Using TCRs to find protective antigens and TB vaccines

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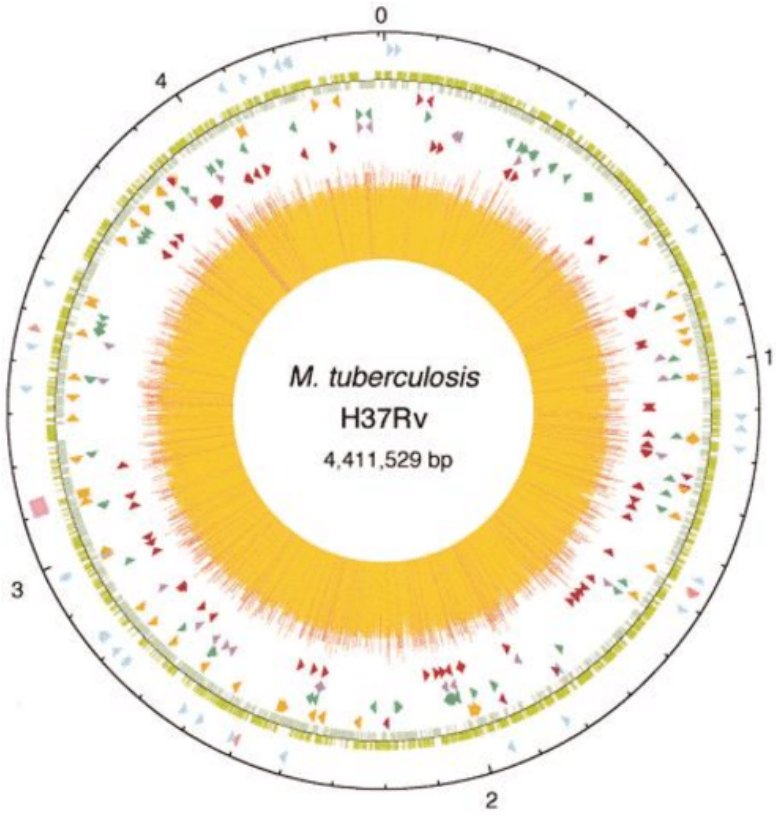
14 June 2023

Challenge: Which antigens to include in a vaccine?

