Lessons in Protection from the Human Model

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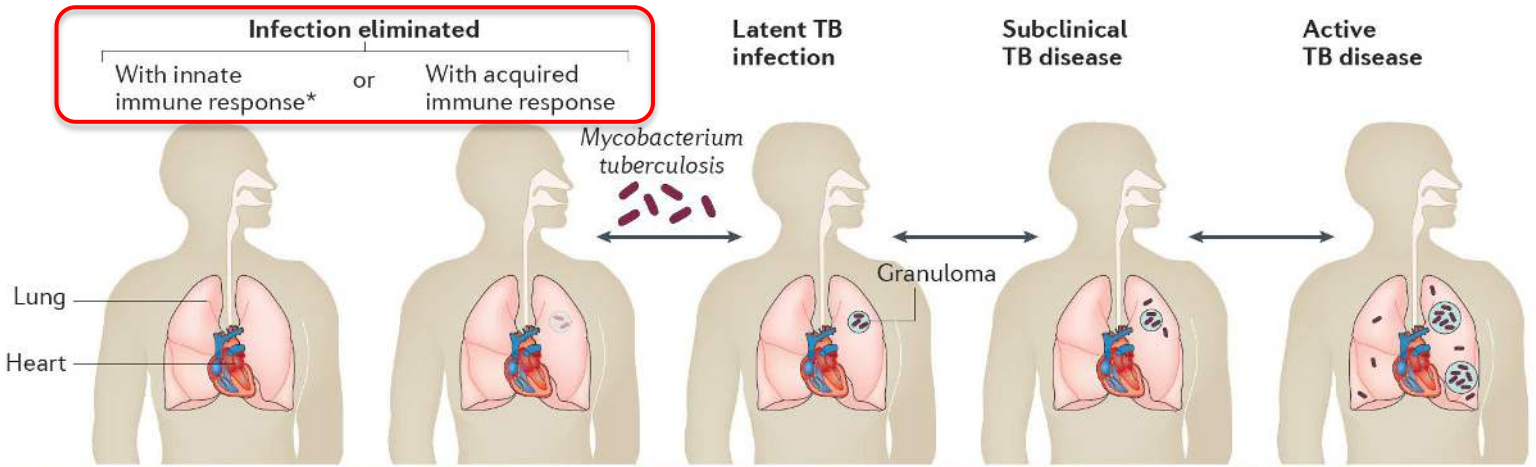
UNIVERSITY of WASHINGTON

SEATRAC
Seattle Tuberculosis Research Advancement Center

The Spectrum of Human TB (Not Animal TB)

No animal model



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai M. Nature Microbiology 2017

