



Identifying And Rationally Modulating Cellular Drivers Of Enhanced And Diminished Immunity

Alex K. Shalek

MIT (Chem, IMES, KI) | Ragon | Broad
2024 SEATRAC Hack Day Talk



Disclosures

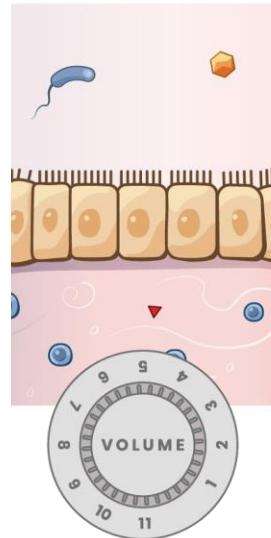
I have the following financial relationships to disclose:

Consultant for: Honeycomb Biotechnologies, Cellarity, Ochre Bio, Bio-Rad Laboratories, Relation Therapeutics, IntrECate Biotherapeutics, Fog Pharma, Passkey Therapeutic, and Dahlia Biosciences

Stockholder in: Honeycomb Biotechnologies, Cellarity, Ochre Bio, Relation Therapeutics, IntrECate Biotherapeutics, Passkey Therapeutics, Santa Ana Bio, and Dahlia Biosciences

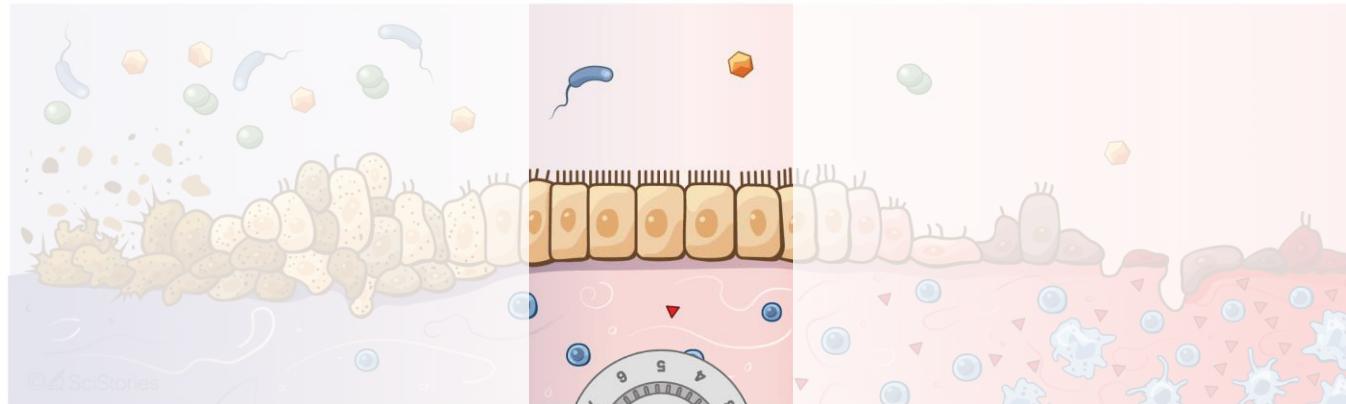
Funding: See acknowledgements

Understanding Balance In Tissue Ecosystems



Immune Activity

Understanding Balance In Tissue Ecosystems



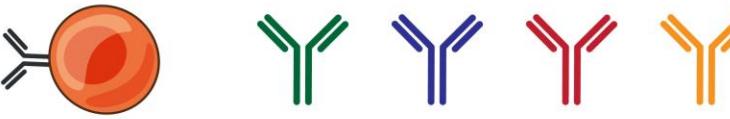
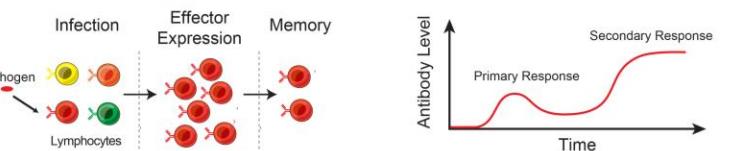
Too little

Too much

Immune Activity

We develop & apply broadly applicable tools to decipher how cells and their interactions inform tissue homeostasis

