

Immunity to Tuberculosis: reevaluating what we think we know



Carolyn King, University of Basel
21 March 2023

Tuberculosis

then...

and now

Chopin



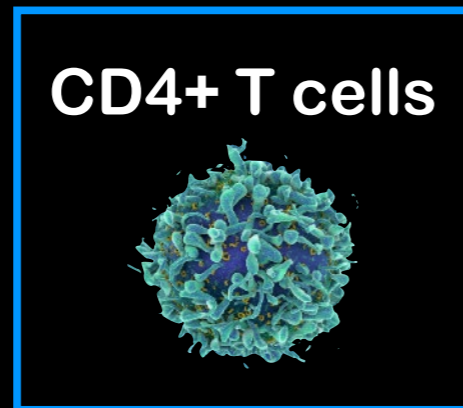
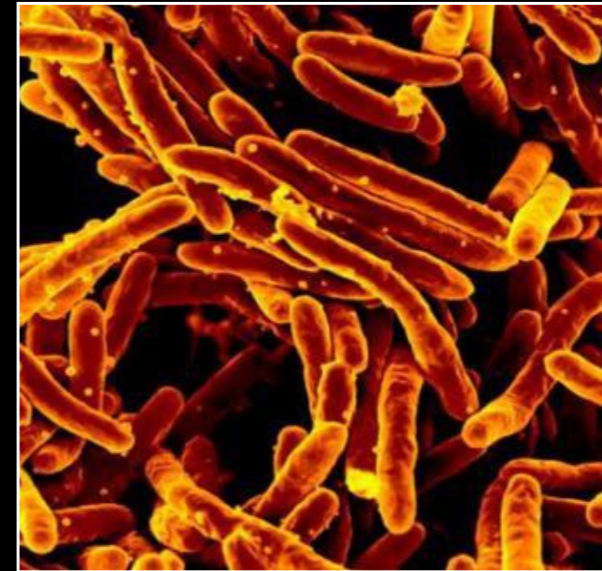
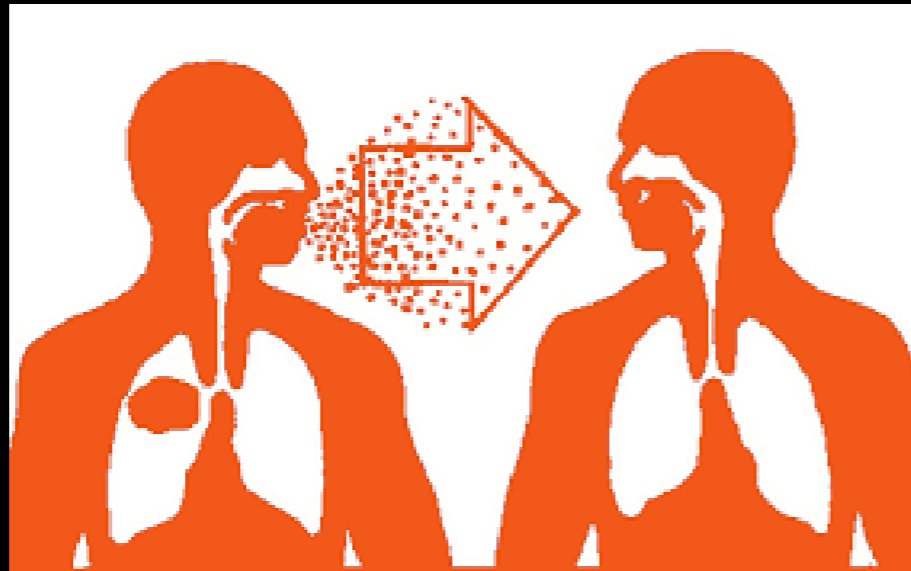
Brontë



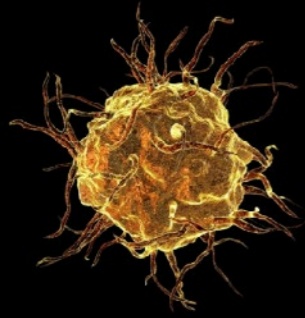
Chekhov



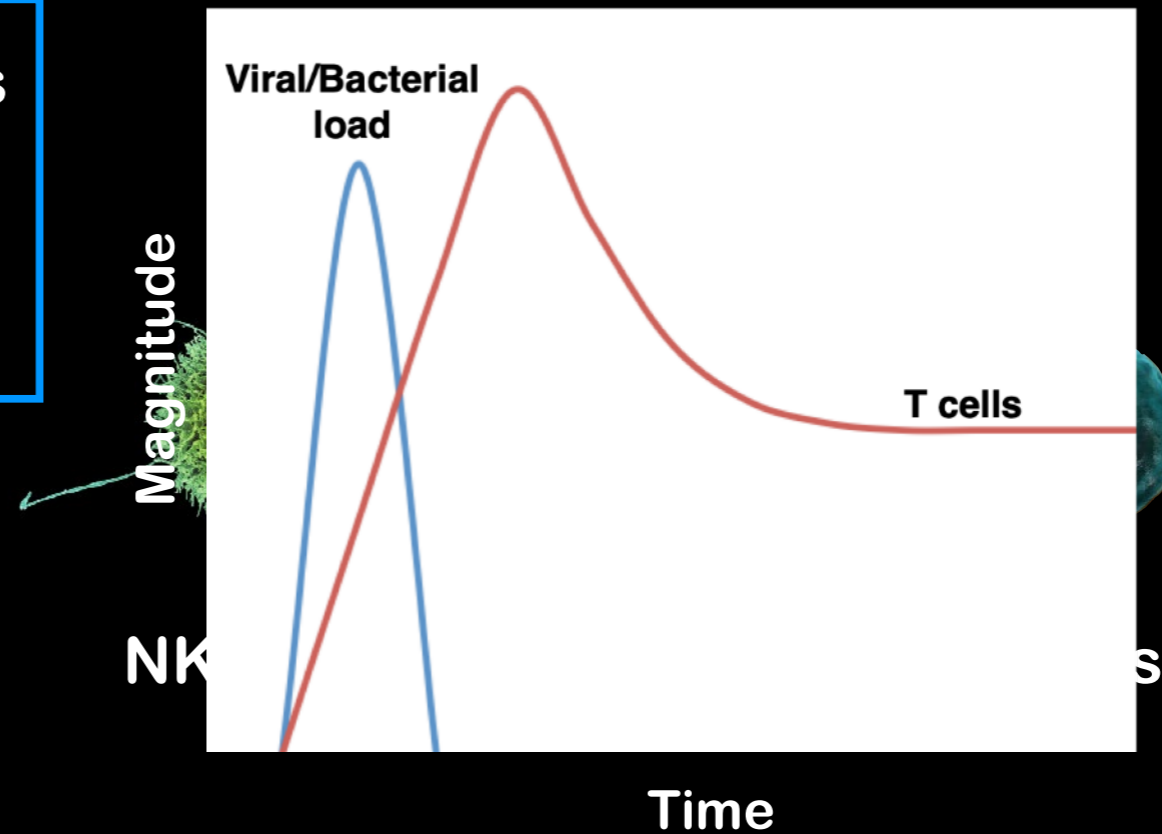
90% of TB infections are well controlled



CD4+ T cells



macrophages



T cell memory and vaccines

nature
medicine

LETTERS

<https://doi.org/10.1038/s41591-018-0319-9>

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

Karin Dijkman^{1*}, Claudia C. Sombroek¹, Richard A. W. Vervenne¹, Sam O. Hofman¹, Charelle Boot¹, Edmond J. Remarque¹, Clemens H. M. Kocken¹, Tom H. M. Ottenhoff², Ivanela Kondova¹, Mohammed A. Khayum¹, Krista G. Haanstra¹, Michel P. M. Vierboom¹ and Frank A. W. Verreck^{1*}



Protection from tuberculosis

T CELL VACCINES

Vaccine-elicited CD4 T cells induce immunopathology after chronic LCMV infection

Pablo Penaloza-MacMaster¹, Daniel L. Barber², E. John Wherry³, Nicholas M. Provine¹, Jeffrey E. Teigler^{1*}, Lily Parenteau¹, Stephen Blackmore¹, Erica N. Borducchi¹, Rafael A. Larocca¹, Kathleen B. Yates⁴, Hao Shen³, W. Nicholas Haining⁴, Rami Sommerstein⁵, Daniel D. Pinschewer^{5,6}, Rafi Ahmed⁷, Dan H. Barouch^{1,8†}



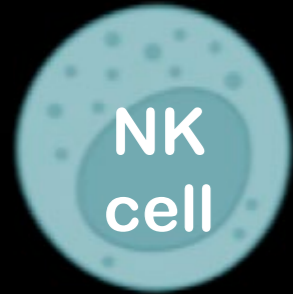
Cytokine storm, immune pathology

Network enablers

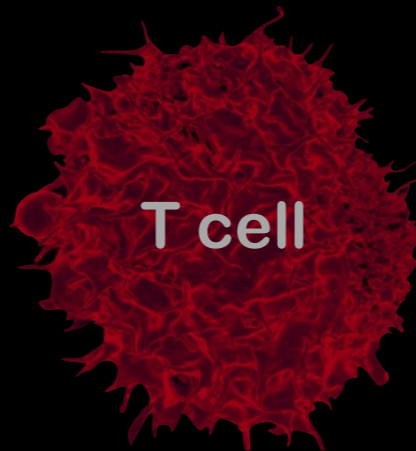
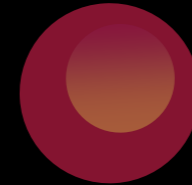


macrophage

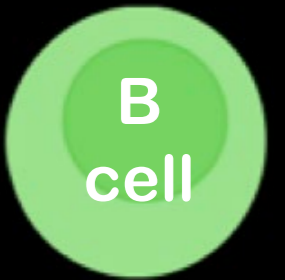
Diversity matters



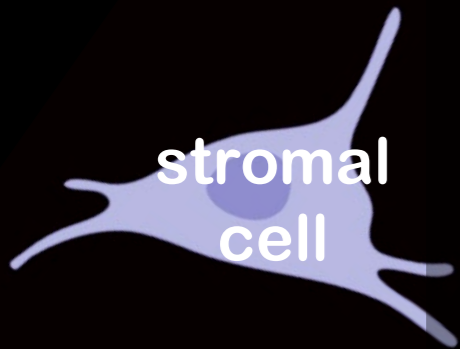
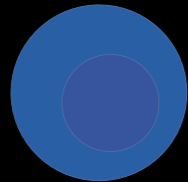
NK cell



