

Dissecting the spectrum of tuberculosis through antibodies

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Virtual Global Forum on TB Vaccines

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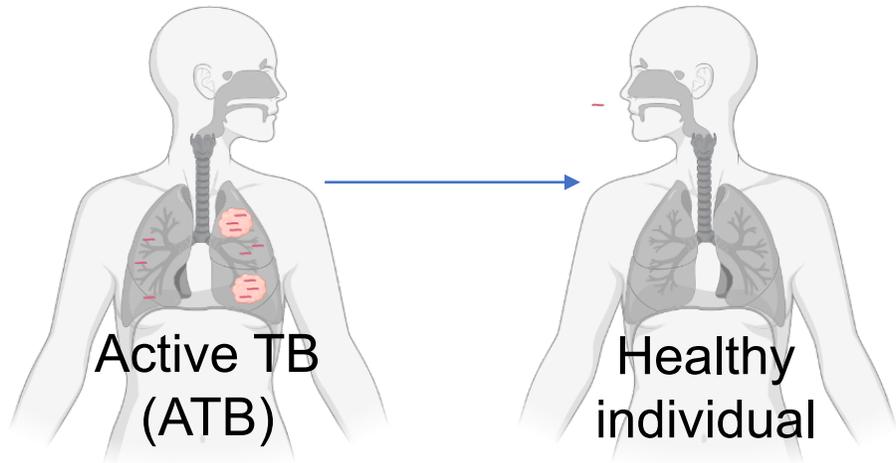
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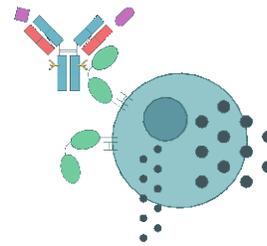
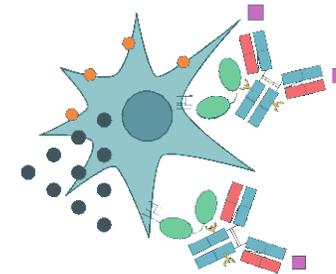
In 15 minutes...

1. Humoral immunity through antibodies fill a gap in what we know about host responses to *Mycobacterium tuberculosis*.
2. Antibody functions diverge in latent and active tuberculosis.
3. Antibodies can identify individuals highly exposed to *Mtb* yet not captured by current clinical diagnostics: “Resisters”.
4. Understanding mechanisms of antibody functions can inform the development of TB diagnostics and vaccines.

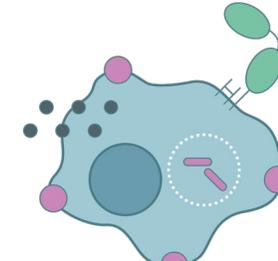
Innate and adaptive immune responses develop in latent and active TB.



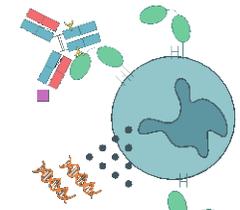
*Innate
immune
cells*



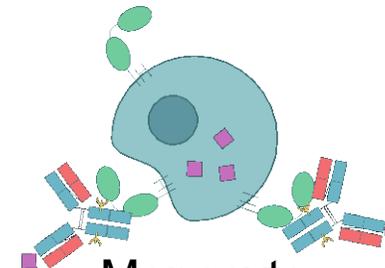
Dendritic cell



Macrophage

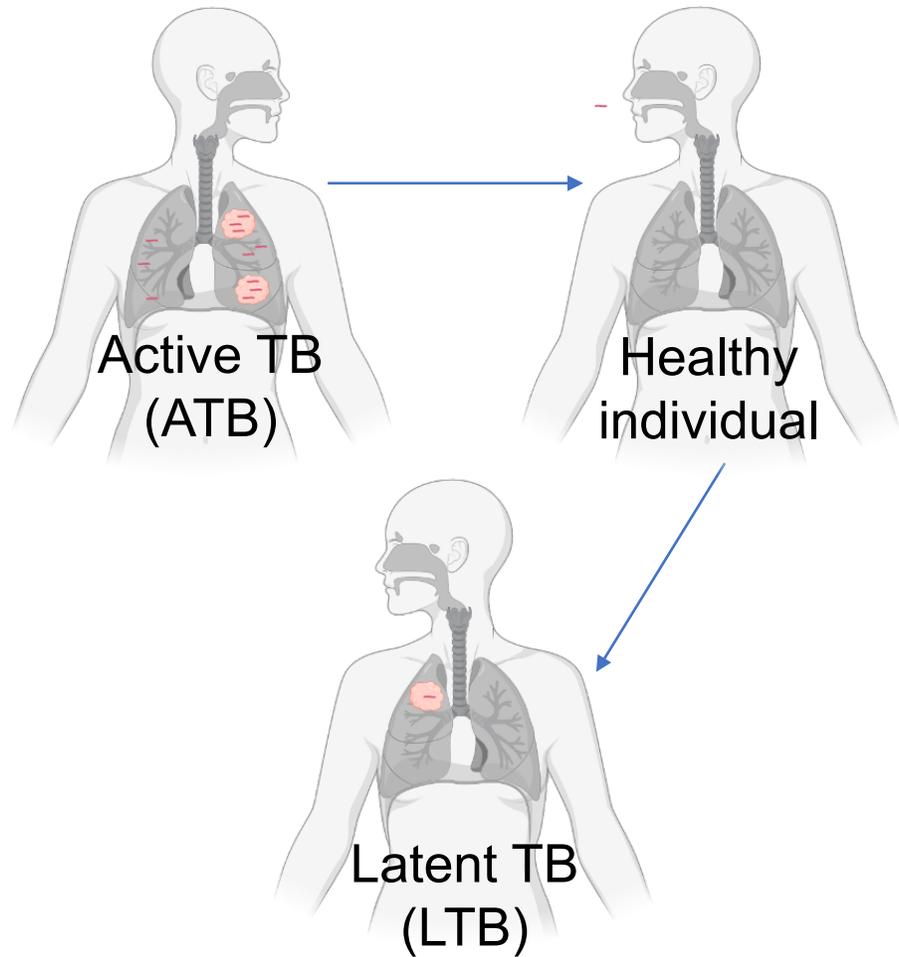


Neutrophil



Monocyte

Innate and adaptive immune responses develop in latent and active TB.



