M. tuberculosis antigens under diversifying evolutionary selection induce Th17 responses in human infection

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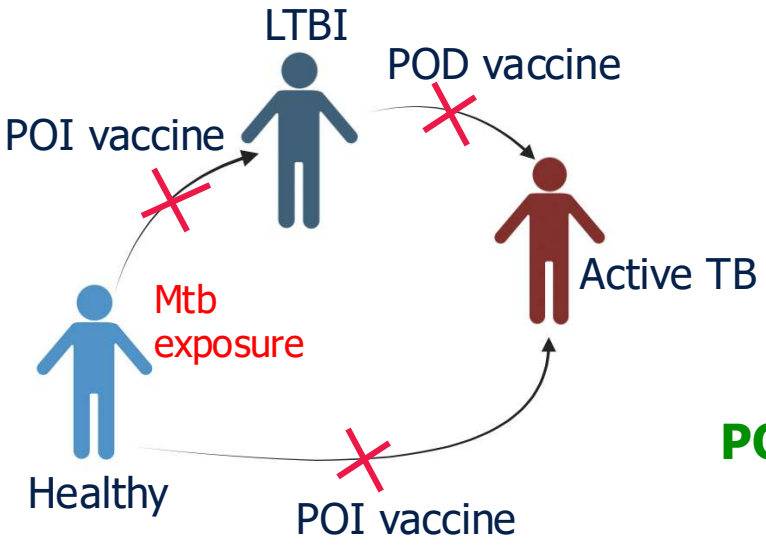
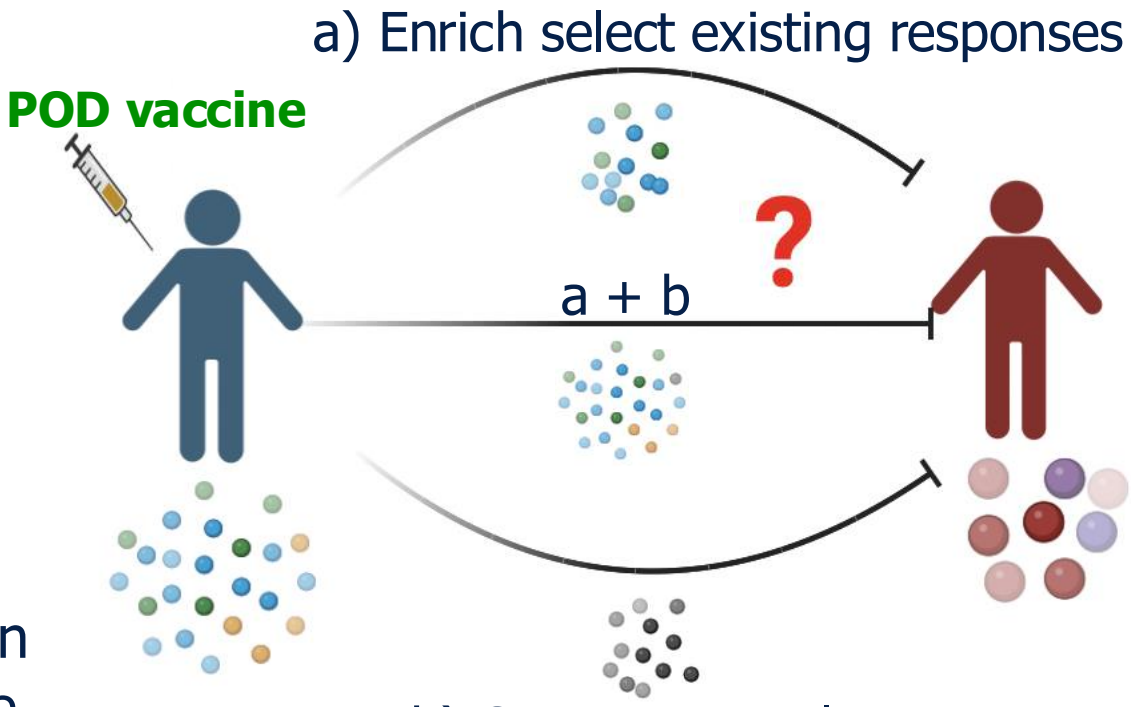
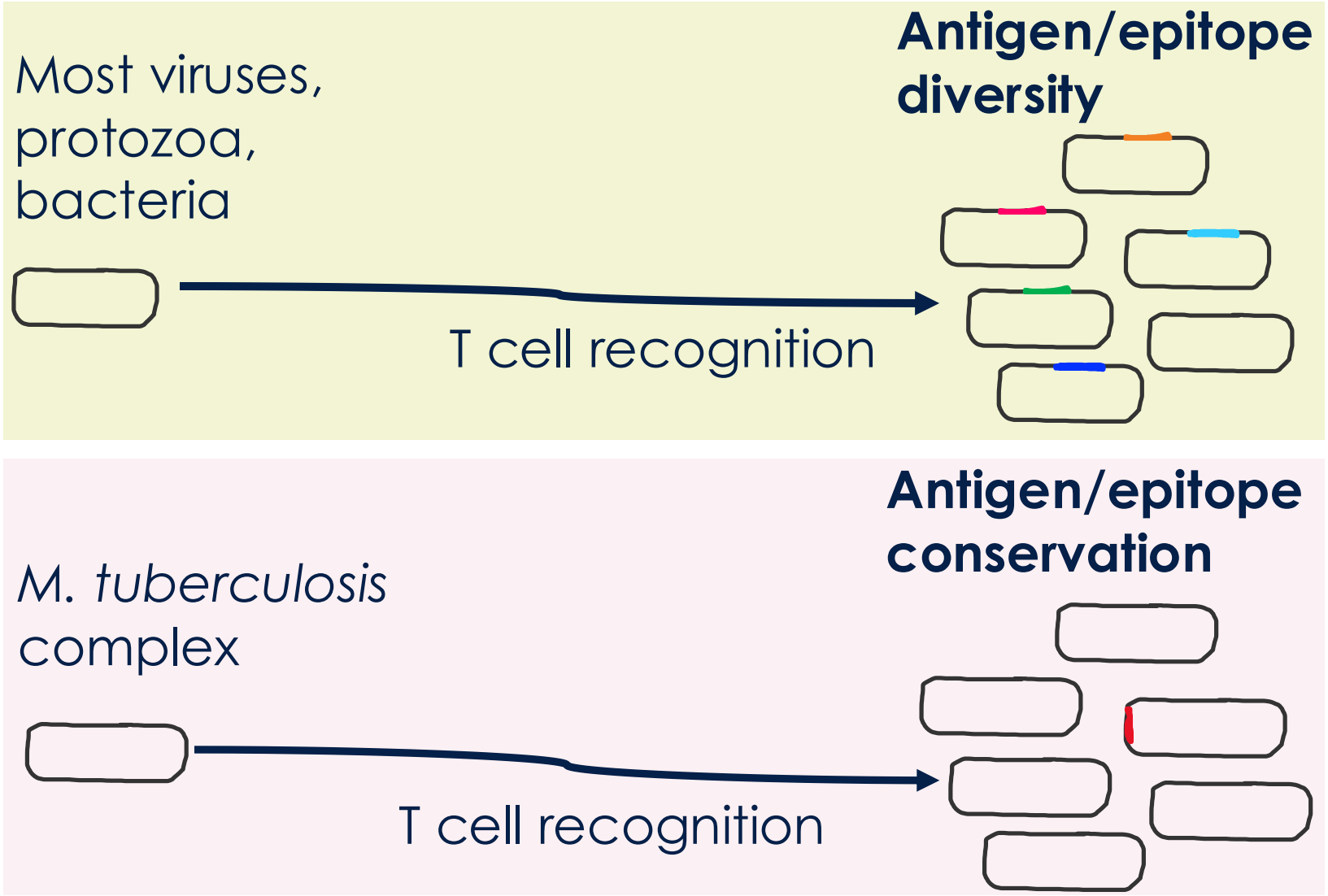
Prevention of Disease TB vaccines