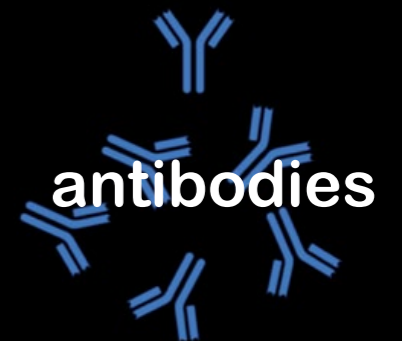
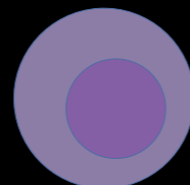
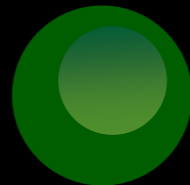
T cell



B cell



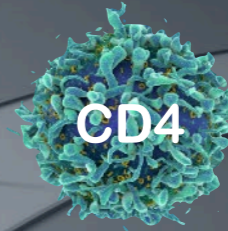
stromal cell



antibodies

Mede padesignT of p r e s e t i o c h # 1

innate
memory



CD4

BCG vaccination

intradermal administration



Alternative BCG vaccination routes



pulmonary instillation



intravenous administration



nature
medicine

LETTERS

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

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Article

Prevention of tuberculosis in macaques after intravenous BCG immunization

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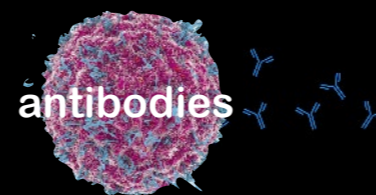
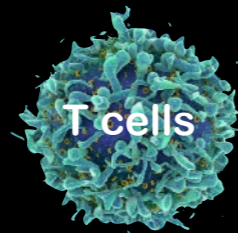
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Patricia A. Darrah¹, Joseph J. Zeppa², Pauline Maiello², Joshua A. Hackney¹, Marc H. Wadsworth II^{3,4,5}, Travis K. Hughes^{3,4,5}, Supriya Pokkali¹, Phillip A. Swanson II¹, Nicole L. Grant⁶, Mark A. Rodgers², Megha Kamath¹, Chelsea M. Causgrove², Dominick J. Laddy⁷, Aurelio Bonavia⁷, Danilo Casimiro⁷, Philana Ling Lin⁸, Edwin Klein⁹, Alexander G. White², Charles A. Scanga², Alex K. Shalek^{3,4,5,10}, Mario Roederer^{1,11}, JoAnne L. Flynn^{2,11} & Robert A. Seder^{1,11*}

