

Differentially recognized T cell epitopes in the spectrum of Mtb infection

WGNV/NIAID workshop

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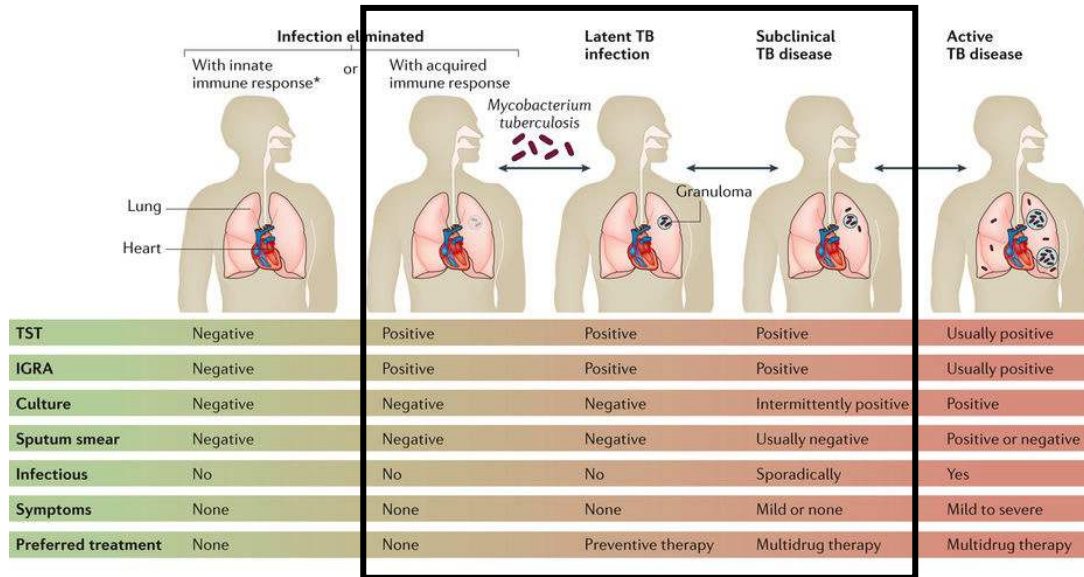
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The complexity of Mtb infection

