], Ragini R. Kudchadkar[2], Steven P. Fling[3,4], Tracey A. Day[5], Julie A. Vergara[5], David Ashkin[6], Jonathan H. Cheng[7], Lisa M. Lundgren[4], Vanessa N. Raabe[8], Colleen S. Kraft[9], Jorge J. Nieva[7], Martin A. Cheever[3,4], Paul T. Nghiem[10], Elad Sharon[11]*

(2019) Science Translational Medicine

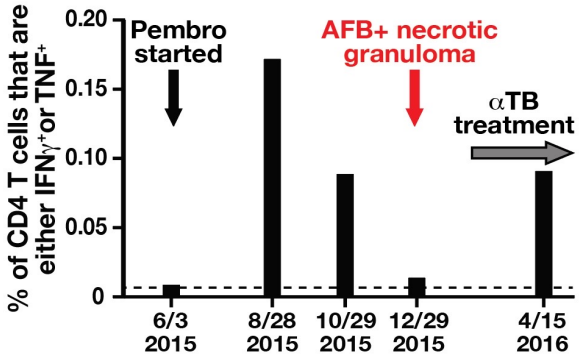
A 83-yr old male treated with Pembrolizumab







Increased *Mtb*-specific Th1 response before granuloma formation



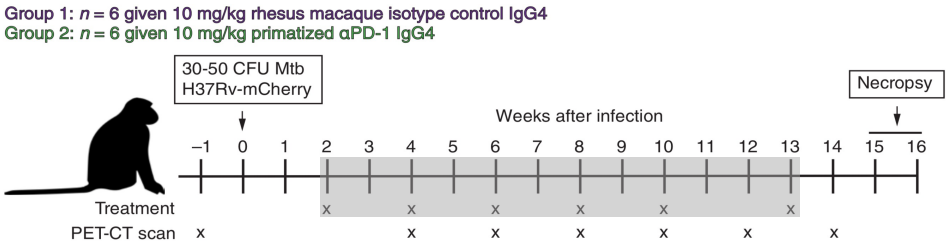
IVReD

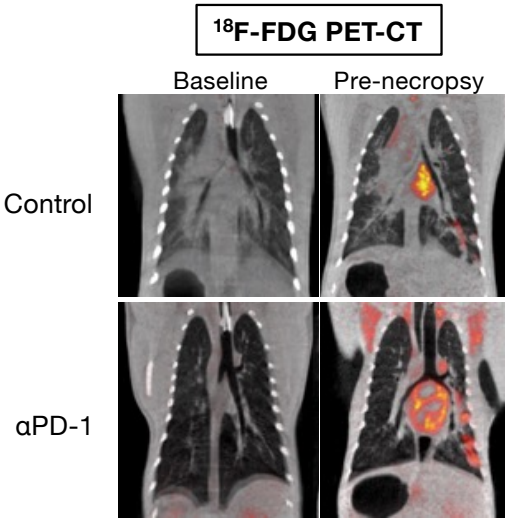
PD-1 blockade increases lung inflammation and bacterial growth in the granulomas of *Mtb*-infected macaques

PD-1 blockade exacerbates *Mycobacterium tuberculosis* infection in rhesus macaques

