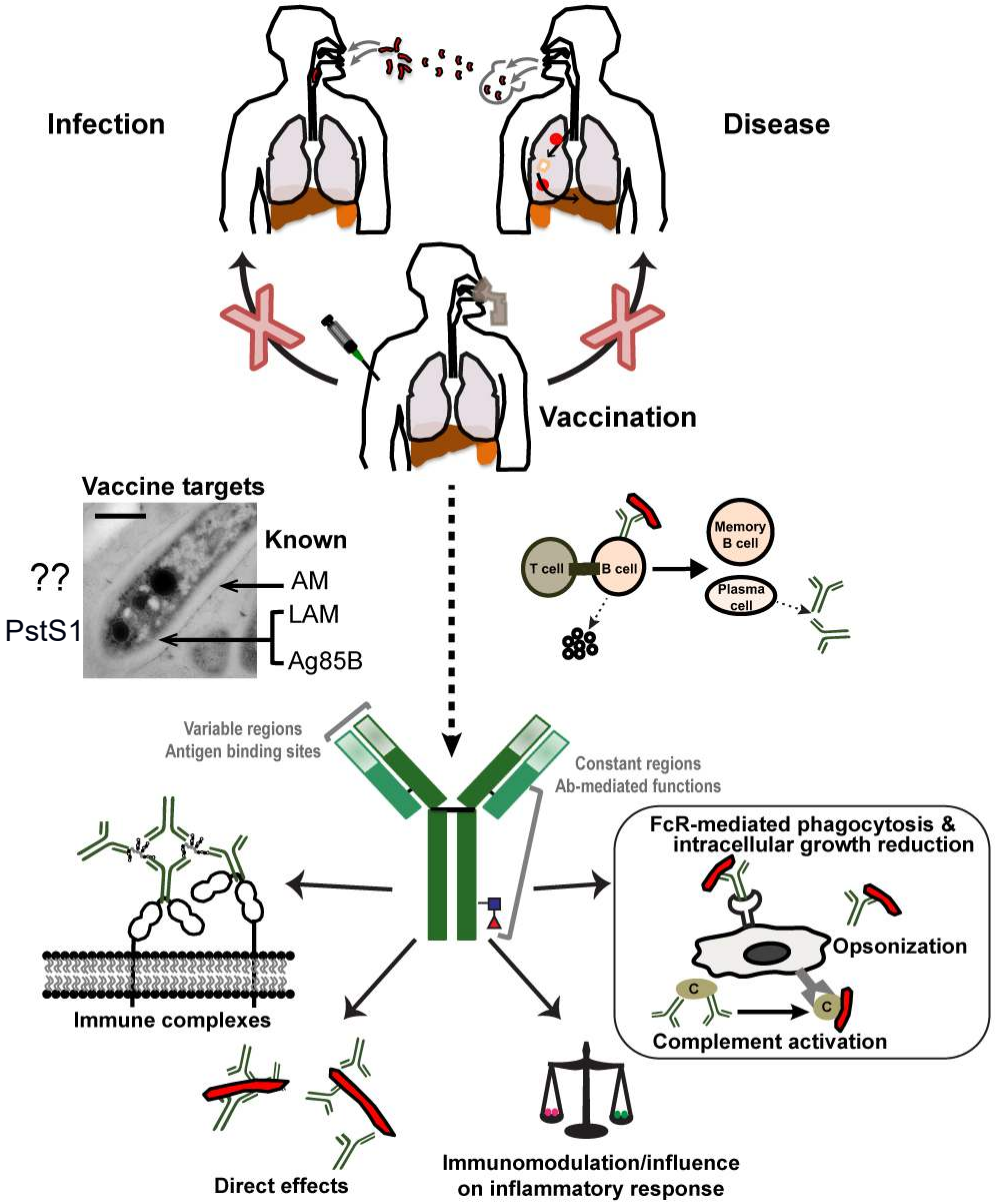
Protective Antigen Specificity of B cells in TB

Jacqueline M. Achkar, MD, MSc, FIDSA
Professor
Departments of Medicine (Div. of Infectious Diseases), Microbiology & Immunology
Albert Einstein College of Medicine

EINSTEIN
Albert Einstein College of Medicine

Montefiore
nspired Medicine



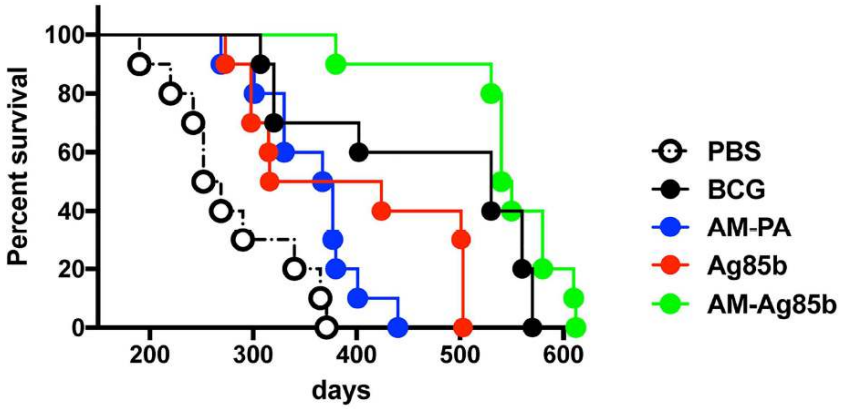
Achkar & Prados-Rosales, *Current Opinions in Immunology* 2018

What are the important antigenic targets for B cells?

- Passive transfer studies in mice (mostly murine IgG mAbs)
  - AM/LAM
  - PstS1 (Ag 38)
  - HSPX (α-crystalin, 16 kDa; IgA)
  - HBHA
  - MPT83
- Murine serum transfer from vaccine studies
  - AM/LAM, Ag 85