Deciphering The Cellular And Molecular Features Of Immune Response

Diversity	
Quality	
Breadth	
Durability	
Location	

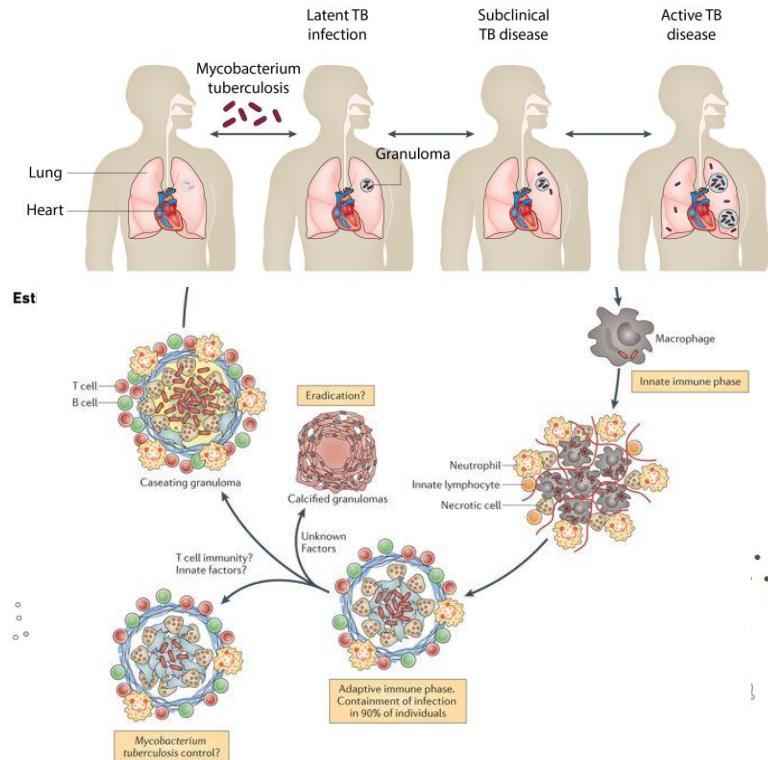
Deciphering The Cellular And Molecular Drivers Of TB Protection

How can we identify restrictive cellular phenotypes?

- 1. Examining natural correlates of immune control**
- 2. Profiling protective vaccine responses**

M. tuberculosis (Mtb) Infection

- WHO estimates 1.7 billion people (23% of the world's population) are latently infected with TB.
- In 2017, there were 10 million new cases of active disease and 1.6 million TB-related deaths.
- Burden of disease concentrated in Sub-Saharan Africa and South-East Asia.
- Pulmonary infection spread by droplet exposure.
- Pulmonary granuloma formation can either eradicate or establish chronic infection.



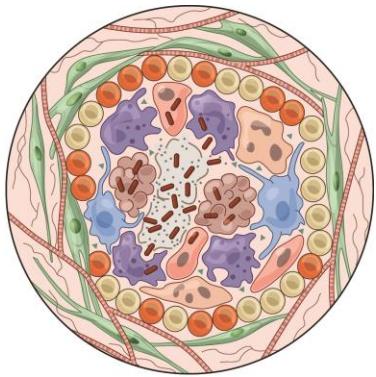
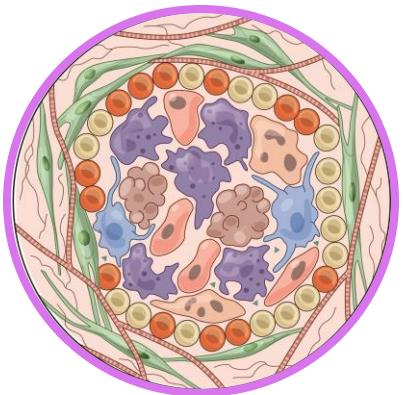
Nature Reviews | Microbiology

To Resolve Or Not?