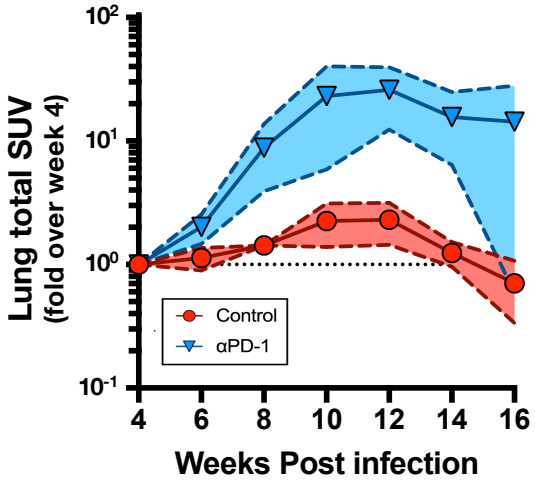
Keith D. Kauffman[1], Shunsuke Sakai[1], Nickiana E. Lora[1], Sivaranjani Namasivayam[2], Paul J. Baker[3], Olena Kamenyeva[4], Taylor W. Foreman[1], Christine E. Nelson[1], Deivide Oliveira-de-Souza[5], Caian L. Vinhaes[5], Ziv Yaniv[6], Cecilia S. Lindestam Arleham[7], Alessandro Sette[7,8], Gordon J. Freeman[9], Rashida Moore[10], NIAID/DIR Tuberculosis Imaging Program*, Alan Sher[2], Katrin D. Mayer-Barber[3], Bruno B. Andrade[5], Juraj Kabat[4], Laura E. Via[11]*, Daniel L. Barber[1†]