Intravenous (iv) BCG prevents TB in macaques

correlates of protection in the lung mucosa



Intravenous (iv) BCG prevents TB in macaques



- BM derived myeloid cells
- epigenetic reprogramming
- glycolytic metabolism

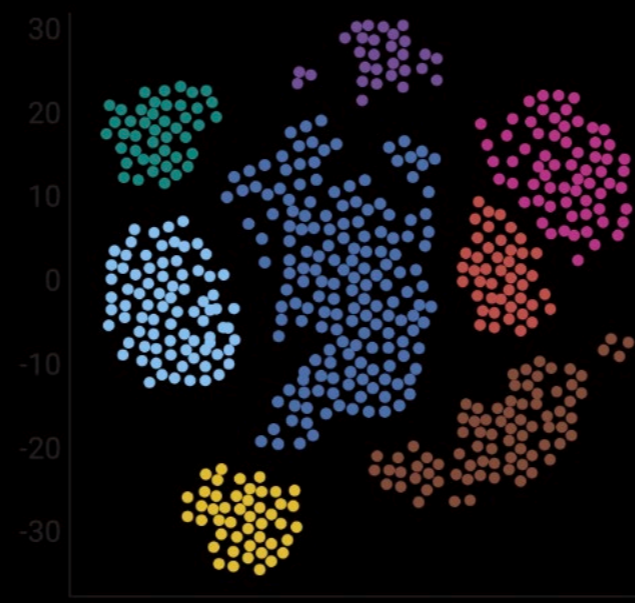
iv BCG



iv BCG remodels lung macrophages in macaques

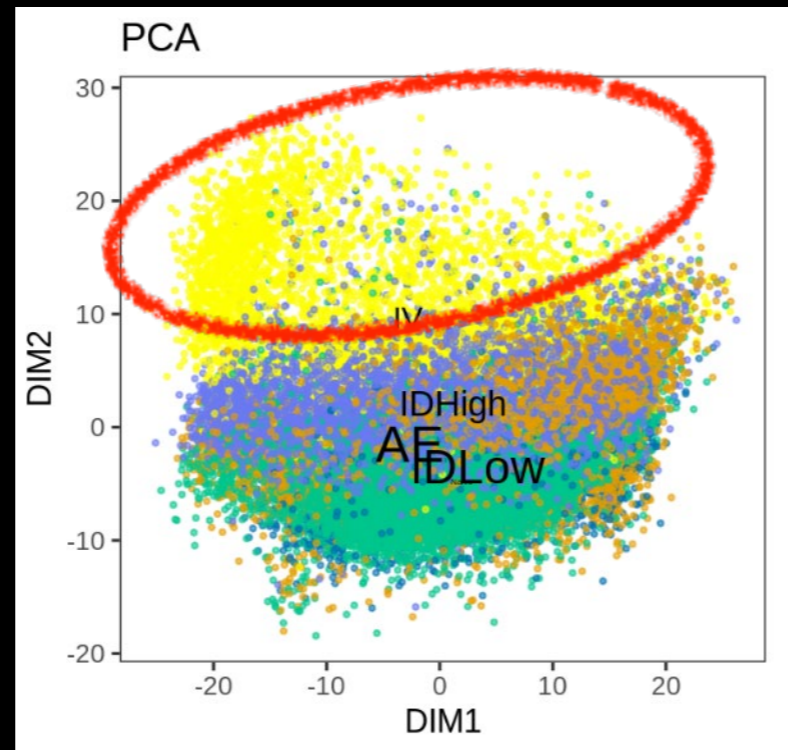


bronchoalveolar lavage fluid

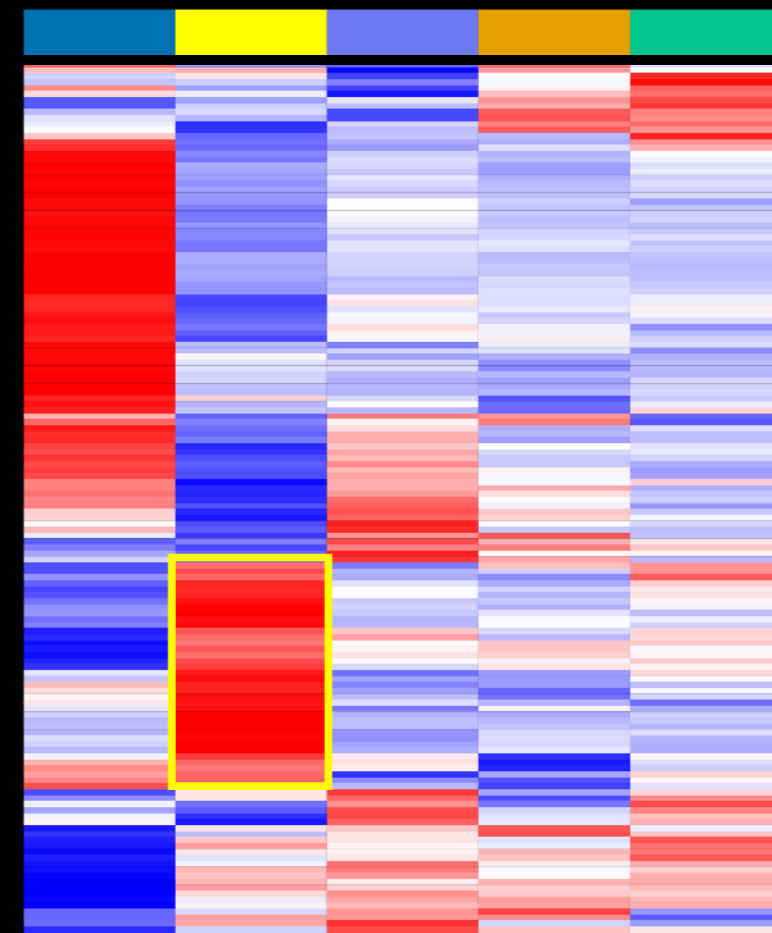


iv BCG remodels lung macrophages in macaques

no vaccine
intravenous
intradermal - low
intradermal - high
aerosol



intravenous



Top 40 cluster-defining genes

iv / it BCG remodels lung macrophages in mice

BCG immunization

naive

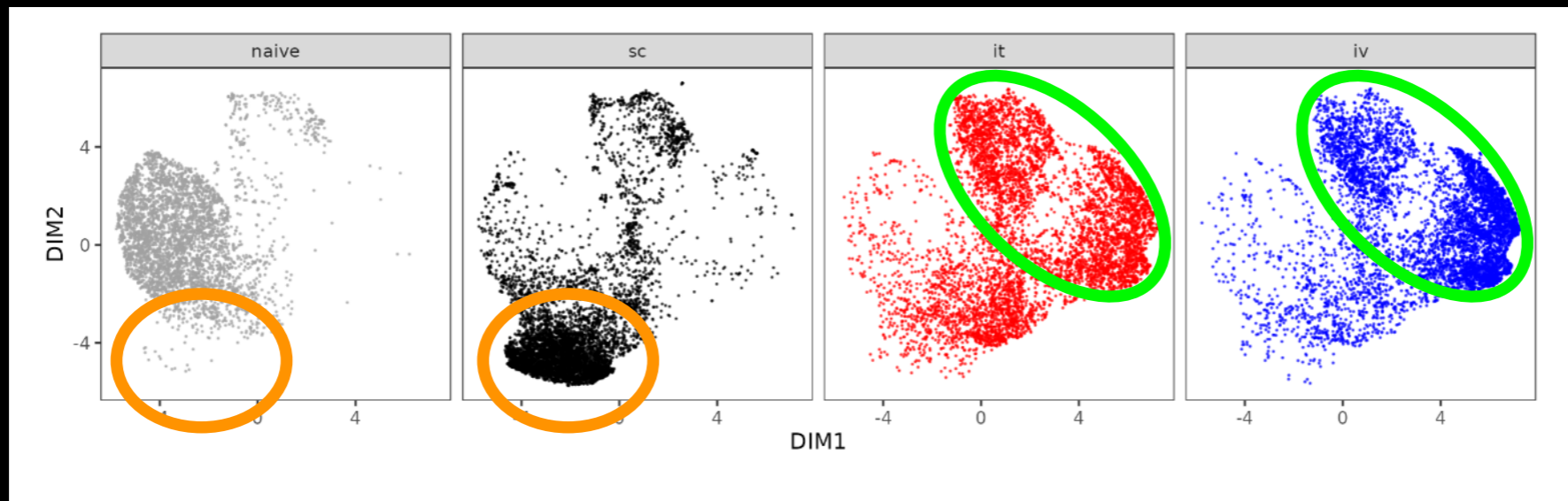
subcutaneous

intratracheal

intravenous



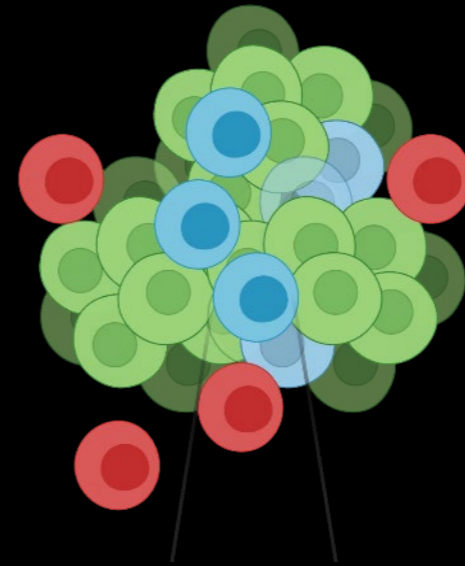
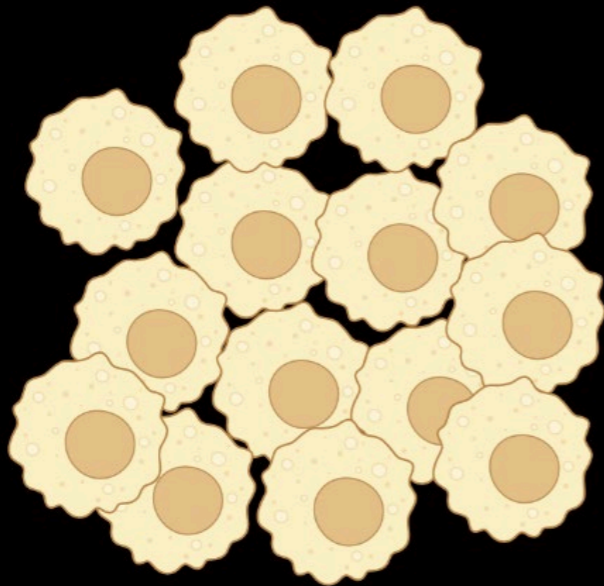
alveolar
macrophages



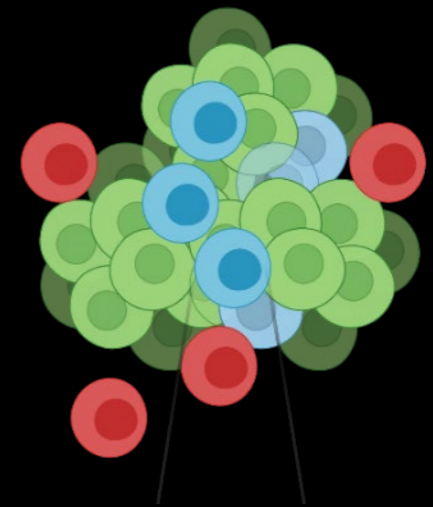
remodeled

BCG remodeling of the lung

alveolar macrophage



iBALT structures
(B & T cells)

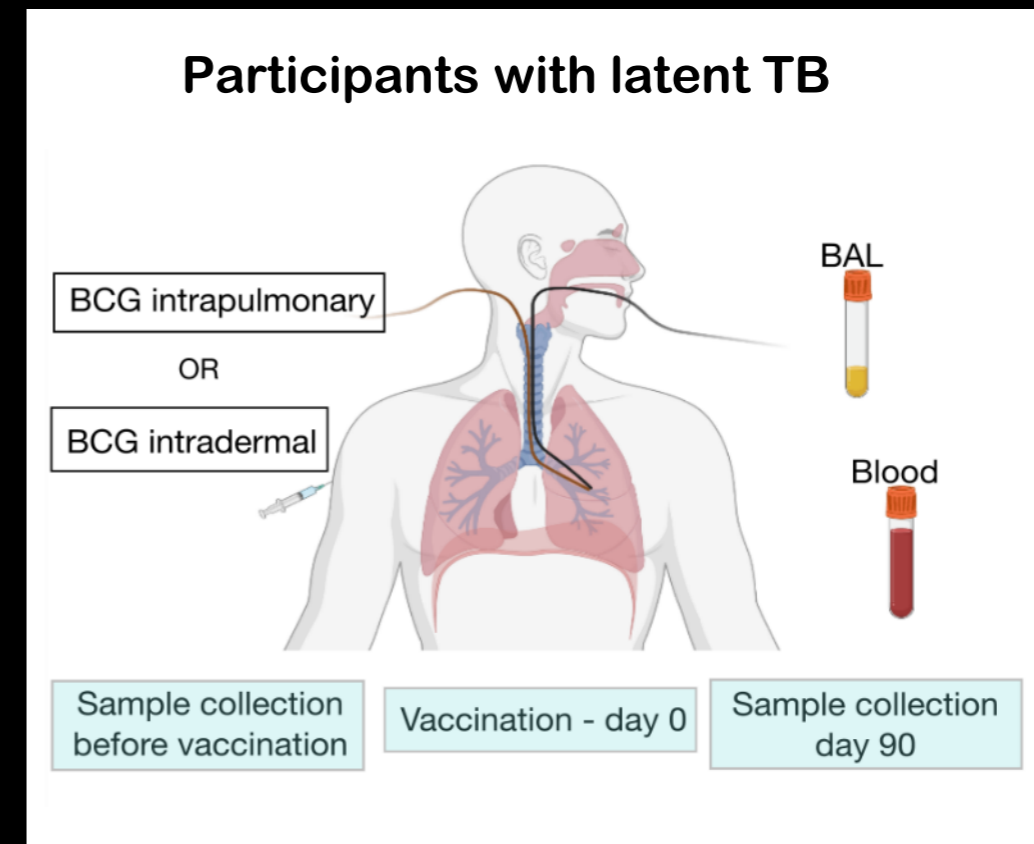


(How) does BCG remodel human macrophages?

TB-CHIM controlled human infection

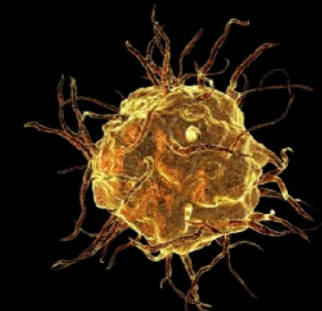


*Prof Keertan Dheda & Dr. Anil Pooran
University of Cape Town
UK MRC funded project*

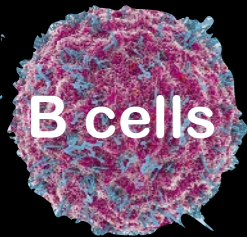


SNSF funded project

innate cell analysis
BALF/blood



New paradigm of protection #2



 TB resisters make protective antibodies

antibody quality differs between health and disease

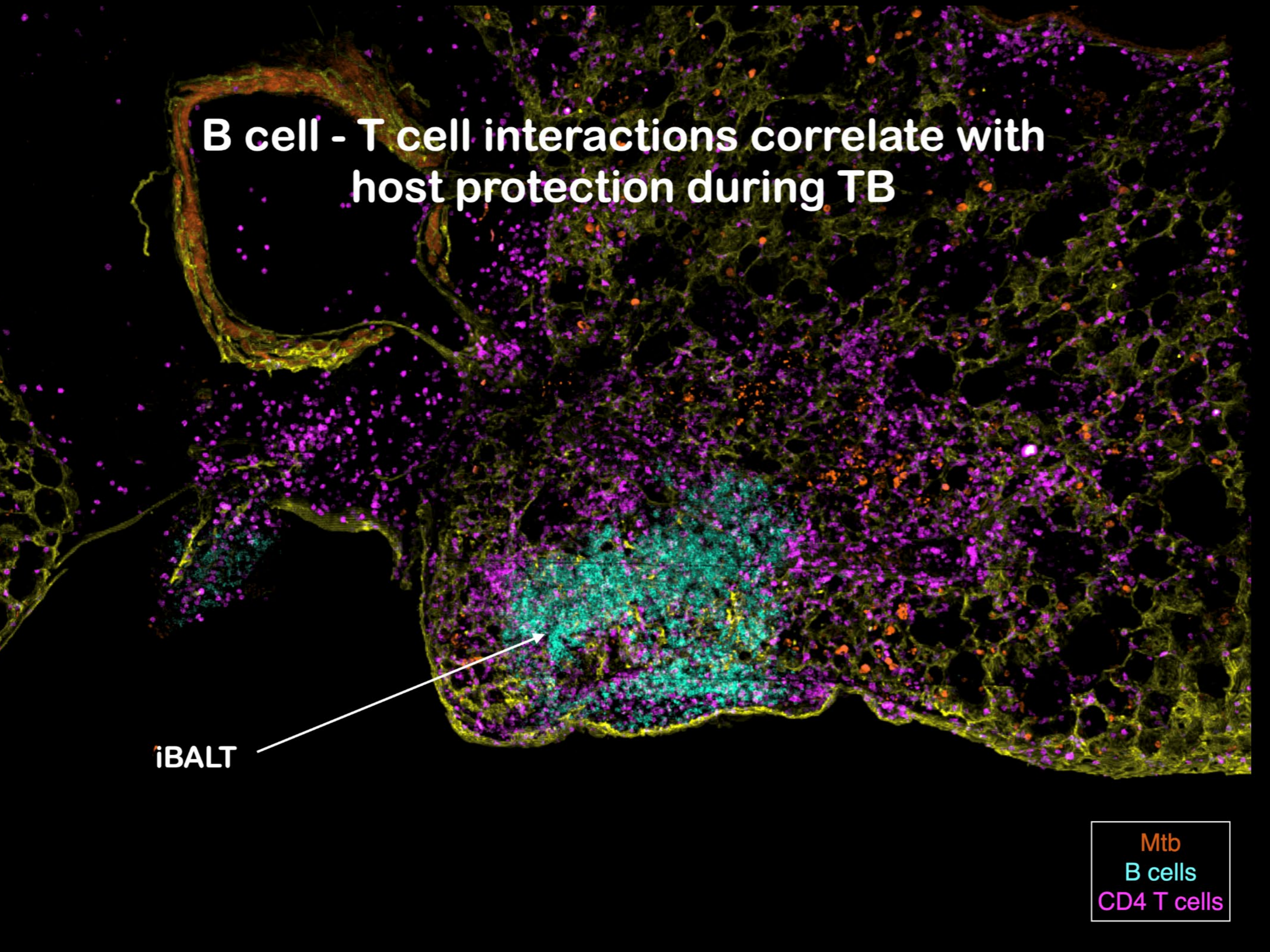
~~intracellular bacteria are not accessible to antibodies~~