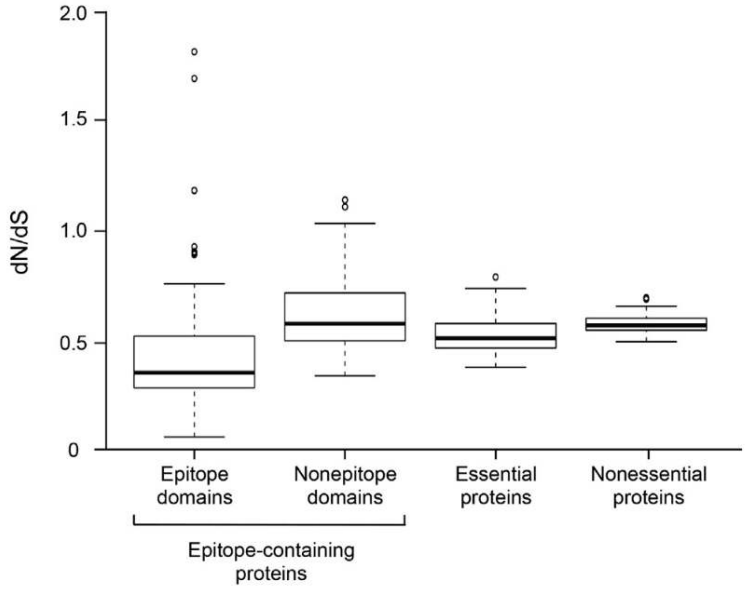


POI = prevention of infection
POD = prevention of disease

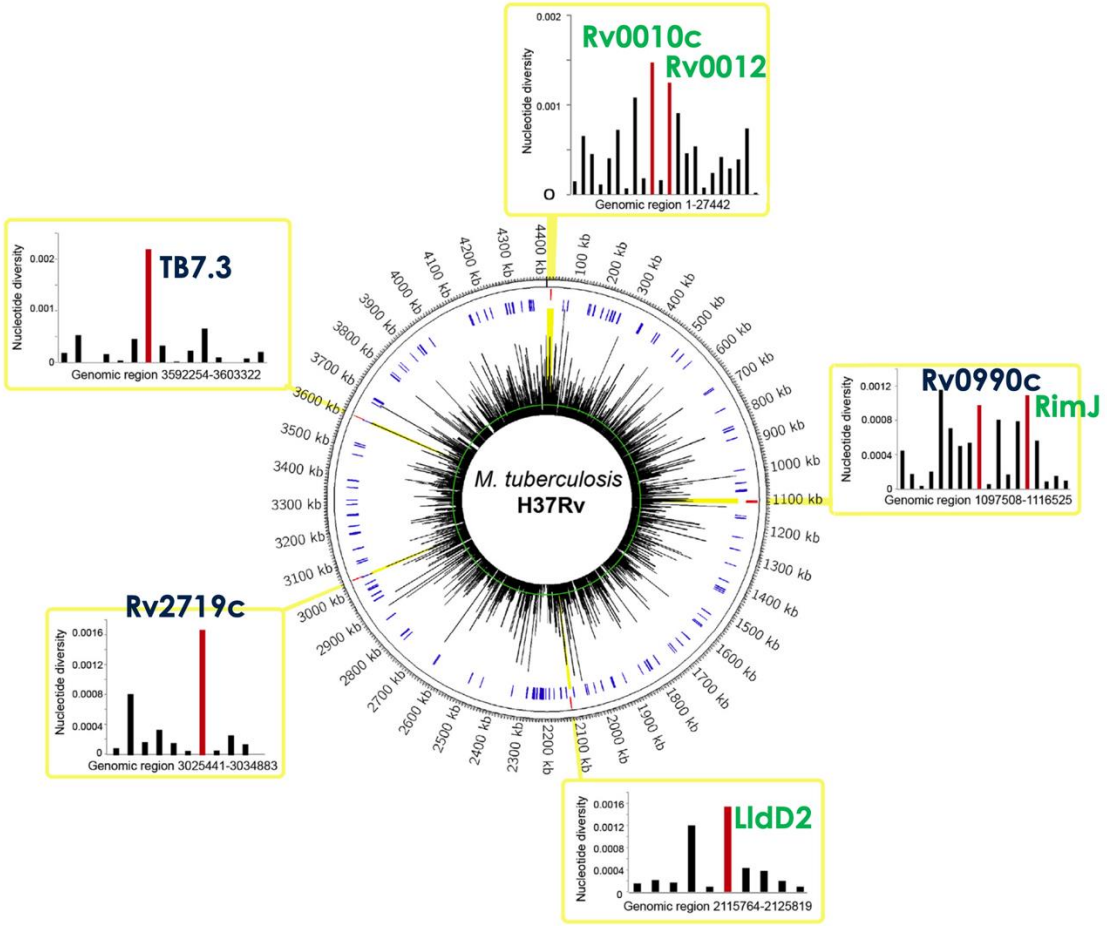
POD vaccines: which *Mtb* antigens should we target?