TB has over 4000 possible vaccine targets



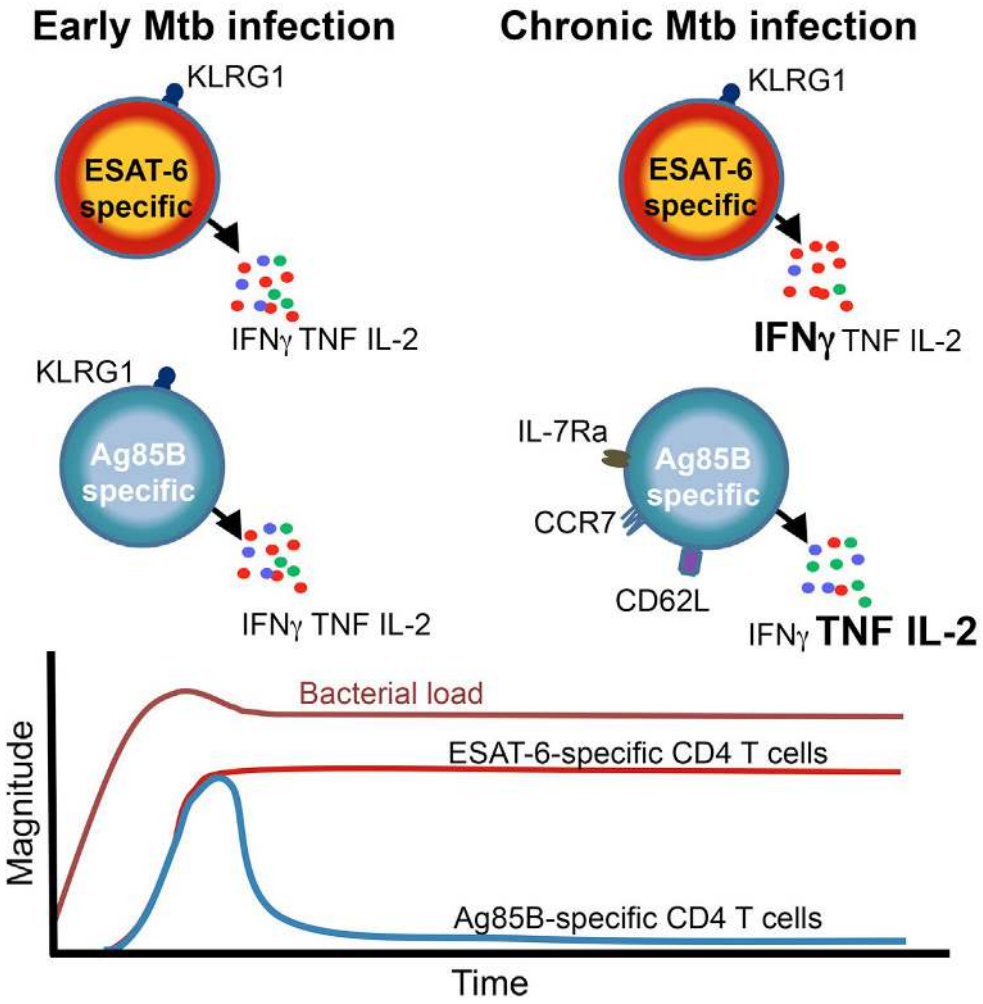
Cole et al., 1998

Table II. *Vaccine-induced protection against Mtb*

CFU Reduction (Log_{10}) ± SEM[a]							
<0.1		0.1–0.3			>0.3		
Rv0164[b]	Rv2450	Rv0496	0.11 ± 0.08	S[c]	Rv0577	0.36 ± 0.07	S[c]
Rv0410	Rv2623	Rv0733	0.23 ± 0.10	S	Rv1626	0.32 ± 0.07	S
Rv0455	Rv2626	Rv0831	0.13 ± 0.06	S	Rv2608	0.58 ± 0.16	P
Rv0655	Rv2801	Rv1411	0.11 ± 0.11	S	Rv2875	0.44 ± 0.18	S
Rv0952	Rv2866	Rv1569	0.12 ± 0.05	M	Rv3044	0.43 ± 0.06	H
Rv1211	Rv2945	Rv1789	0.15 ± 0.16	P	Rv3478	0.66 ± 0.15	P
Rv1270	Rv3029	Rv1813	0.14 ± 0.14	H	BCG	0.78 ± 0.07	
Rv1410	Rv3133	Rv1860	0.19 ± 0.07	S			
Rv1590	Rv3204	Rv1886	0.20 ± 0.04	S			
Rv1738	Rv3407	Rv2220	0.25 ± 0.11	S			
Rv1818	Rv3541	Rv3020	0.17 ± 0.07	E			
Rv1884	Rv3620	Rv3619	0.24 ± 0.05	E			
Rv1926	Rv3628						
Rv1984	Rv3810						
Rv2032	CpG						
Rv2389	(−0.09 ± 0.05)						