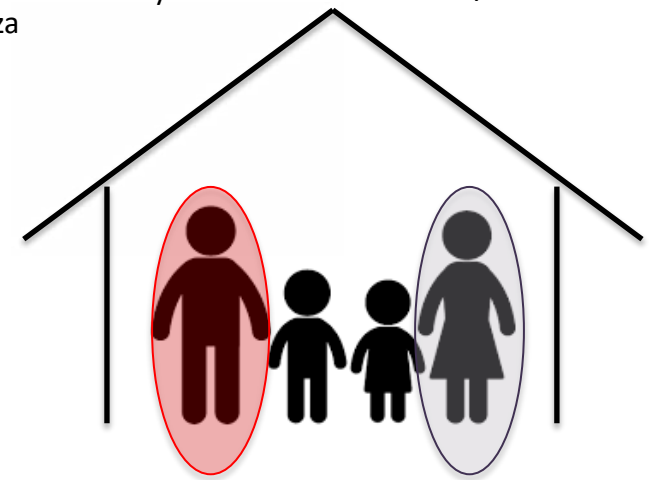
‘Resistance’ to M.tb infection

Harriet Mayanja-Kizza

Henry Boom

Cathy Stein

Tom Hawn



Lenette Lu

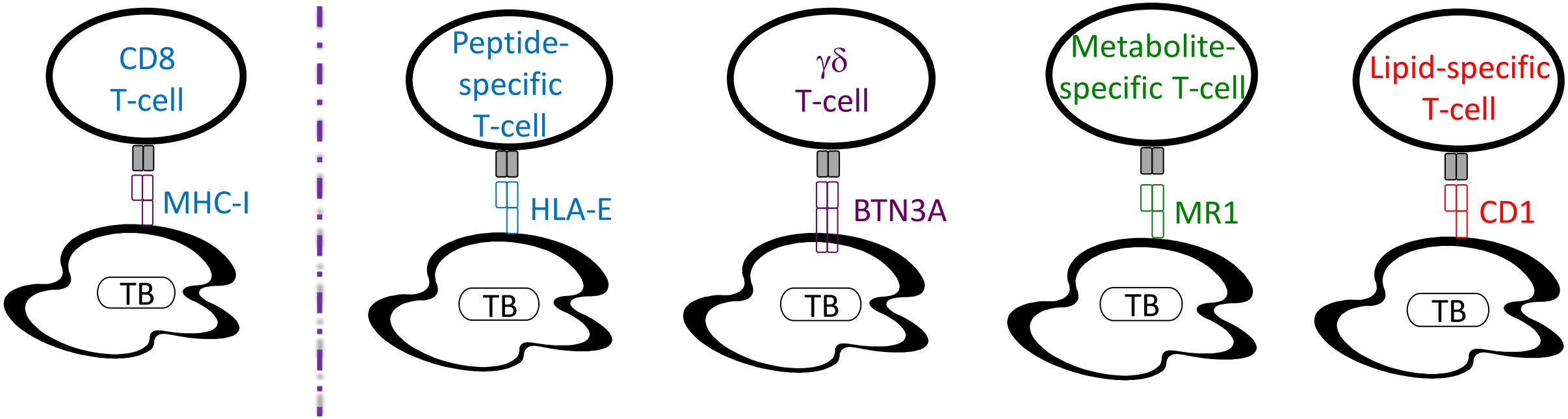
Galit Alter

- “Resisters” (RSTRs)
  - Exposure (high risk score)
  - Diagnostic Testing (TST x 6 and IGRA x 3)
  - Durability (median 9 years)
- Adaptive immune responses to ESAT-6 andf CFP-10 in RSTRs
  - IFN-γ independent T cells
  - Class-switched Abs (IgG and IgA)

Stein et al. Clinical Infectious Diseases 2018; Lu et al. Nature Medicine 2019

WikiClipArt
Medium.com

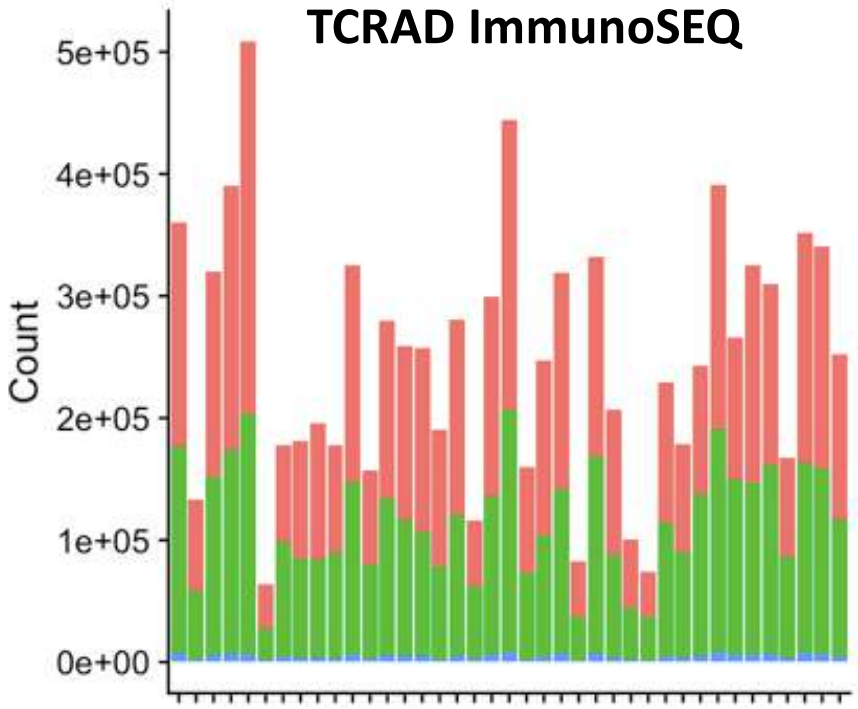
T cells also recognize non-peptide antigens