~~the main (only) role of B cells is to produce antibodies~~

B cell - T cell interactions correlate with host protection during TB

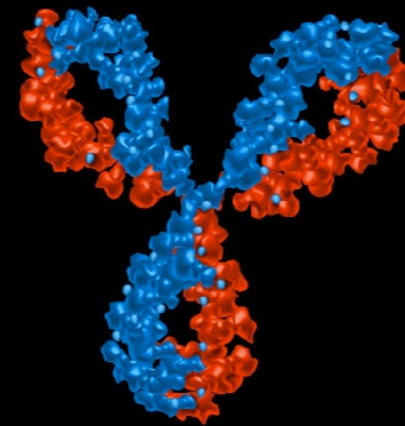
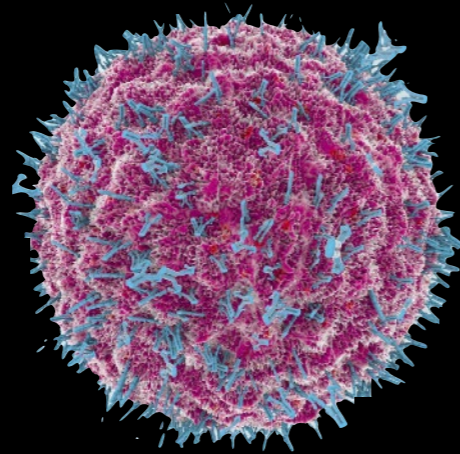
iBALT

Mtb
B cells
CD4 T cells



DEBATE

Deciphering the role of B cells and antibodies during tuberculosis



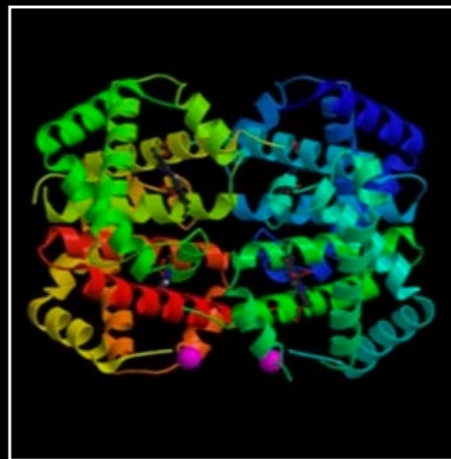
microbiology



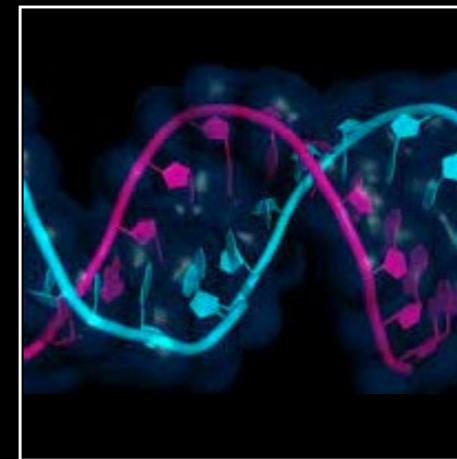
immunology



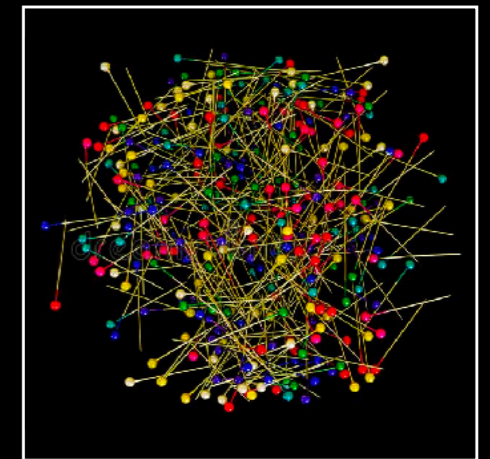
proteomics



transcriptomics



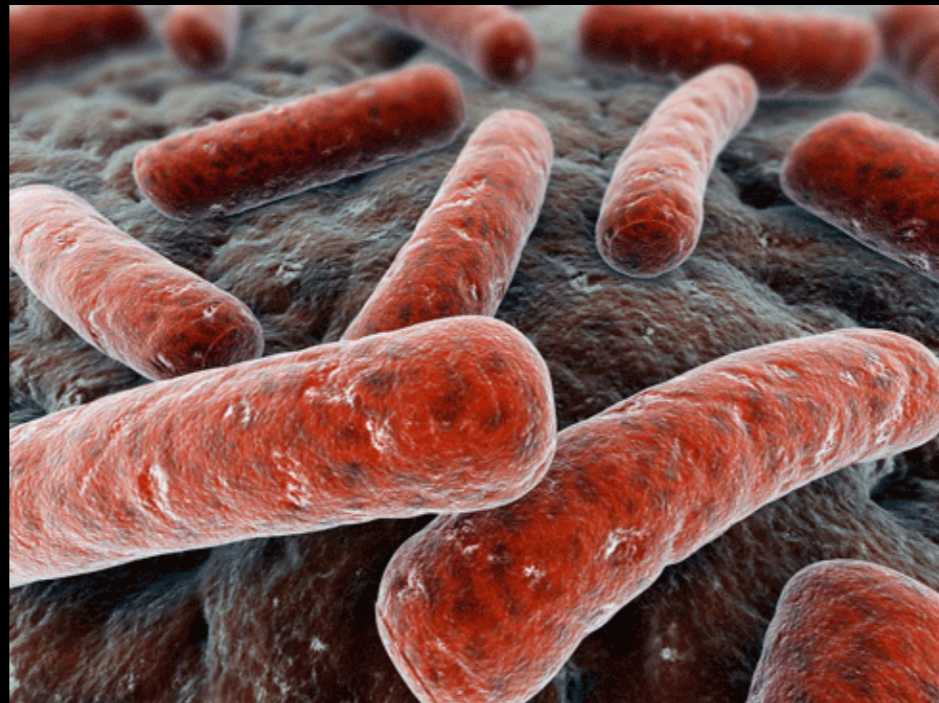
bioinformatics



What Mtb antigens do B cells recognize?

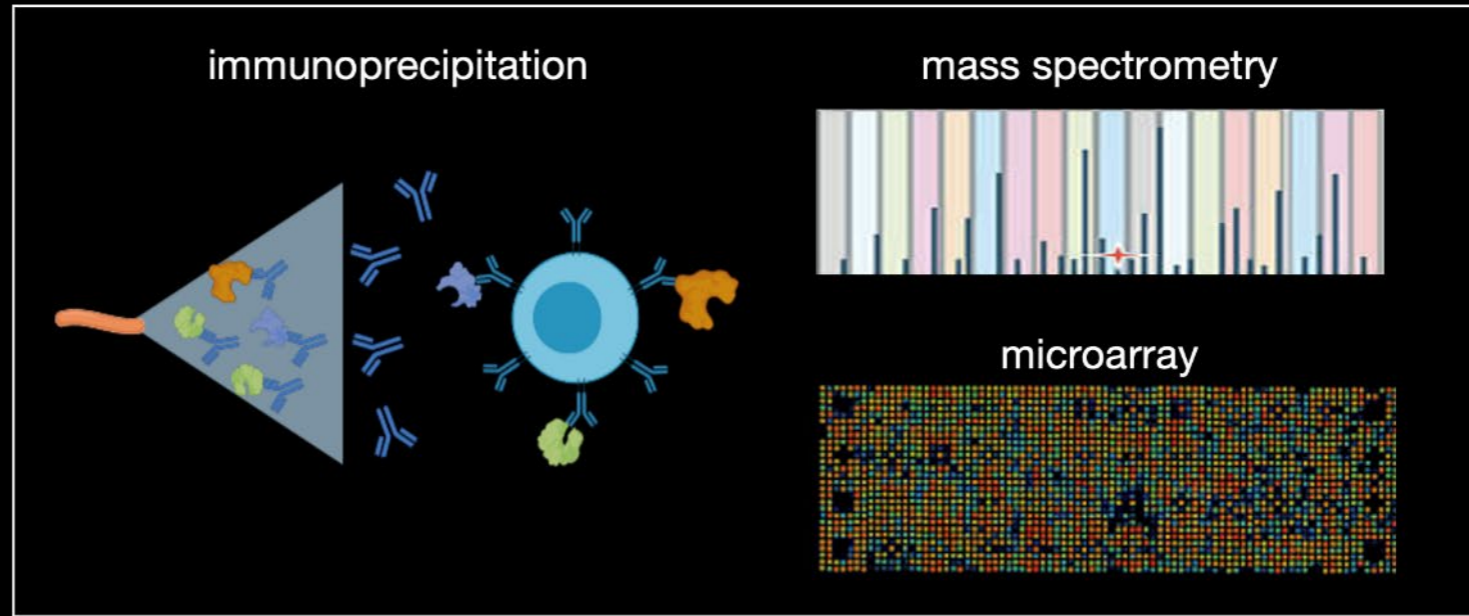
State of the field:

focus on antigens that are abundant in culture filtrate

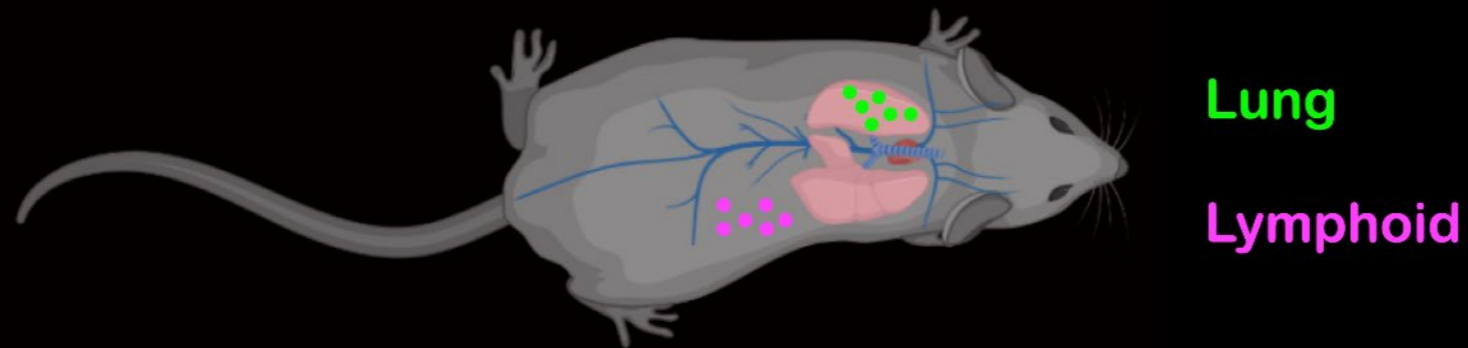


? specificity of **disease relevant** antibodies ?

What Mtb antigens do B cells recognize?