Reviewed in
Achkar & Casadevall,
CHM 2013

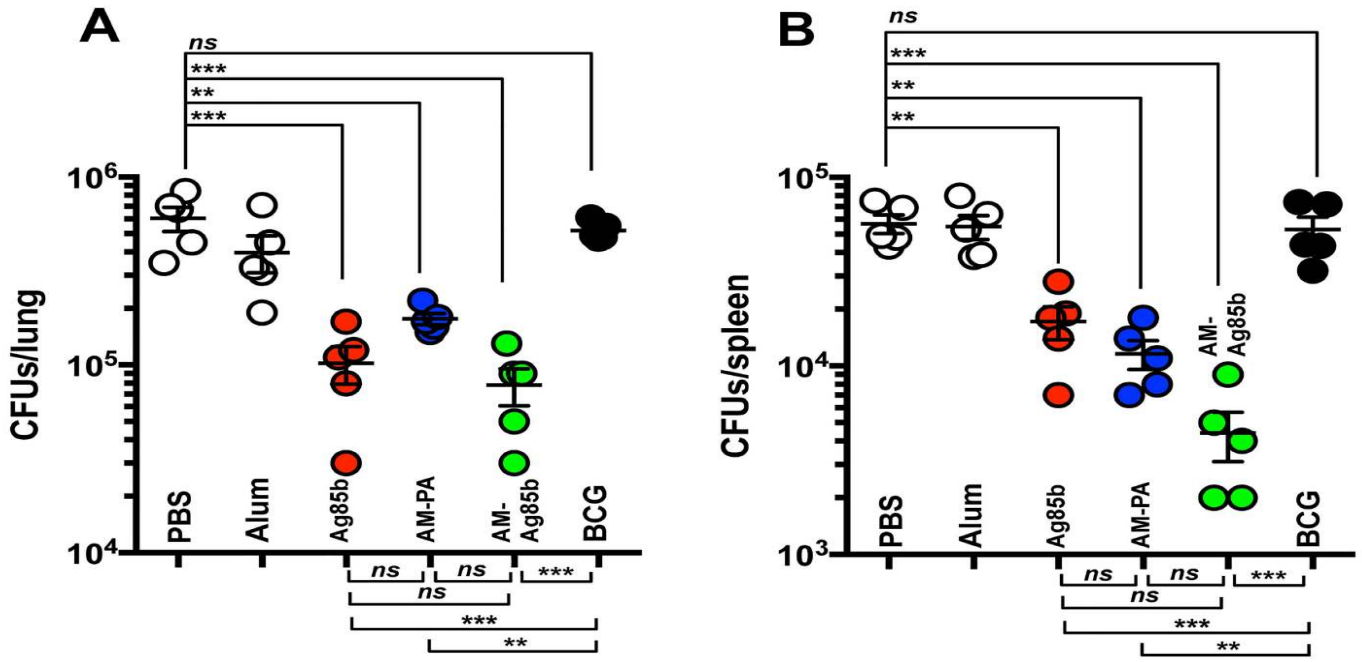
PLOS | PATHOGENS



RESEARCH ARTICLE

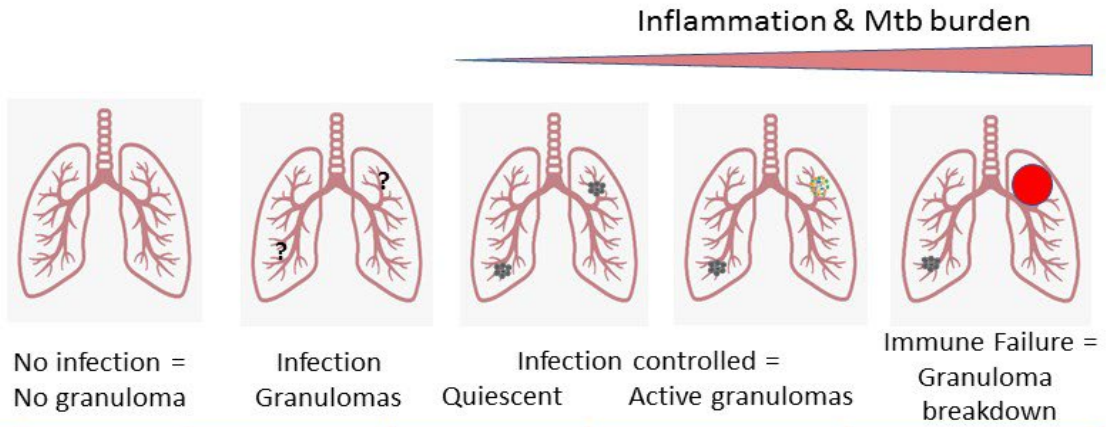
Enhanced control of *Mycobacterium tuberculosis* extrapulmonary dissemination in mice by an arabinomannan-protein conjugate vaccine

Rafael Prados-Rosales[1,2‡*], Leandro Carreño[1,3], Tingting Cheng[1,4], Caroline Blanc[1,4], Brian Weinrick[1,5], Adel Malek[1,5], Todd L. Lowary[6], Andres Baena[7], Maju Joe[6], Yu Bai[6], Rainer Kalscheuer[8], Ana Batista-Gonzalez[1], Noemi A. Saavedra[1], Leticia Sampedro[2], Julen Tomás[2], Juan Anguita[2,9], Shang-Cheng Hung[10], Ashish Tripathi[10], Jiayong Xu[1,4], Aharona Glatman-Freedman[11,12], Williams R. Jacobs, Jr.[1,5], John Chan[1,4], Steven A. Porcelli[1], Jacqueline M. Achkar[1,4], Arturo Casadevall[1,13‡]



Prados-Rosales et al., *PLoS Pathog* 2017

Human defense mechanisms in *Mtb* exposure & infection



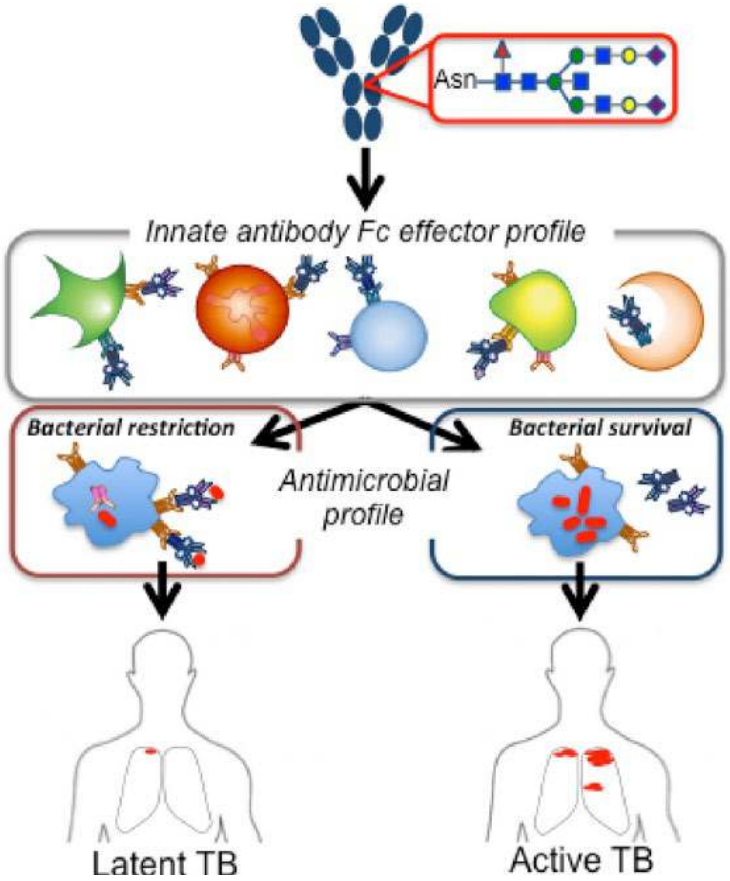
X = failure and/or imbalance and/or pro-inflammatory dominance

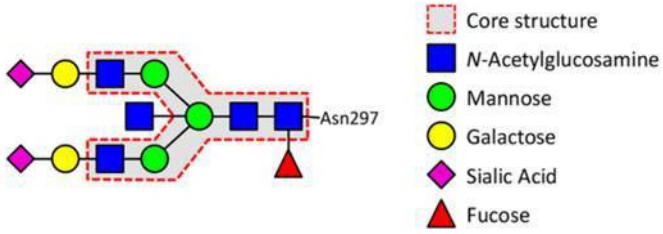
Host Defense Mechanisms		Colonization & Early Clearance	Non-traditional LTBI/Resisters	Traditional LTBI	At Risk for Reactivation	Progressor/ Incipient TB
Mechanical	Cilia/Defensins	+?	?	-	-	-
Innate Immunity	Recruited Macrophages	-	+/-	?	?	X?
	Neutrophils	-	?	?	+/-	X
Adaptive Immunity	T cells	-	-/+	++	+	X
	B cells/Abs	-	-/+	+	?	X?