(2021) Science Immunology

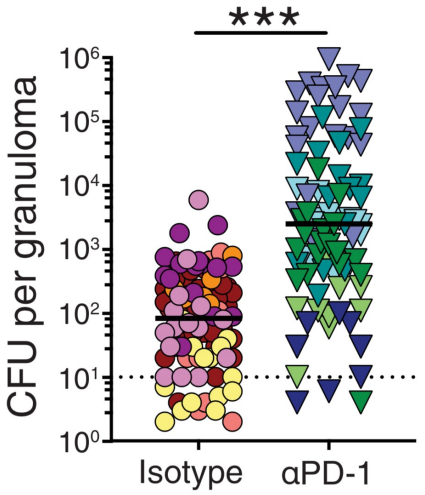




Pulmonary inflammation



Bacterial load



IVReD

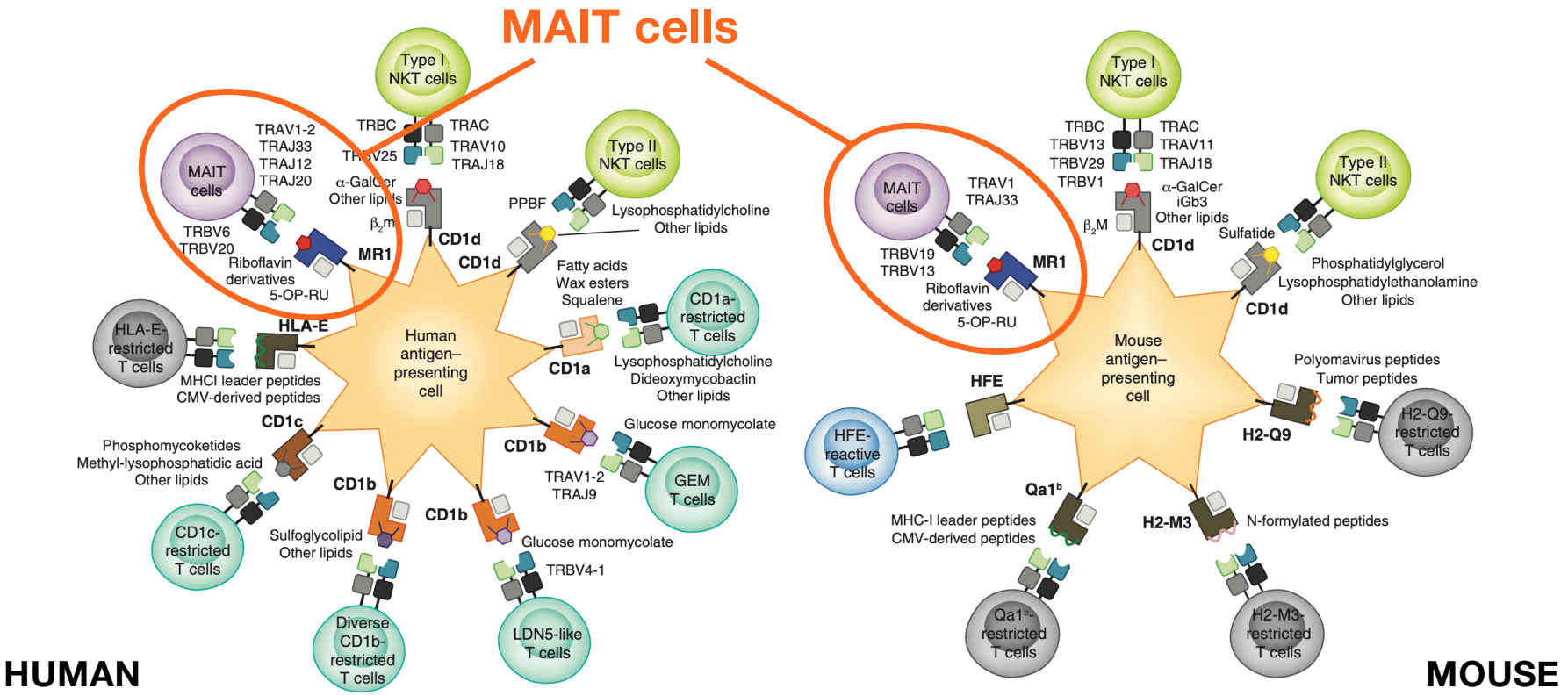
SUMMARY - I

Evidence from mice, humans, and non-human primates indicate that PD-1 blockade exacerbates tuberculosis.

PD-1 is required for preventing T cell-driven immunopathology in *M. tuberculosis* infection.

IVReD

Can we target Donor Unrestricted T cells (DURTs) to treat *M. tuberculosis* infection ?



Godfrey et al. (2015) *Nat Immunol*.

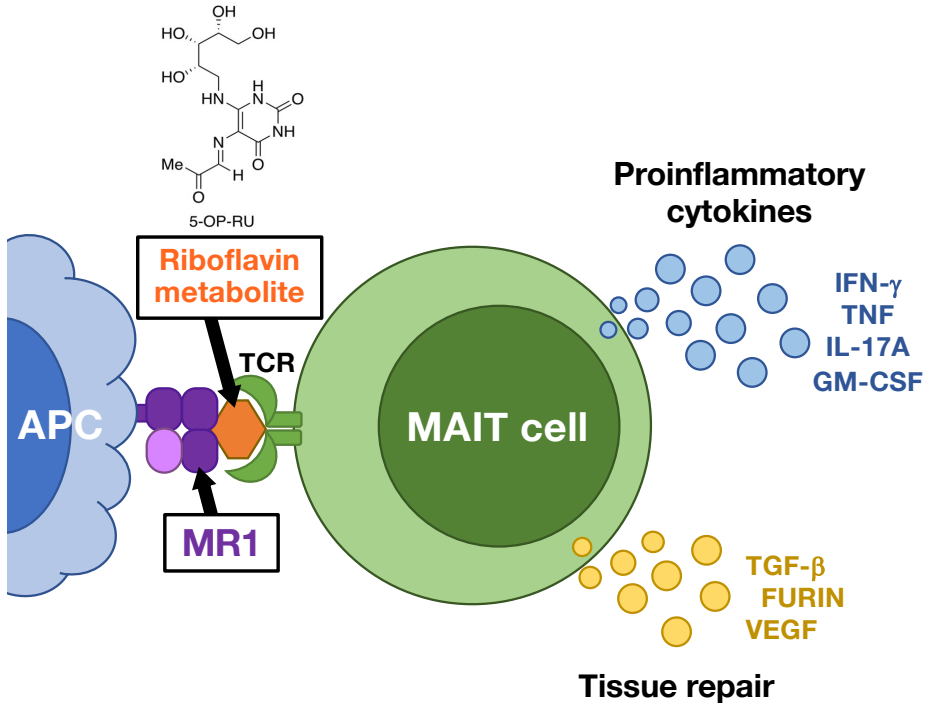
IVReD

Targeting mucosal-associated invariant T (MAIT) cells as a potential new host-directed therapy for TB

- MAIT cells express semi-invariant TCRs and recognize microbe-derived riboflavin metabolites (e.g. 5-OP-RU) presented by MHC class I-like molecule MR1.