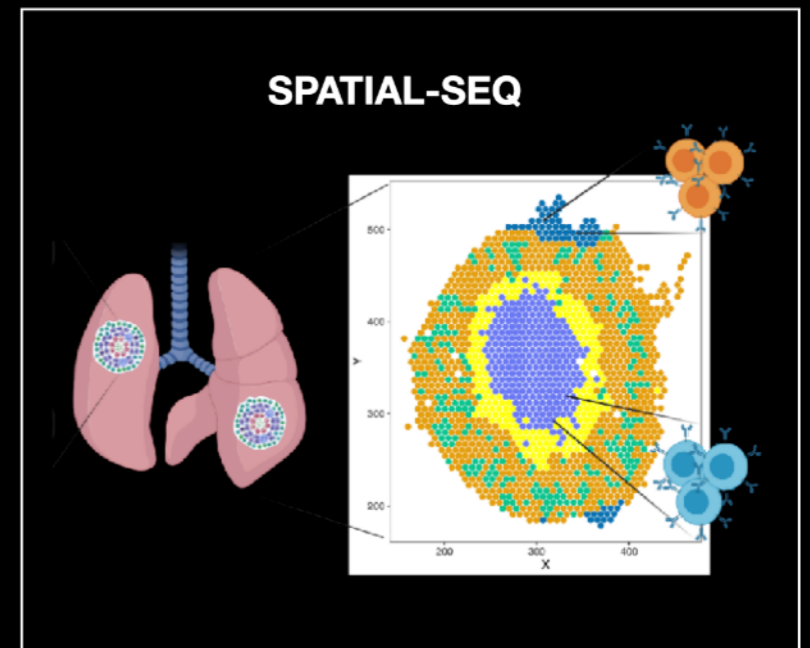
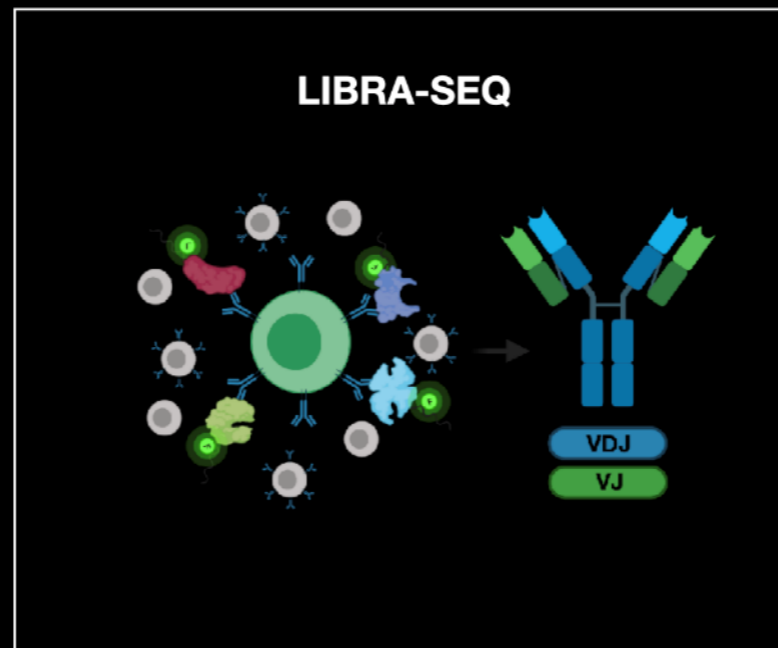
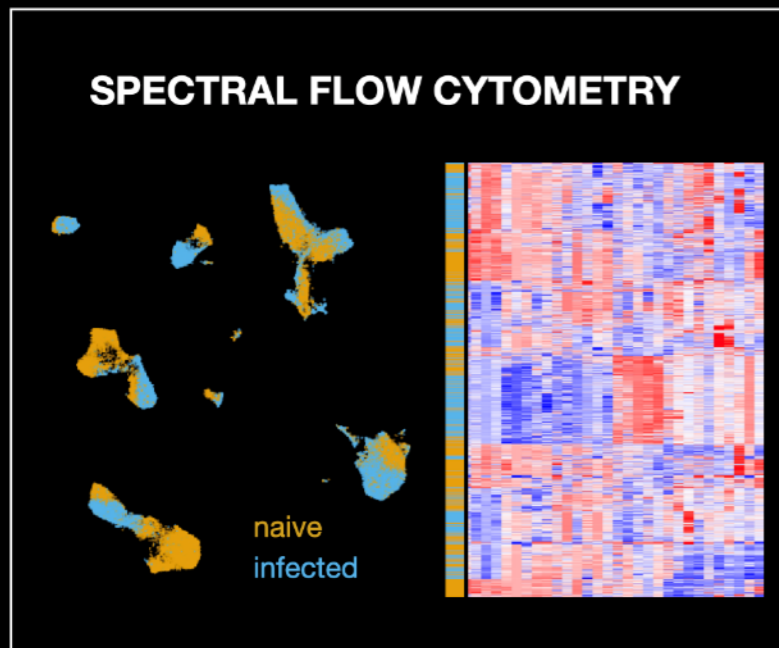
What Mtb-B cells look like?



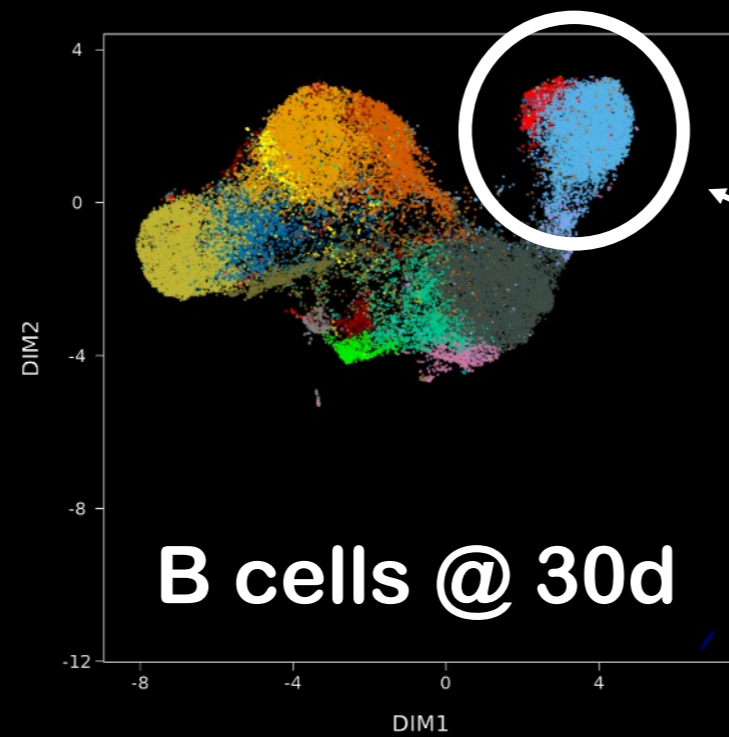
phenotype

transcriptome

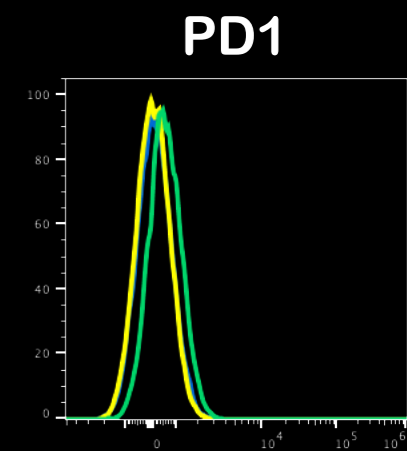
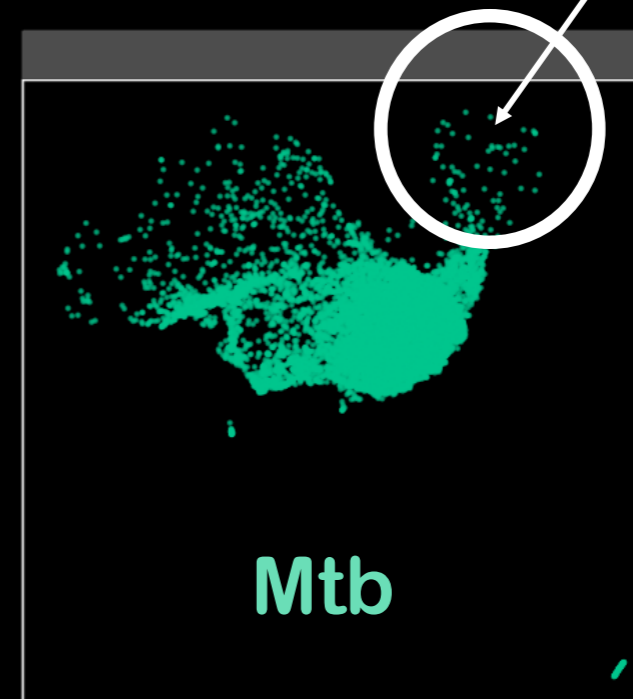
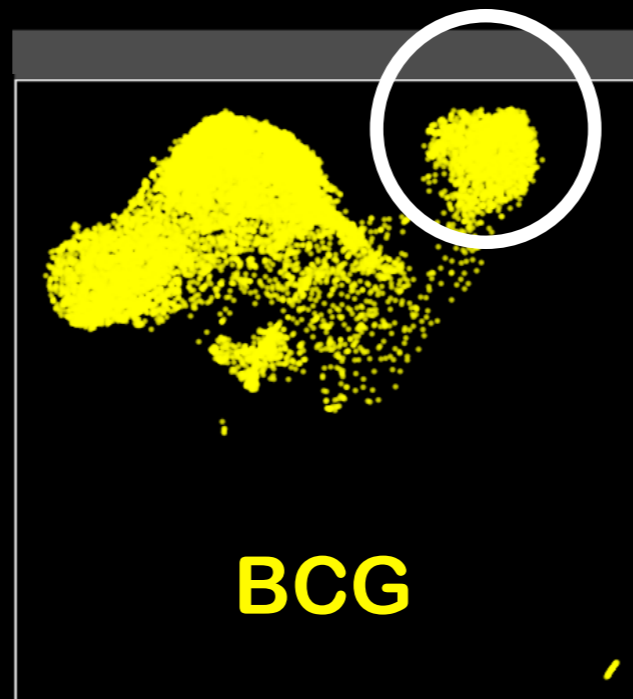
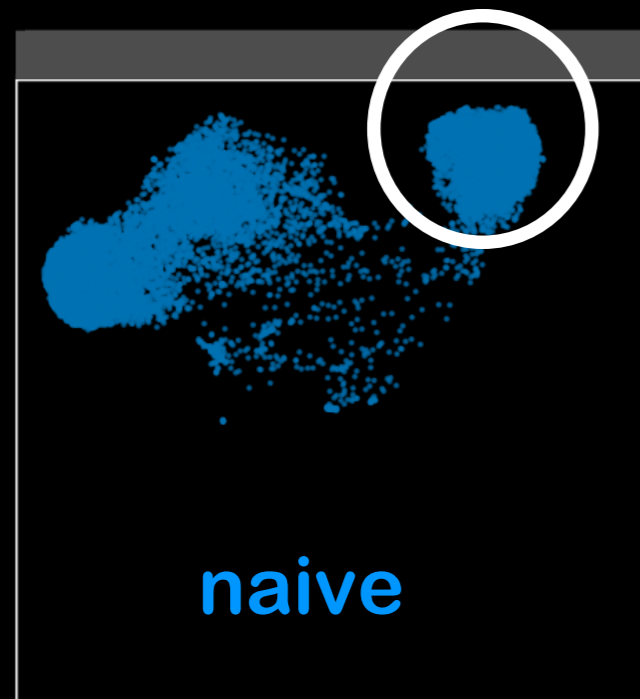
immune cell network