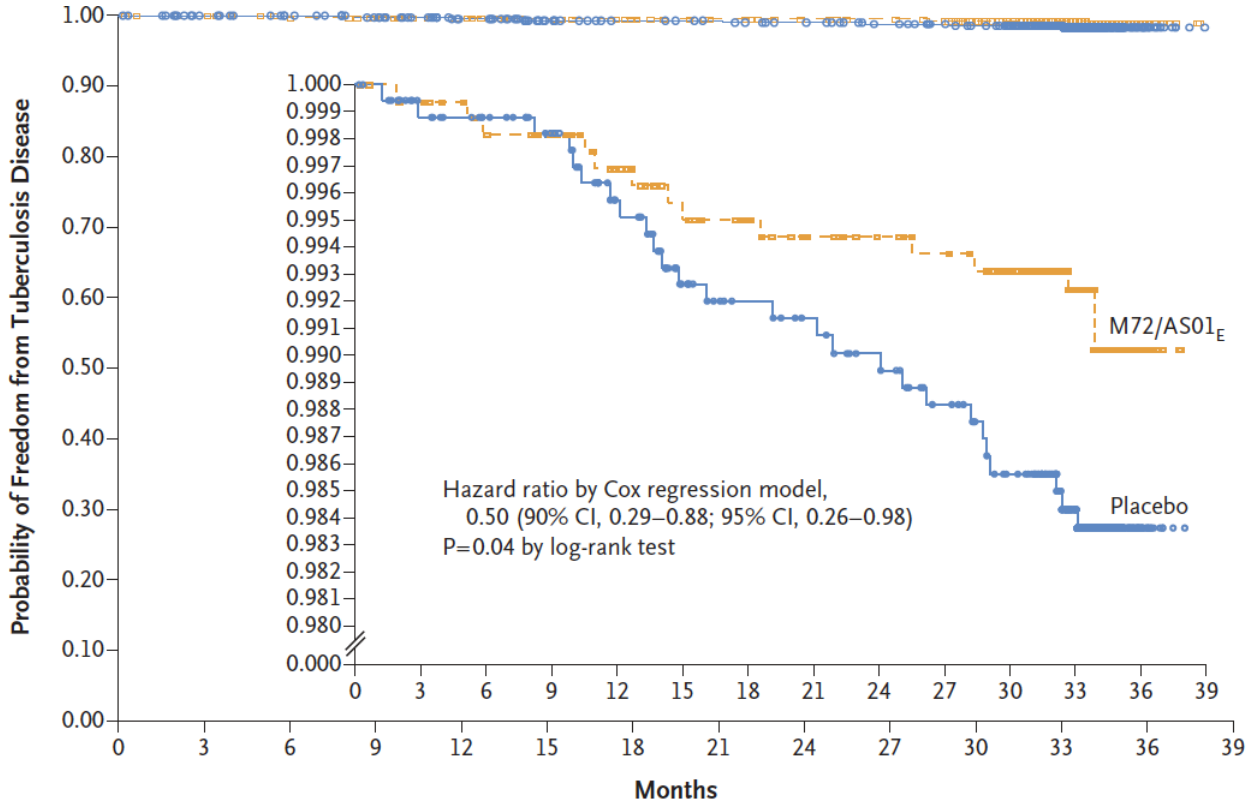
Bertholet et al., 2008

Different antigens may drive a distinct response.



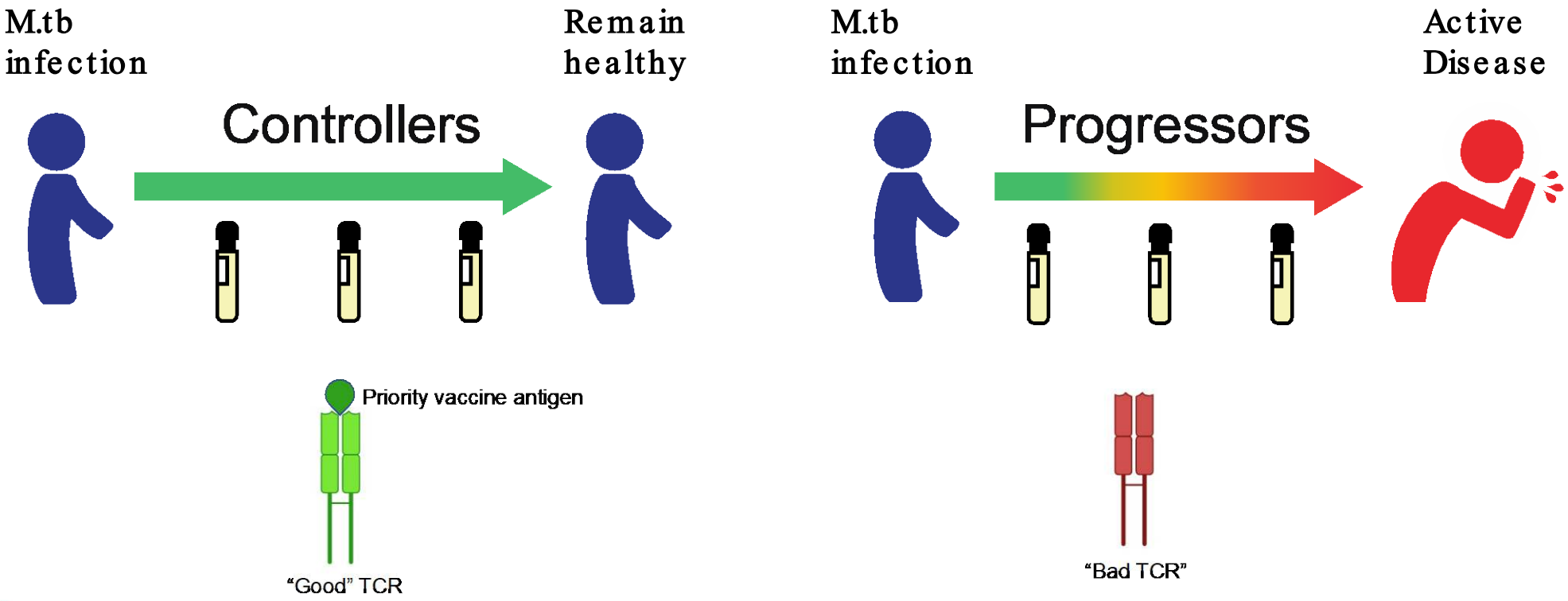
Musvosvi et al., 2017, Cell Host & Microbe doi.org/10.1016/j.chom.2017.05.012