Rare variable *Mtb* antigens as POD vaccine candidates



Coscolla M *et al* 2015



Antigens with variable T cell epitopes = RVMA

- Hotspots of variable regions suggestive of diversifying evolutionary selection

Distinct *Mtb* antigen-specific CD4 T cell responses in controlled human TB

Hypothesis:
Human CD4 T cells with distinct *Mtb* antigen specificities differ in their functional responses that contribute to protective CD4 T cells

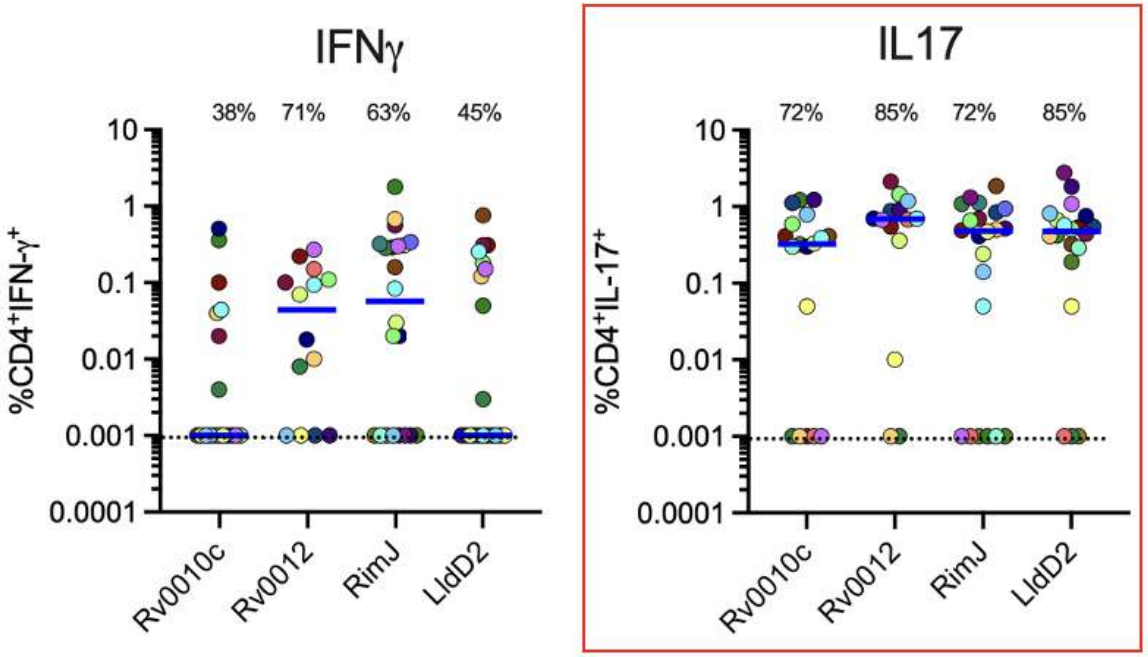
Household contacts (QFT+/HIV-) of confirmed index TB case(smear+/Xpert)