Donor-unrestricted T cells (DURTs) mediate 'universal' responses independent of genetic background

Van Rhijn & Moody, J Immunology 2015

TCR-α clonotypes are associated with RSTR status



Productive
Out of frame
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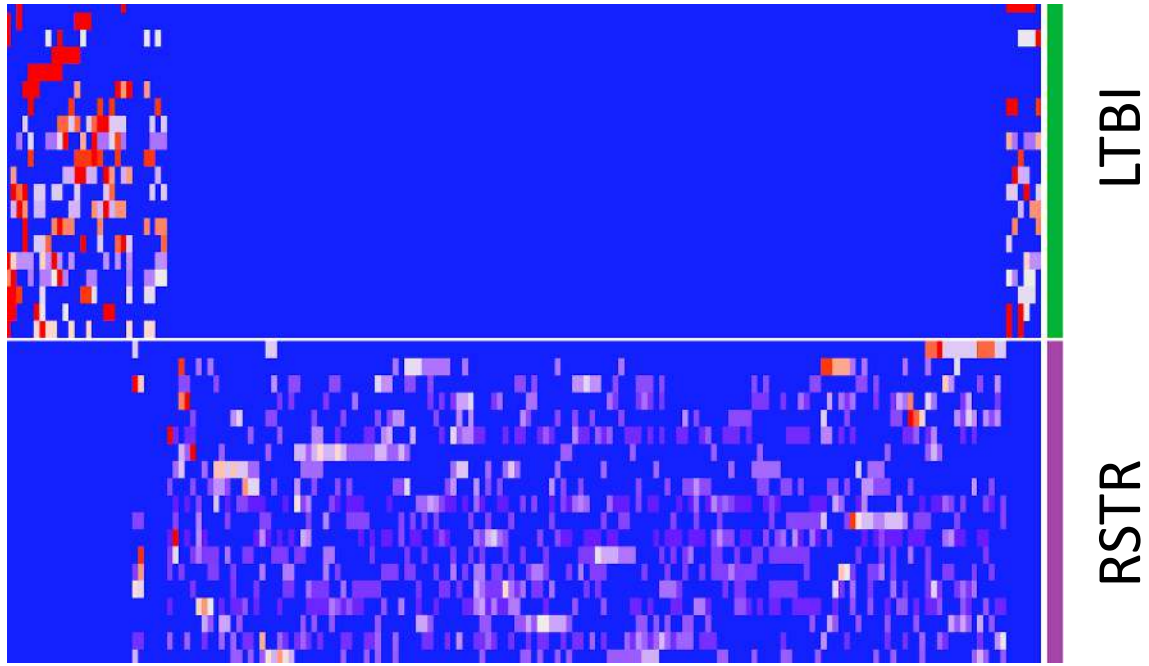
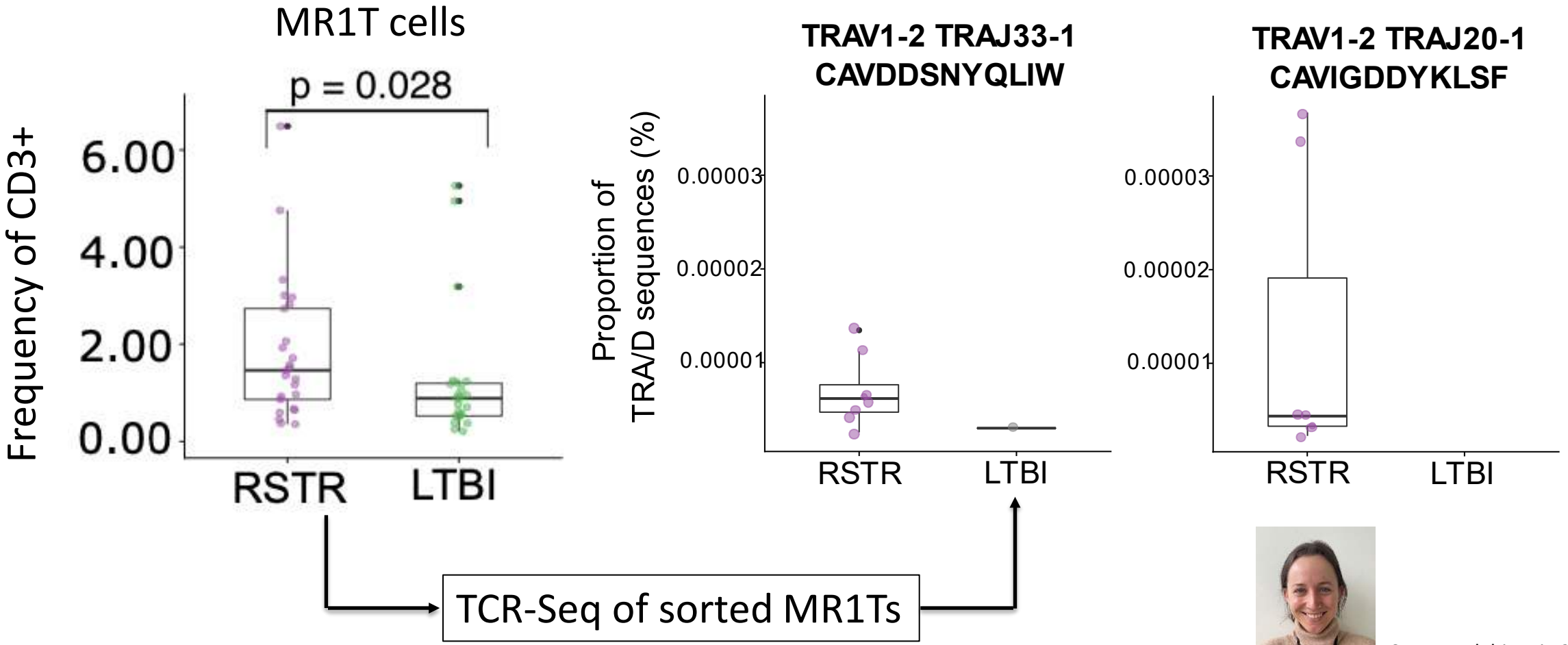