*Adaptive
immune
cells*

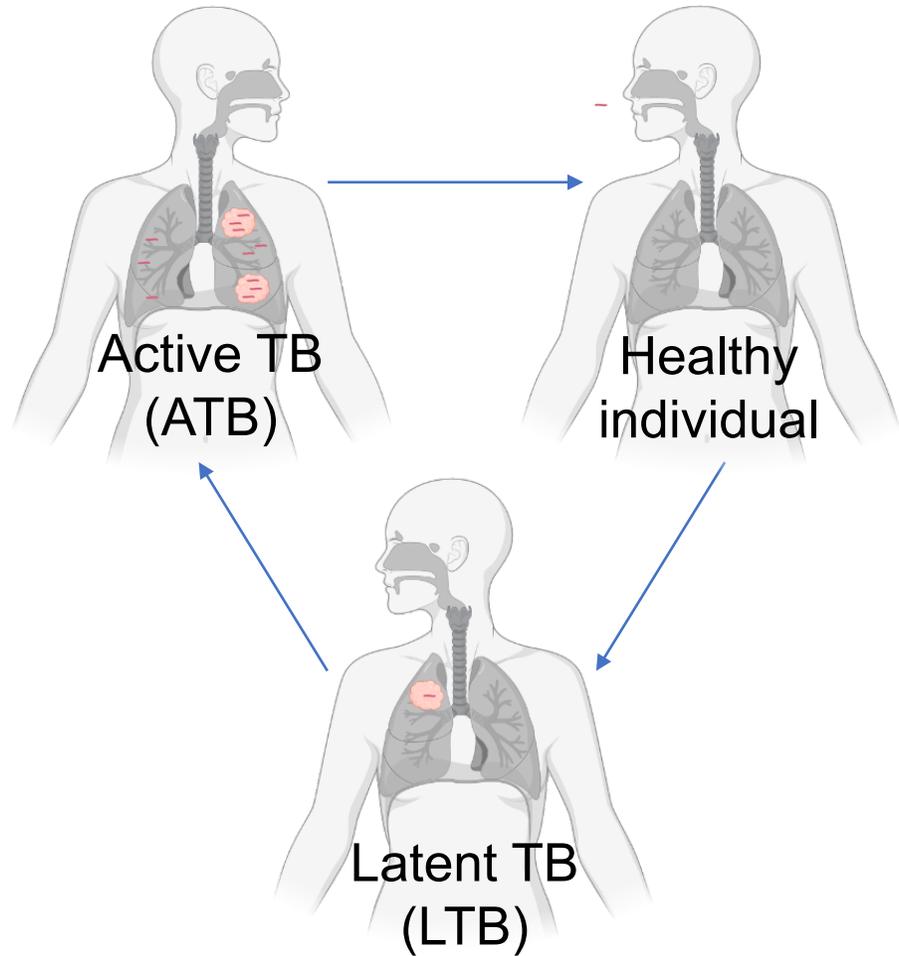


B cell

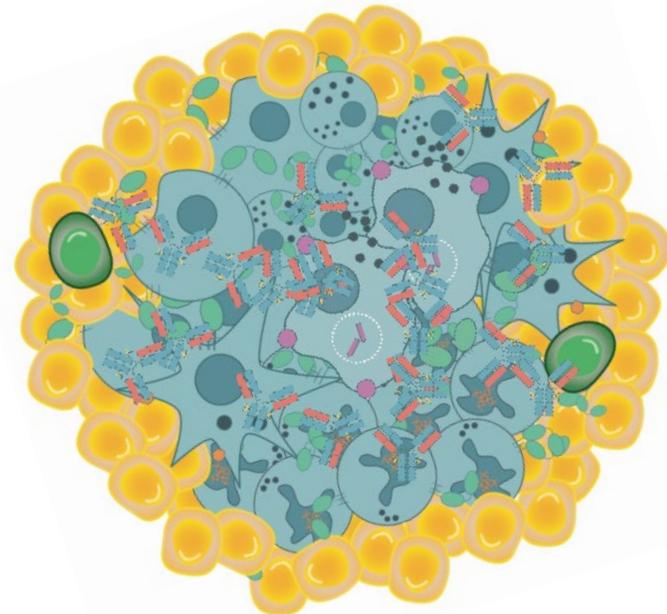


T cell

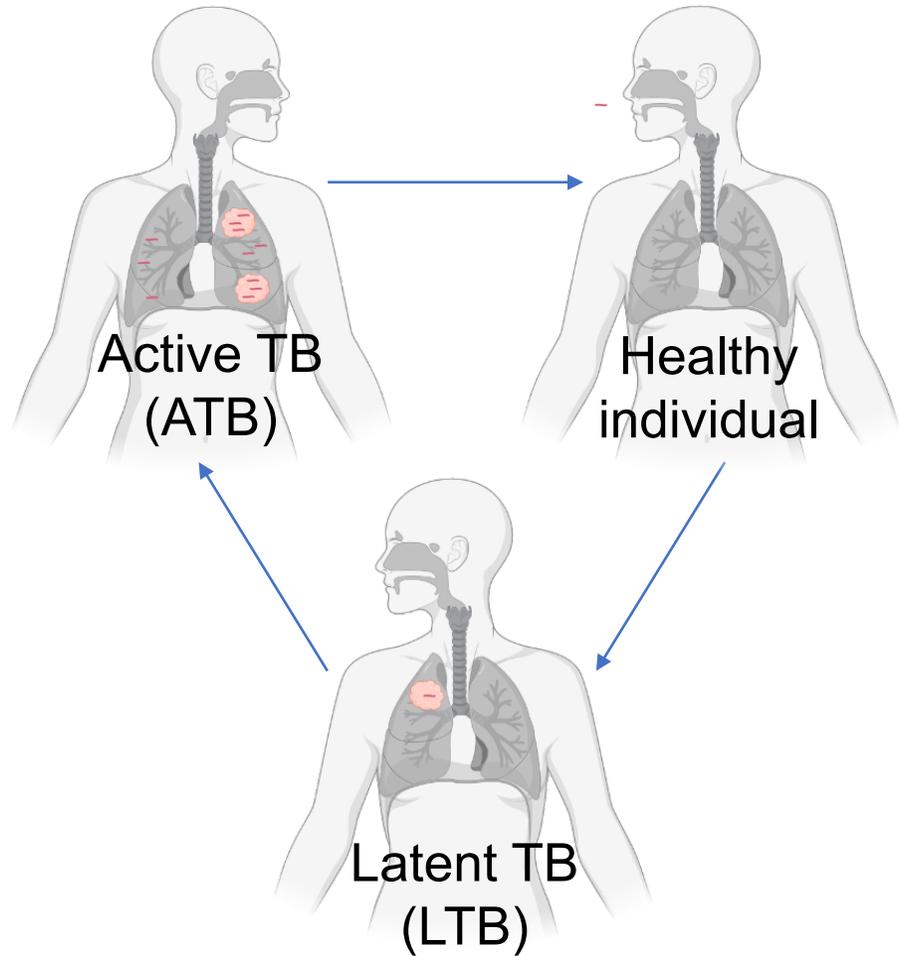
Innate and adaptive immune responses develop in latent and active TB.



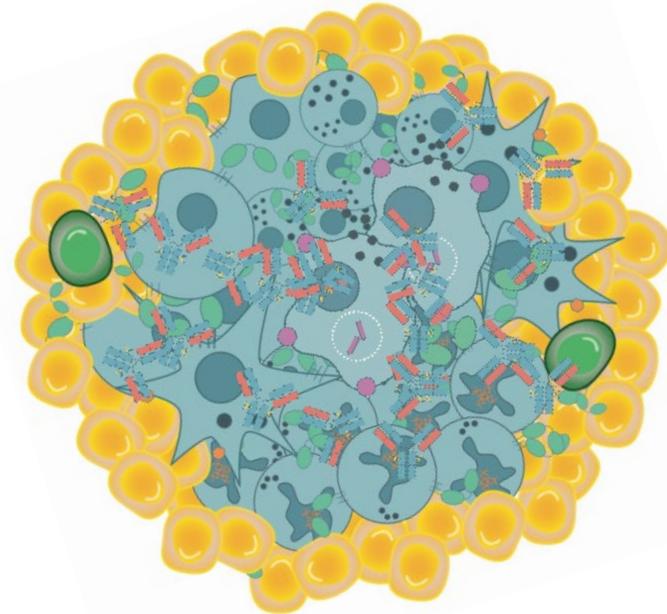
Innate and adaptive immune cells surround Mtb infected macrophages in a granulomatous lesion.



Innate and adaptive immune responses develop in latent and active TB.

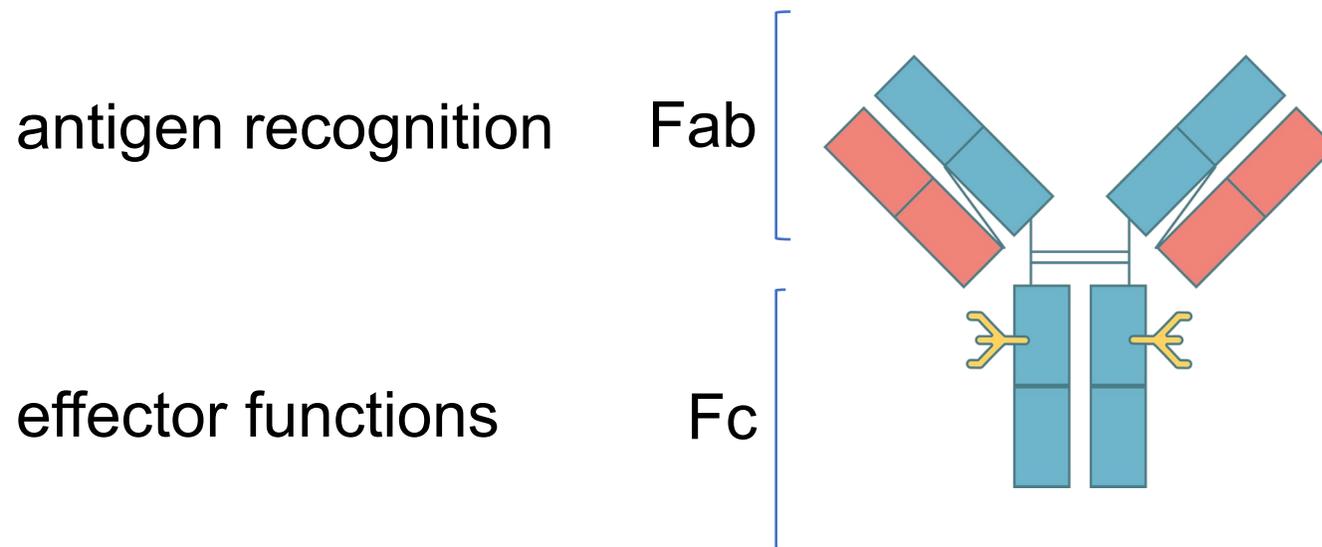


Antibodies surround innate and adaptive immune cells and Mtb infected macrophages in a granulomatous lesion.