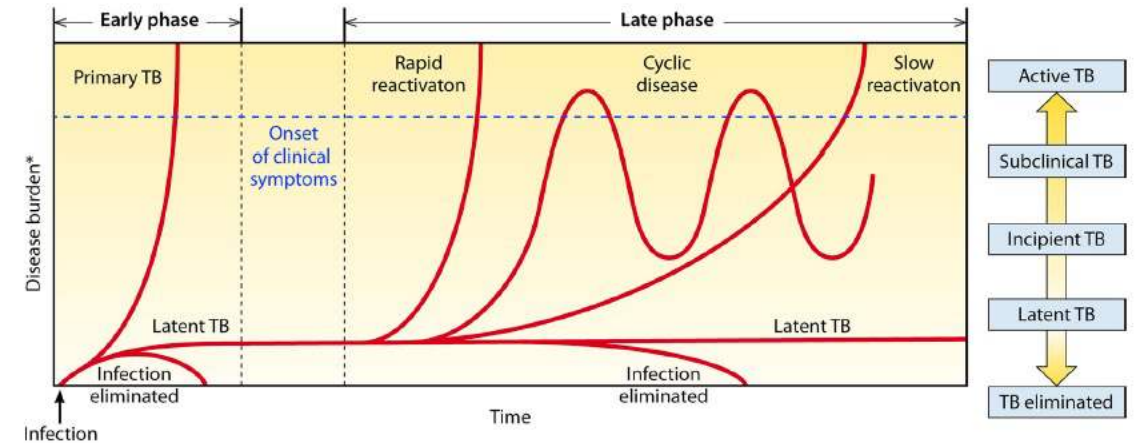


No TB

Latent TB

Active TB

Pai et al., Nature Rev Dis Prim 2016



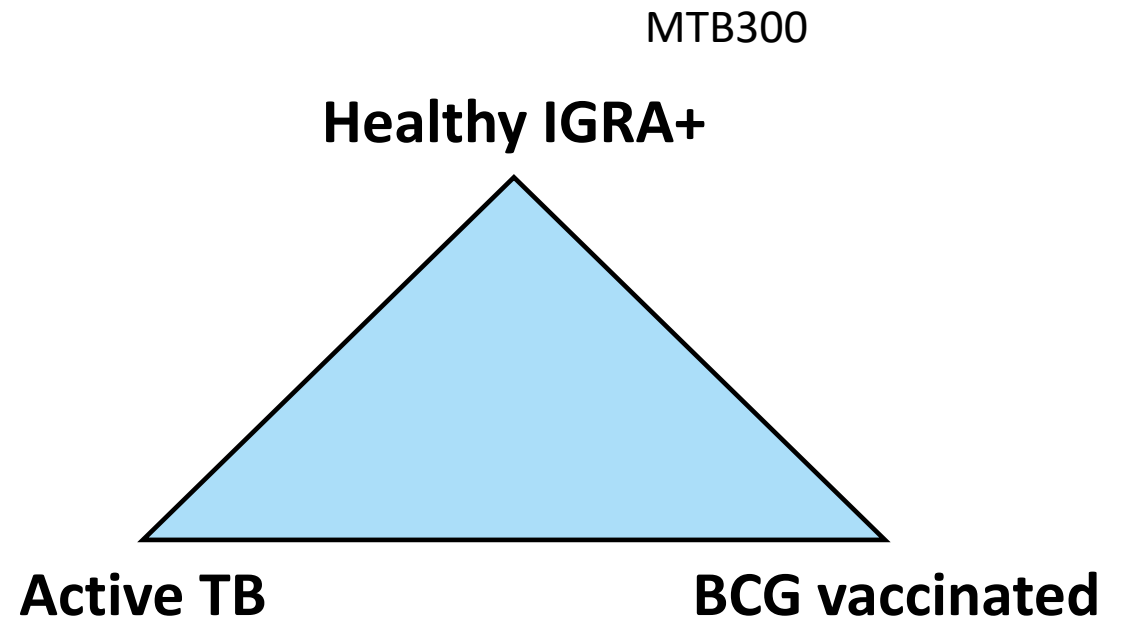
Drain et al., CMR 2018

IGRA – Interferon Gamma Release Assay

- TB blood test
- Measures cell mediated immune response against Mtb-derived antigens ESAT-6 and CFP10
- Not influenced by BCG vaccination