- Significantly more clonotypes associated with RSTR than would be expected by chance alone ($p<0.0001$)

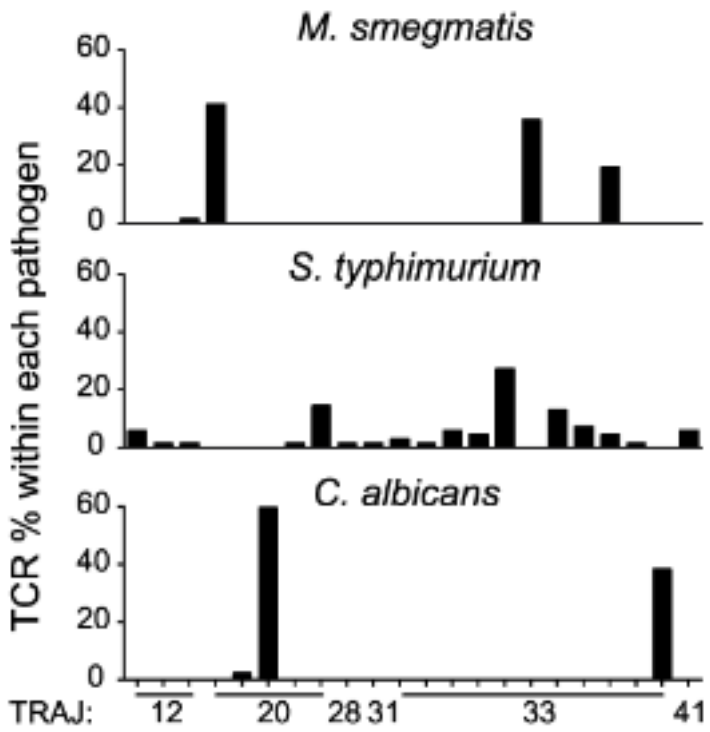
Cross et al. bioRxiv 2022

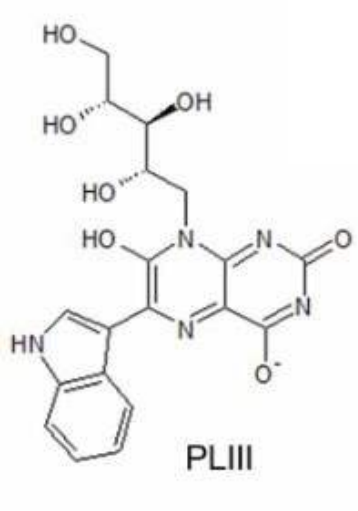
Association between MR1Ts and RSTR Status

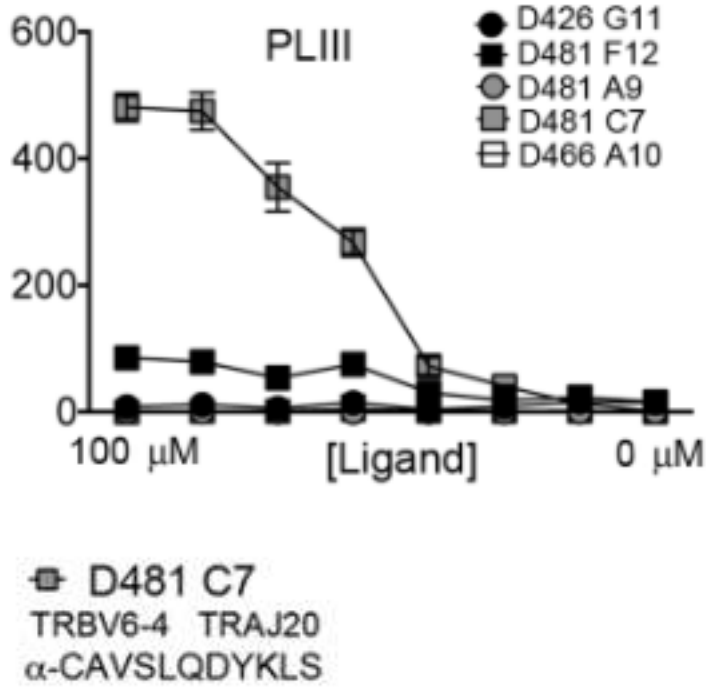


Cross et al. bioRxiv 2022

MR1Ts display ligand discrimination





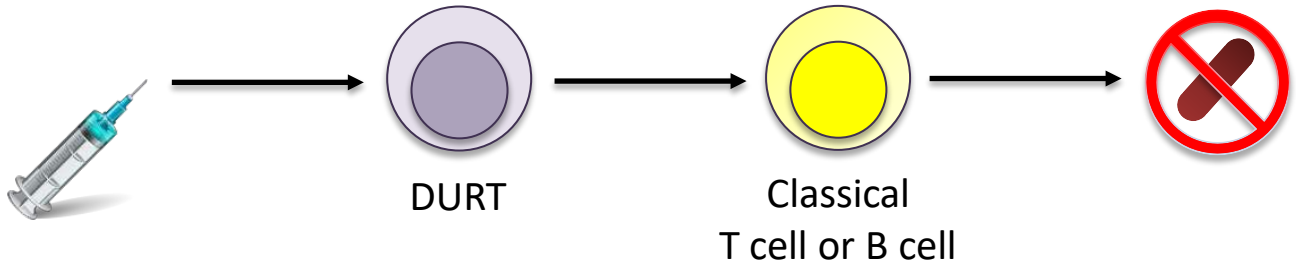


Most ligands are undiscovered and/or undefined!