- Human MAIT cells recognize Mtb-infected cells and produce IFN-γ in vitro.

- MAIT cells in the peripheral blood are reduced in active TB patients compare to healthy controls.



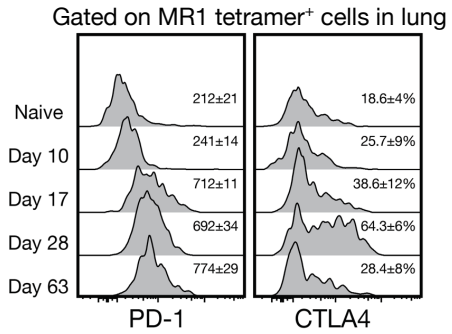
Therapeutic vaccination of MAIT cells with 5-OP-RU enhances control of *Mtb* infection in mice

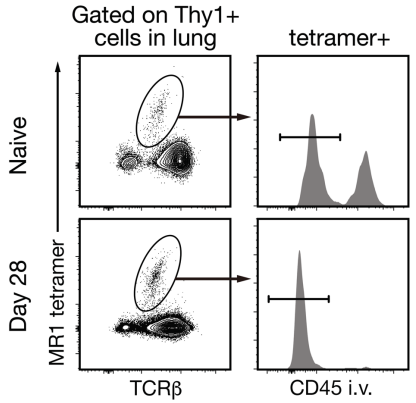
MAIT cell-directed therapy of *Mycobacterium tuberculosis* infection

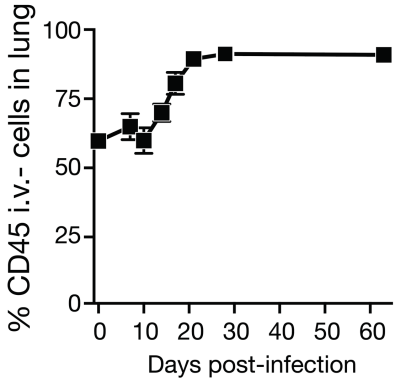
Shunsuke Sakai[1], Keith D. Kauffman[1], Sangmi Oh[2], Christine E. Nelson[1], Clifton E. Barry III[2] and Daniel L. Barber[1]