Characterization of epitope-specific T cells

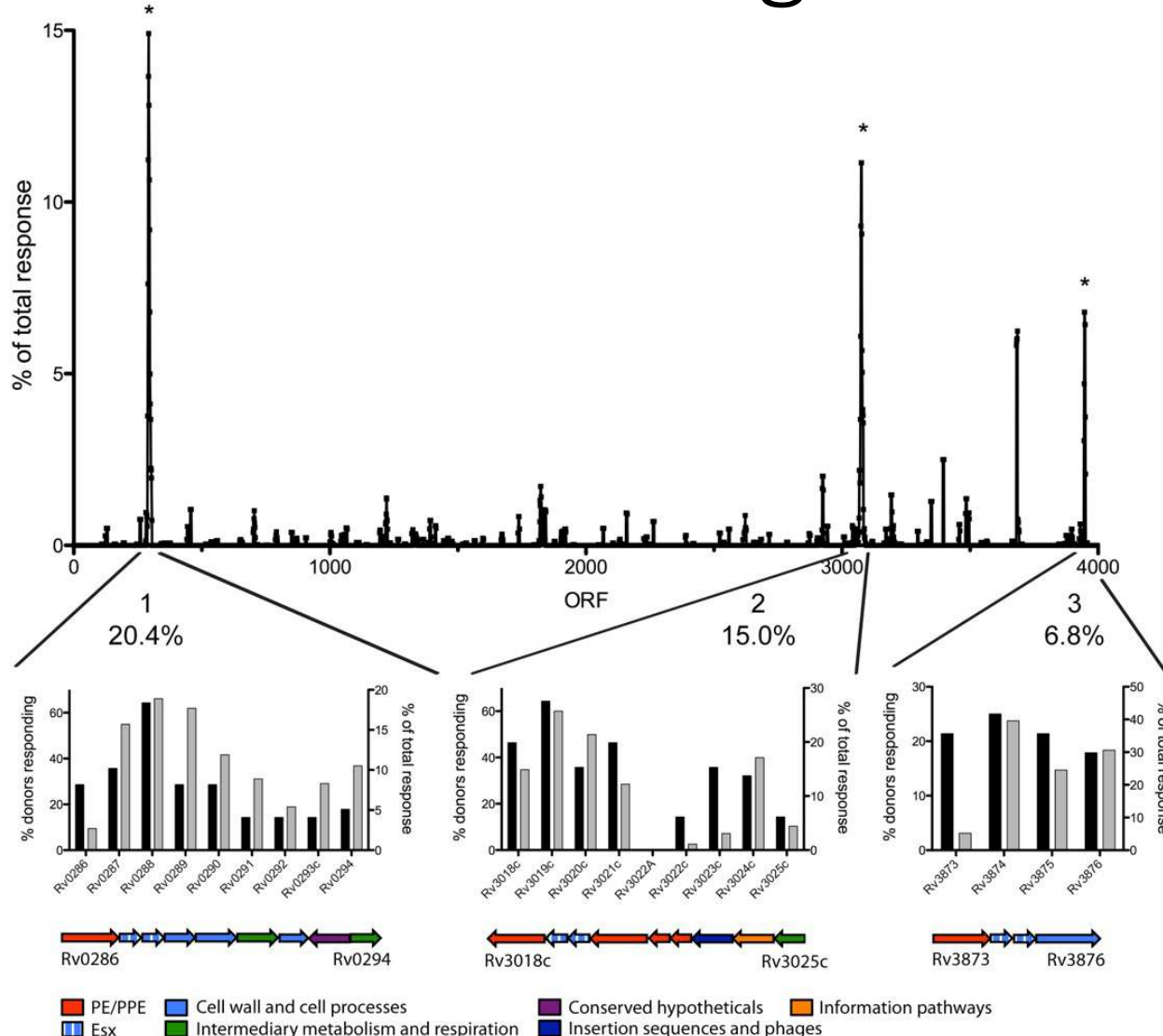
- Magnitude (higher or lower)
- Specificity (antigens and immunodominance)
- Breadth (diversity of response)
- Functionality (T cell subsets)



21,220 Mtb- and BCG-derived peptide library

- 20,610 Mtb-derived peptides, representing every ORF with 2-10 peptides per ORF
 - Including 1,660 variant sequences present in selected Mtb genomes
- 93 peptides present in BCG (not in Mtb)
- 517 overlapping 15-mers spanning the entire sequence of 12 vaccine candidate and IGRA antigens

A Genome-wide Library (20,610 peptides) defined the targets of CD4 responses in LTBI