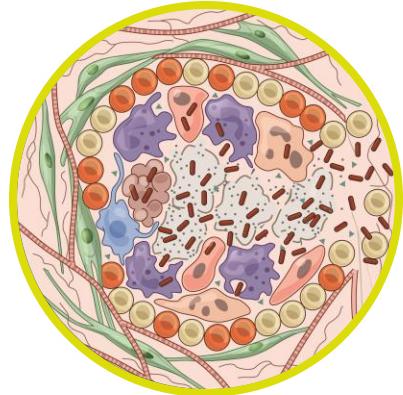


Sarah
Fortune Travis
Hughes

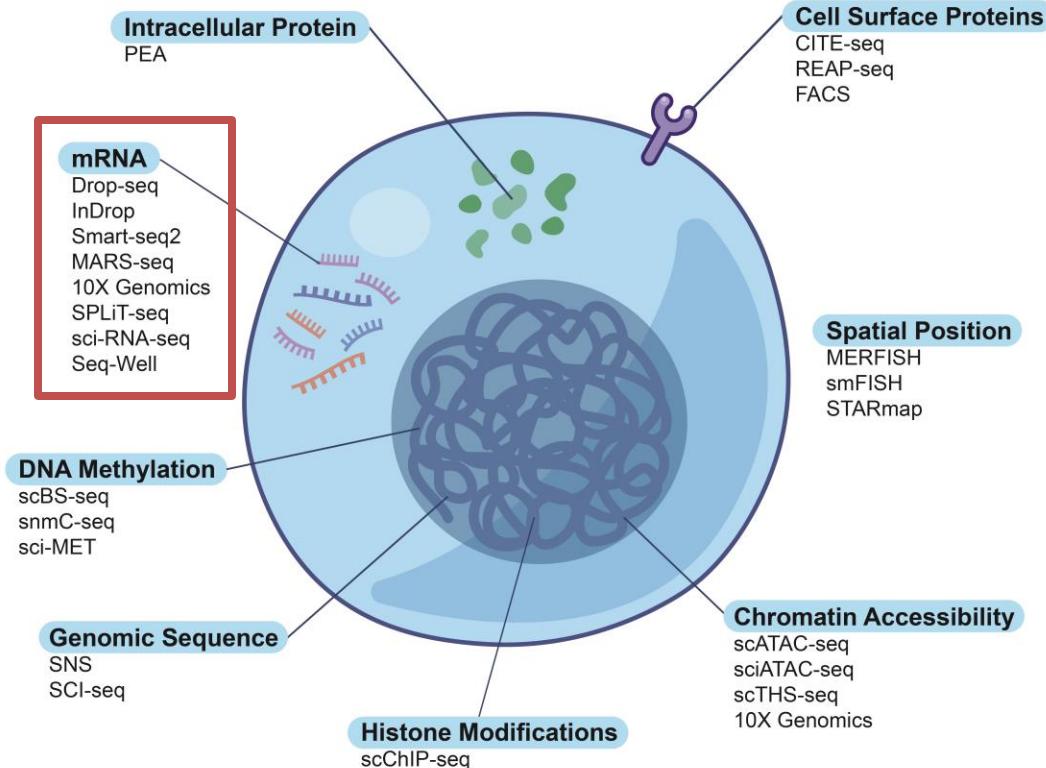
Resolving Granuloma



Progressing Granuloma

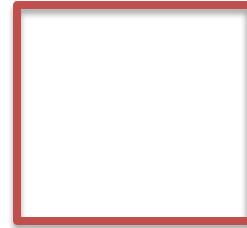
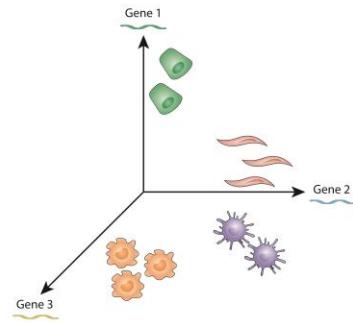
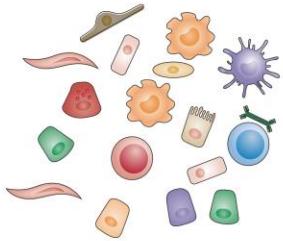


Profiling Cellular and Molecular Diversity

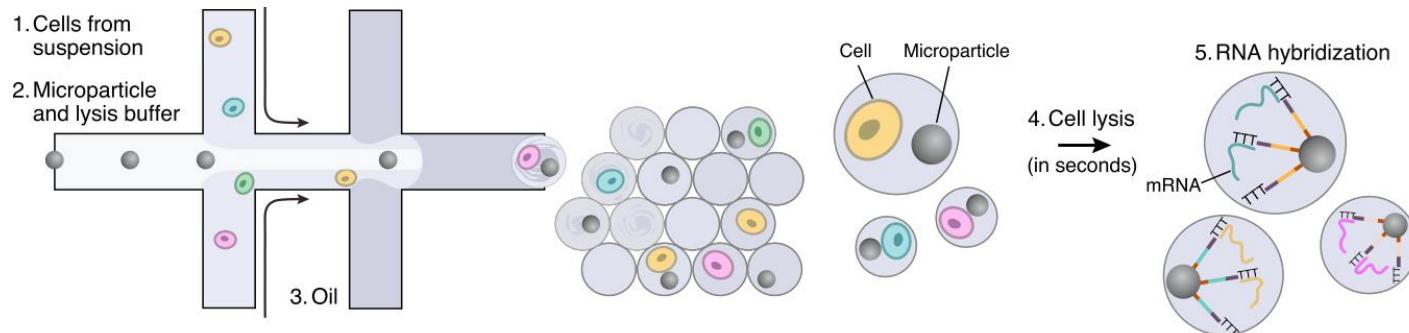
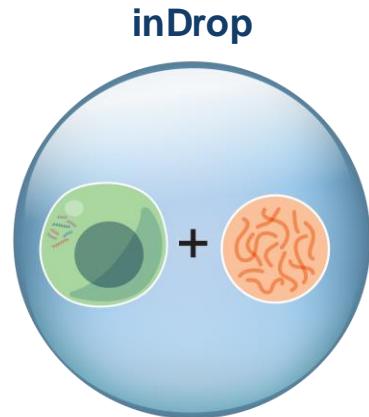
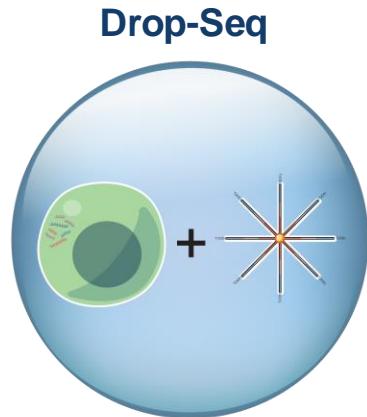