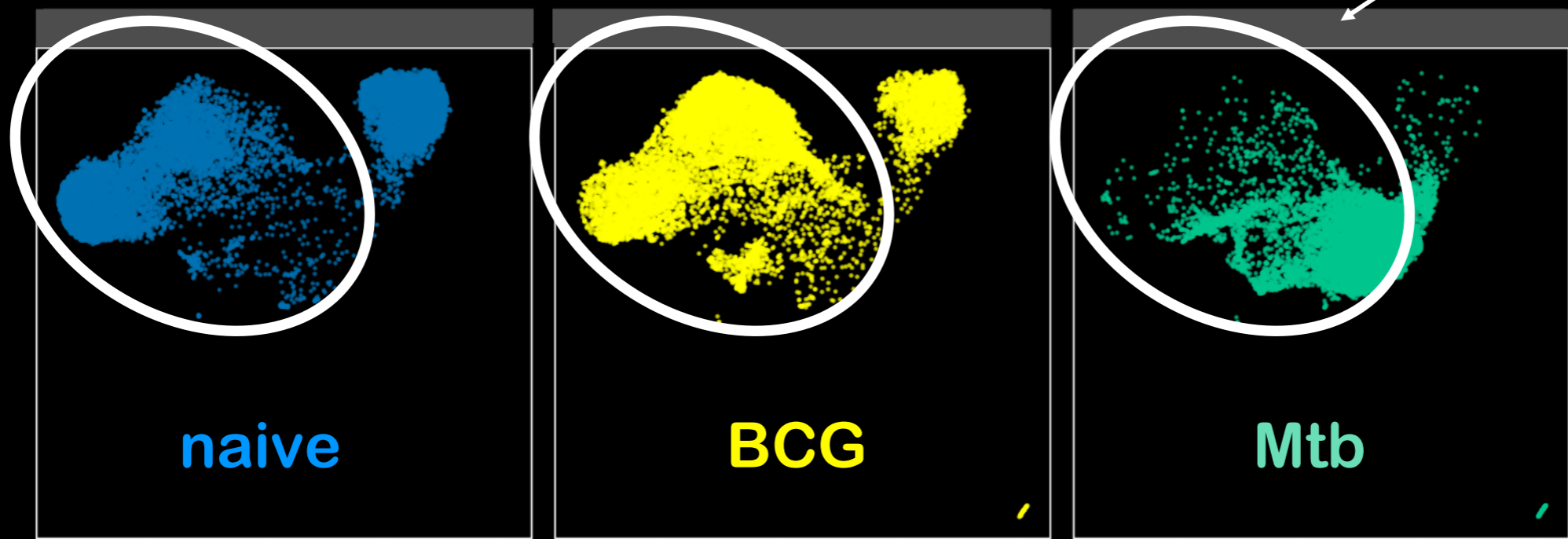
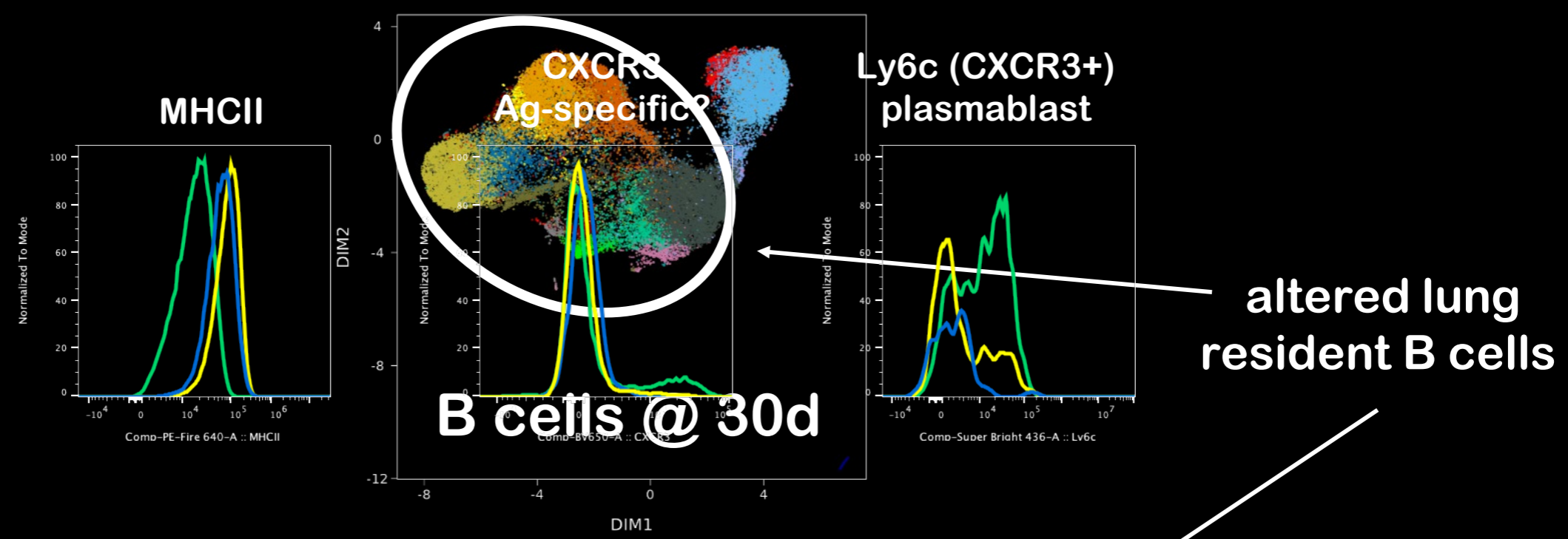
Total lung B cells: BCG vs. Mtb