8 distinct Mtb antigens; synthesized as peptide pools

- 4 Rare variable Mtb antigen (RVMA)
- 4 classical conserved Mtb antigens

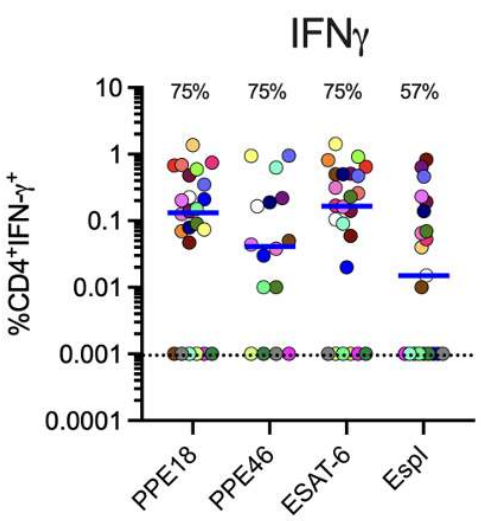
RVMA preferentially elicit Th17 responses

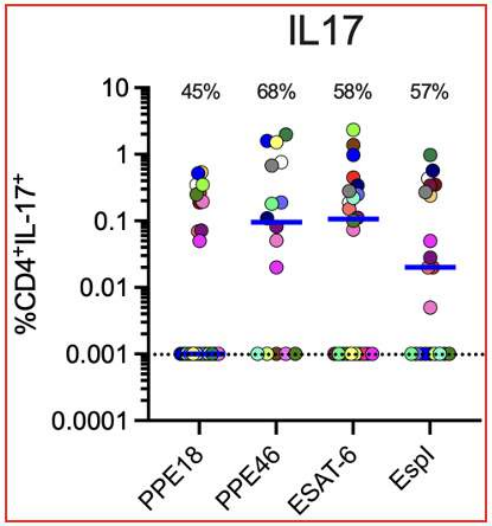
RVMA



Ogongo P et al 2024
(*bioRvix,* PMID: 38496518)