Tools For Characterizing Complex Cellular Systems

Complex
Cellular Mixture

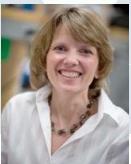


Massively-Parallel Early Barcoding Strategies

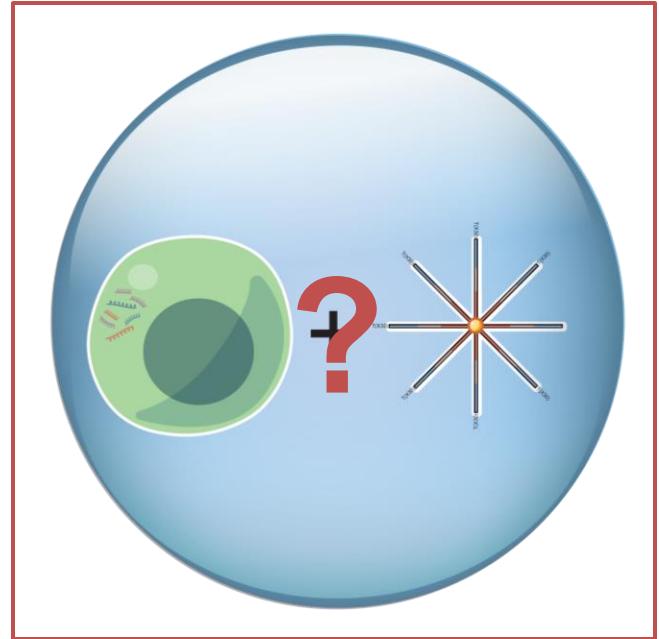
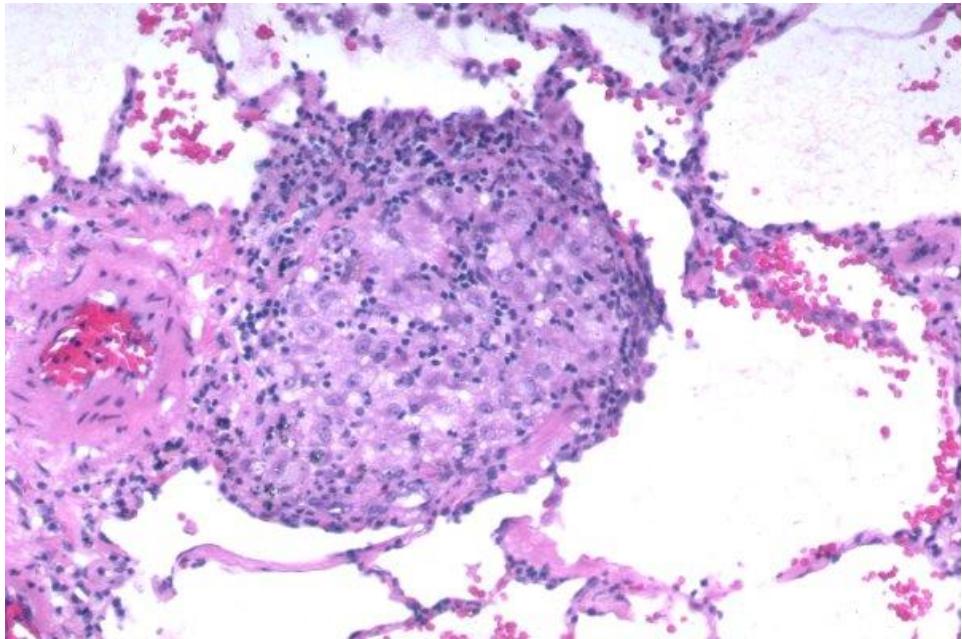


Macosko et al, *Cell* (2015); Klein et al, *Cell* (2015); Zheng et al, *Nat Commun* (2016).

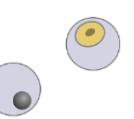
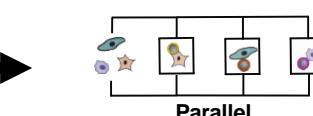
Understanding Infectious Ecosystems



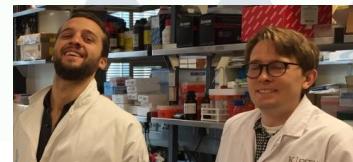
Sarah
Fortune



Drop-Based Methods Have Clinical Complications

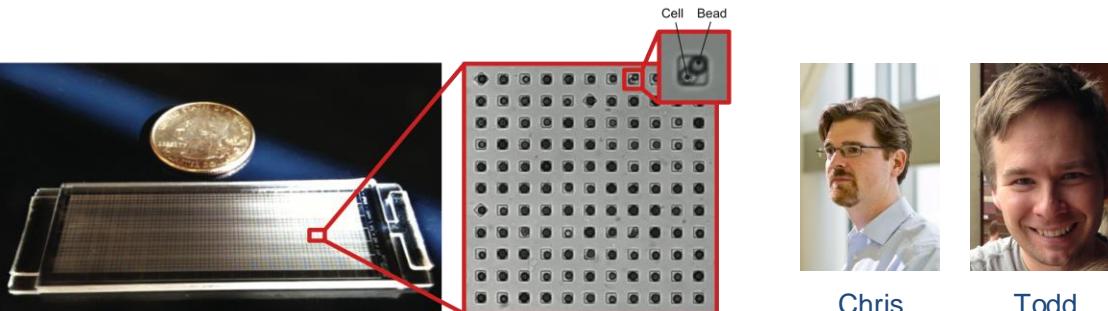
		Drop-Seq	InDrop	10X
Scalability	 	X	X	~
Portability	  	X	X	~
Capture Efficiency	    	X	~	✓
Cost	\$ \$ \$	✓	✓	X
Temporal Uniformity	 	X	X	~