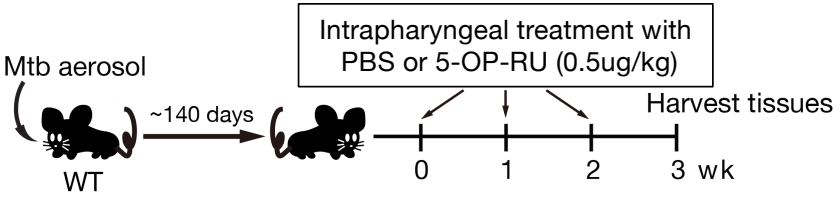
(2020) MUCOSAL IMMUNOLOGY

Up-regulation of TCR-stim markers and migration into the pulmonary tissues

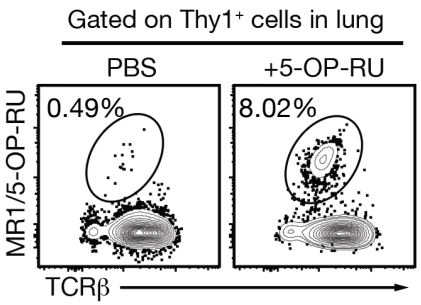


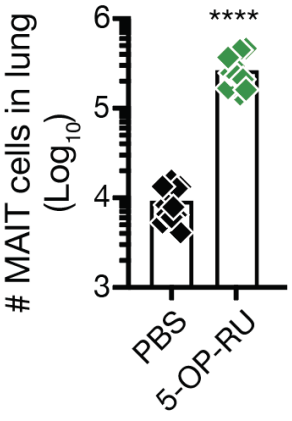


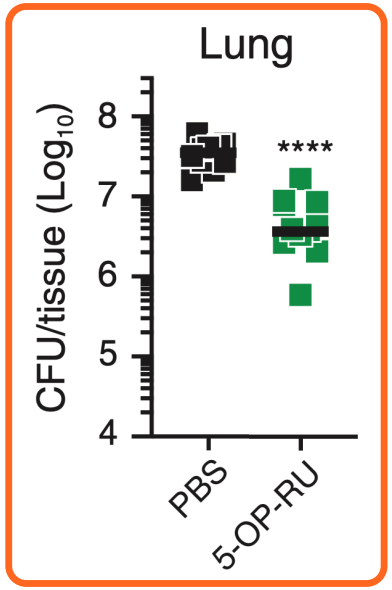




Expansion by pulmonary instillation of MAIT cell antigen





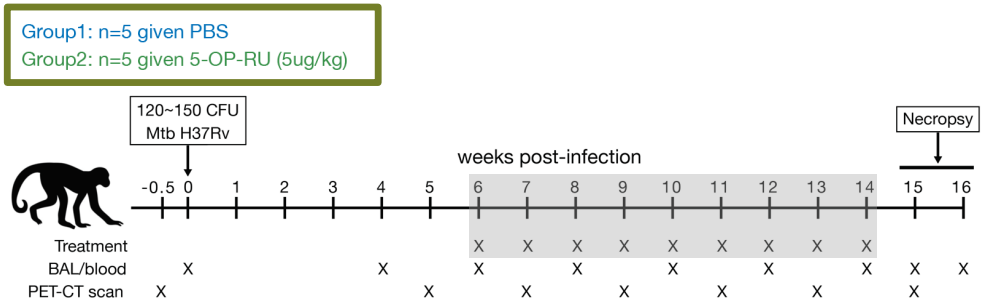


5-OP-RU instillation has little impact on disease severity and control of *Mtb* infection in macaques

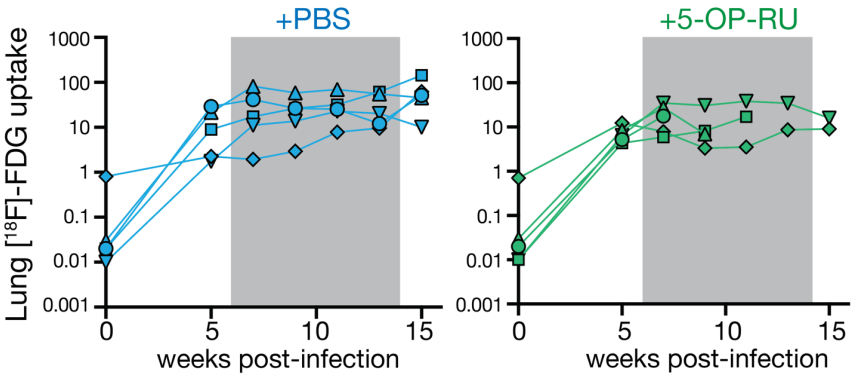
Functional inactivation of pulmonary MAIT cells following 5-OP-RU treatment of non-human primates