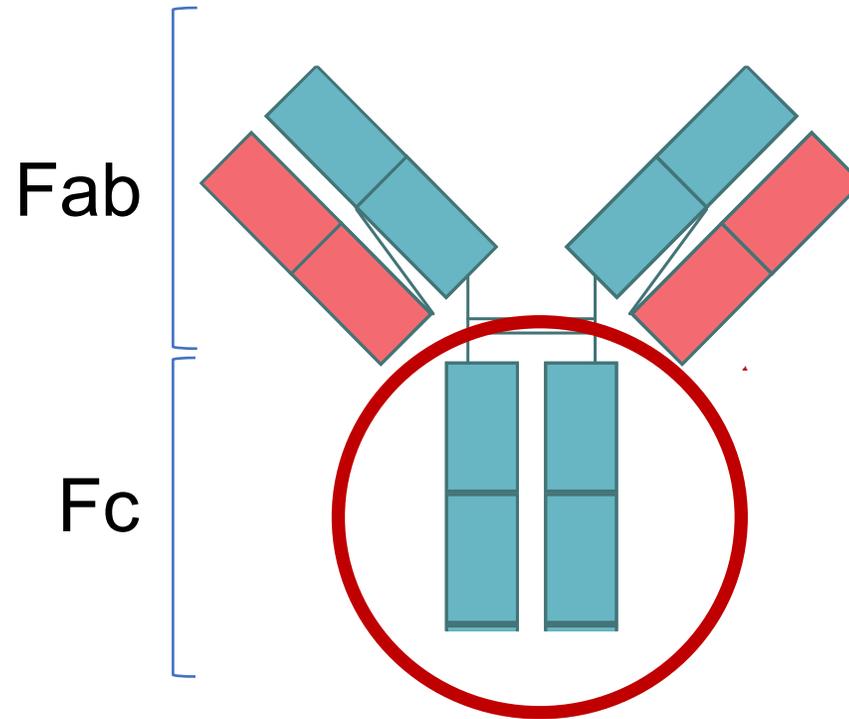
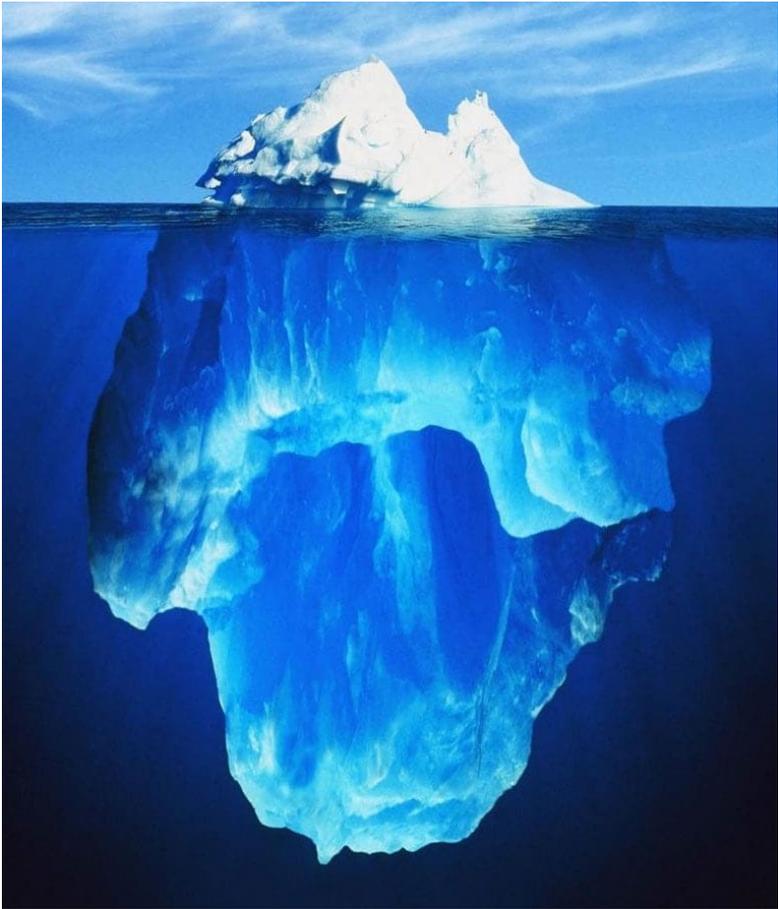
Unclear role of antibodies in TB in Fab focused studies.

- *Mtb* associated titers alone are insufficient as diagnostics.
- Transfer of antibodies inconsistently confers protection.

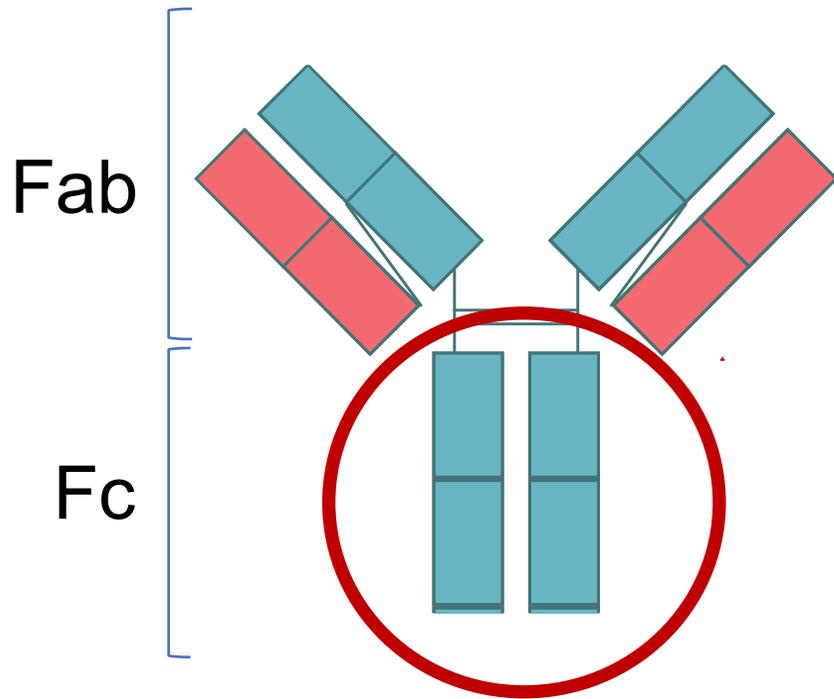


Adapted from Lu et al. 2018. Nature Reviews Immunology.

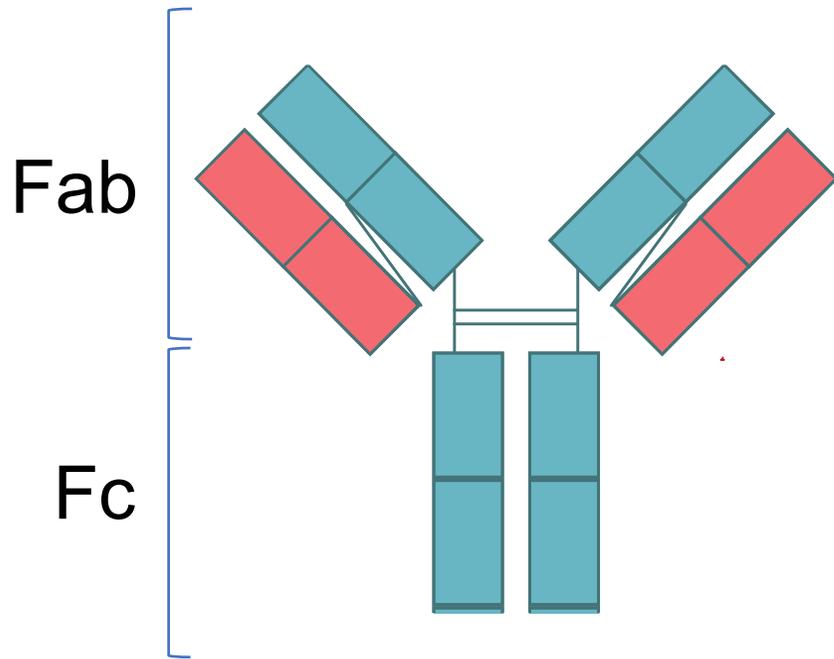
The back end matters.



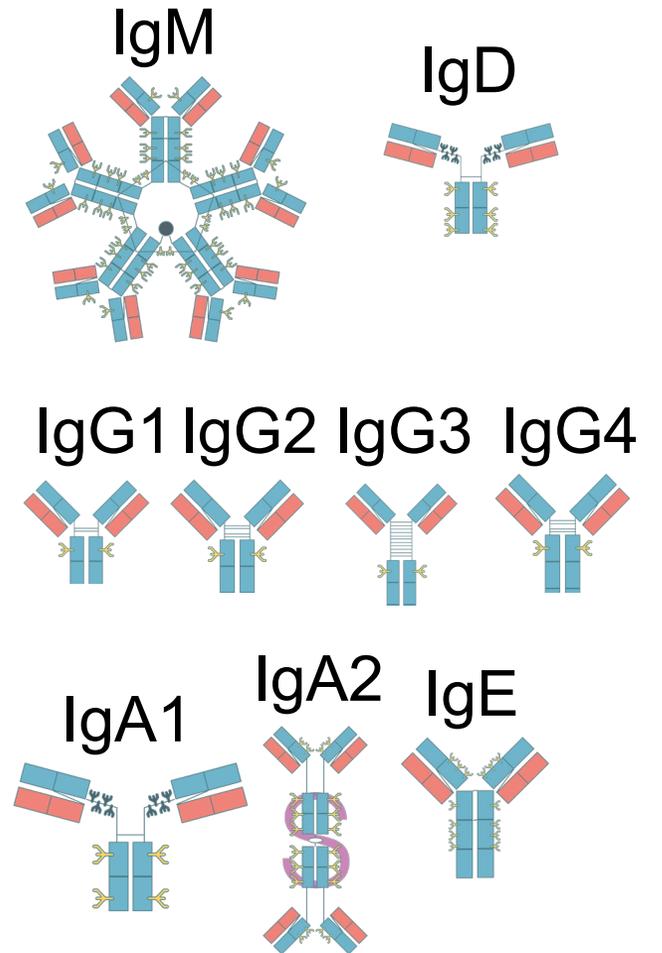
Antibodies function through the combination of diverse Fab and Fc domains.