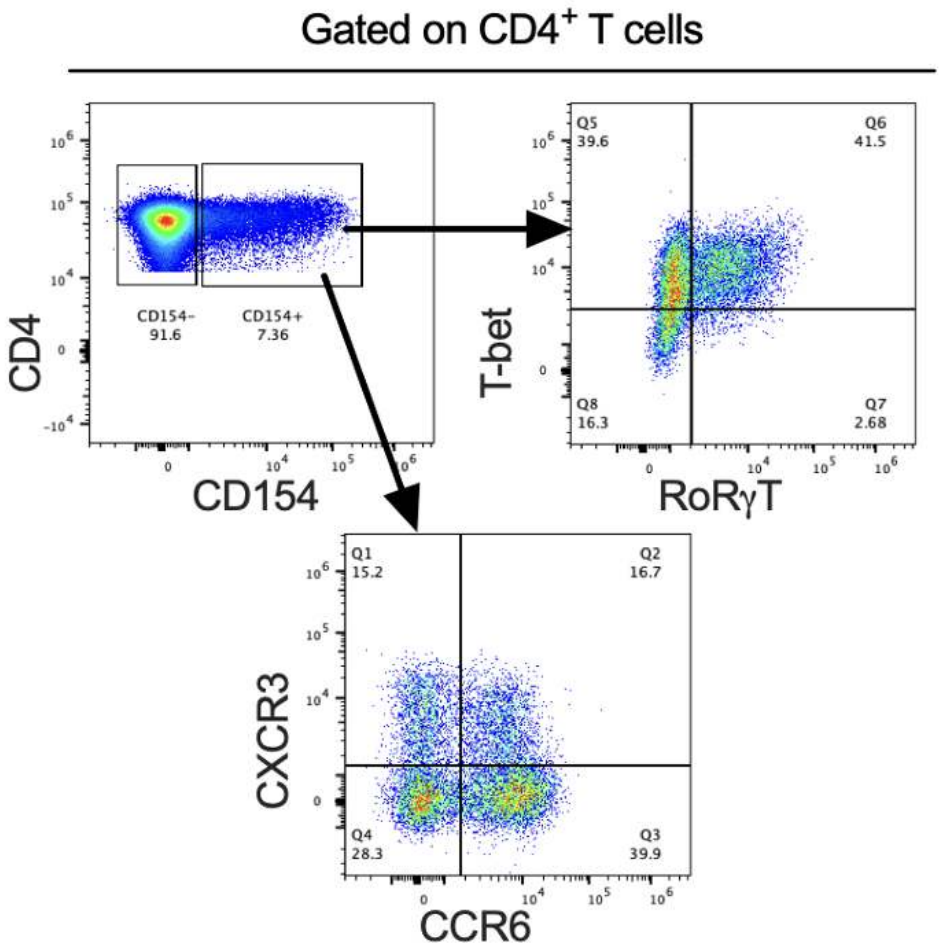
Classical antigens

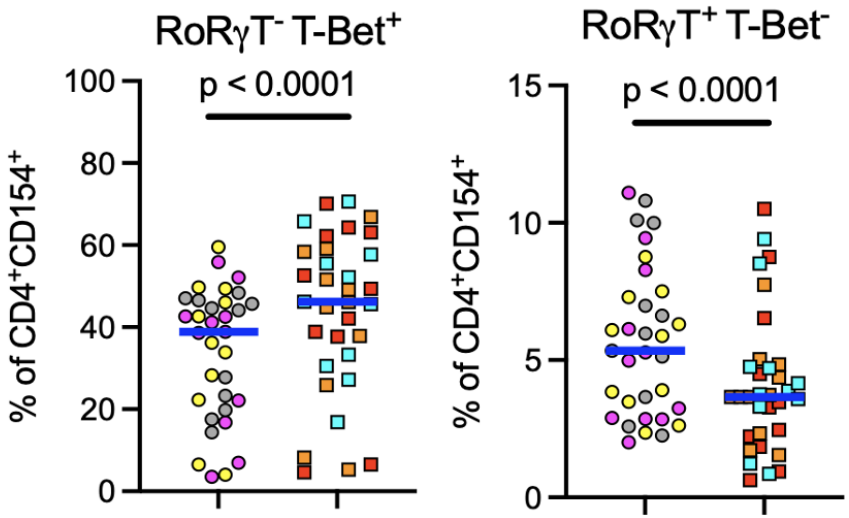


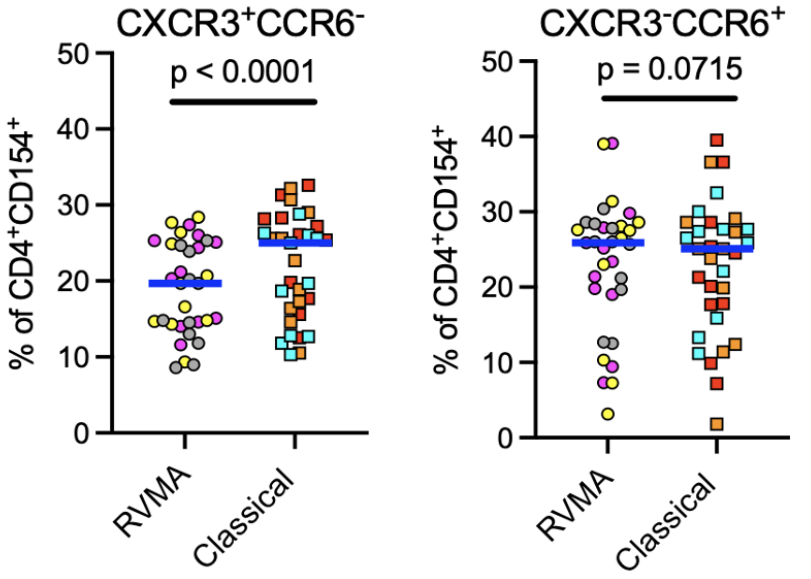


2 East African cohorts of people with contained *Mtb* infection

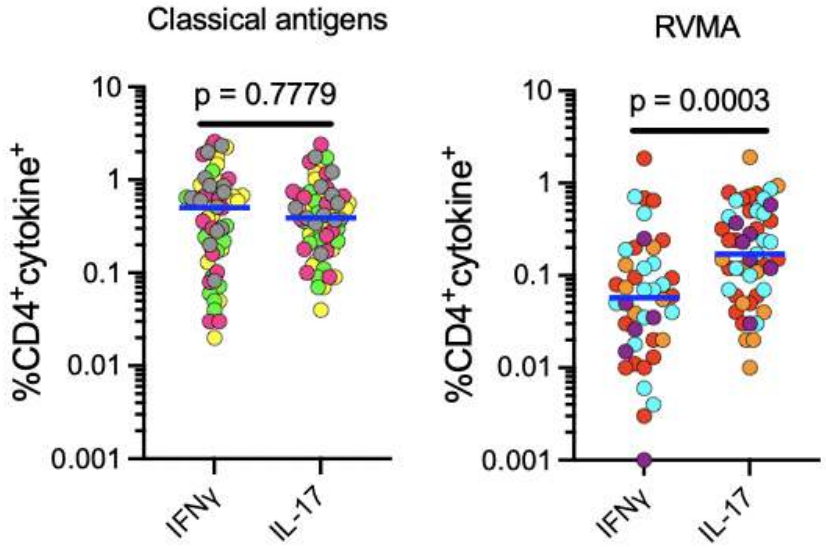
RVMA preferentially elicit Th17 responses