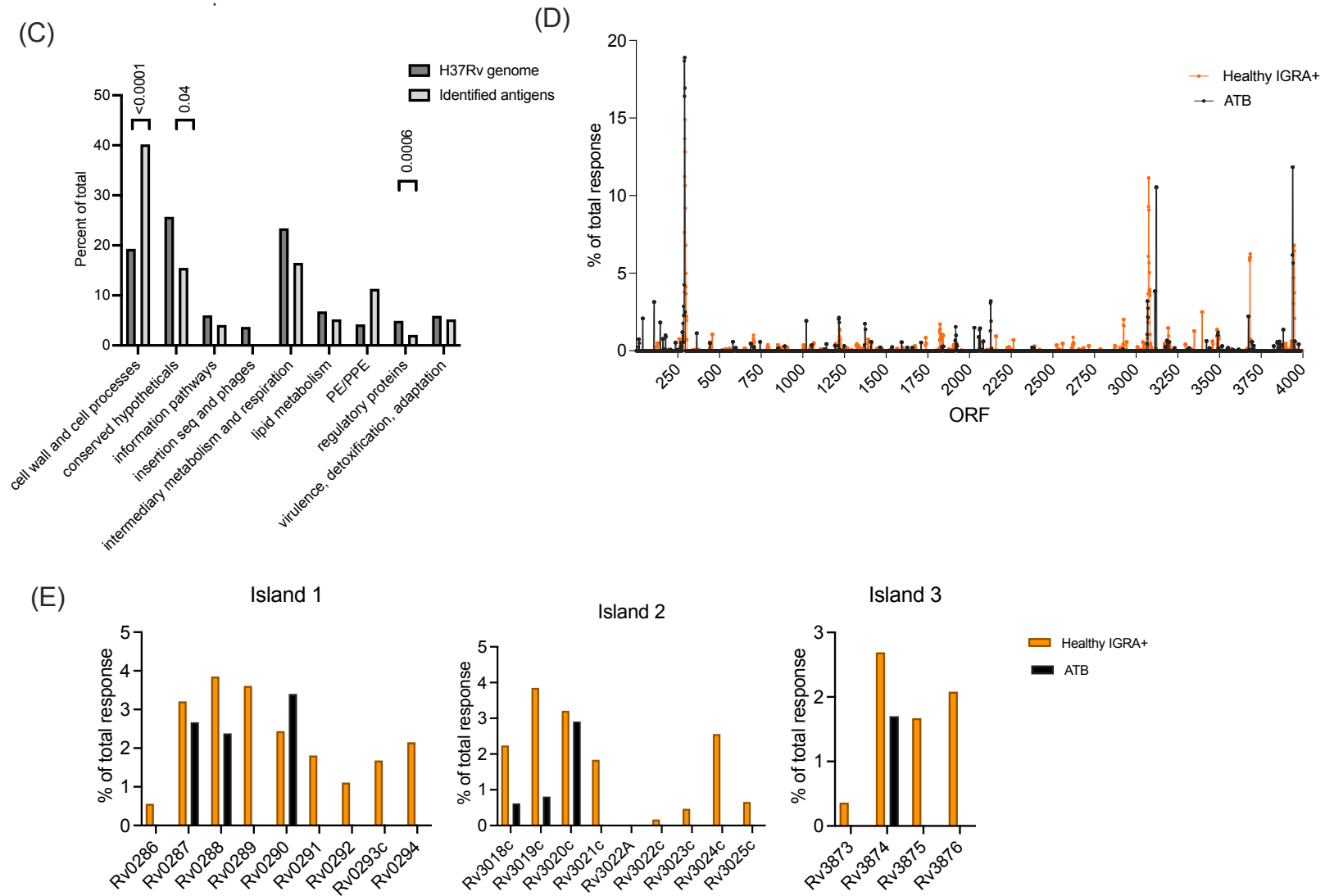
- Identified ~400 epitopes
- 82 antigens were recognized by >10% of subjects and accounted for ~80% of the total response
- Each subject recognizes on average 24 epitopes – heterogeneity of immunity to Mtb