Boom, Schaible & Achkar, JCI 2021

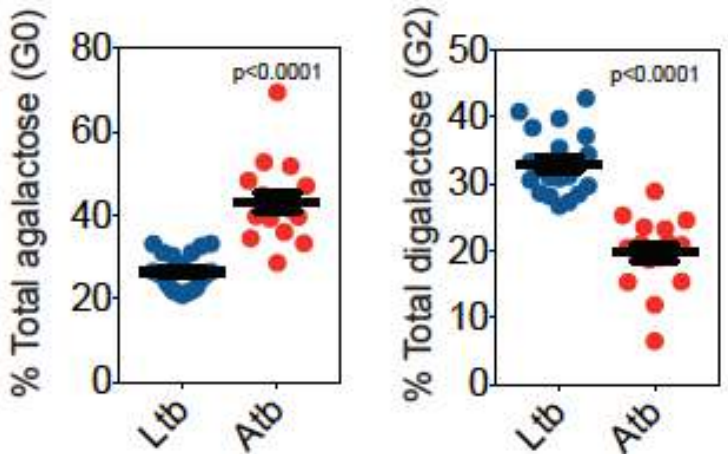
A Functional Role for Antibodies in Tuberculosis

Lenette L. Lu,[1,2,11] Amy W. Chung,[1,3,11] Tracy R. Rosebrock,[2,11] Musie Ghebremichael,[1] Wen Han Yu,[1,4] Patricia S. Grace,[1] Matthew K. Schoen,[1] Fikadu Tafesse,[1] Constance Martin,[2] Vivian Leung,[2] Alison E. Mahan,[1] Magdalena Sips,[1,6] Manu P. Kumar,[4] Jacquelynne Tedesco,[1] Hannah Robinson,[1] Elizabeth Tkachenko,[1] Monia Draghi,[1] Katherine J. Freedberg,[1] Hendrik Streeck,[5] Todd J. Suscovich,[1] Douglas A. Lauffenburger,[4] Blanca I. Restrepo,[7] Cheryl Day,[8,9,10] Sarah M. Fortune,[2,*] and Galit Alter[1,12,*]





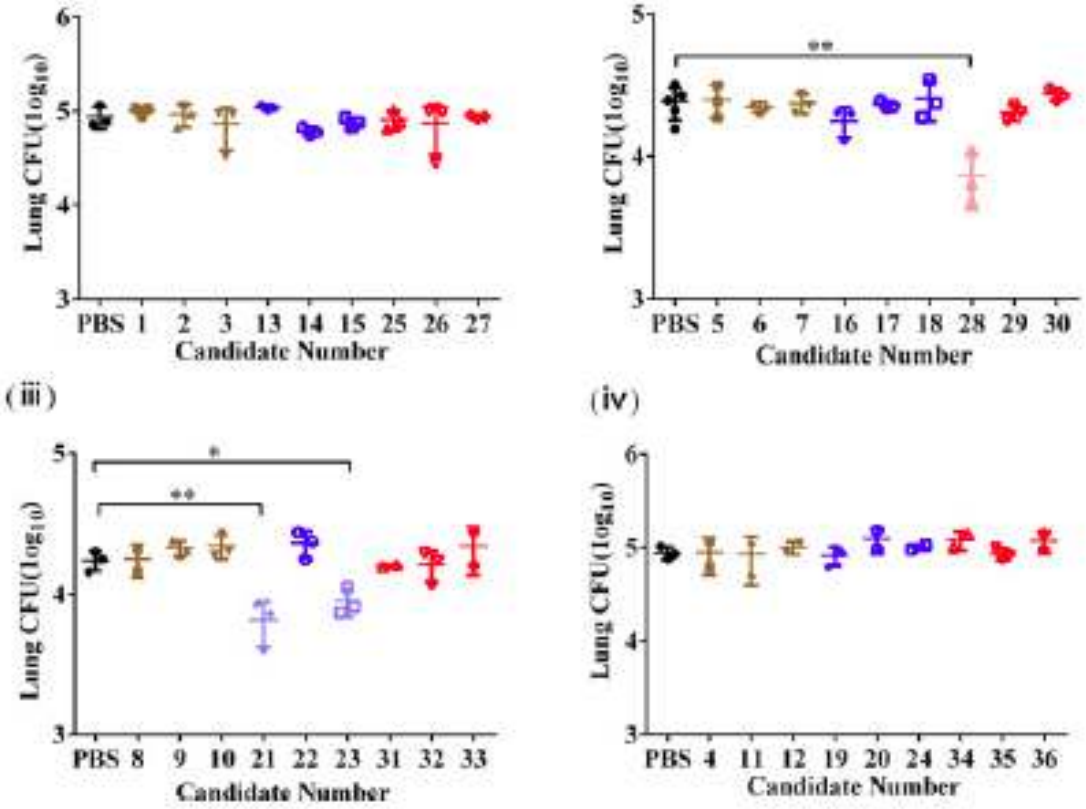
Dekkers et al., *Sci Rep* 2016



Lu et al, *Cell* 2016

Latently and uninfected healthcare workers exposed to TB make protective antibodies against *Mycobacterium tuberculosis*

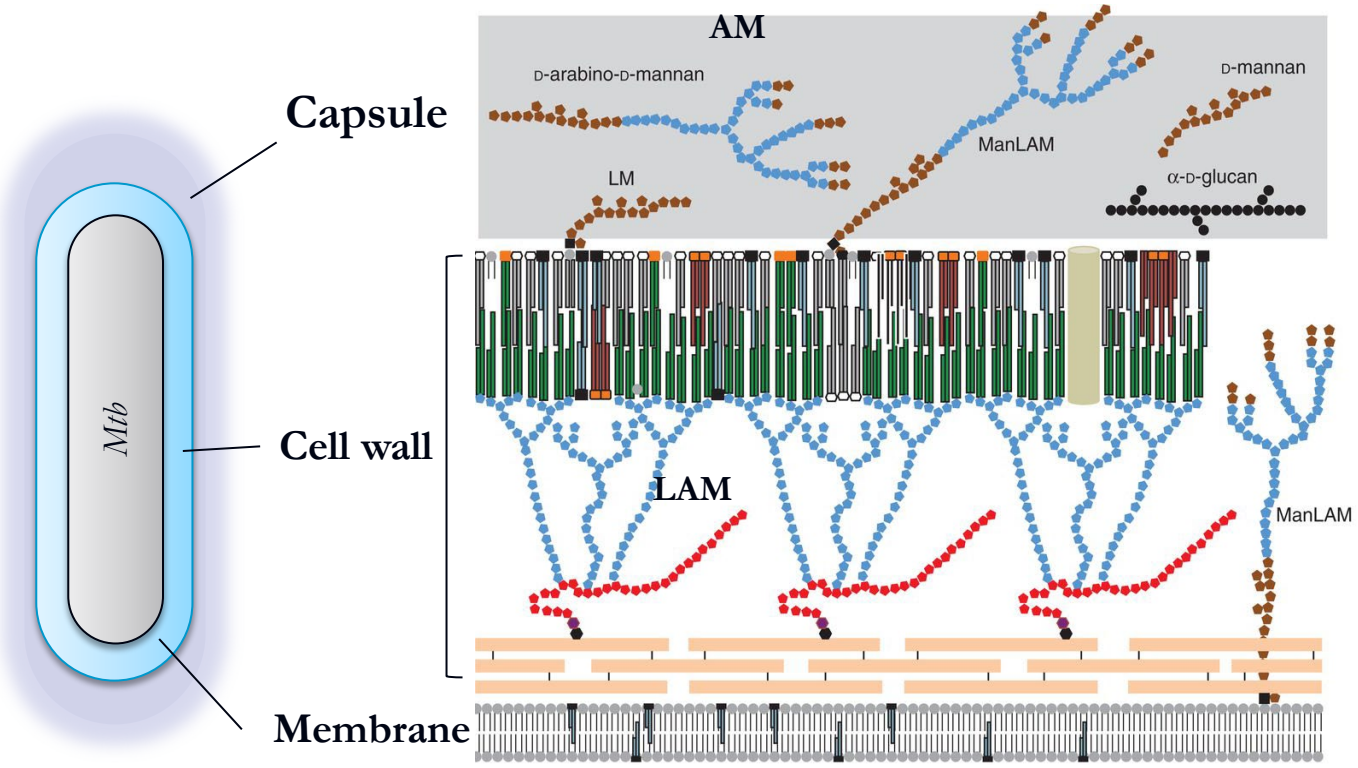
Hao Li[a], Xing-xing Wang[a], Bin Wang[b], Lei Fu[b], Guan Liu[c], Yu Lu[b], Min Cao[c], Hairong Huang[c,1], and Babak Javid[a,1]