RVMA skew T cells towards IL17 responses



Color legends

Classical Antigens:

Yellow (PPE18),
Green. (PPE-46),
Strawberry (ESAT-6),
Grey (Esp-I)

Novel Antigens:

Red (Rv0010c),
Orange (Rv0012),
Turquoise (RimJ),
Plum (LldD2)

Cohort 2

Cohort 2: IL17 vs IFNγ responses to individual RVMA

	Response Frequencies (% of participants with detectable cytokine+ CD4 T cells)		Response Magnitudes (% of CD4 T cells that are cytokine+) Median (interquartile range)		
	IL-17	**IFNγ**	**IL-17**	**IFNγ**	p*
Rv0010c	58	35	0.02 (0.001, 0.115)	0.001 (0.001, 0.047)	0.2437
Rv0012	58	58	0.07 (0.001, 0.385)	0.012 (0.001, 0.0775)	0.0054
RimJ	62	55	0.06 (0.001, 0.32)	0.01 (0.001, 0.087)	0.2157
LldD2	63	46	0.03 (0.001, 0.255)	0.001 (0.001,0.0305)	0.0391
*p values for the comparison of IL17 vs IFNγ magnitudes (Wilcoxon matched pairs)					

Th17 cells play a protective role in human TB

Suppression of Th17 responses is associated with progression to TB disease

Mtb-exposed individuals who remain IGRA negative display enrichment of Th17 cell-like functional programs

The Th17 cell-like functional programs were associated with a lack of progression to TB disease

Mtb-specific $CD4^{+}IL17^{+}$ T cells are enriched in Mtb-infected human lungs compared to matched blood and inversely correlate with plasma IL1-β

Scriba *et al* 2017; Nathan *et al* 2021; Sun *et al* 2024; Ogongo *et al* 2021

Vaccines that induce Th17 responses confer superior protection against Mtb

The Journal of Immunology

Mucosal Vaccination with Cyclic Dinucleotide Adjuvants Induces Effective T Cell Homing and IL-17–Dependent Protection against *Mycobacterium tuberculosis* Infection

Robyn M. Jong,*,[1] Erik Van Dis,*,[1] Samuel B. Berry,* Xammy Nguyenla,[†] Alexander Baltodano,[†] Gabrielle Pastenkos,[‡] Chenling Xu,[§] Douglas Fox,* Nir Yosef,[§,¶,‖] Sarah M. McWhirter,[#] and Sarah A. Stanley*,[†]

nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0319-9

Prevention of tuberculosis infection and disease by local BCG in repeatedly exposed rhesus macaques

Karin Dijkman[1*], Claudia C. Sombroek[1], Richard A. W. Vervenne[1], Sam O. Hofman[1], Charelle Boot[1], Edmond J. Remarque[1], Clemens H. M. Kocken[1], Tom H. M. Ottenhoff[2], Ivanela Kondova[1], Mohammed A. Khayum[1], Krista G. Haanstra[1], Michel P. M. Vierboom[1] and Frank A. W. Verreck[1*]

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www.nature.com/npjvaccines

ARTICLE OPEN

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A protective, single-visit TB vaccination regimen by co-administration of a subunit vaccine with BCG

Karin Dijkman[1,4,5], Thomas Lindenstrøm[1,5], Ida Rosenkrands[1], Rikke Søe[2], Joshua S. Woodworth[1], Cecilia S. Lindestam Arlehamn[3] and Rasmus Mortensen[1]✉