Study subjects

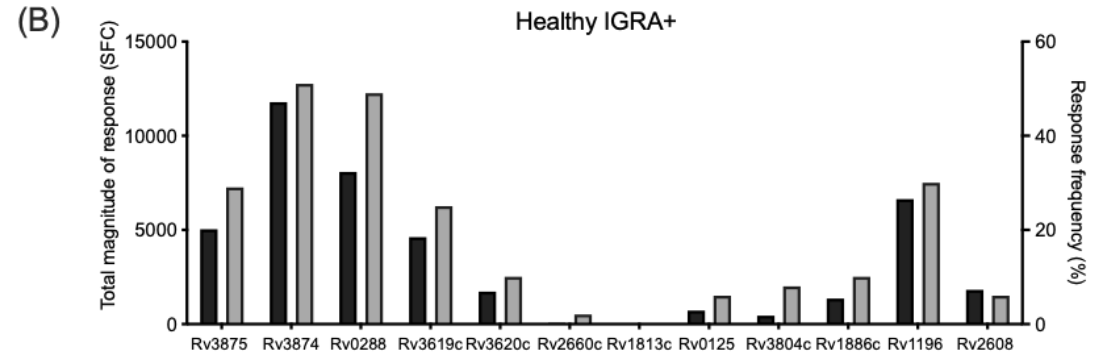
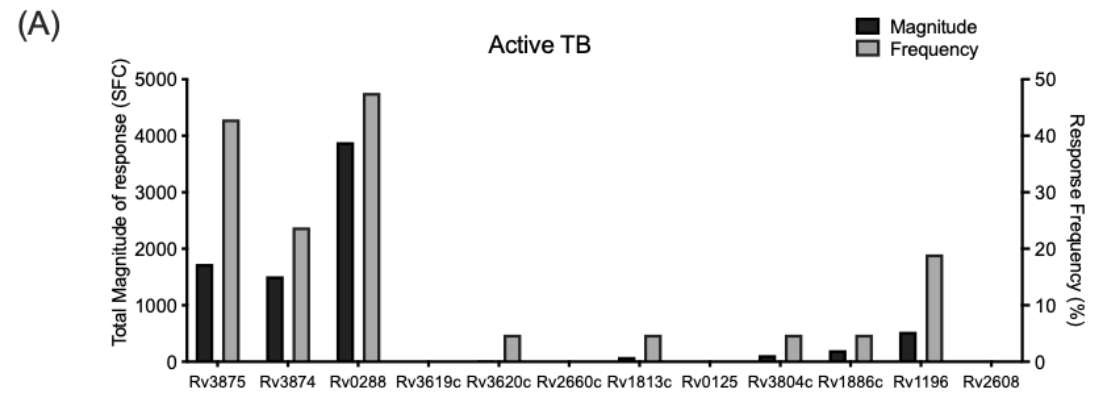
- 31 subjects from Peru (presumed BCG vaccinated at birth)
 - 21 pulmonary ATB 3-4m post diagnosis
 - 10 IGRA- controls
- Age: median 32, range 25-57
- 38% Female, 62% Male

- IFN γ Fluorospot

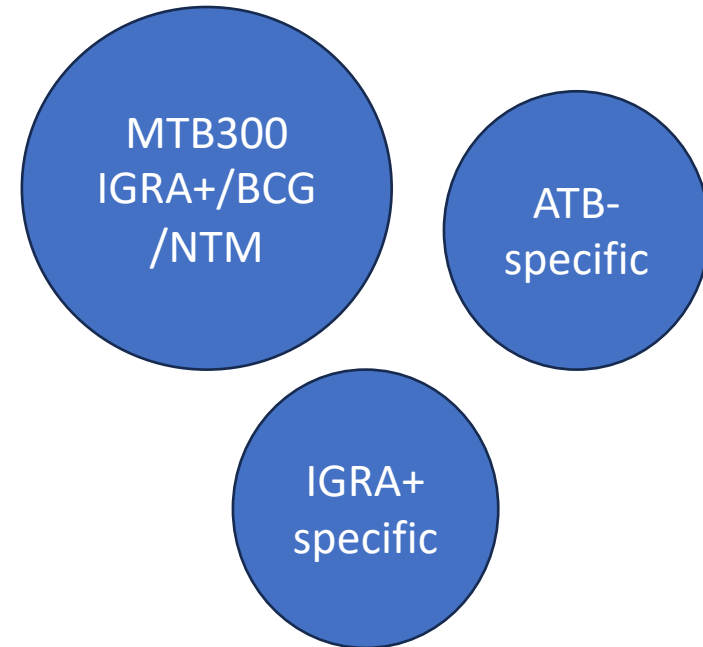
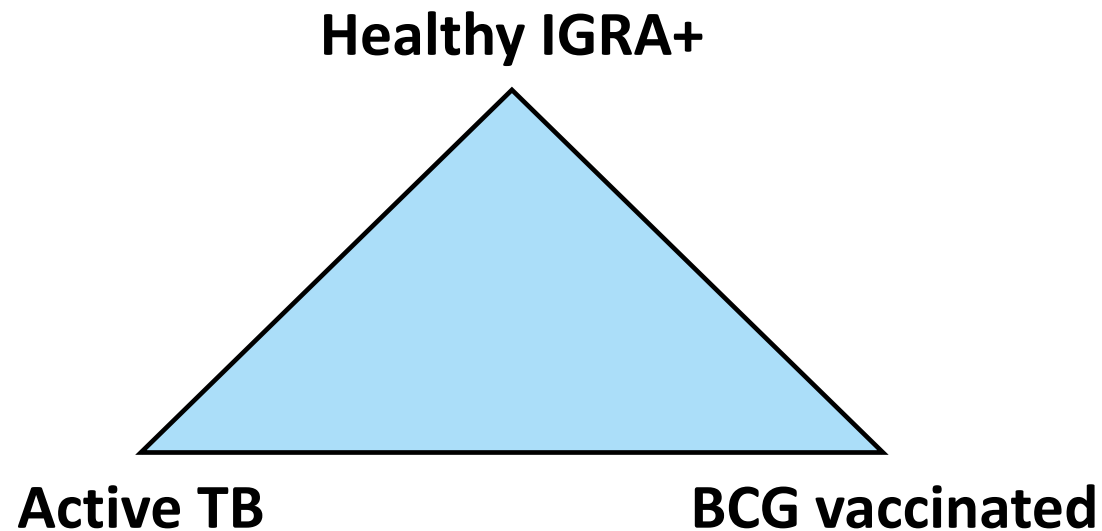
Antigenic islands differ between cohorts