20 mg serum IgG i.p. 5 hrs prior to 100-200 CFU aerosolized Mtb

Li *et al.,* PNAS 2017

Mycobacterial Surface Polysaccharide AM & LAM

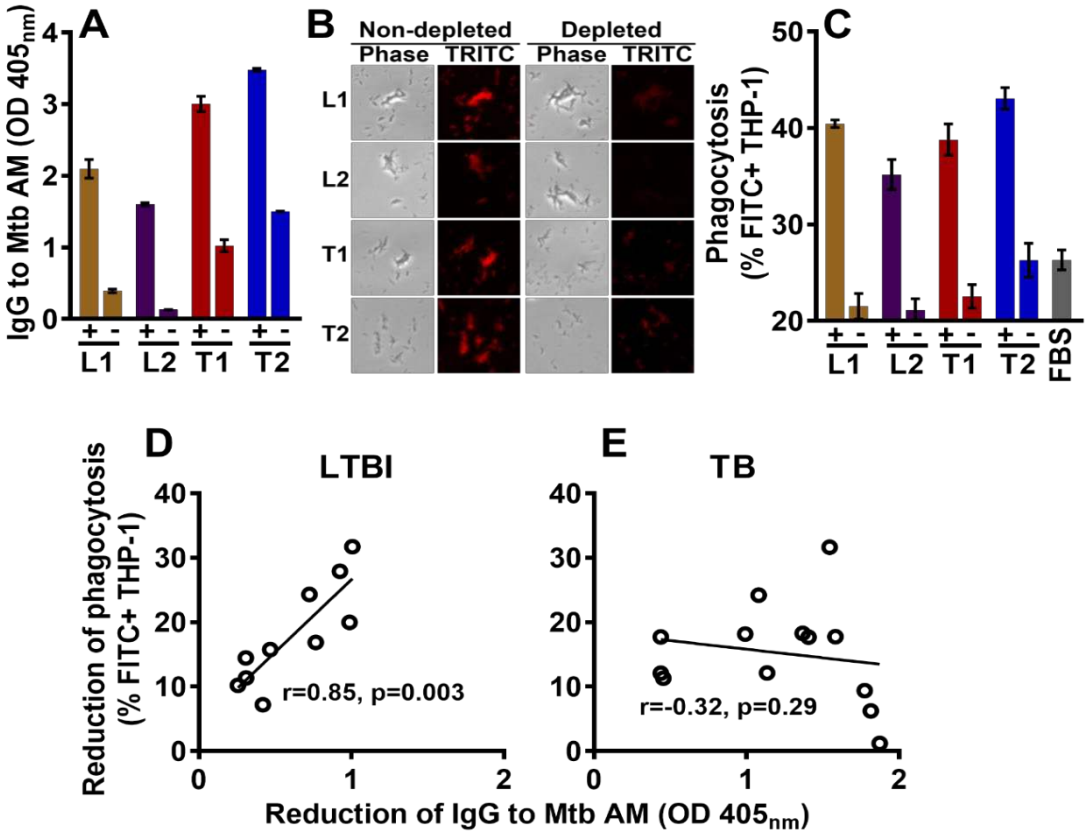


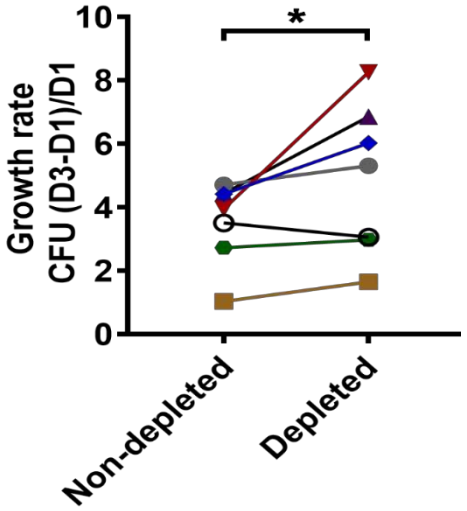
Jackson *Cold Spring Harb,* 2014

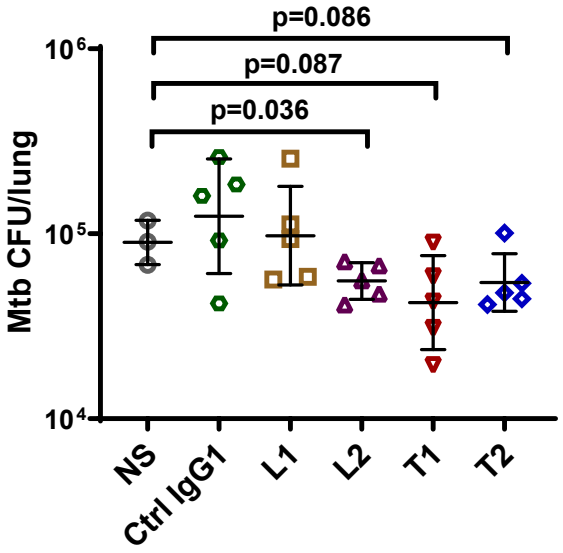
JCI The Journal of Clinical Investigation

Capsular glycan recognition provides antibody-mediated immunity against tuberculosis