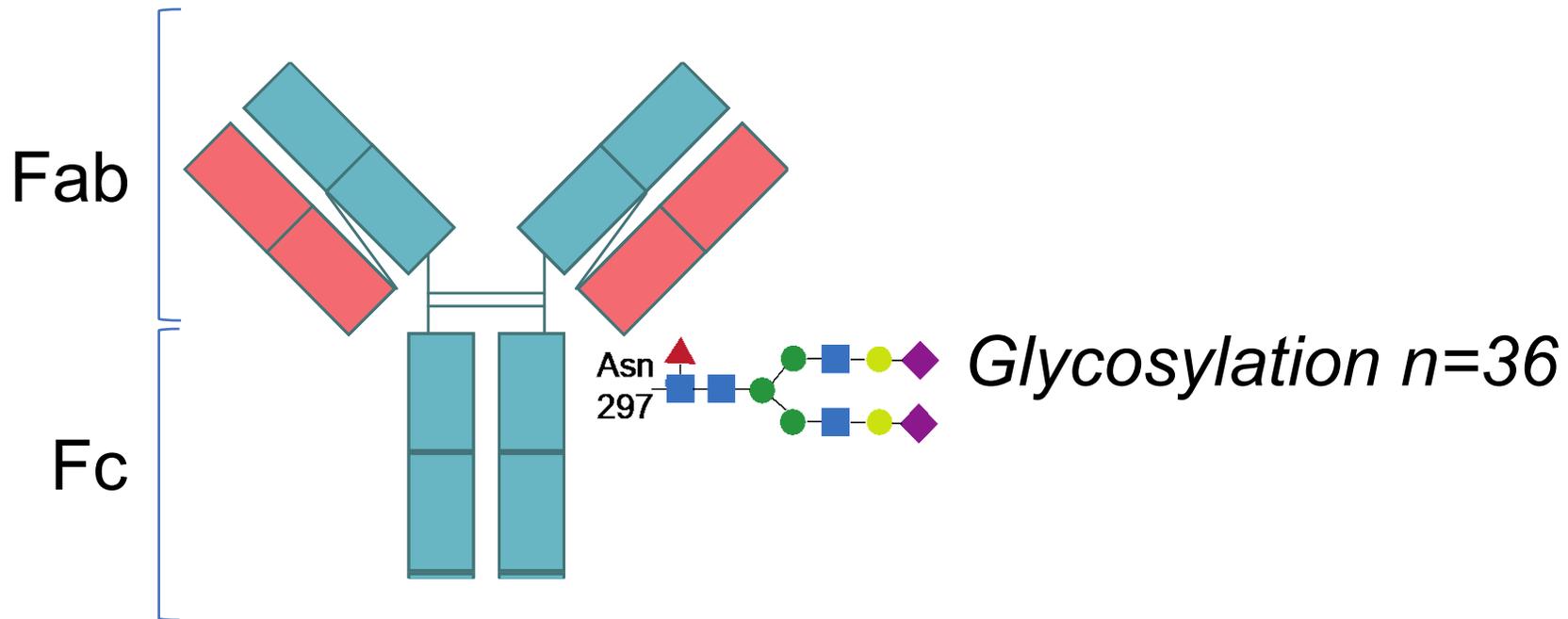
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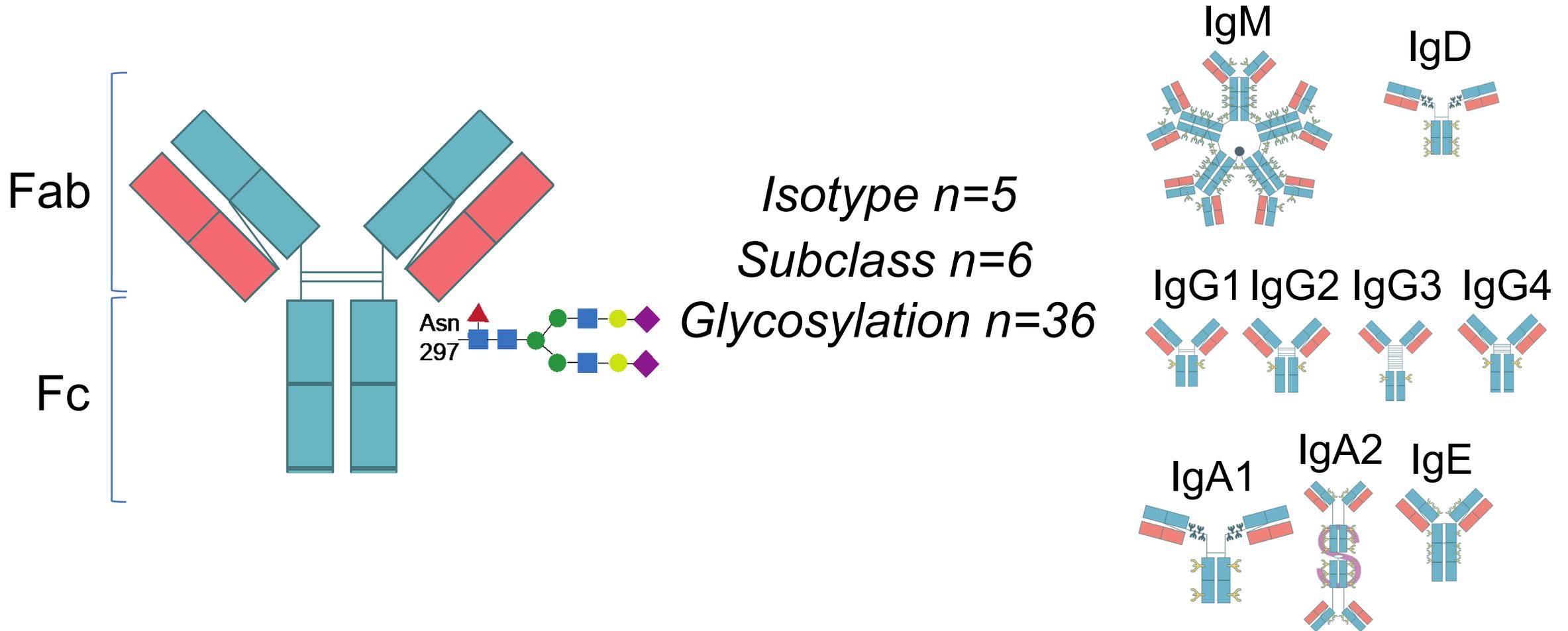
Isotype n=5
Subclass n=6



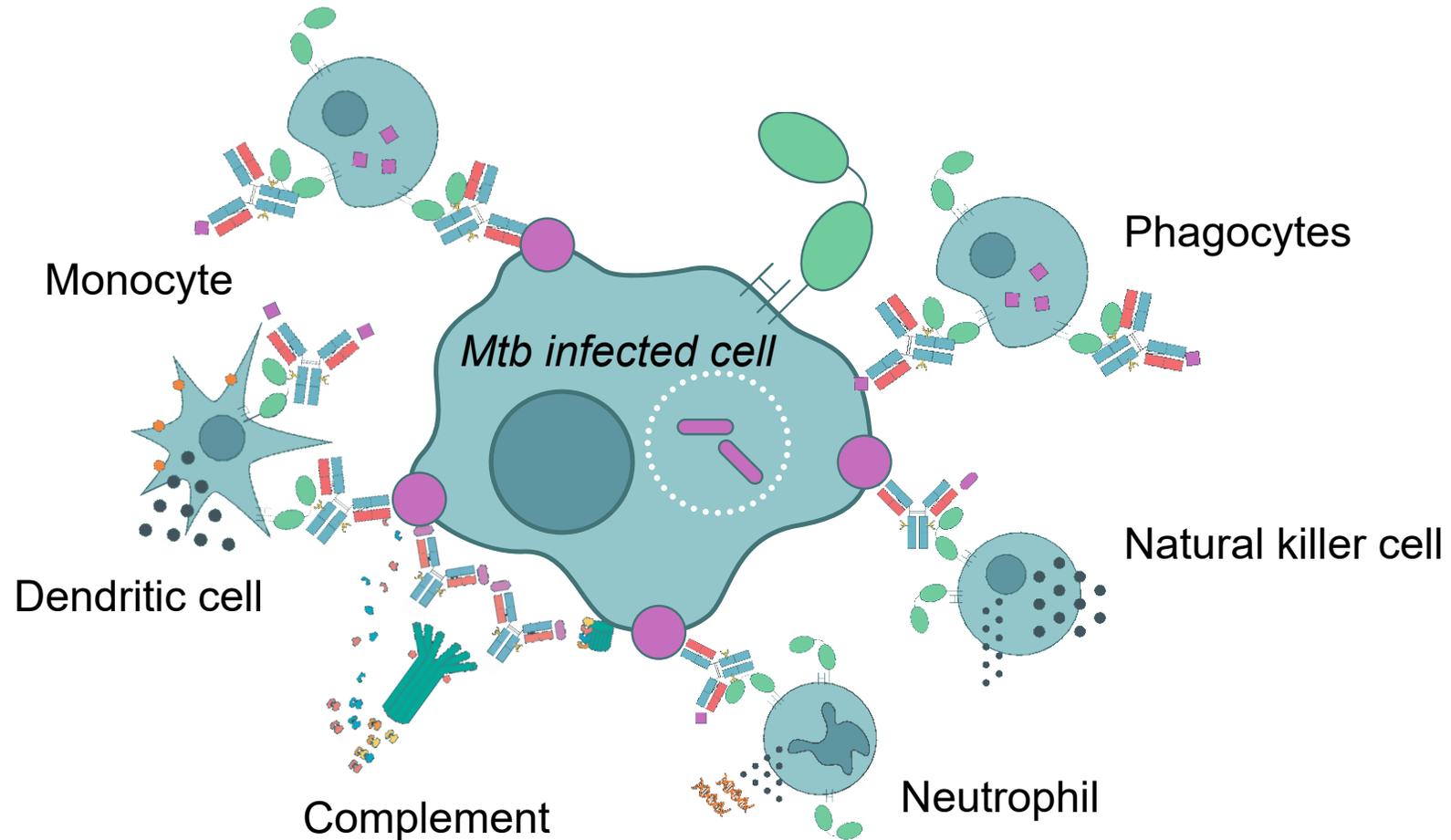
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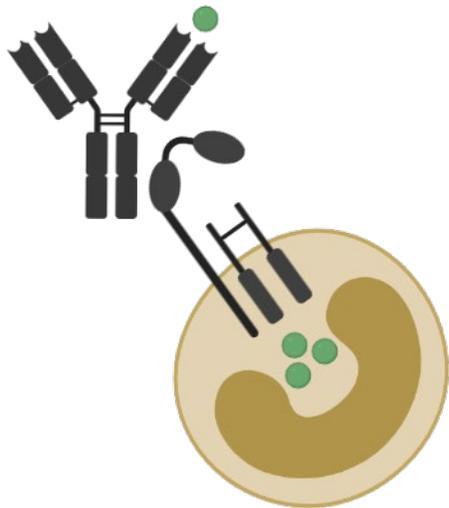


Antibody Fc recruits many innate and adaptive immune effector cells and functions.