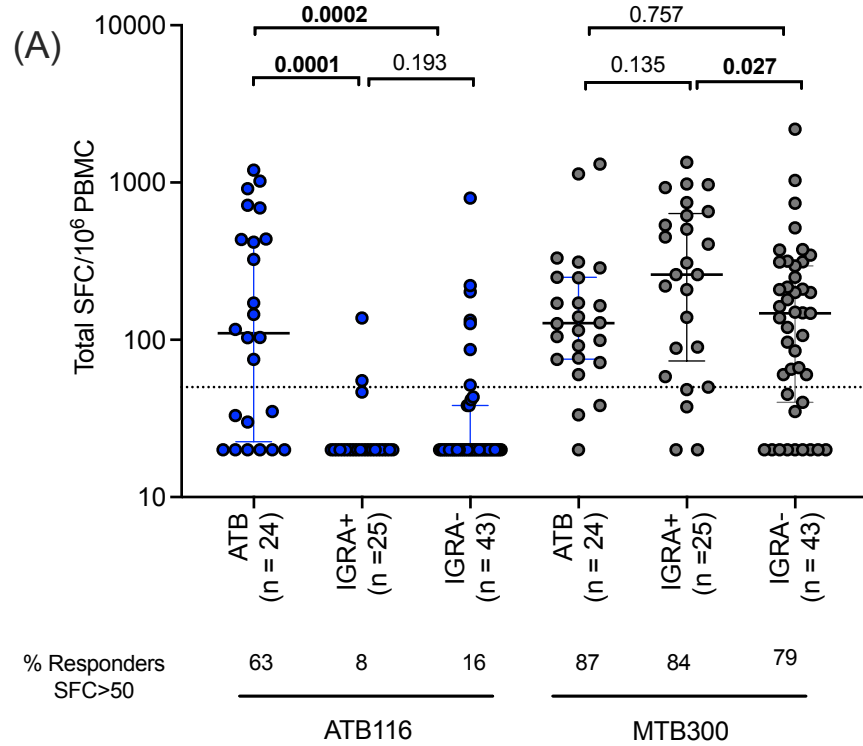
Hierarchy in T cell reactivity against vaccine candidate and IGRA antigens