Gold et al. J Exp Med 2014
Harriff et al. Science Immunol 2018

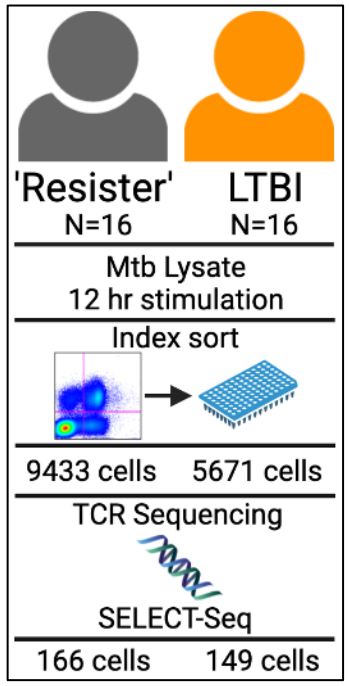
DURTs as Helpers (Not Effectors)

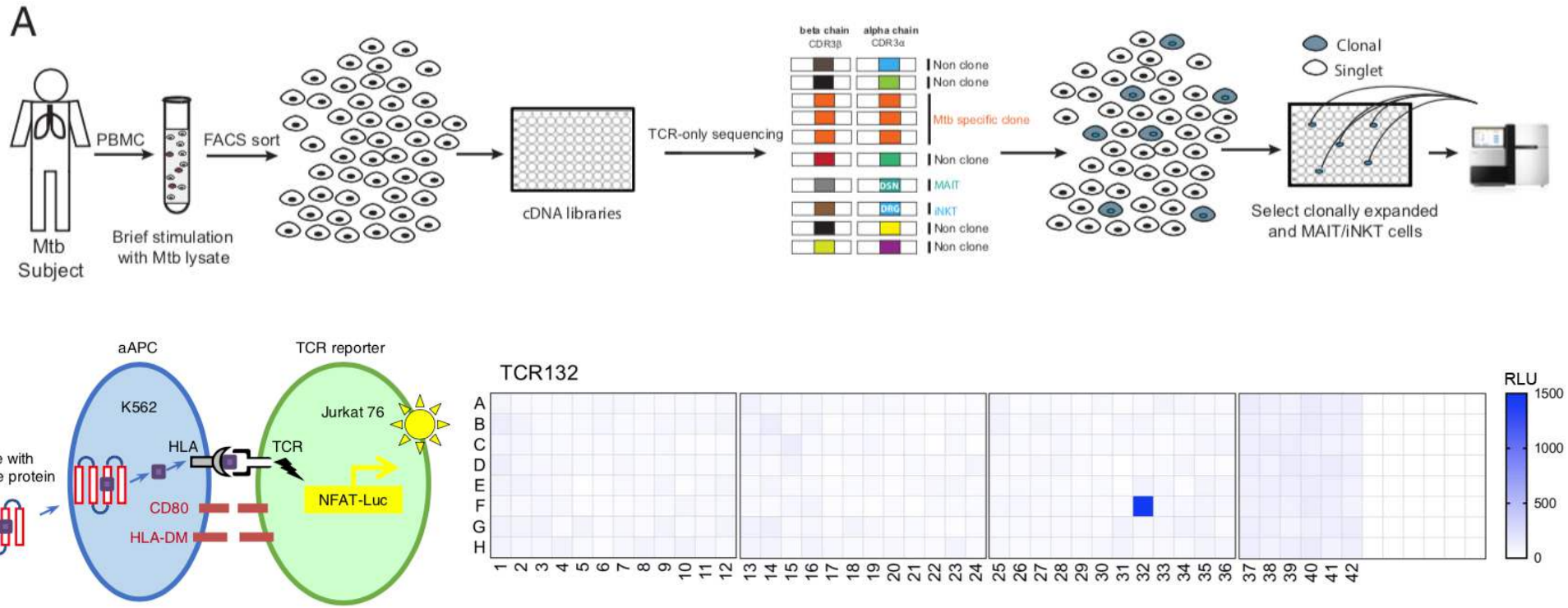
- iNKT cells (not Tfh cells) constitute ~70% of IL-4 producing cells during early viral infection and is correlated with anti-Zika neutralizing Abs in macaques.
- γδ T cells are required for priming a protective CD8 T cell in response to IV PfSPZ and malaria challenge in mice
- Tfh-like MAIT cells mediate B cell help to generate mucosal IgA responses to *V. cholerae* in mice.