Tingting Chen, … , Todd L. Lowary, Jacqueline M. Achkar 2020

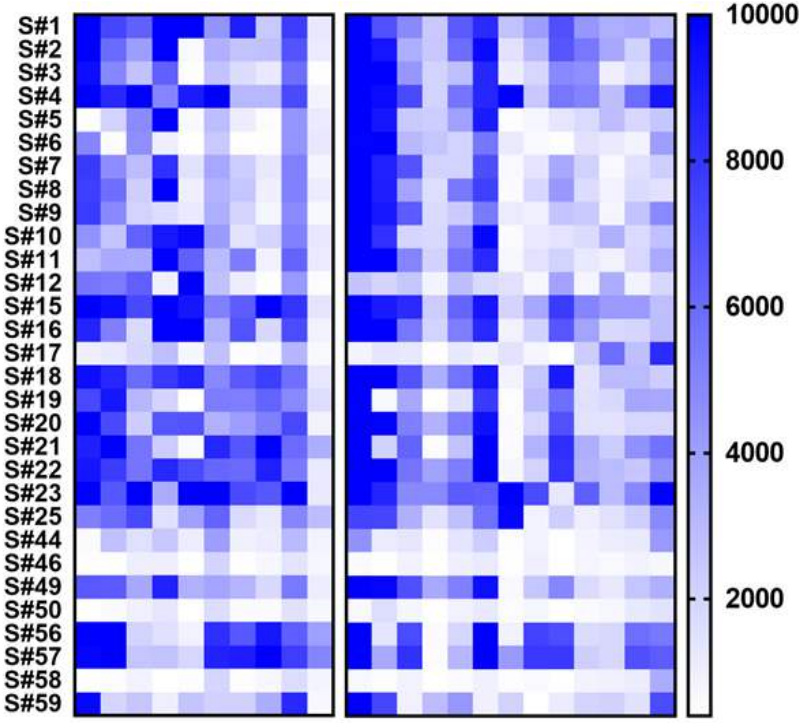


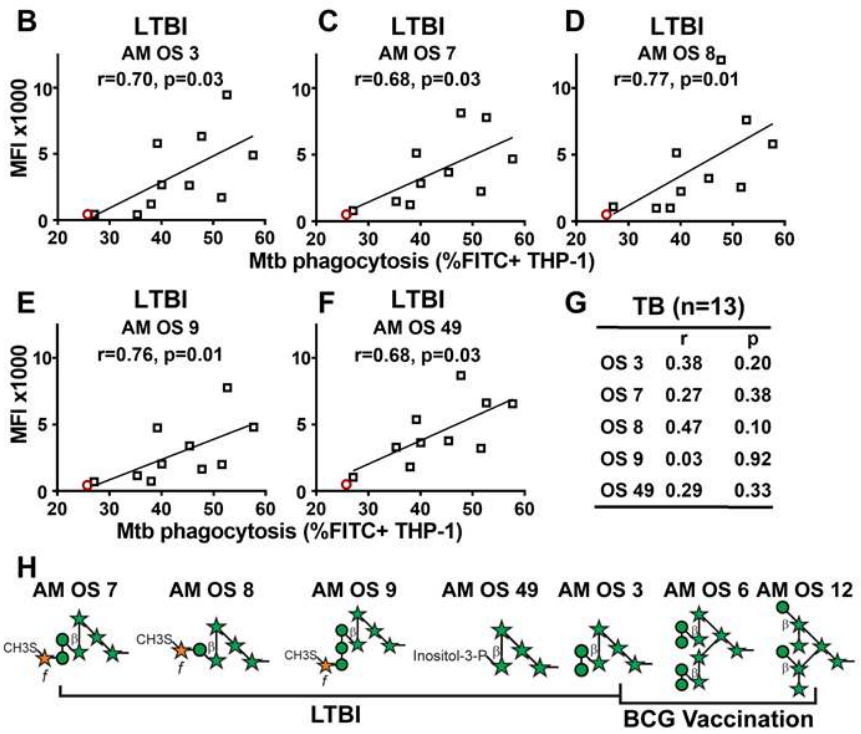




12 ug AM-specific serum IgG i.p.
Prior to Mtb infection of B6 mice

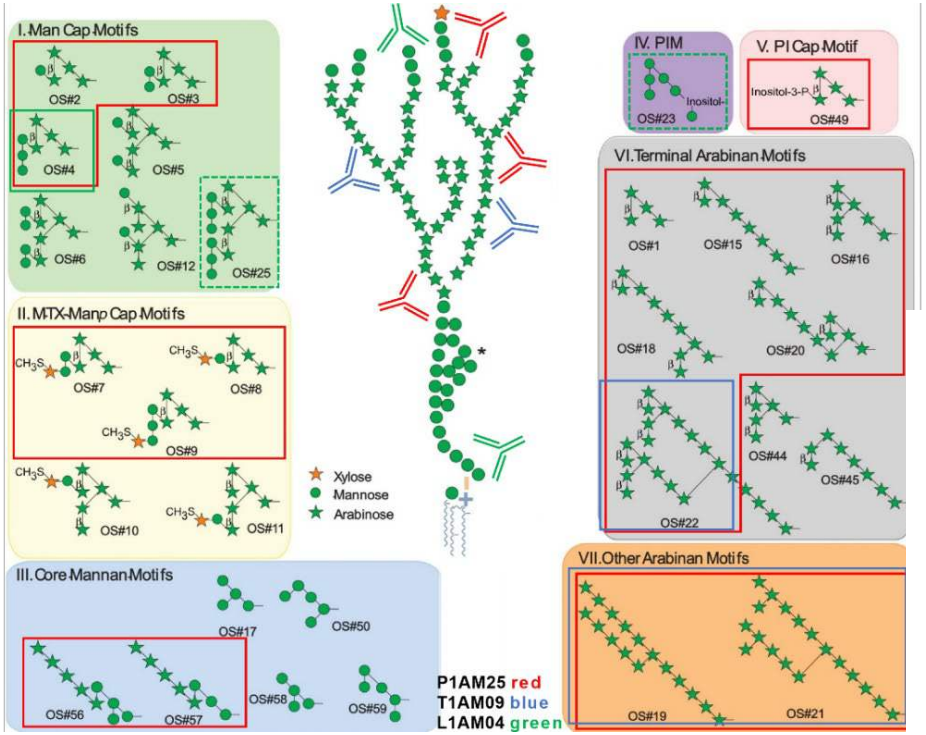
Association of AM oligosaccharide recognition with IgG function against Mtb infection

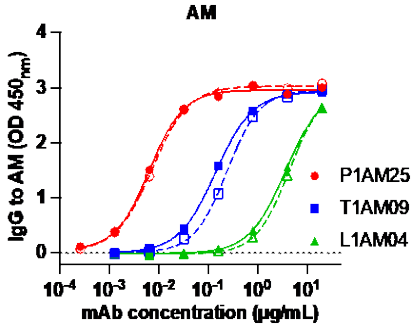




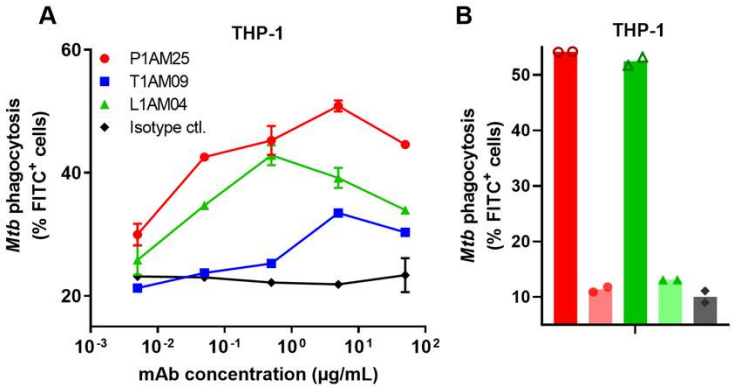
Chen et al., *J Clin Investigation* 2020

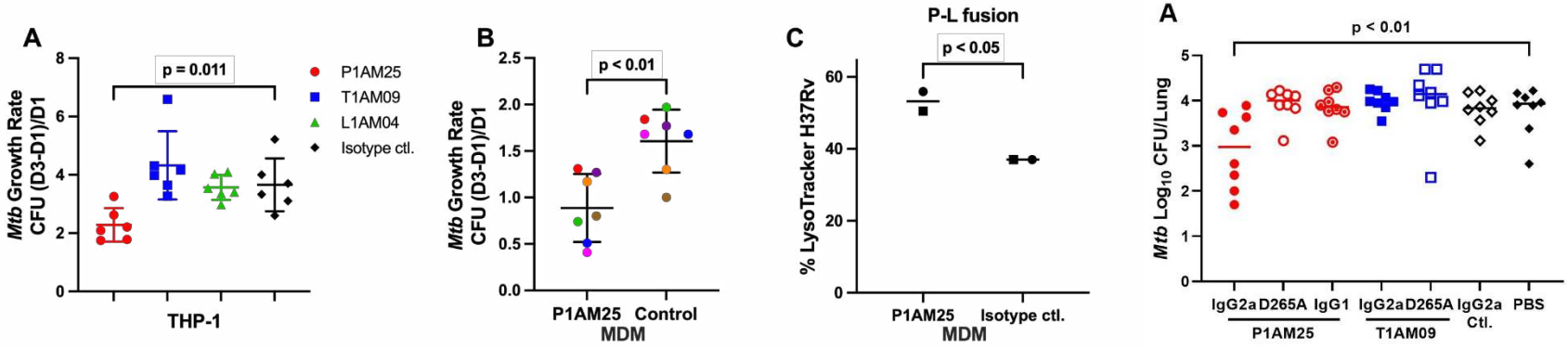
Binding to glycan epitopes affects functions of anti-AM mAbs against *Mtb*