The M72/ AS01E vaccine provided 54.0% protection



Tait et al N engl j med 381;25

Leveraging controller and progressor cohorts to identify protective antigens



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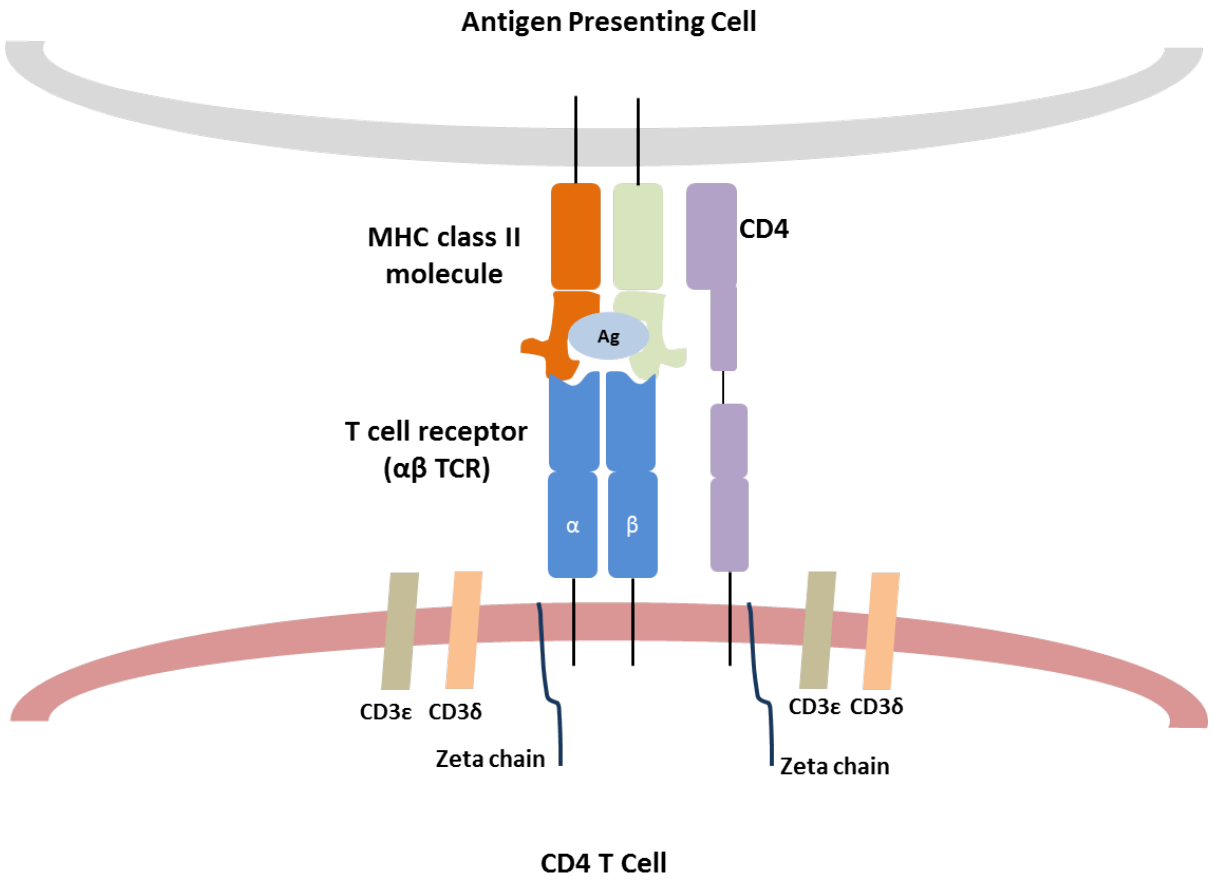
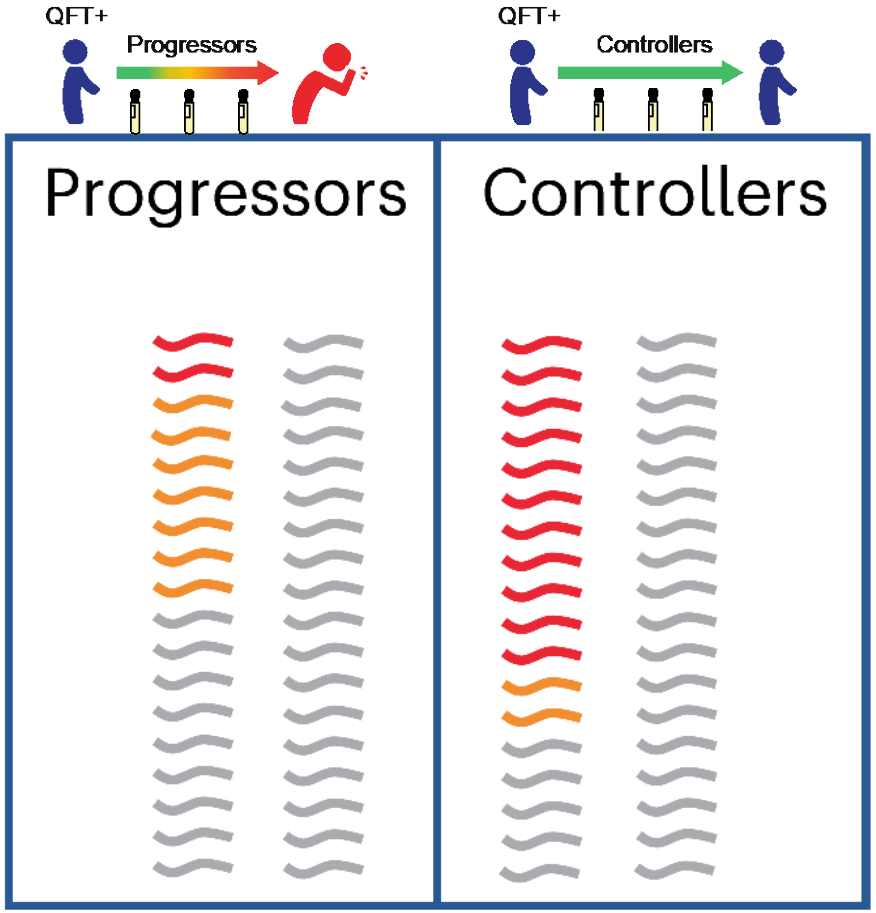
Can T cells from controllers tell us which antigens are best?