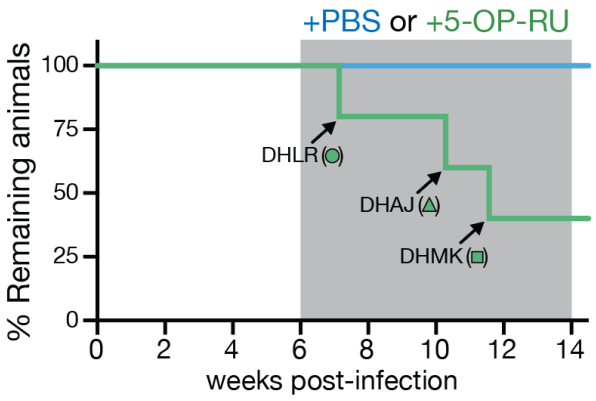
Shunsuke Sakai[1], Nickiana E. Lora[1], Keith D. Kauffman[1], Danielle E. Dorosky[1], Sangmi Oh[2], Sivaranjani Namasivayam[3], Felipe Gomez[4], Joel D. Fleegle[4], Tuberculosis Imaging Program*, Cecilia S. Lindestam Arlehamn[6], Alessandro Sette[6,7], Alan Sher[3], Gordon J. Freeman[8], Laura E. Via[2,4,5], Clifton E. Barry III[2,5] and Daniel L. Barber[1]✉

MUCOSAL IMMUNOLOGY (2021)



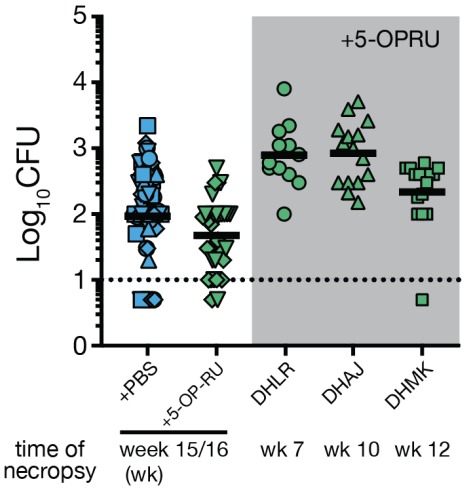
Pulmonary inflammation





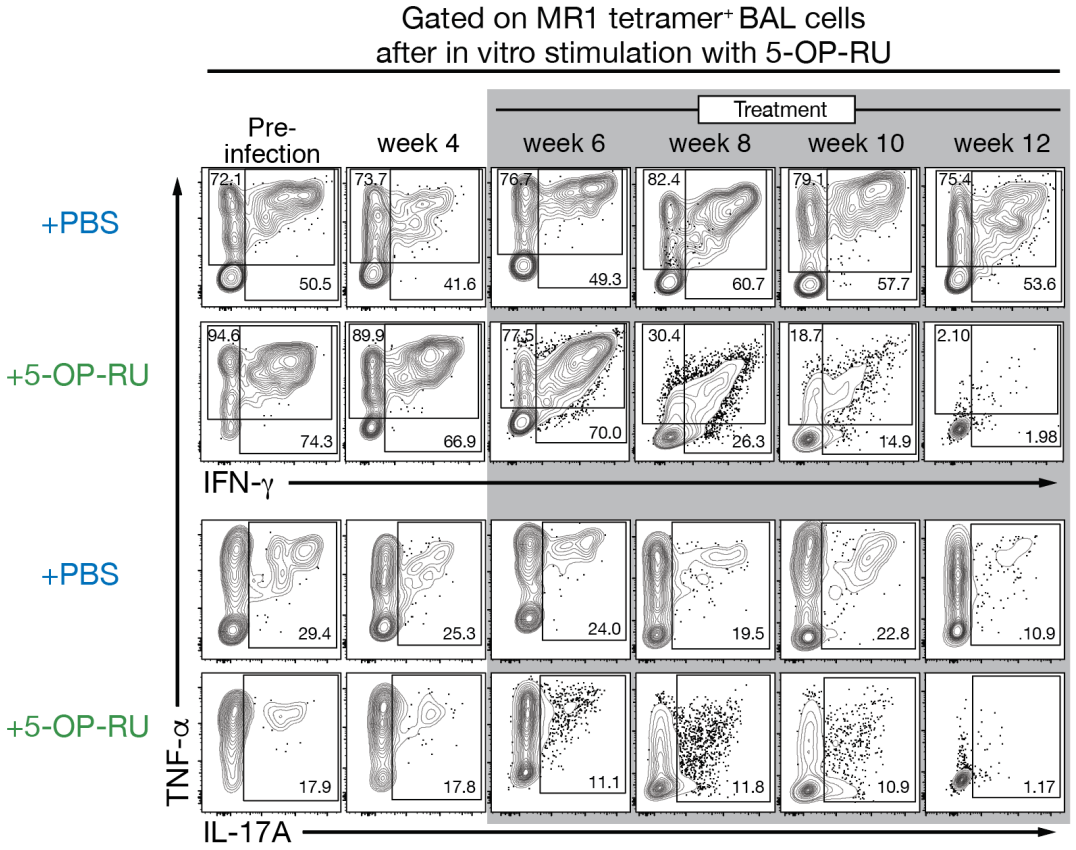
3 out of 5 treated animals needed to be humanely euthanized early.