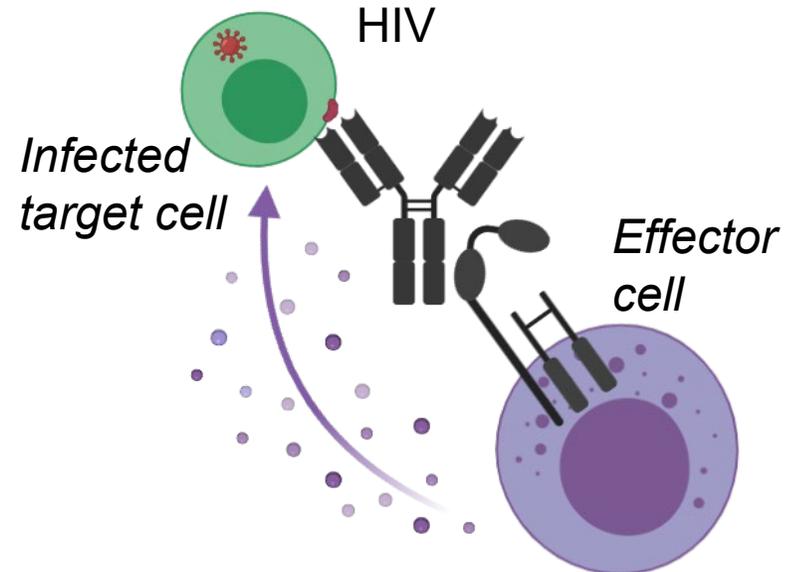
Antibodies protect and enhance infections.

Promote
opsonophagocytosis
Pneumococcal vaccine



Plotkin 2013 Clinical
Infectious Diseases

Directly neutralize and
induce antibody dependent
cellular cytotoxicity

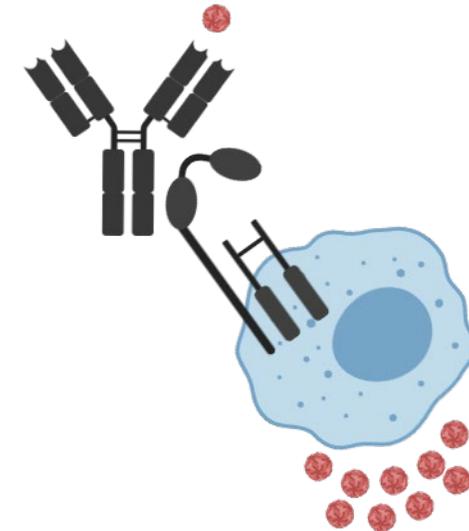


Bournazos et al 2014 Cell

Chung et al 2014 Science
Translational Medicine

Ackerman et al 2016 PLoS Pathogens

Enhance viral entry into
a macrophage
Dengue virus

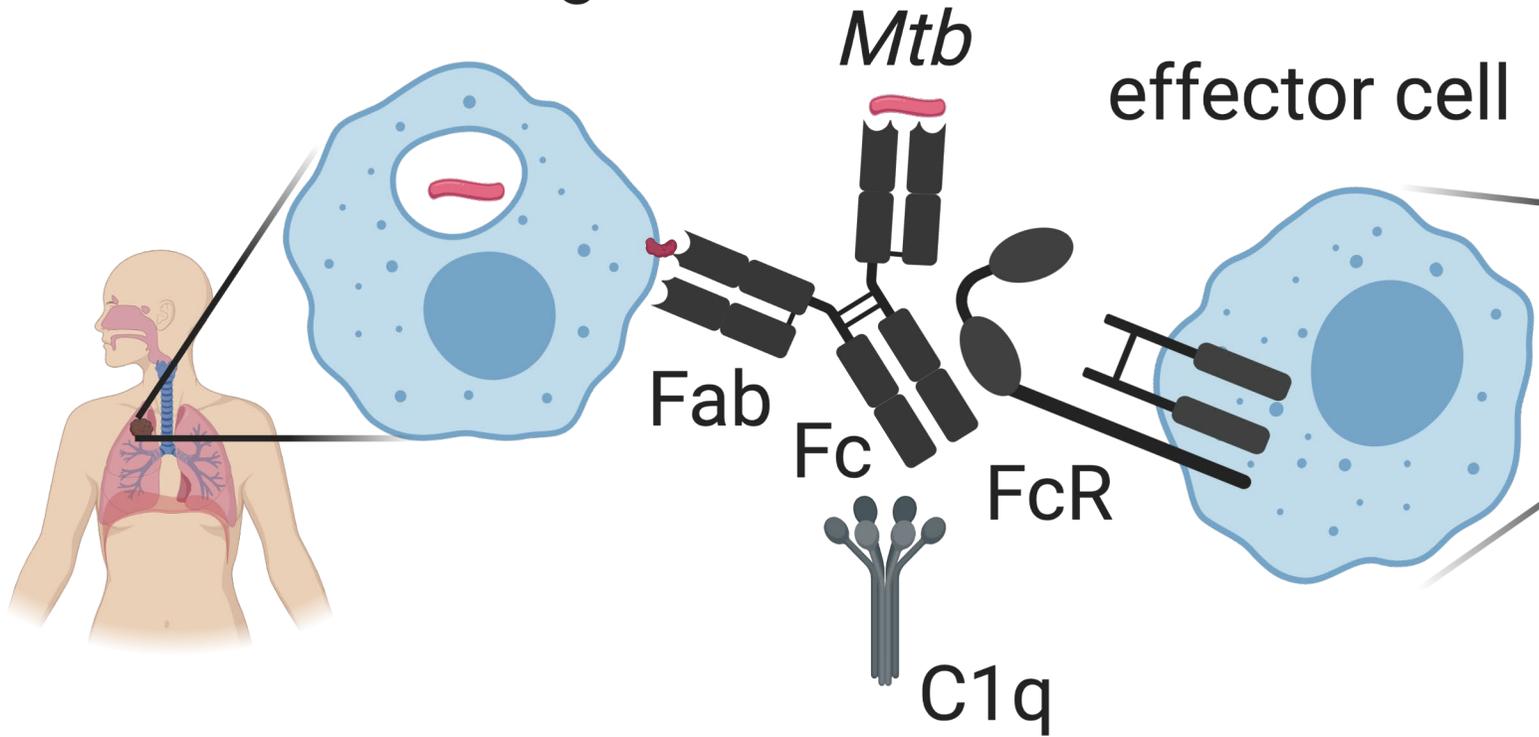


Wang et al 2017 Science

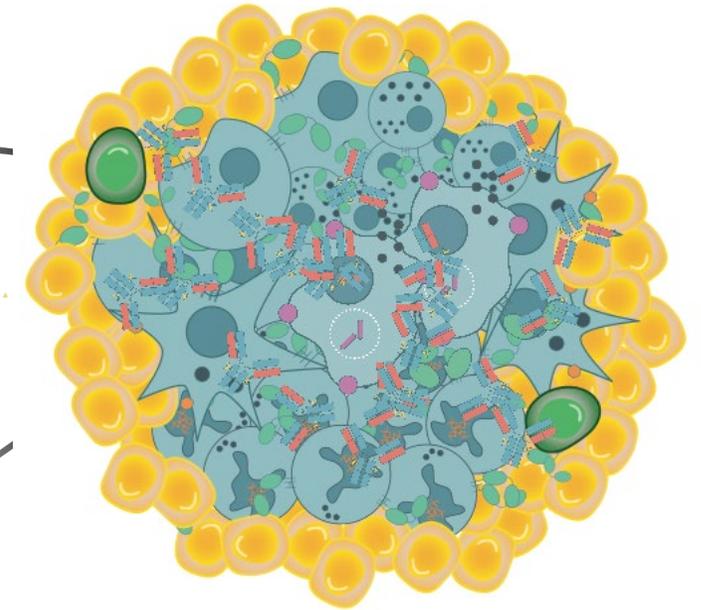
Halstead and O'Rourke 1977
Nature

Antibodies are poised at the interface of host and *Mtb* to bridge innate and adaptive immunity.