https://www.bio-rad-antibodies.com/static/2016/innate/an-overview-of-t-cell-receptors.pdf

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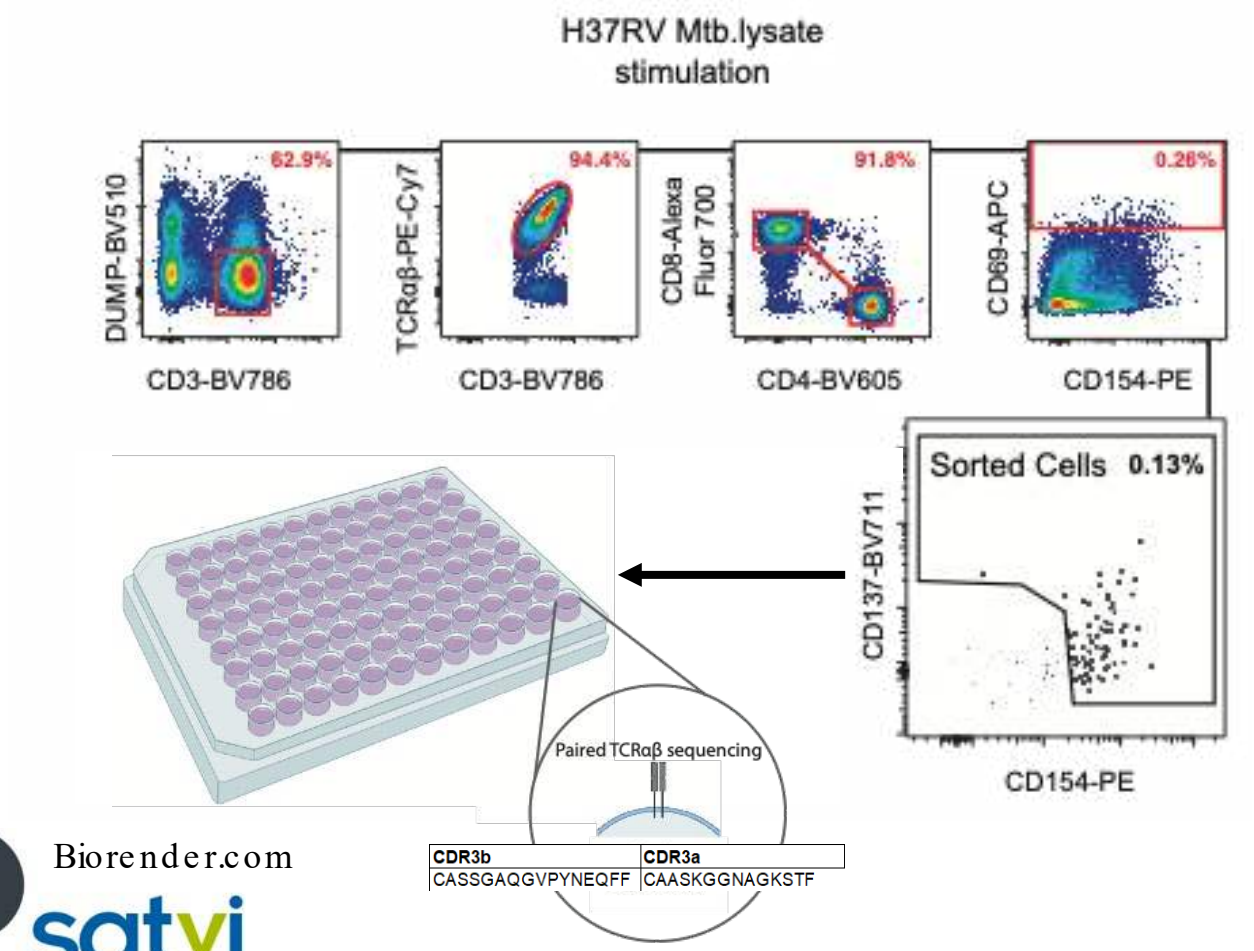