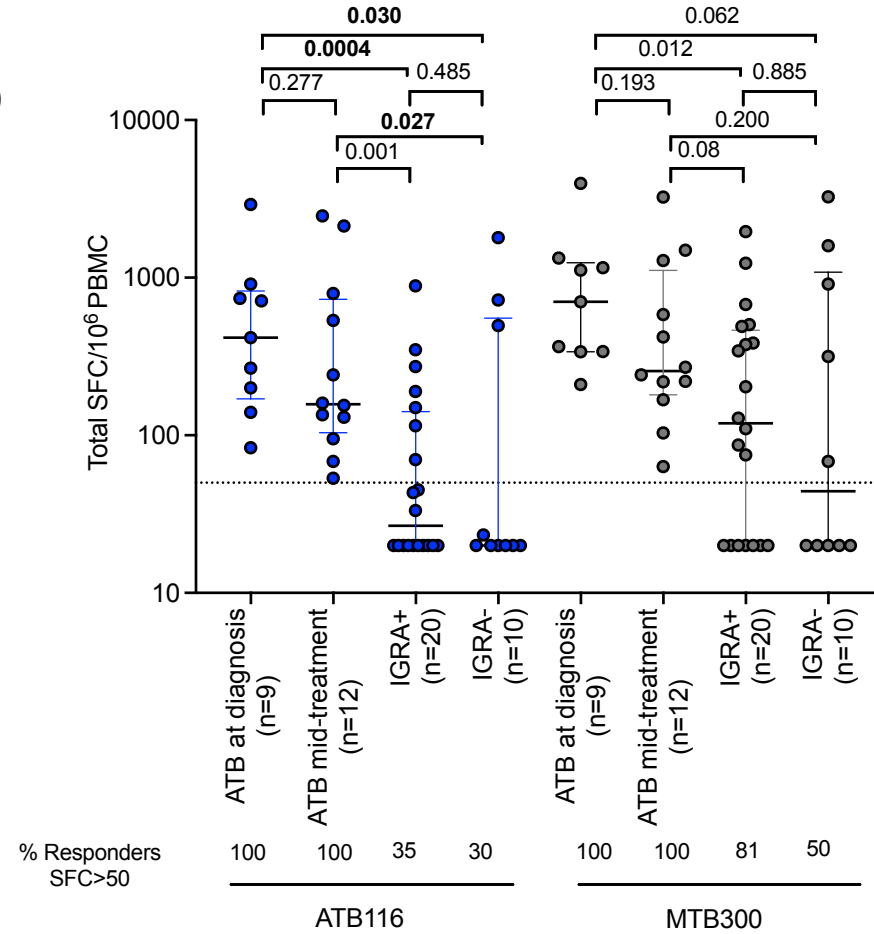
Can we design peptide pools that can distinguish different Mtb infection states?



An ATB-specific peptide pool

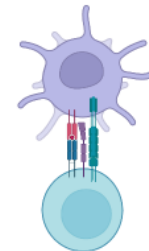
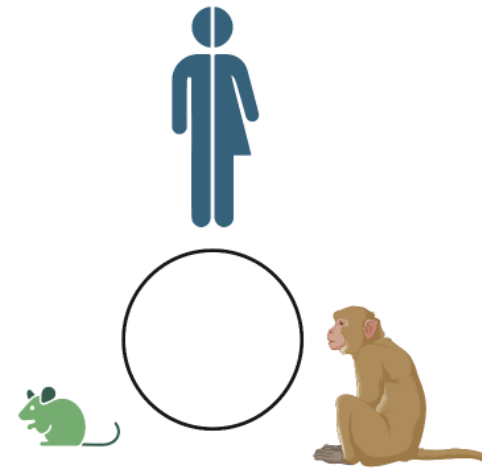
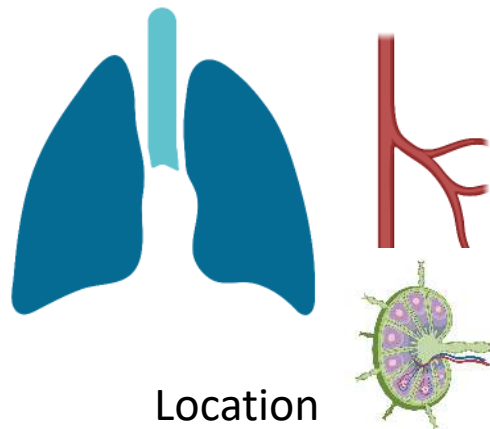


(C)