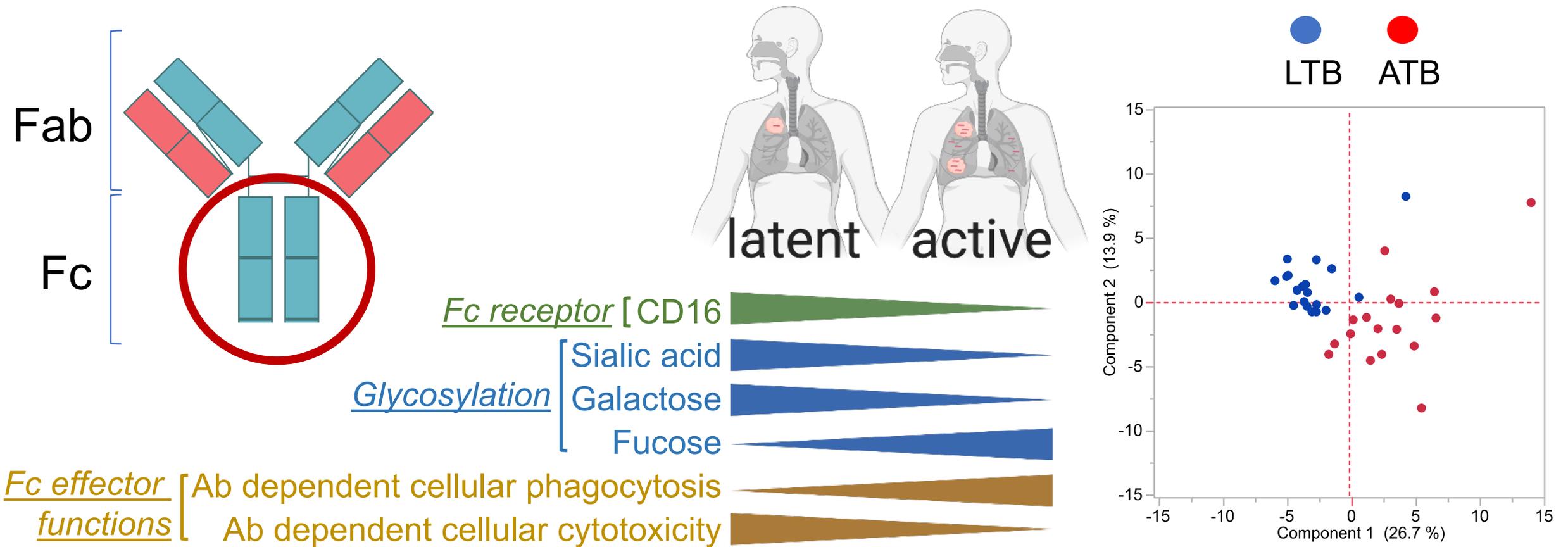
Mtb infected target cell



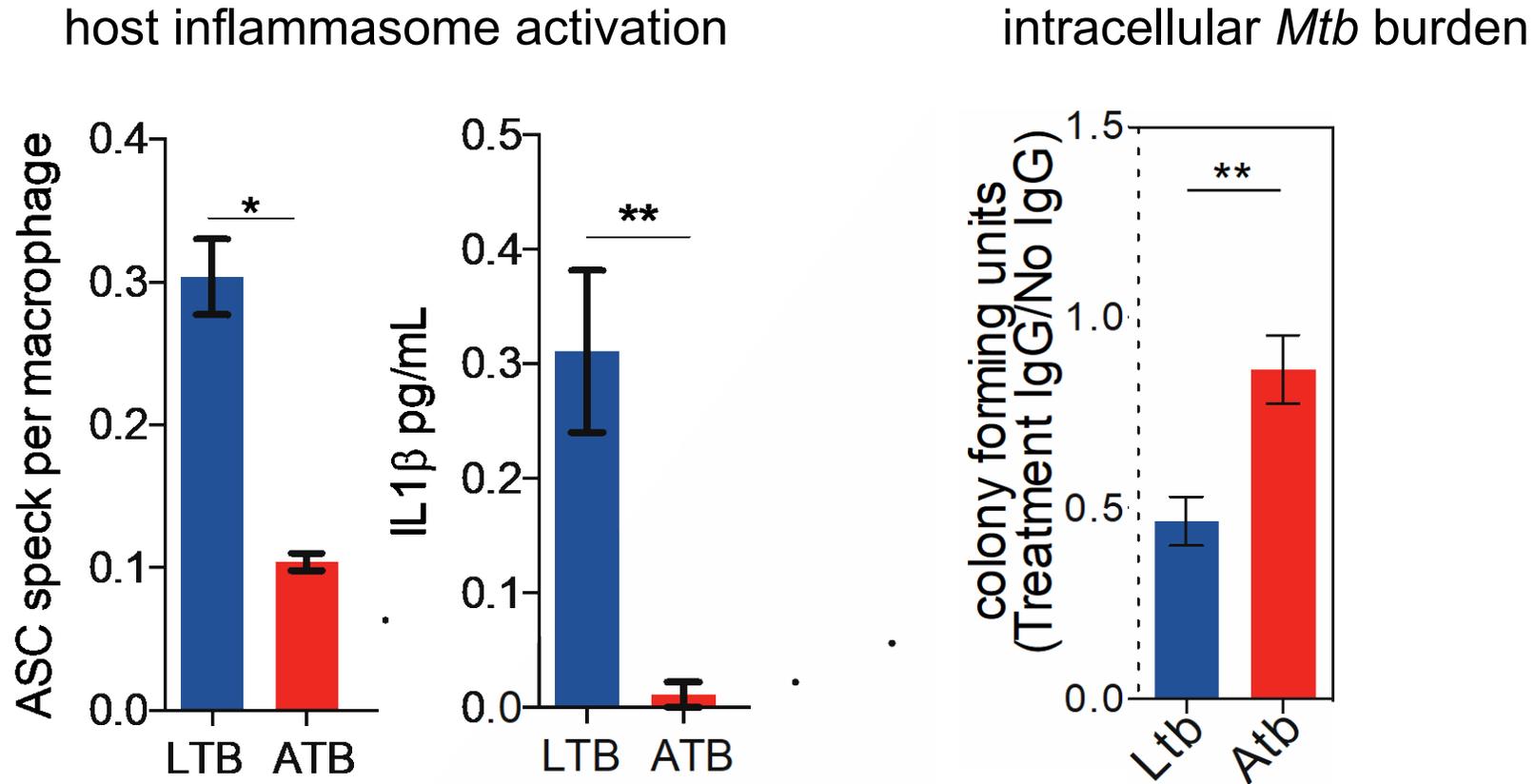
granuloma



Divergent Fc features in latent and active TB are discriminatory.

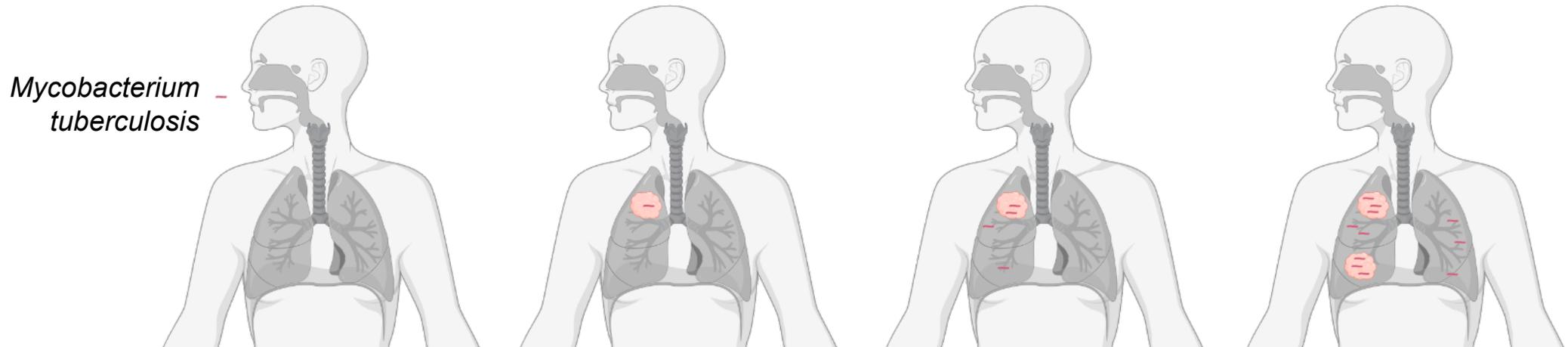


Distinct Fc profiles differentially impact host-*Mtb* interactions.



Antibody Fc effector functions diverge in latent and active TB.

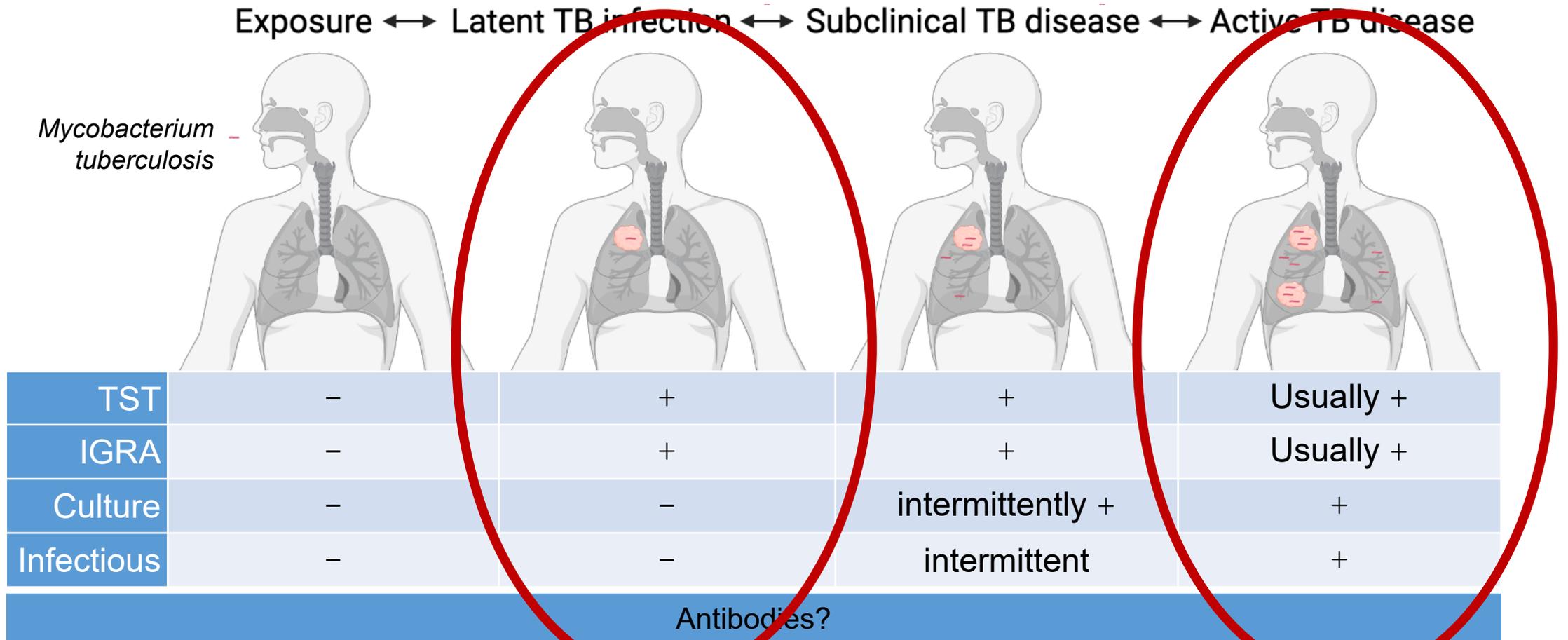
Exposure ↔ Latent TB infection ↔ Subclinical TB disease ↔ Active TB disease



TST	-	+	+	Usually +
IGRA	-	+	+	Usually +
Culture	-	-	intermittently +	+
Infectious	-	-	intermittent	+

Antibodies?