Cell Host & Microbe

CellPress

Article

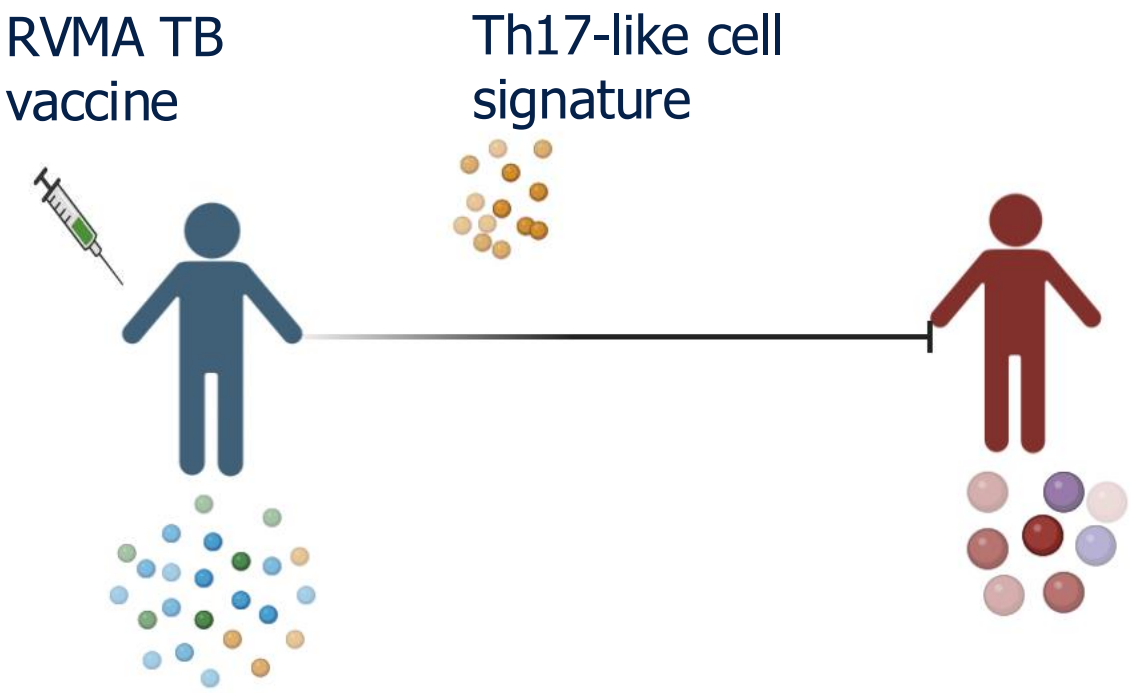
Airway T cells are a correlate of i.v. Bacille Calmette-Guerin-mediated protection against tuberculosis in rhesus macaques

Patricia A. Darrah,[1,9] Joseph J. Zeppa,[2,9] Chuangqi Wang,[3,8,9] Edward B. Irvine,[4,7] Allison N. Bucsan,[1] Mark A. Rodgers,[2] Supriya Pokkali,[1] Joshua A. Hackney,[1] Megha Kamath,[1] Alexander G. White,[2] H. Jacob Borish,[2] L. James Frye,[2] Jaime Tomko,[2] Kara Kracinovsky,[2] Philana Ling Lin,[5] Edwin Klein,[6] Charles A. Scanga,[2] Galit Alter,[4] Sarah M. Fortune,[4,7] Douglas A. Lauffenburger,[8] JoAnne L. Flynn,[2] Robert A. Seder,[1] Pauline Maiello,[2,10] and Mario Roederer[1,10,11,*]

Summary/Conclusions

- Rare variable *Mtb* antigens induce human Th17 responses in controlled TB

- Th17 cell responses are associated with a lack of progression to TB disease in human cohorts



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Study participants

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  - Julia Huffaker
  - ***Zach Howard - PD20***

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UCSF University of California San Francisco

UCSF AIDS Research Institute

UCSF-BAY AREA CFAR CENTER FOR AIDS RESEARCH

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NIH/NIAID P30AI168440

TBRU | ASTRa Antigen Specific T-cell Responses and the control of TB

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