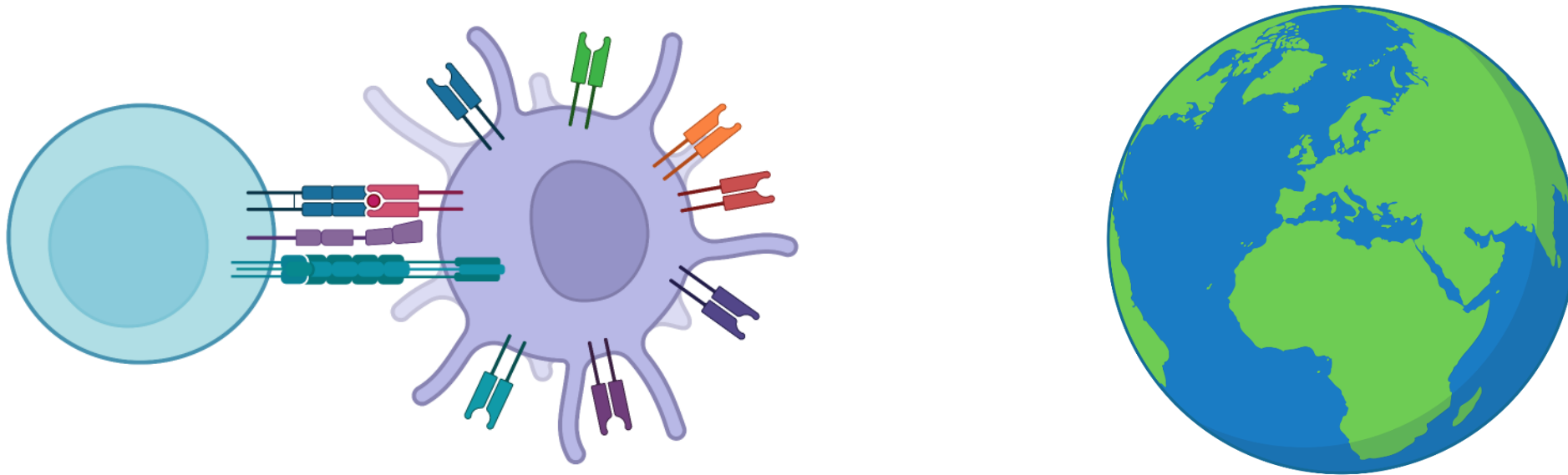


Mtb infection stage-specific T cell responses

- Participants have a large heterogeneity of epitope-specific responses
- The number of frequently recognized antigens are more restricted compared to LTBI
- Active-specific antigens and peptide pool



HLA diversity as a source of heterogeneity



Can we identify HLA alleles associated with active TB?

HLA allele	No. subjects with allele		No. subjects lacking allele		Odds ratio	P-value	Corrected
	Active TB	QFT+ & QFT-	Active TB	QFT+ & QFT-			p-value
DQA1*03:01	24	21	75	516	7.9	8.0E-10	6.9E-08
DPB1*04:02	25	40	74	495	4.2	2.0E-06	1.7E-04
DRB4*01:01	42	127	57	401	2.3	0.0003	0.03
DPB1*105:01	12	150	87	385	0.4	0.0006	0.05
A*23:17	0	43	99	494	0.0	0.0008	>0.05
C*12:02	7	7	92	529	5.8	0.002	n/a
DQA1*01:05	0	34	99	503	0.0	0.006	>0.05
DPB1*05:01	6	8	93	527	4.3	0.01	n/a
DPB1*19:01	3	1	96	534	16.7	0.01	n/a
DRB1*11:01	21	61	78	474	2.1	0.01	>0.05
A*66:01	10	21	89	516	2.8	0.02	n/a
B*52:01	6	9	93	527	3.8	0.02	n/a
DQA1*03:03	13	125	86	412	0.5	0.02	>0.05
C*03	2	0	97	536	inf	0.02	n/a
B*15:02	5	7	94	529	4.0	0.03	n/a
B*15:03	16	47	83	489	2.0	0.03	>0.05
DQB1*02:01	8	90	90	447	0.4	0.03	>0.05
A*33:03	0	22	99	515	0.0	0.04	n/a
DRB5*01:02	5	8	94	520	3.5	0.04	n/a
DRB1*03:01	10	101	89	434	0.5	0.04	>0.05
DRB1*07:01	25	88	74	447	1.7	0.04	>0.05

DQA1*03:01 also identified in a previous study (Sveinbjornsson 2016 Nature Genetics)


HLA association

- 3 HLA alleles were found to be associated with susceptibility to ATB
- Expression of susceptibility alleles causes a decrease in Mtb-specific responses
- Expression of susceptibility alleles leads to decreased expression of APC-related genes.

ORIGINAL ARTICLE

HLA
Immune Response Genetics WILEY

Expression of specific HLA class II alleles is associated with an increased risk for active tuberculosis and a distinct gene expression profile

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