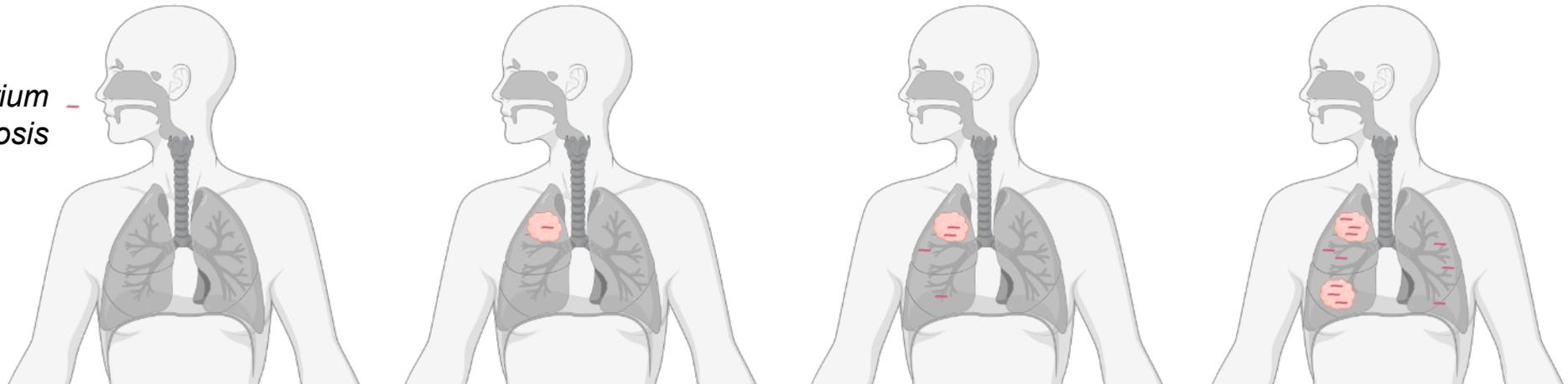
Antibody Fc effector functions diverge in latent and active TB.



Can antibodies capture other host states beyond latent and active TB?

Exposure ↔ Latent TB infection ↔ Subclinical TB disease ↔ Active TB disease

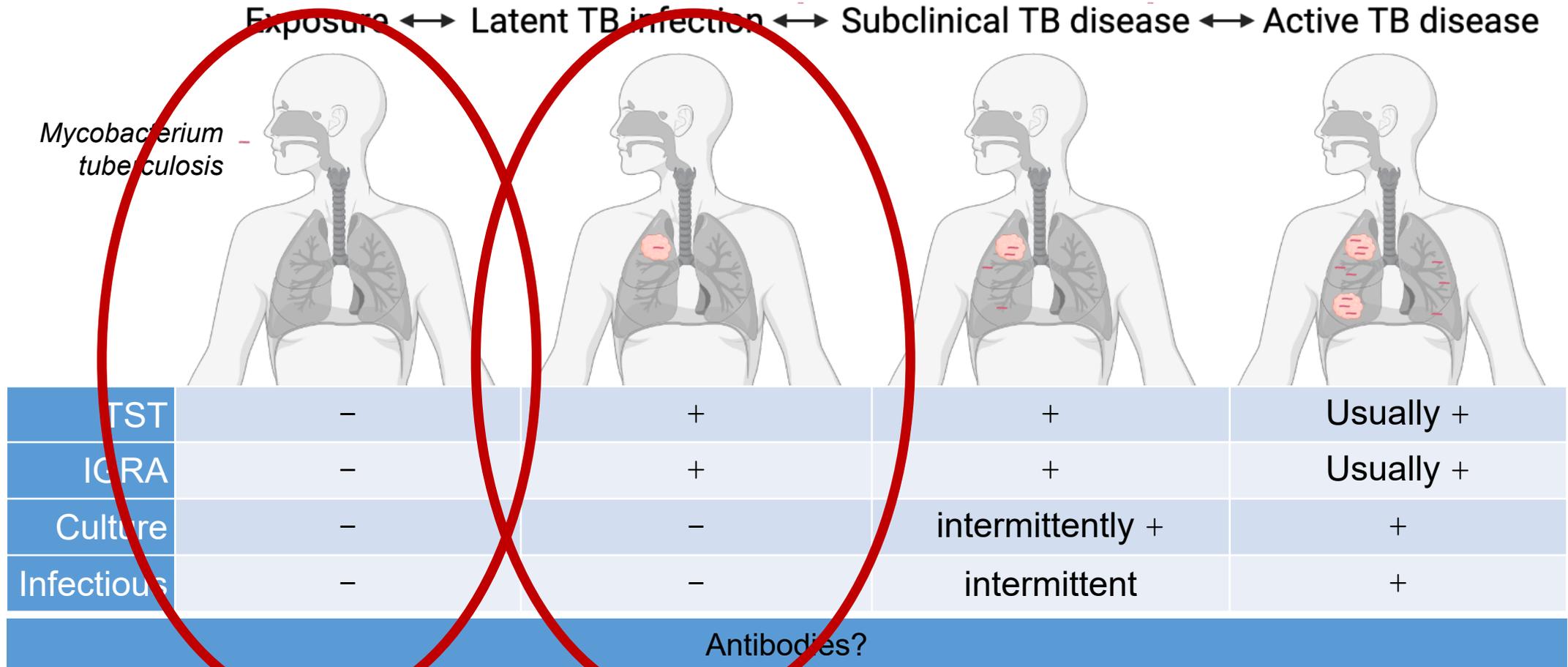
Mycobacterium tuberculosis -



TST	-	+	+	Usually +
IGRA	-	+	+	Usually +
Culture	-	-	intermittently +	+
Infectious	-	-	intermittent	+

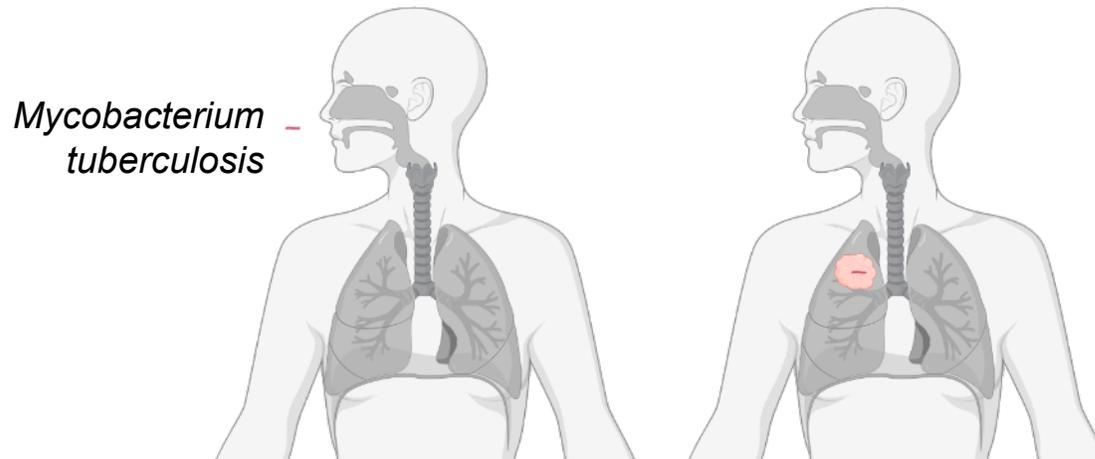
Antibodies?

Can antibodies capture other host states beyond latent and active TB?



“Resisters” are highly exposed to *Mtb* but tuberculin skin test (TST)/IFN γ negative.