Affinity to AM by Bio-layer interferometry			
MAb ID	P1AM25	T1AM09	L1AM04
K_D (M)	3.4E-09	2.6E-08	9.6E-08

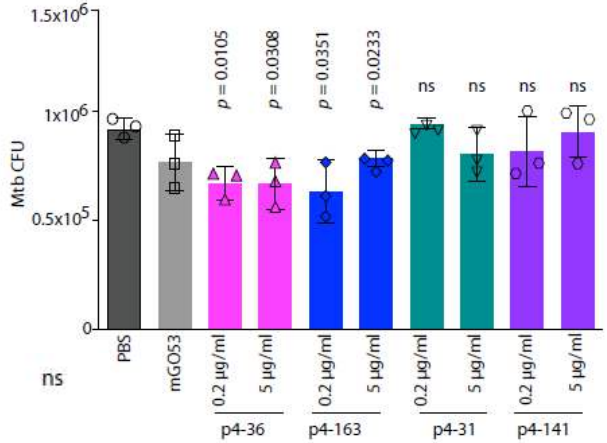


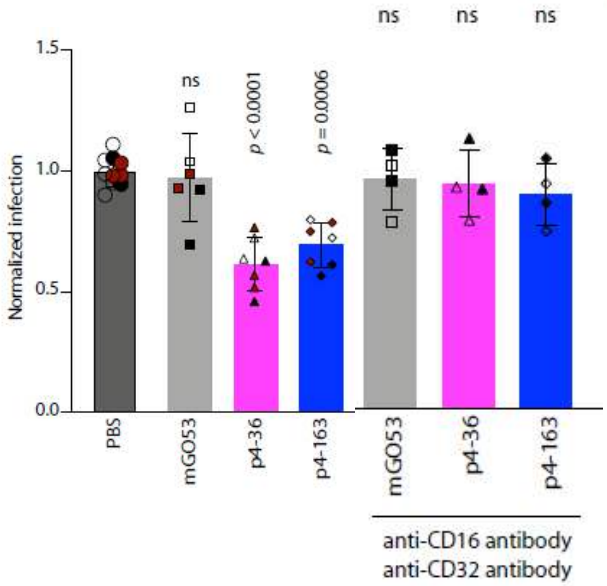


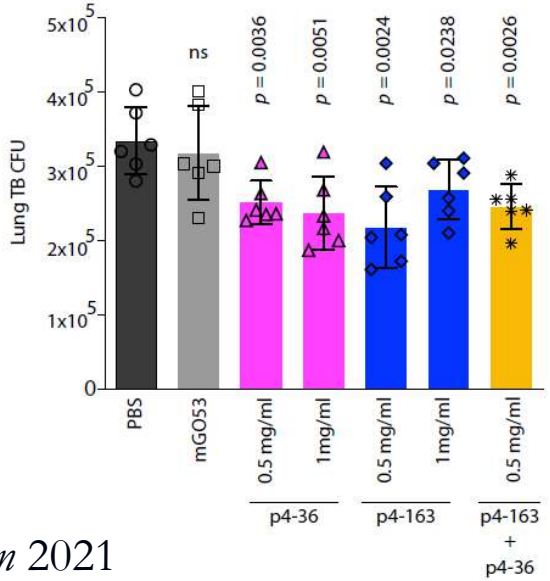
Liu et al., under review

Human antibodies targeting a *Mycobacterium* transporter protein mediate protection against tuberculosis

Avia Watson[1,13], Hao Li[2,3,13], Bingting Ma[4,13], Ronen Weiss[1], Daniele Bendayan[5], Lilach Abramovitz[1], Noam Ben-Shalom[1], Michael Mor[1], Erica Pinko[5], Michal Bar Oz[6], Zhenqi Wang[2], Fengjiao Du[7], Yu Lu[7], Jan Rybniker[8,9], Rony Dahan[10], Hairong Huang[11], Daniel Barkan[6], Ye Xiang[4]✉, Babak Javid[2,12]✉ & Natalia T. Freund[1]✉