Identifying M.tb-specific T cell receptor (TCR) sequences.



Biorender.com

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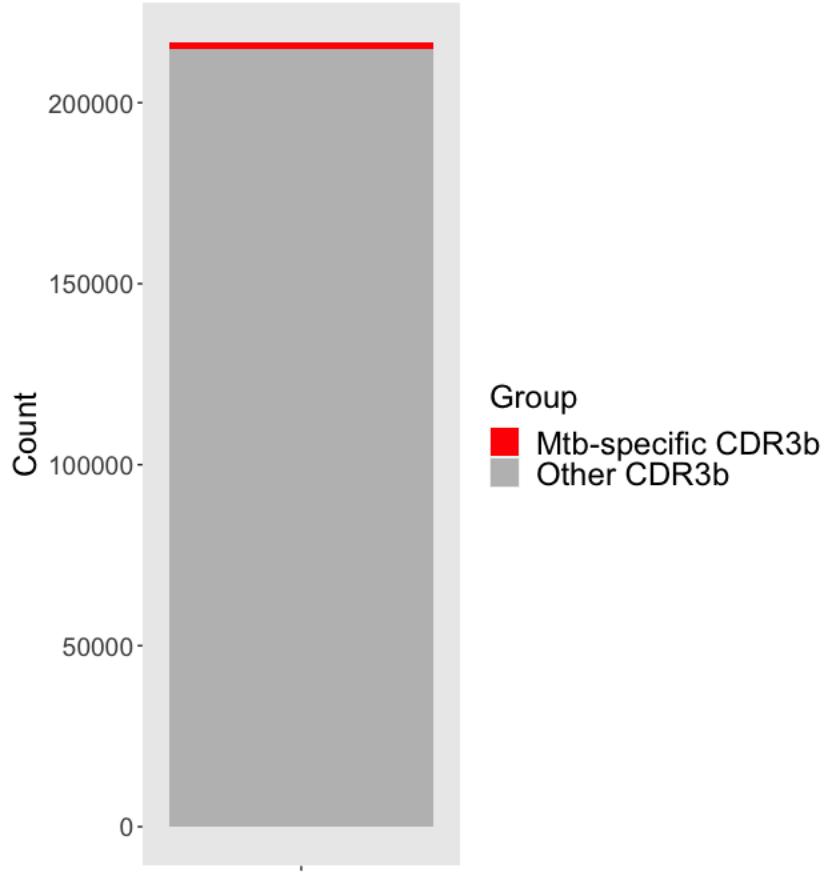
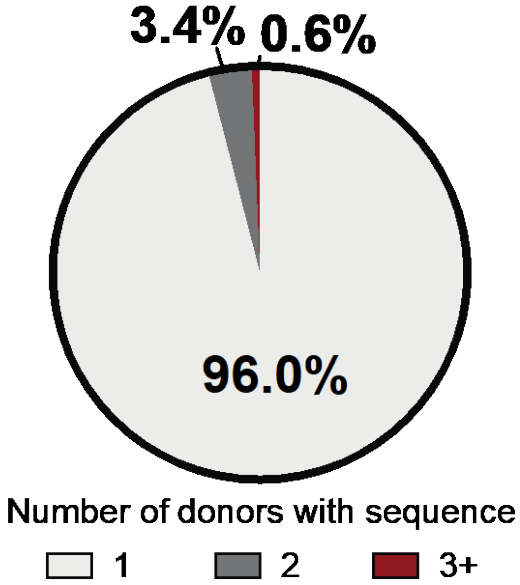
Bulk TCR sequencing