A Solution: Seq-Well



Marc
Wadsworth

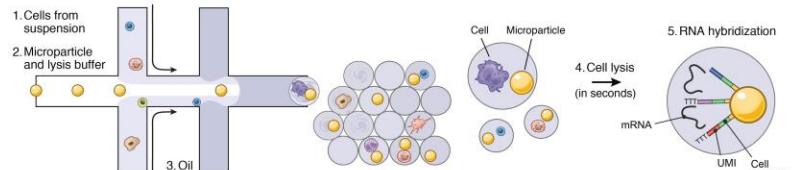
Travis
Hughes



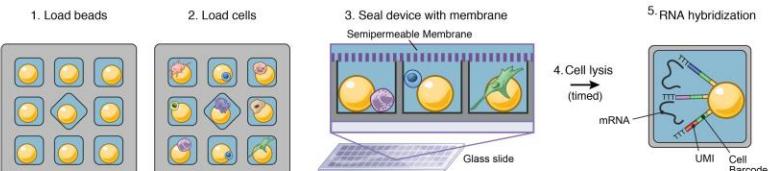
Chris
Love

Todd
Gierahn

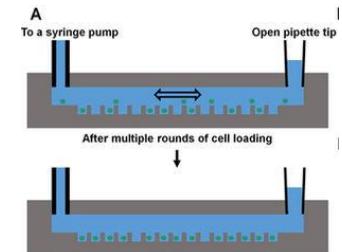
Drop-Seq



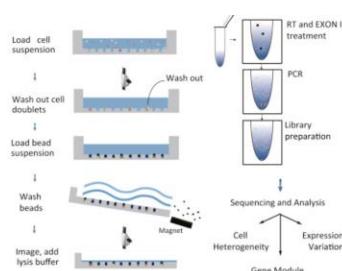
Seq-Well



Gierahn et al, *Nat Methods* (2017)

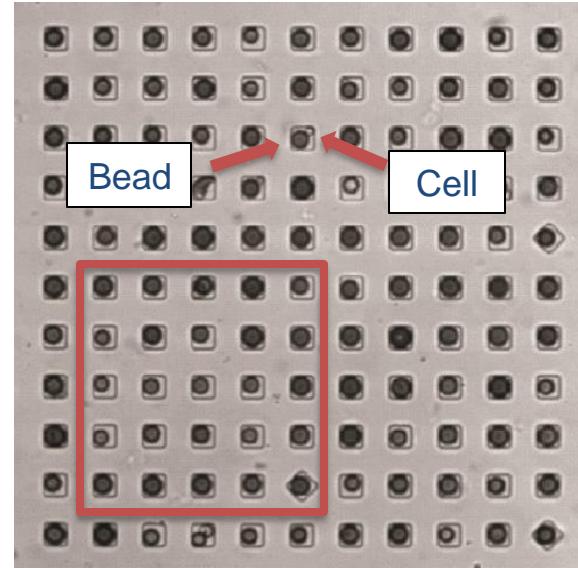
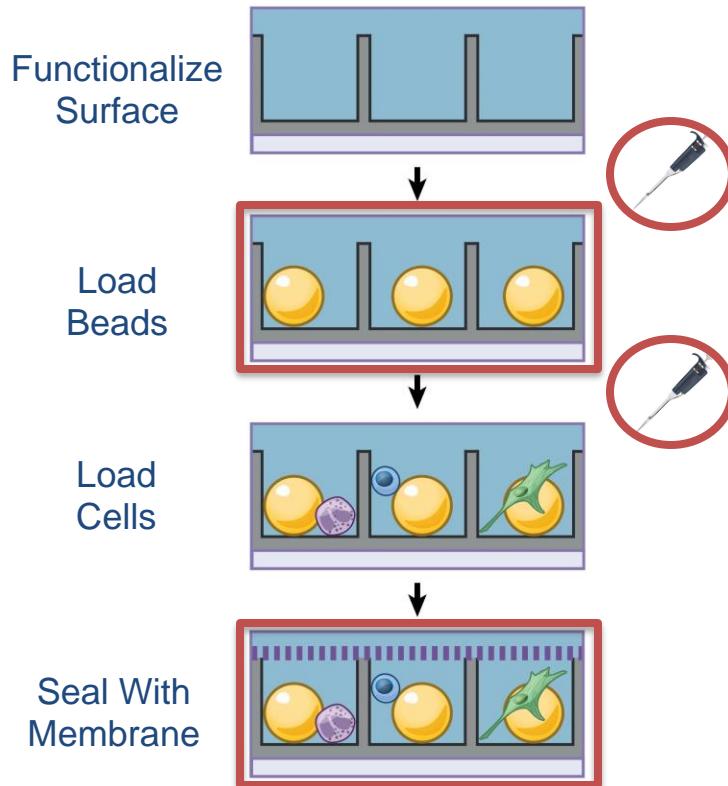