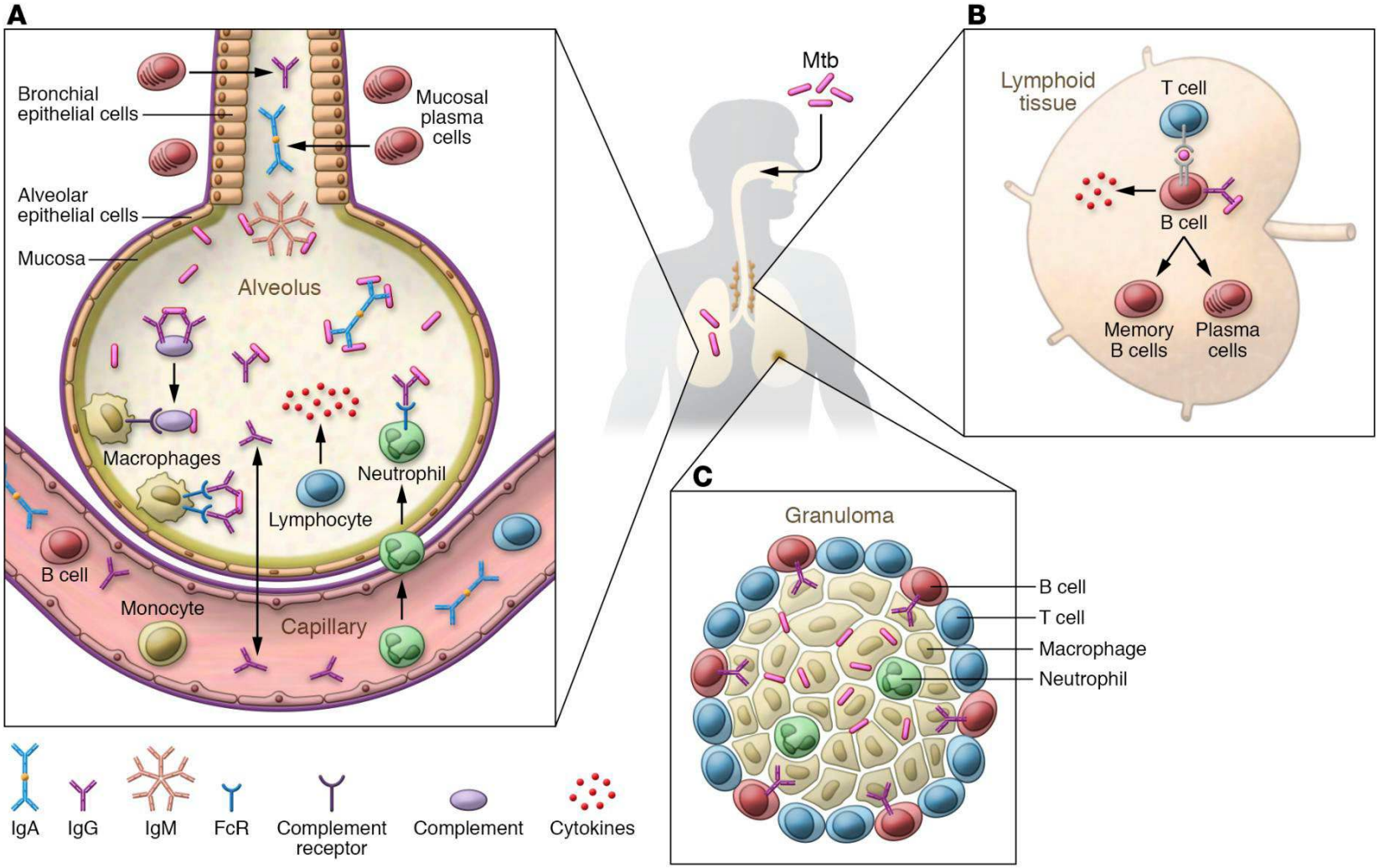






Watson et al., *Nat Commun* 2021

Potential protective roles of antibodies and B cells in the lung during initial *Mtb* exposure and LTBI



Boom, Schaible & Achkar, *J Clin Investigation* 2021

BCG vaccine studies in NHPs showed associations of mucosal airway antibodies with protection against TB

nature medicine

Letter | Published: 21 January 2019

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

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

Nature Medicine **25**, 255–262(2019) | Cite this article

Increased IgA to PPD in the broncho-alveolar lavage fluid (BALF).

nature

Article | Open Access | Published: 01 January 2020

Prevention of tuberculosis in macaques after intravenous BCG immunization

Patricia A. Darrah, Joseph J. Zeppa, Pauline Maiello, Joshua A. Hackney, Marc H. Wadsworth II, Travis K. Hughes, Supriya Pokkali, Phillip A. Swanson II, Nicole L. Grant, Mark A. Rodgers, Megha Kamath, Chelsea M. Causgrove, Dominick J. Laddy, Aurelio Bonavia, Danilo Casimiro, Philana Ling Lin, Edwin Klein, Alexander G. White, Charles A. Scanga, Alex K. Shalek, Mario Roederer, JoAnne L. Flynn & Robert A. Seder

Nature **577**, 95–102(2020) | Cite this article

IV BCG induced **higher titers of IgG and IgA against *Mtb* whole cell lysate in BALF** and plasma than other vaccination routes.

Presence of plasma IgM to LAM, PstS1, and Apa and **BALF IgA, IgG, and IgM to LAM and PstS1 correlated with reduced *Mtb* burden**

nature immunology

ARTICLES

https://doi.org/10.1038/s41590-021-01066-1

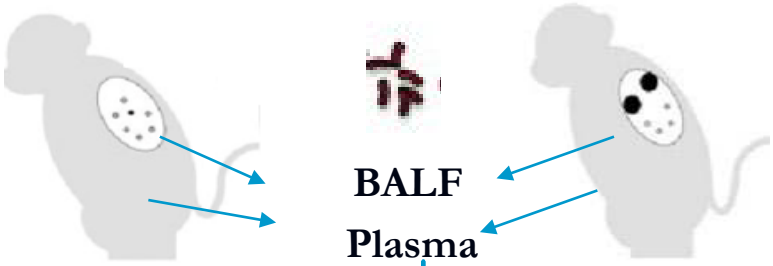
Check for updates

OPEN

Robust IgM responses following intravenous vaccination with Bacille Calmette–Guérin associate with prevention of *Mycobacterium tuberculosis* infection in macaques

Edward B. Irvine[1,2], Anthony O'Neil[1], Patricia A. Darrah[3], Sally Shin[1], Alok Choudhary[4], Wenjun Li[5], William Honnen[4], Smriti Mehra[6], Deepak Kaushal[7], Hannah Priyadarshini Gideon[8], JoAnne L. Flynn[8], Mario Roederer[3], Robert A. Seder[3], Abraham Pinter[4], Sarah Fortune[1,2,9] and Galit Alter[1,9]

Mtb antigen-unbiased approach to investigate antibody correlates of protection against TB in cynomolous macaques



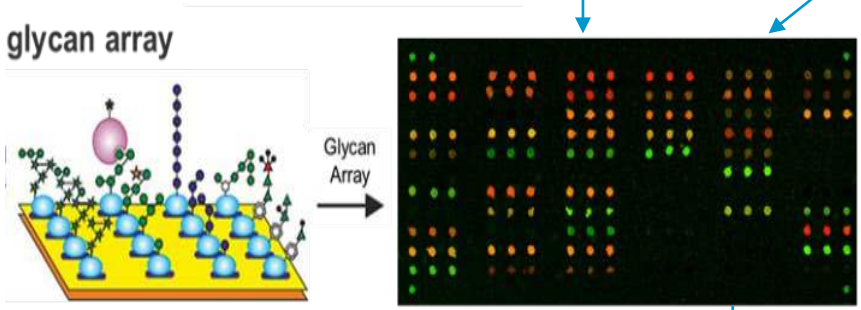
LTBI
(n = 35)

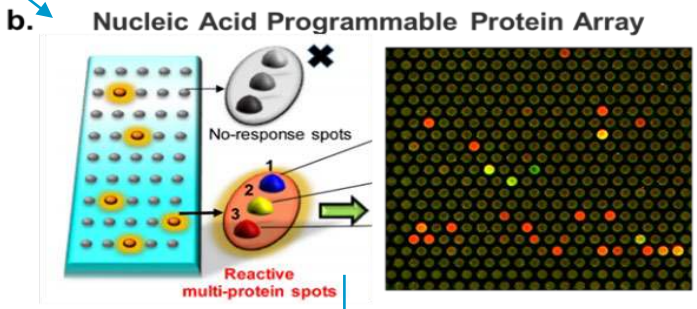
BALF
Plasma

TB
(n = 21)

Pre-infection | **Early infection (2 – 3 months)** | **Late infection (5 – 6 months)**