Jensen et al. Sci Immunol 2022
Gaya et al. Cell 2018
Zaidi et al. J. Immunol 2017

T cell Peptide Antigen Discovery – In Progress



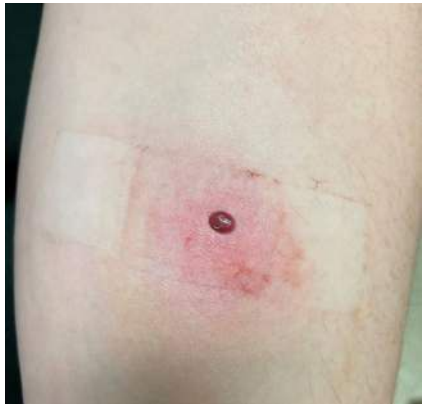


How to validate and prioritize for pre-clinical and clinical development?

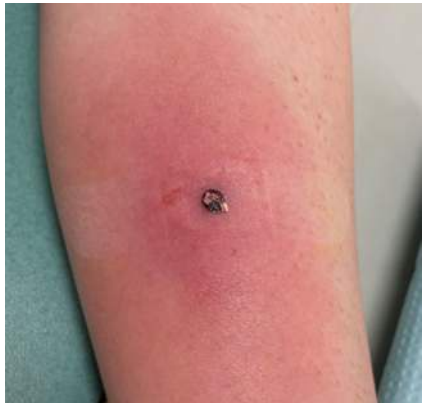
Huang et al. PNAS 2019
Huang et al. Nature Biotech 2020

Controlled Human Infection with Mycobacteria (CHIM)

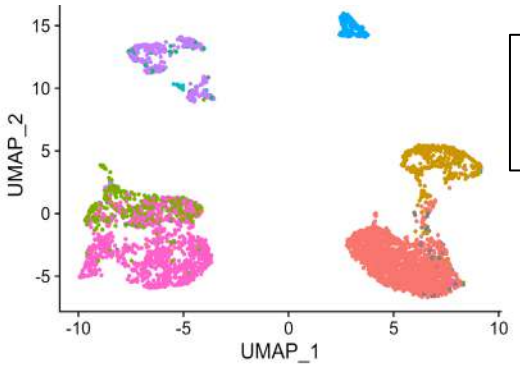
Grade 1



Grade 3



scRNA-Seq + TCR-Seq



Analysis of *in-situ* T cell clonotypic expansions

Jim Kublin

Chetan Seshadri

Chandler Church

David Sherman

Sean Murphy

UW Medicine SCHOOL OF MEDICINE

Fred Hutch Cancer Center

Summary

- ‘Resistance’ to M.tb infection is an important clinical phenotype for which there is no good animal model
- MR1Ts are expanded in RSTRs compared to LTBI controls, including at least two MAIT cell clonotypes
- Significantly more TCR-α clone sharing among RSTRs compared to LTBI suggests a role for DURTs in mediating ‘resistance’ to M.tb infection
- The dearth of known non-peptide T cell antigens (and assays) limits progress
- DURTs can be helpers as well as effectors
- Peptide antigen discovery in RSTRs is ongoing (GLIPH2)
- CHIM provides a mechanism to characterize the true antigenic breadth of *in situ* T cell responses to mycobacteria in humans.

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FRED HUTCH CURES START HERE

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HI IMPAcTB

Questions?

Post-doctoral applications welcome!

TEMPLATE