depletion of circulating B cells

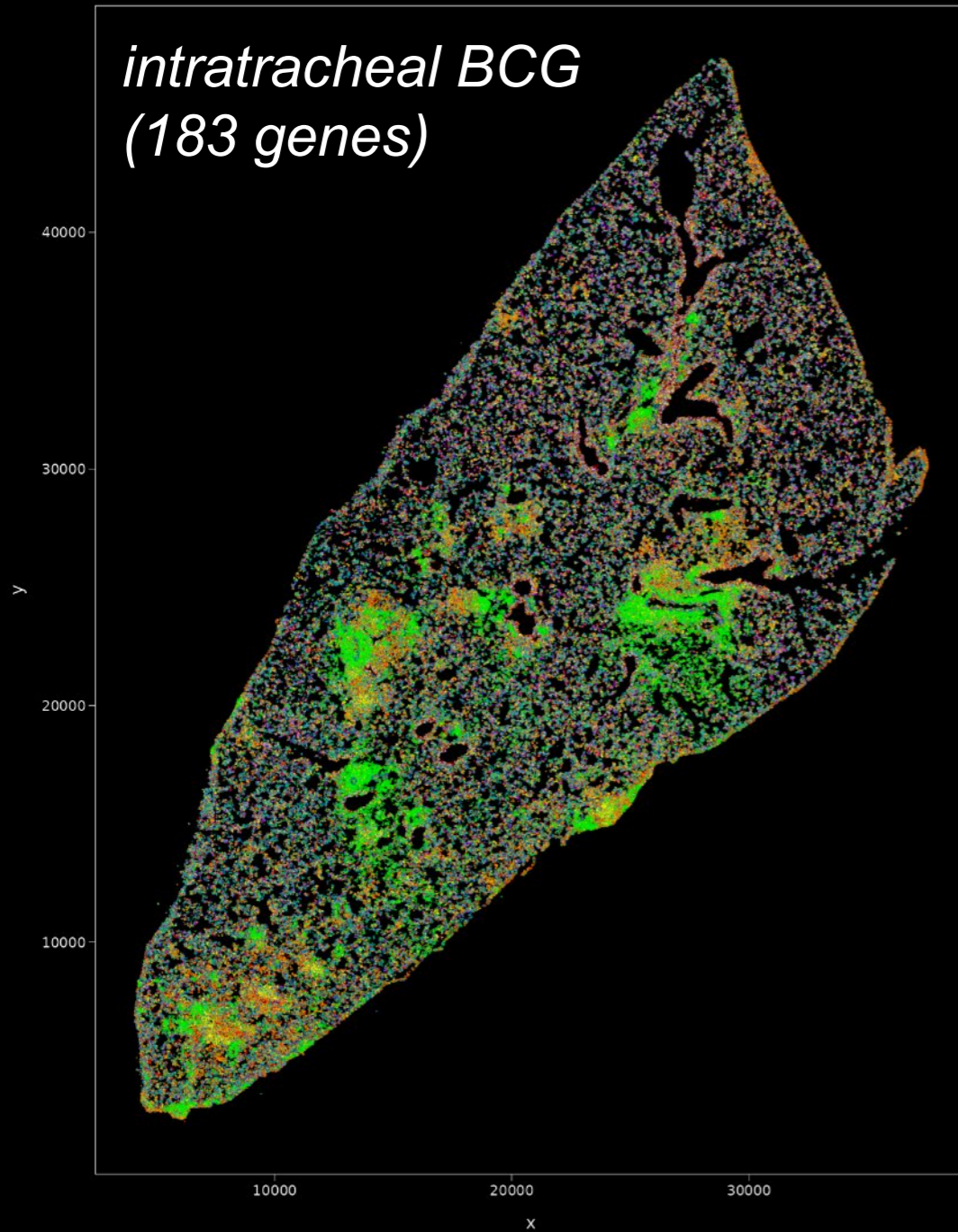


Total lung resident B cells: BCG vs. Mtb

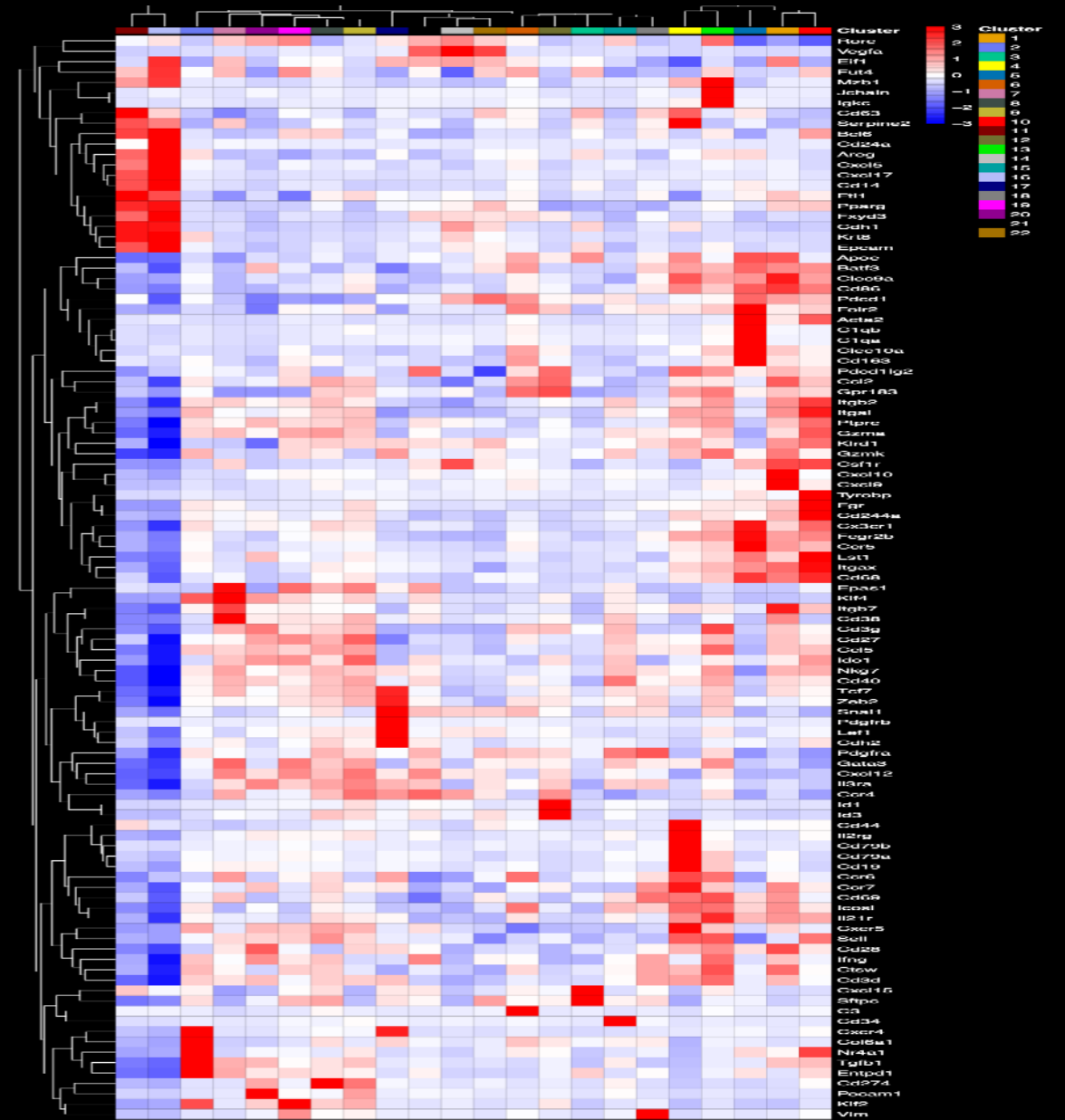


Spatial immune cell network in the lung

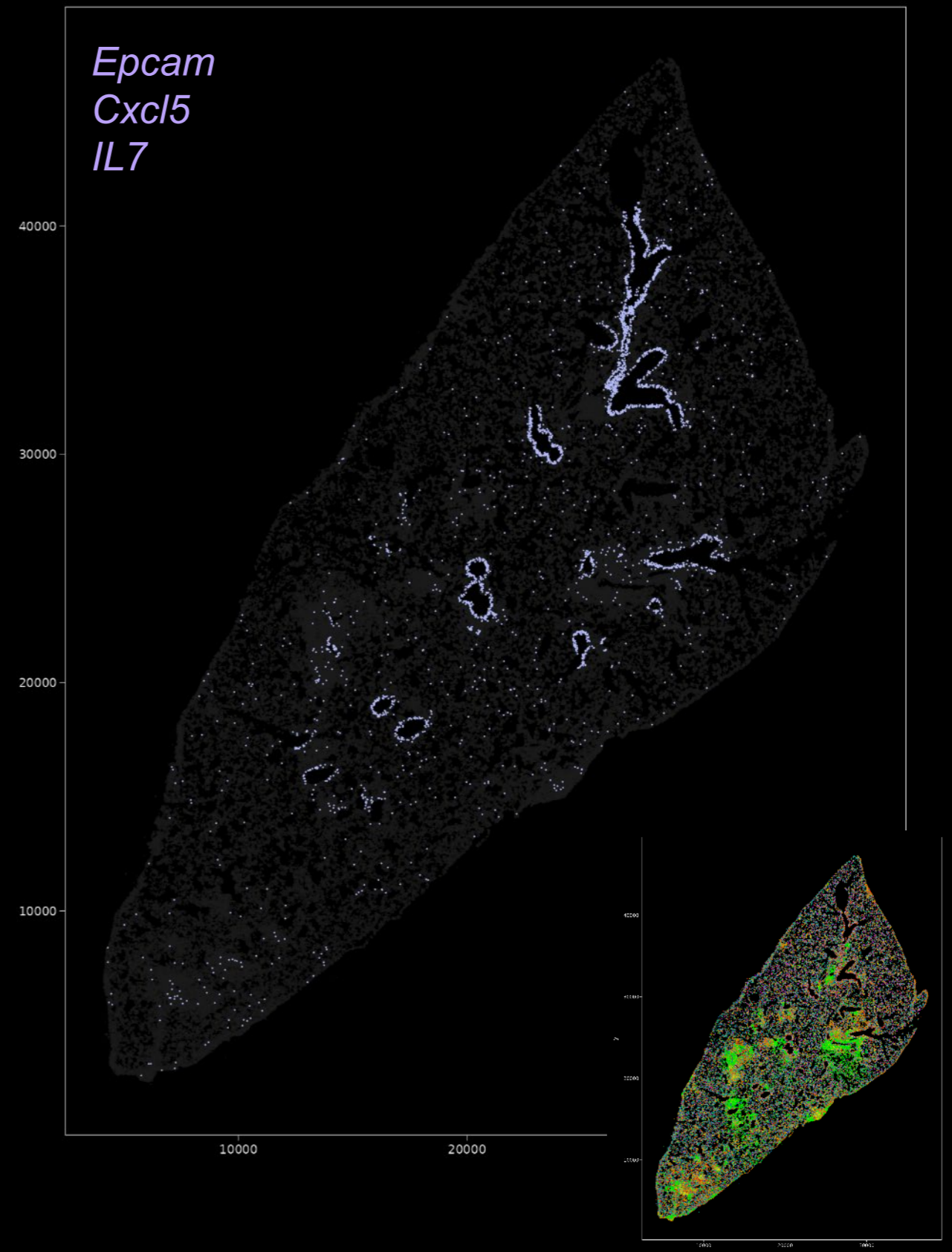
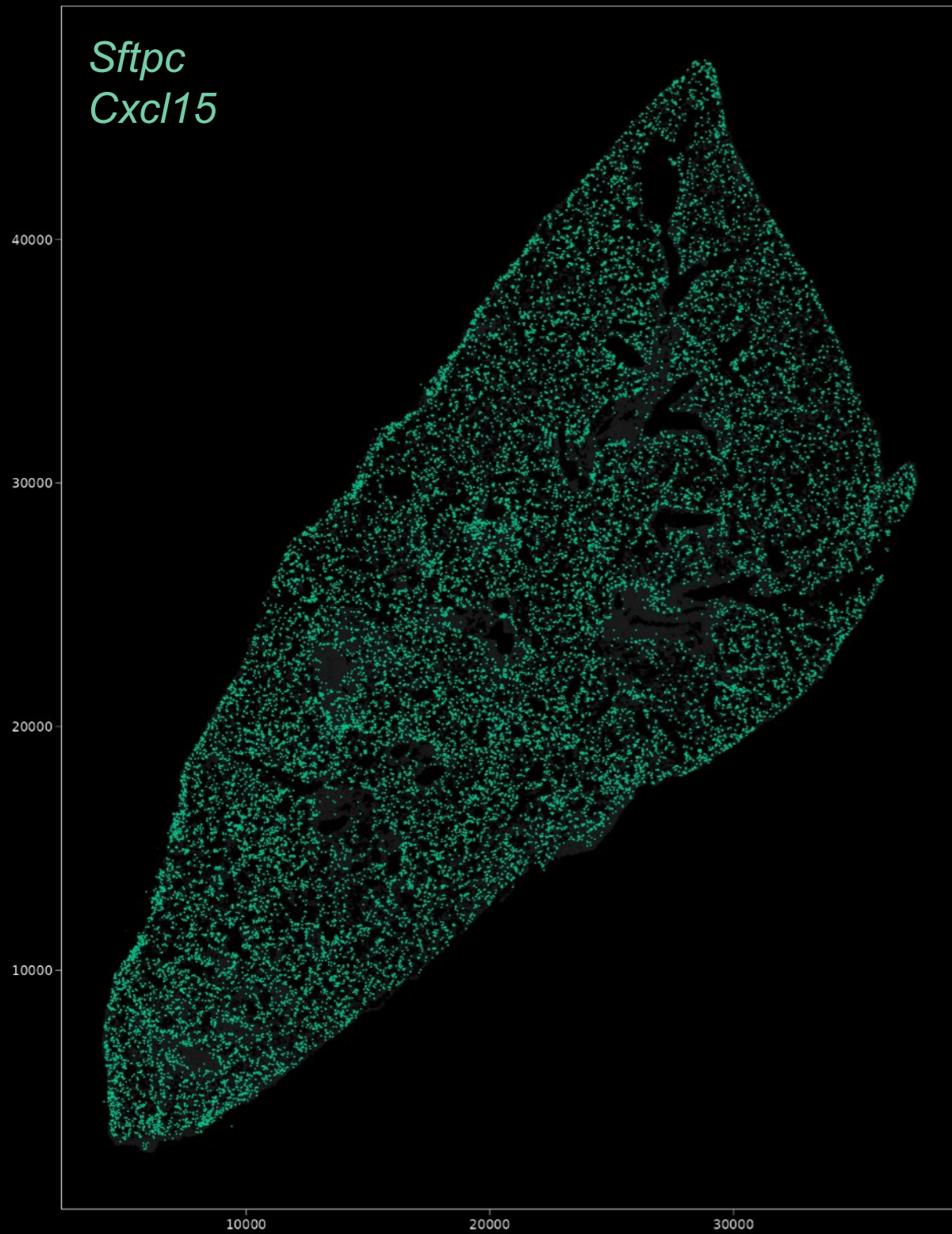
intratracheal BCG
(183 genes)