IgM | **IgG & IgA**





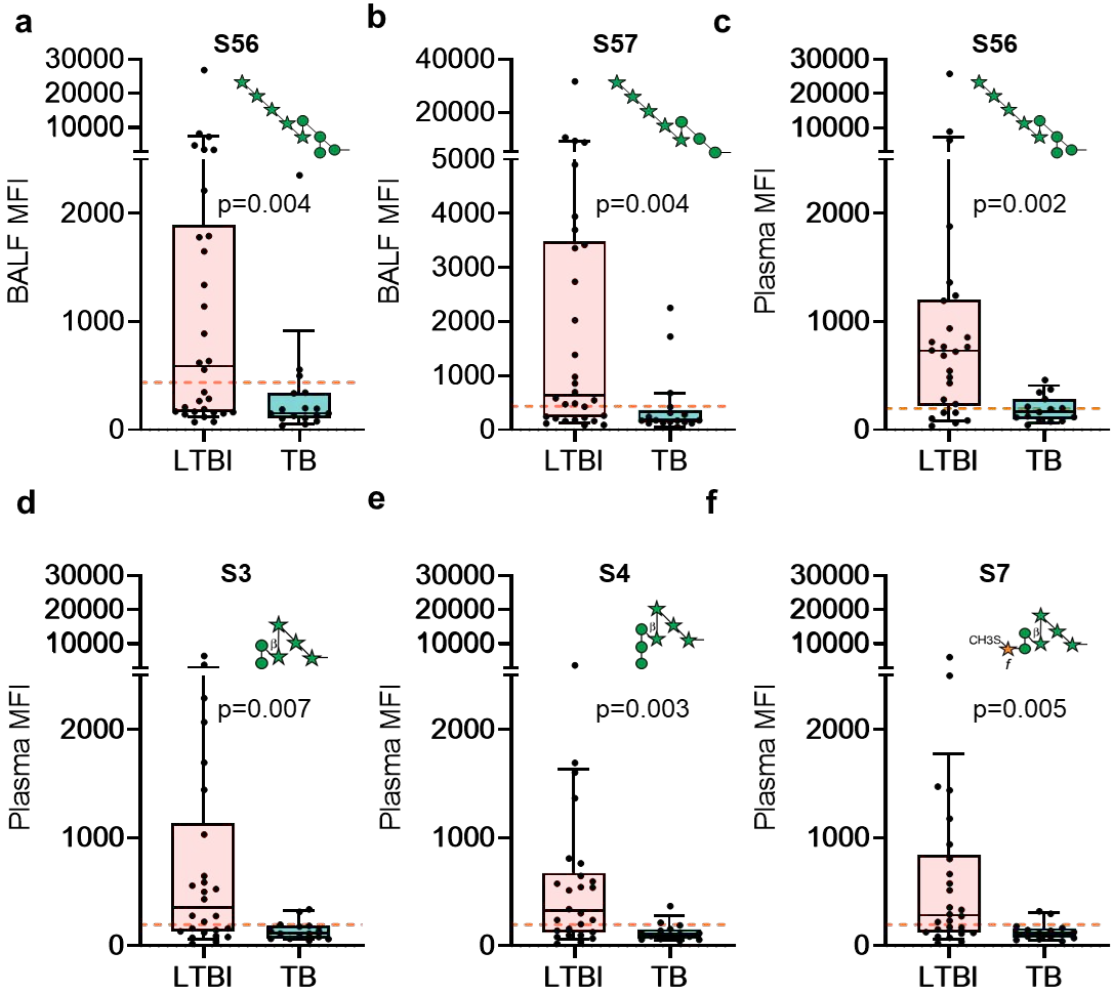
Data processing with normalization & Filtering for reactive *Mtb* glycans and proteins

↓

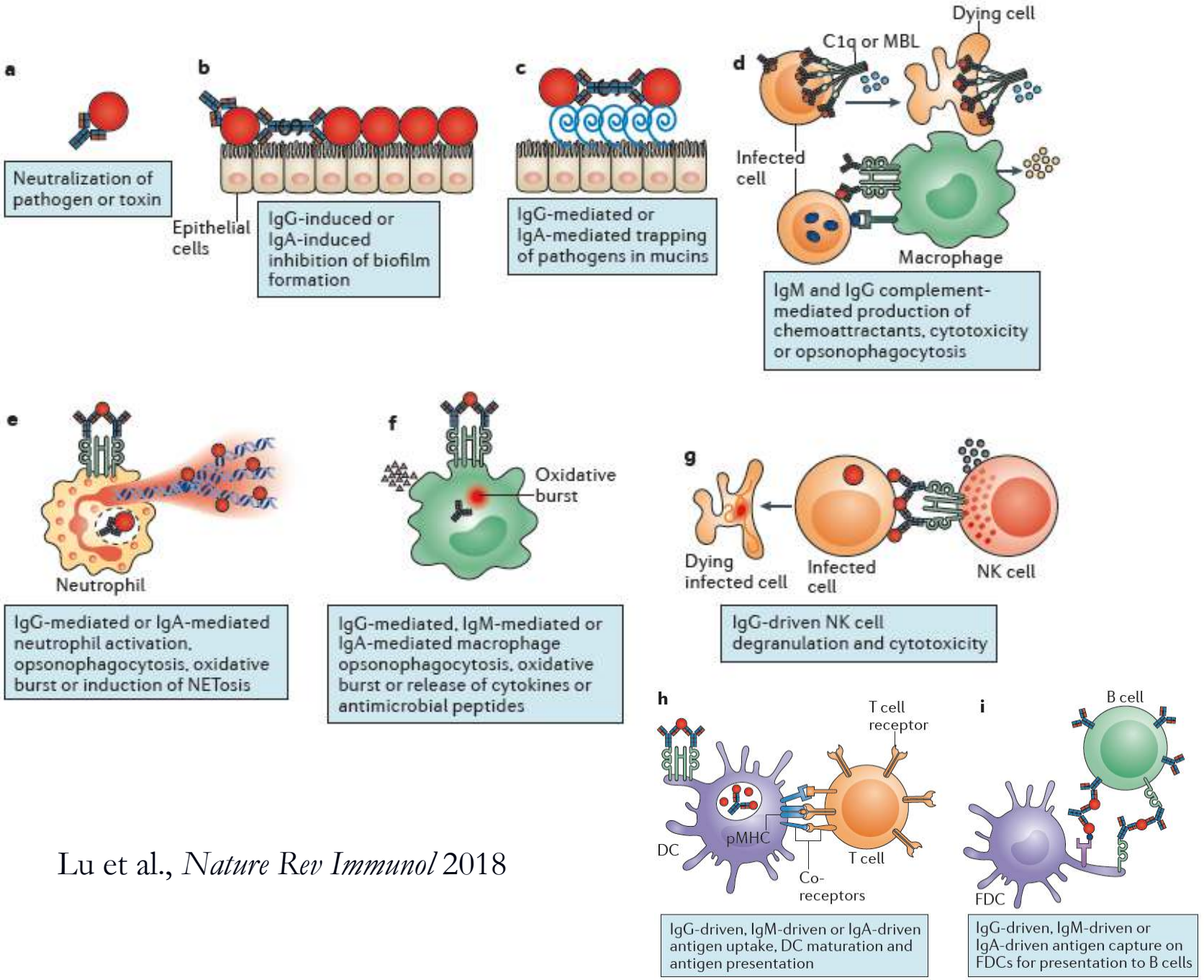
Analysis with identification of *Mtb* glycans and proteins associated with LTBI outcome

Ishida et al, in revision

Pre-existing mucosal airway and systemic IgA responses to specific AM motifs correlate with control of *Mtb* infection



Ishida et al, in revision



Lu et al., *Nature Rev Immunol* 2018

Major remaining gaps of knowledge

- Most critical B cell antigens/epitopes
- Antigen expression on infected cells
- Interactions with other immune arms and mechanisms of protection
- B cells vs antibody effects
- Mucosal vs systemic antibody responses and their likely different mechanism of protection
- Role of isotypes at different stages of *Mtb* infection
- Natural vs vaccine induced immunity

Acknowledgements

Achkar Lab

- **Tingting Chen**
- **Yanyan Liu**
- **Elise Ishida**
- Sushmitha Aliathe
- Devin Corrigan
- Aisha Furey
- Cristal Finkenberg
- Yonqi Zhu
- Sarah Singer
- Caroline Blanc

Einstein Collaborators

- Jon Lai
- John Chan (Rutgers)

Other collaborators

- Todd Lowary (U of Alberta)
- Maju Joe (U of Alberta)
- Jeffrey Ravetch (Rockefeller)
- Stylianos Bournazos (Rockefeller)
- Philana (Ling) Lin
- Helen McShane (Oxford)
- Helen Fletcher (Oxford)
- Rachel Tanner (Oxford)
- Rafael Prados-Rosales (Universidad Autonoma de Madrid)
- Arturo Casadevall (J Hopkins)
- Elisabeth Jenny-Avital (JMC)

Funding

- NIAID AI146329, AI117927, AI127173
- FDA; AERAS