Yuan & Sims, *Sci Reports* (2016)



Han et al, *Cell* (2017)

Seq-Well: A User's Guide



Load with any pipetting device
Size exclusion → ≤ 1 bead per well
Sealing → Cross-contamination

At The Bench: Seq-Well On Cell Lines





Sam
Kazer

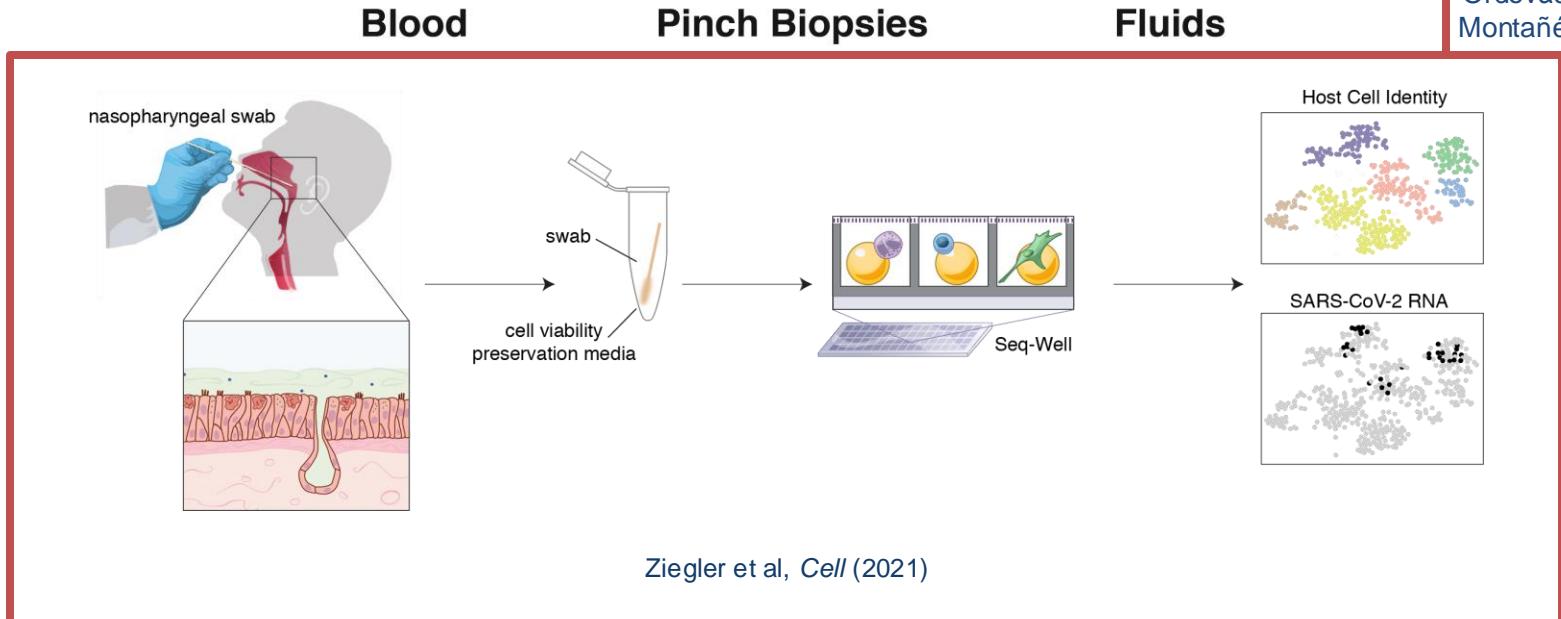
At The Bedside: Profiling Challenging Low-Input Clinical Biopsies