- 1 (31879) ● 14 (6636)
- 13 (29154) ● 18 (5274)
- 3 (26251) ● 19 (5196)
- 2 (17449) ● 12 (5186)
- 5 (15862) ● 17 (4981)
- 4 (12417) ● 15 (4844)
- 6 (12208) ● 7 (4741)
- 8 (11344) ● 22 (4449)
- 10 (10306) ● 21 (4310)
- 9 (7672) ● 16 (3580)
- 11 (6929) ● 20 (3217)

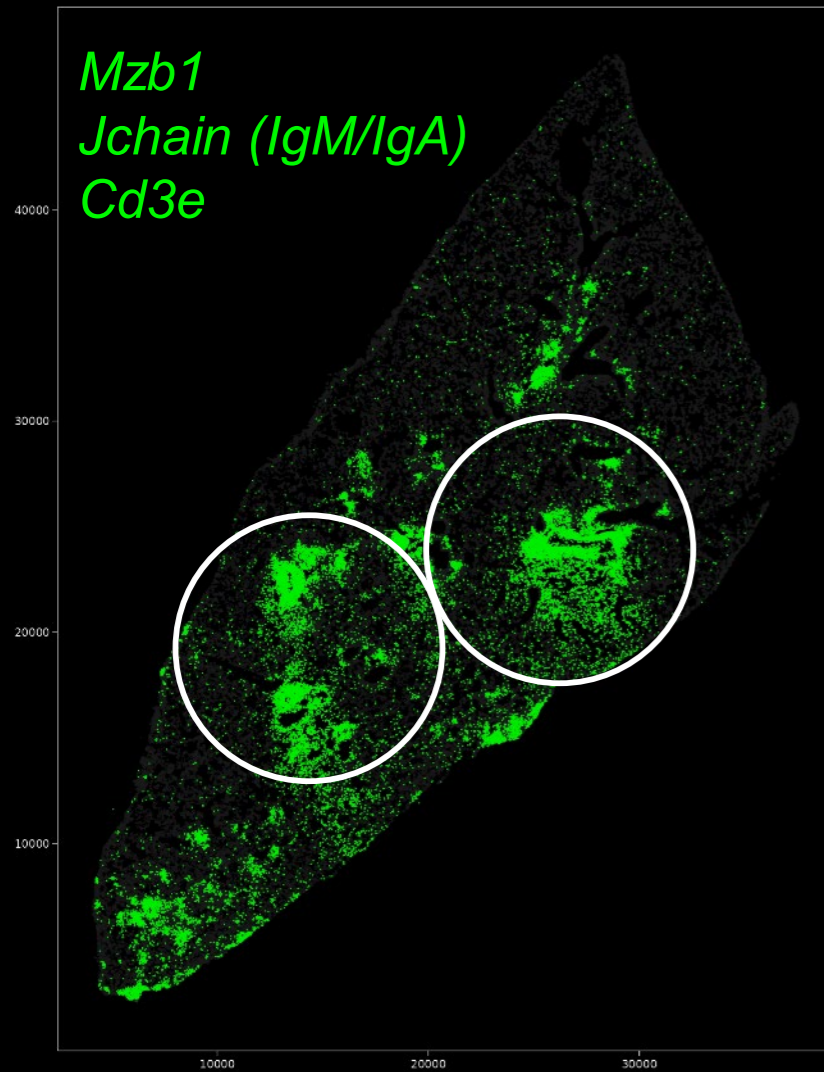


Spatial immune cell network in the lung

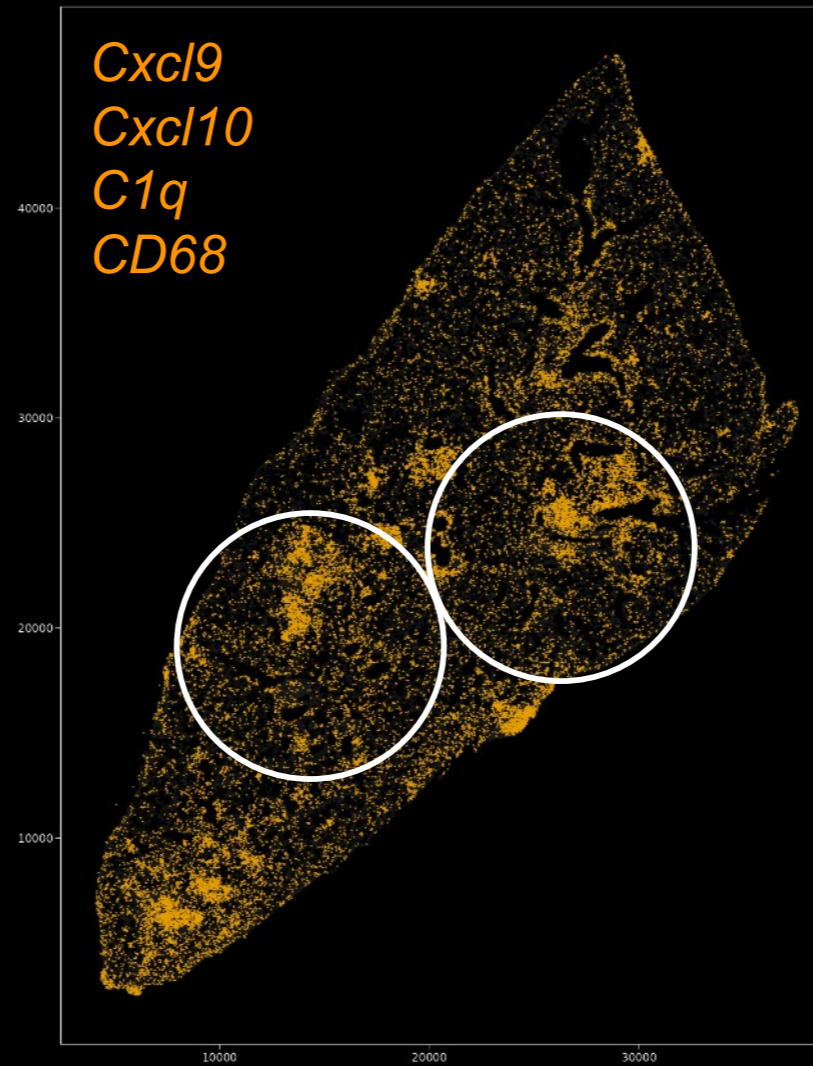


Spatial immune cell network in the lung

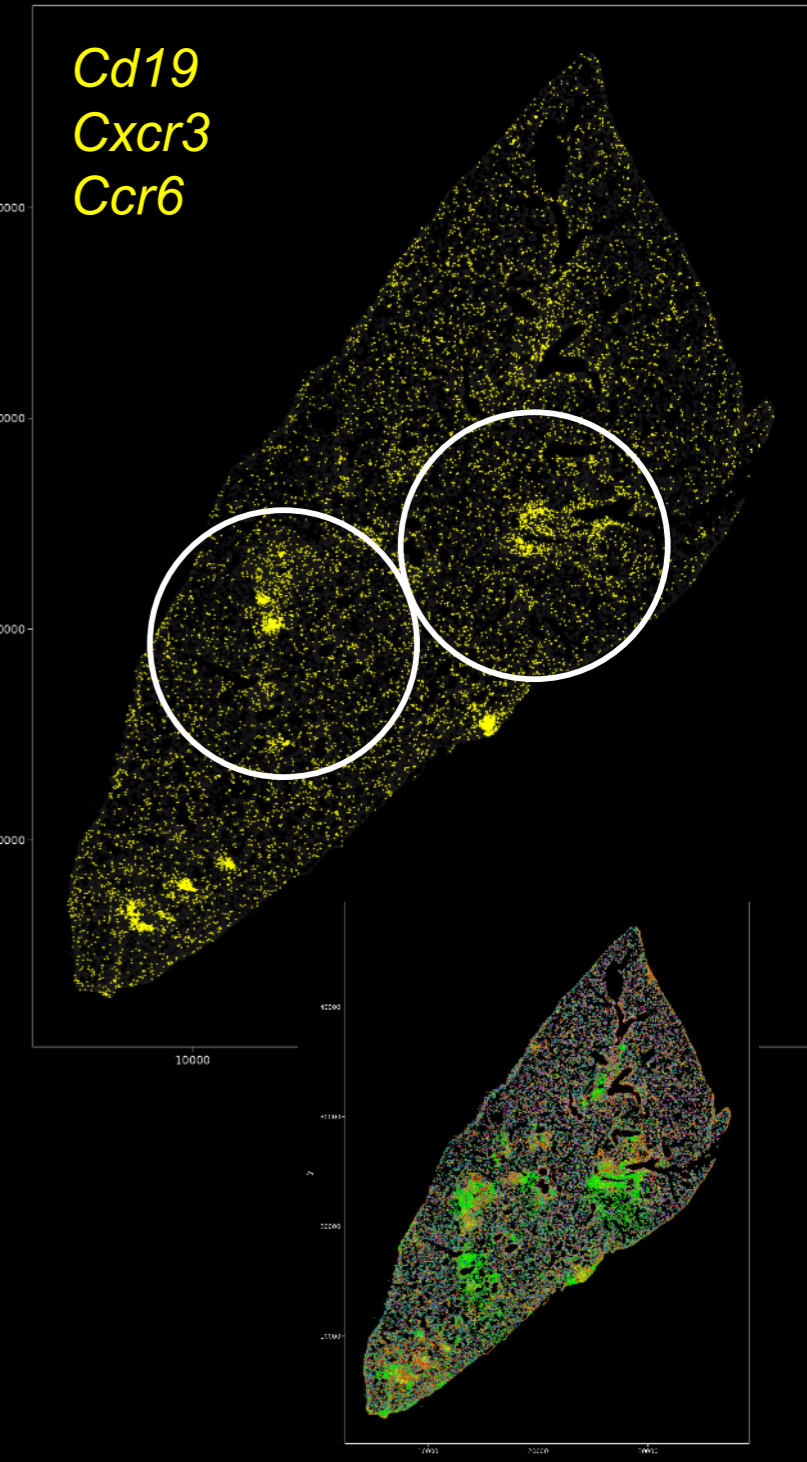
iBALT I



iBALT II / myeloid



B "resident" cells



Thank you

KING LAB

Jean de Lima
Maïke Erber
Mara Esposito
Clemens Hermann
Wadschma Naderi
Nikos Pantouloufos
Gian Pietro Pietri
David Schreiner
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TBVAC-HORIZON

University of Basel

Maxime Quebatte
Petra Chiquet
Dominik Viscardi & team