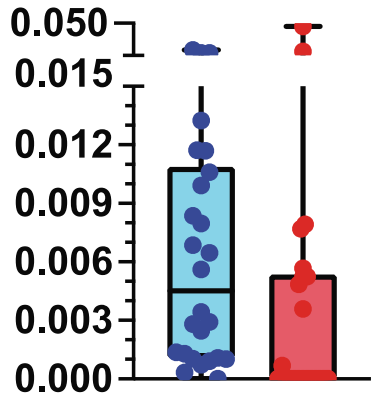
Identifying differentially abundant M.tb T cell clones in controllers and progressors.



GLIPH2 clusters TCRs with likely shared specificity

CDR3β
CASSVALSNYGYTF
CASSVALFSNTQYF
CASSVALLAGTQYF
CASSVALSGSGYTF
CASSVALFGETQYF
CASSVALGAGEQYF
CASSVALAGANGYTF

Compare cluster frequencies in controllers and progressors



DRB1*15 participants only

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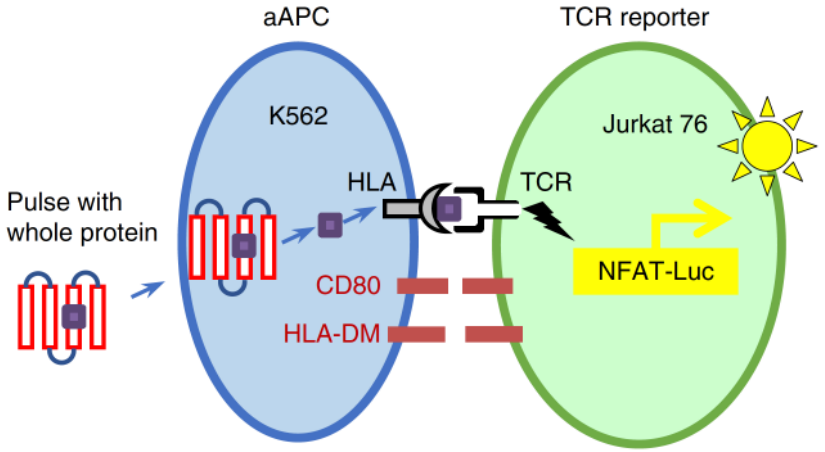
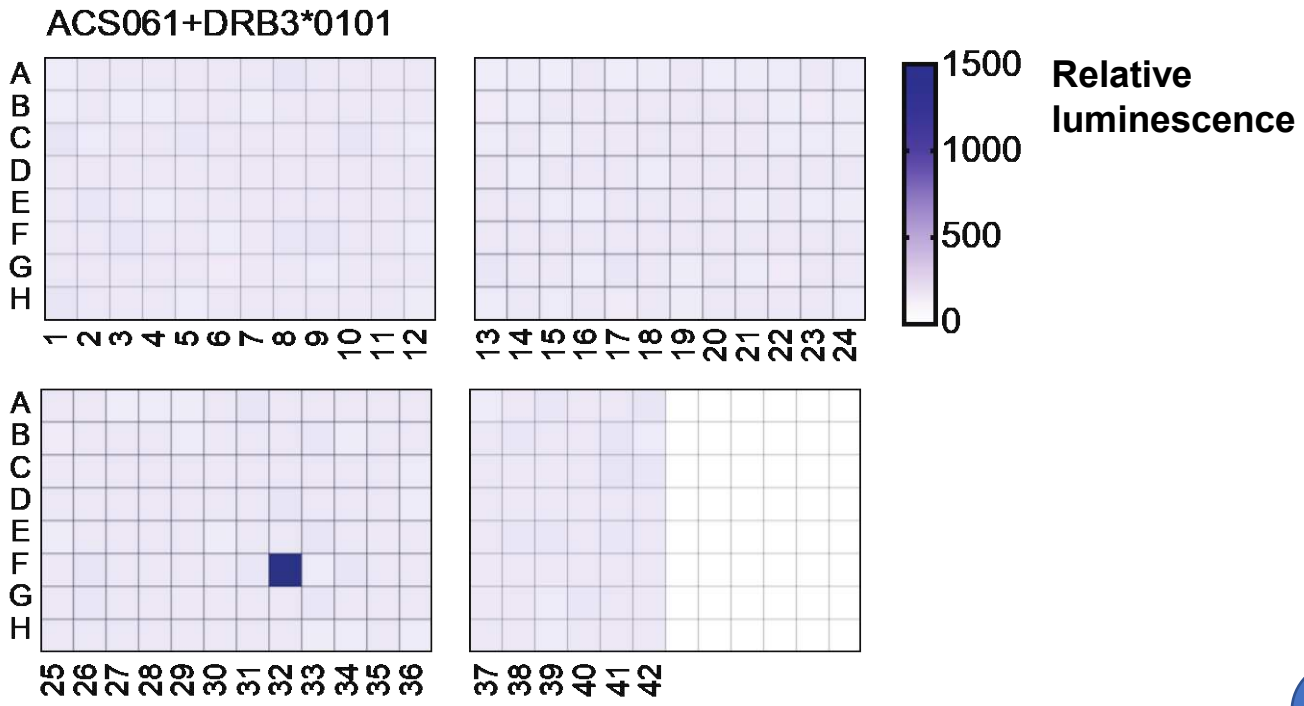
Reporter system to perform Mtb genome wide protein screening

Cluster	Clone ID	CDR3α	TRAV	TRAJ	CDR3β	TRBV	TRBJ	HLA-a	HLA-b
S%EDRGNTE	ACS060	CAVPNSGYSTLTF	21	11	CAISQEDRGNTEAFF	10-3	1-1	DRA*01:01	DRB3*01:01
	ACS061	CAAPNSGYSTLTF	21	11	CAISGEDRGNTEAFF	10-3	1-1	DRA*01:01	DRB3*01:01



Huang et al. Nature biotechnology 2020



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Take home message 1

- Using TCRs TCRs to find priority antigens has applications for clinical studies of specific T cell responses to vaccination, infection, and other immunological indications.

- May represent a platform for rational antigen selection for candidate subunit vaccines.

Take home message 2

- Establishing well characterized clinical cohorts is crucial
  - Multiple cohorts will need for validation.
- Overcoming TCR repertoire diversity
  - Establish the "universe" of M.tb-specific TCRs
  - GLIPH and TCRdist3 – important for clustering
- Additional antigen discovery platforms required for identifying target epitopes.
- Animal model with limited MHC diversity may miss key antigens.

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Thank You

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Thomas Scriba
Constance Schreuder
Onke Nombida
Elisa Nemes
Pia Steigler
Anele Gela
.and many more

Virginie Rozot
Tim Reid
Michelle Fisher
Ashley Veldsman
Melissa Murphy
Mark Hatherill

CAPE TOWN HVTN IMMUNOLOGY LABORATORY

Shamiska Rohith
One Dintwe
Erica Andersen-Nissen

Stanford MEDICINE

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