Exposure \leftrightarrow Latent TB infection



	Resister	Latent TB
TST	-	+
IGRA	-	+
Culture	-	-
Infectious	-	-

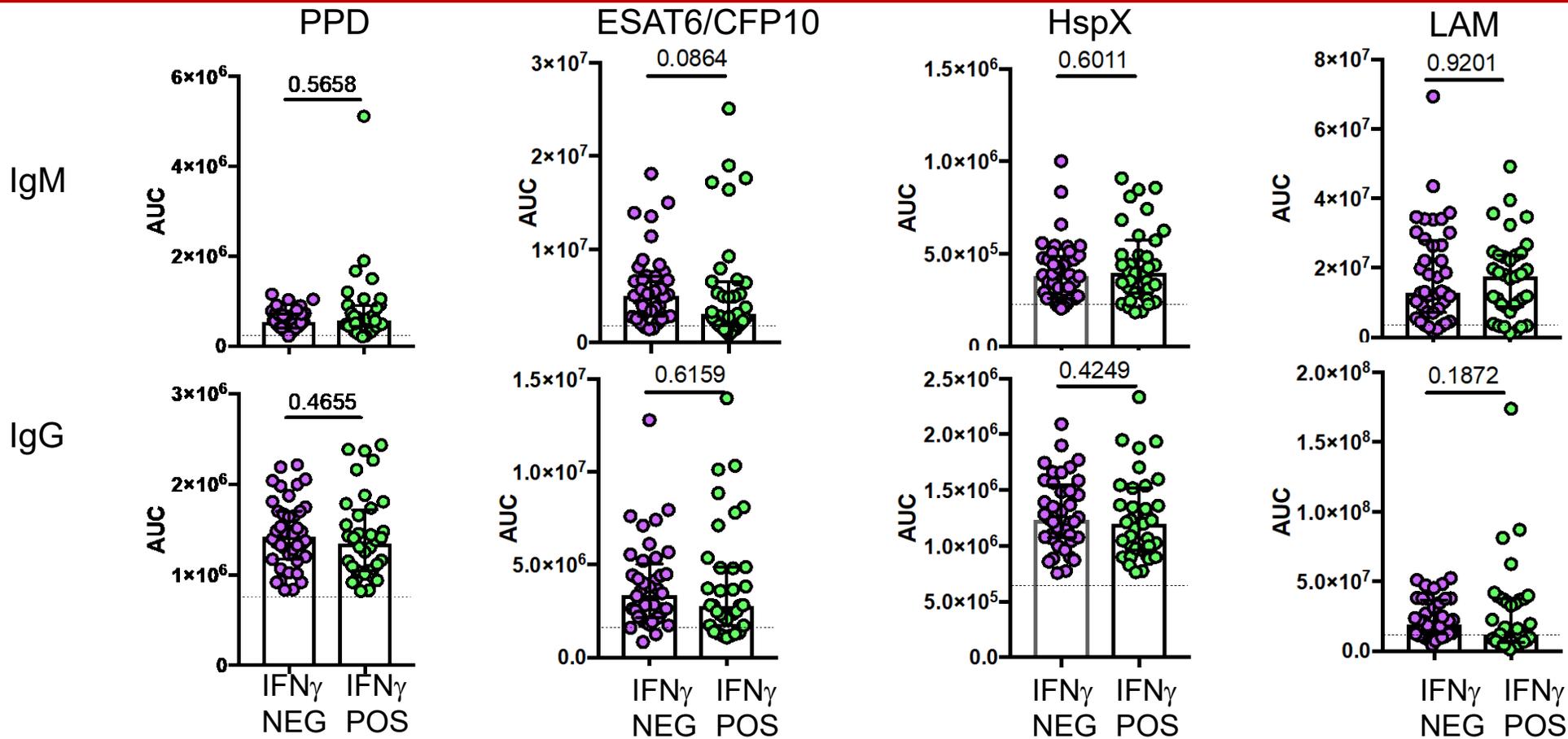
Similar risk score between “Resisters” and latent TB

	“resister” TST-/IGRA-	LTBI TST+/IGRA+	p-value
Current age (median)	20.00	22.50	0.371
Age at recruitment (median)	13	13.5	0.502
Sex (% Female)	42.9%	43.5%	0.951
% with BCG scar	61.2%	65.2%	0.830
Pediatric risk score (mean)	6.07	6.35	0.113
Adult risk score (mean)	6.26	6.70	0.296
Duration of follow-up in years (median)	9.31	8.47	0.780
BMI (median)	20.92	21.83	0.388

No statistically significant difference in active TB

	PTST- TST-/IGRA-	LTBI TST+/IGRA+
Total cases	144	303
Person-years of follow-up	1020	2212
Cases of active TB	2	4
Incidence rate [95% CI]	0.00196 [0-0.0047]	0.00180 [0.000036-0.00357]

“Resisters” have detectable levels of *Mtb* specific adaptive immunity.

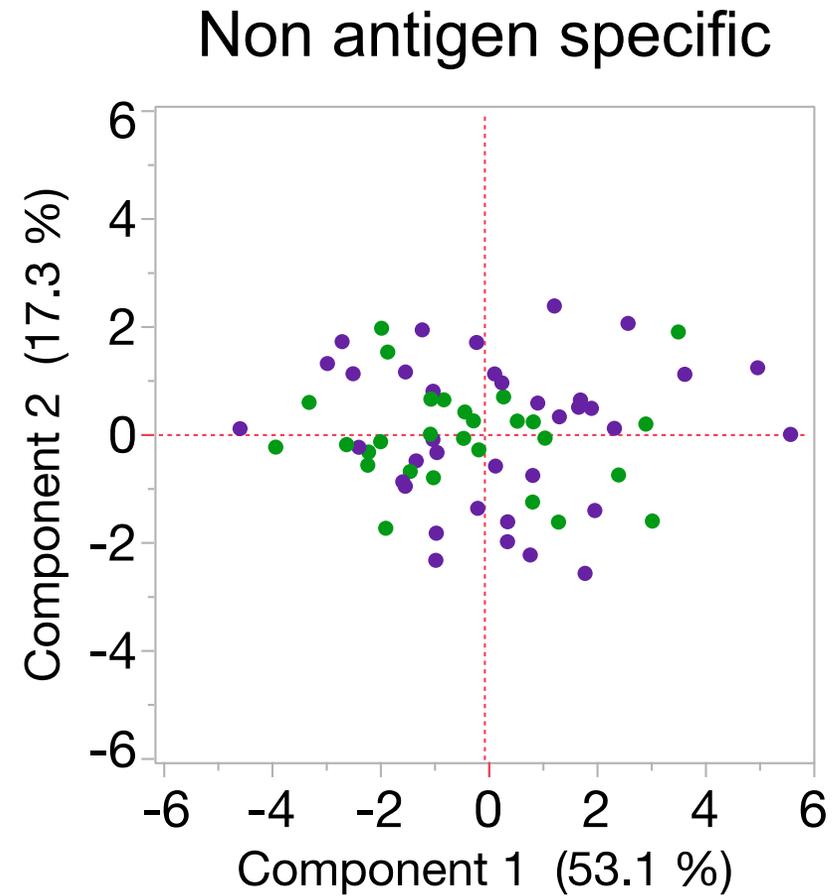
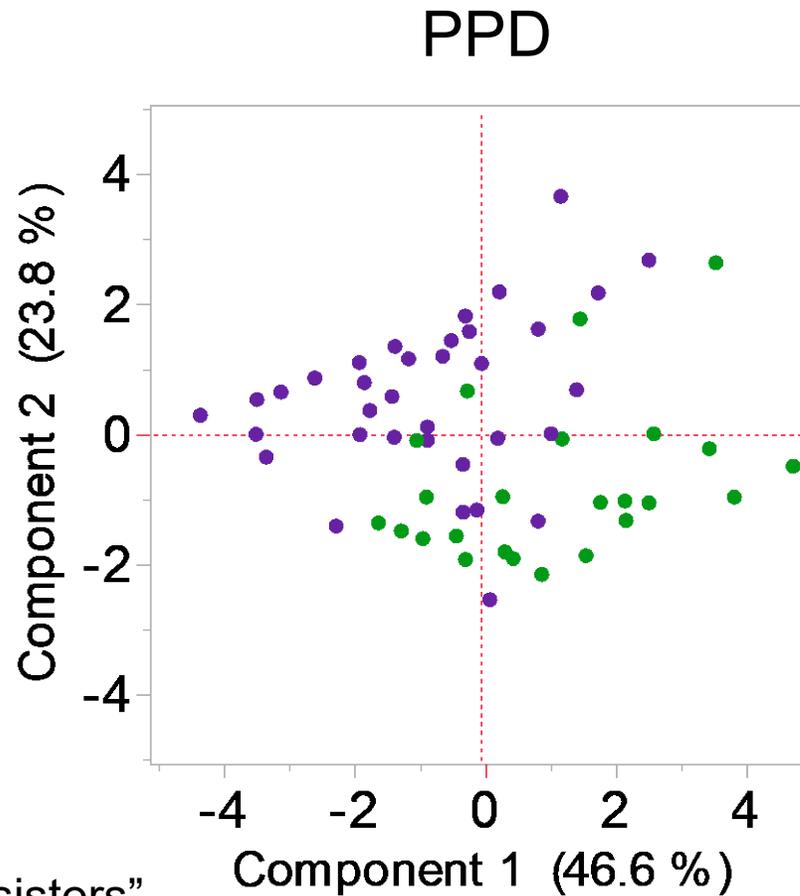


● IFN γ negative/ “Resisters”

● IFN γ positive/ latent TB

--- Healthy negative

Mtb antibody glycosylation can potentially separate “Resisters” and latent TB.



- IFN γ negative/ “Resisters”
- IFN γ positive/ latent TB

What have we learned?

1. Diverse Fab and Fc domains in antibody responses generated during infection mediate host-*Mtb* interactions.
2. The spectrum of human TB offers opportunities to dissect mechanisms of humoral immunity.
3. Focused testing in models in combination with human immune correlates inform on humoral immunity in TB.



Where can we go from here?

1. Leverage antibody functions to understand the spectrum of human TB phenotypes
2. Harness antibody glycosylation to enhance development of diagnostics
3. Utilize antibody features as immune correlates or mediators of protection in vaccine studies and design



Thank you!

Harvard TH Chan School of Public Health: Sarah Fortune

Ragon Institute of MGH, MIT and Harvard: Galit Alter

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University of Washington: Chetan Seshadri and Tom Hawn

Emory University: Cheryl Day

UT Brownsville: Blanca Restrepo

University of Melbourne: Amy Chung

UT Southwestern Medical Center:

Pei Lu

Joshua Miles

Gabrielle Lessen