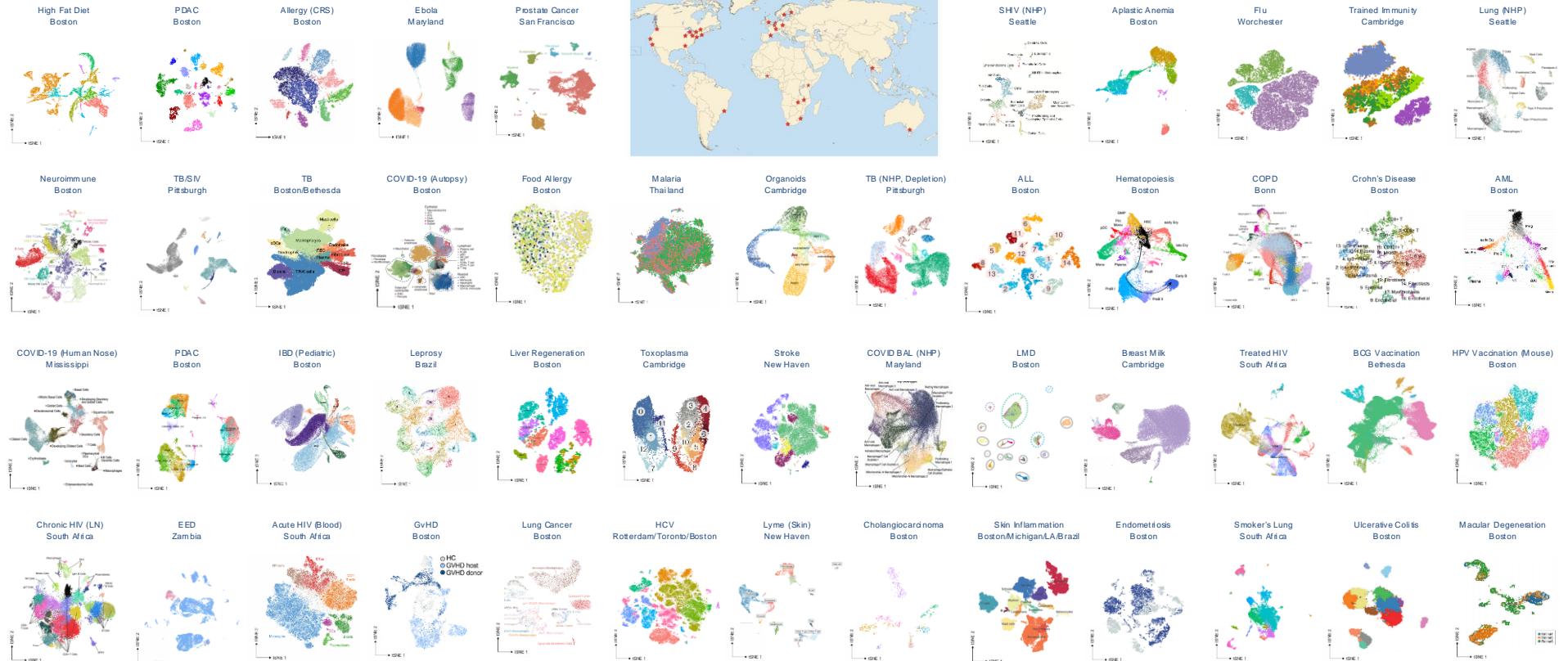
José
Ordovás-
Montañés



Jay
Prakadan



And Beyond: 6 Out Of 7 Continents Ain't Bad ...



A Partial List

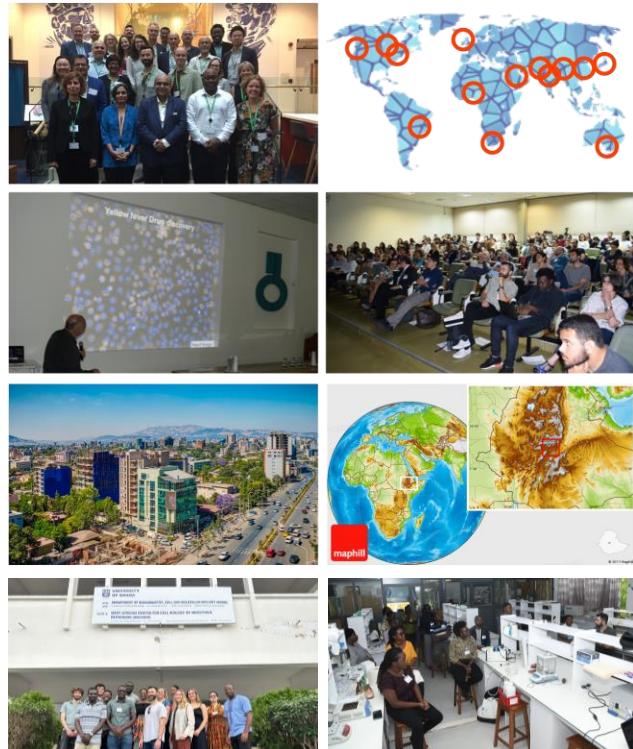
HCA Equity Working Group (EqWG) & SCAP Capacity Creation

HCA EqWG:

- Promote and support progress towards equity in the HCA
- Engage the global community to drive inclusive representation and participation, and promote equal benefit from the HCA
- Empower to participate in the HCA through outreach, education, and training

SCAP Capacity Creation:

- Empower equitable participation of global scientists in experimental creation and computational consumption of single-cell and bulk genomics data.