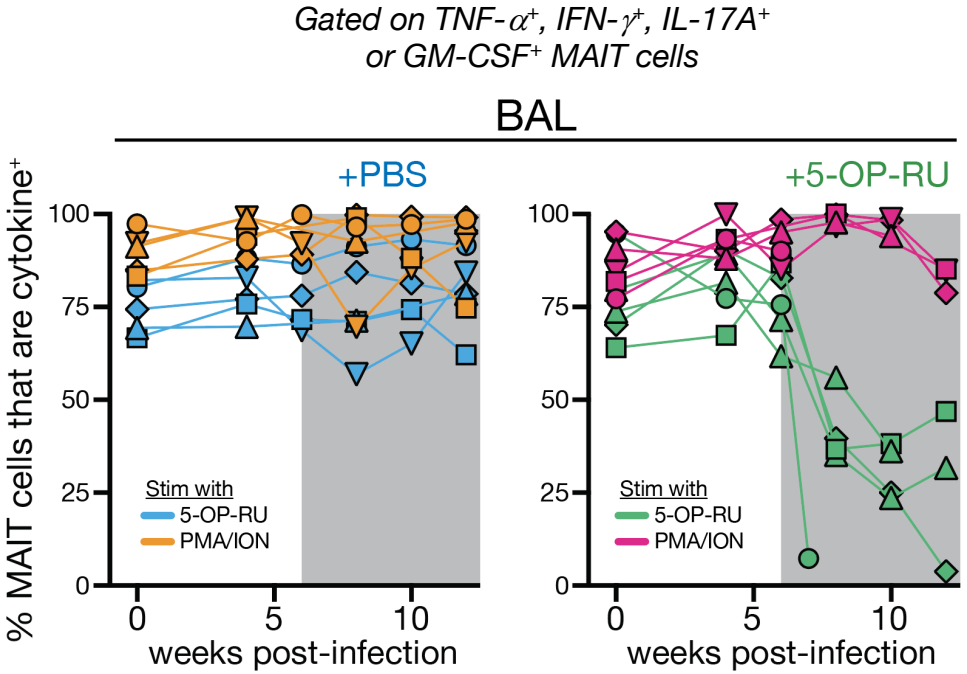
Mtb growth in granulomas



IVReD

5-OP-RU treatment leads to antigen-specific MAIT cell exhaustion in *Mtb*-infected macaques





MAIT cells highly expressed PD-1 after 5-OP-RU treatment.

IVReD

SUMMARY - II

Therapeutic (post-exposure) MAIT cell vaccination with 5-OP-RU enhances control of *M. tuberculosis* infection in mice (through IL-17A).

Similar MAIT cell-directed therapy in macaques had no clinical benefit and rather led to MAIT cell exhaustion.

IVReD

T cell-directed therapy for TB

➤ Blocking the immune checkpoint PD-1

- Unlikely to be a feasible approach to treat TB, but might be beneficial with adjunct TB drug treatment or for less virulent mycobacterial infections.

➤ Stimulating MAIT cells

- Looks promising in mice, but need to figure out how to expand MAIT cells in primates (*importance of macaque models to evaluate its clinical potential*).

IVReD