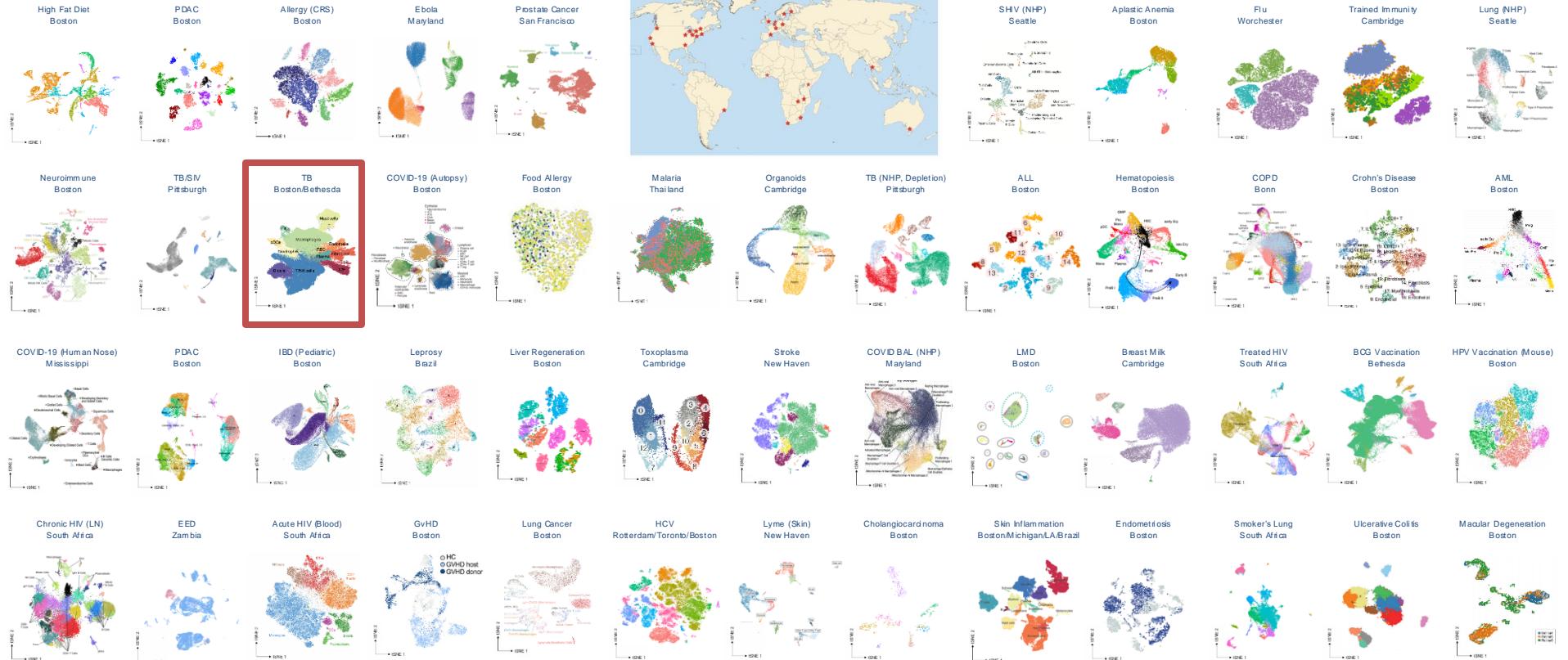
[Check for updates](#) [comment](#)

The Human Cell Atlas and equity: lessons learned

The Human Cell Atlas has been undergoing a massive effort to support global scientific equity. The co-leaders of its Equity Working Group share some lessons learned in the process.

Partha P. Majumder, Musa M. Mhlanga and Alex K. Shalek

And Beyond: 6 Out Of 7 Continents Ain't Bad ...

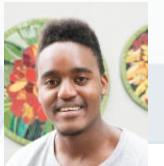


A Partial List

Looking At Fresh TB Infected Human Lung Tissue In South Africa



Al
Leslie

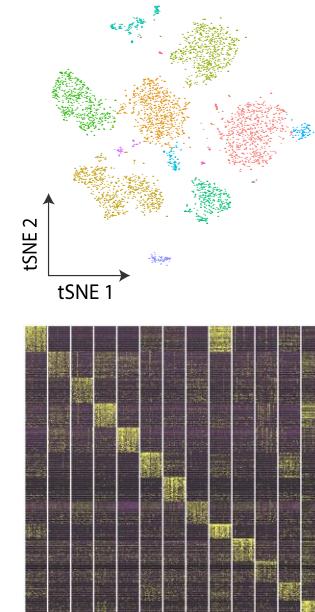
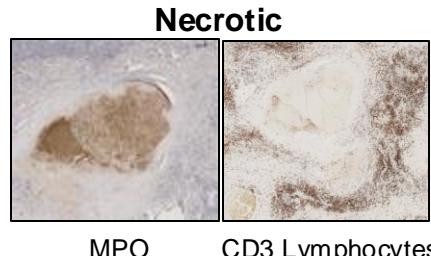
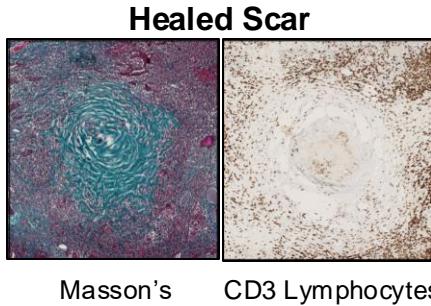
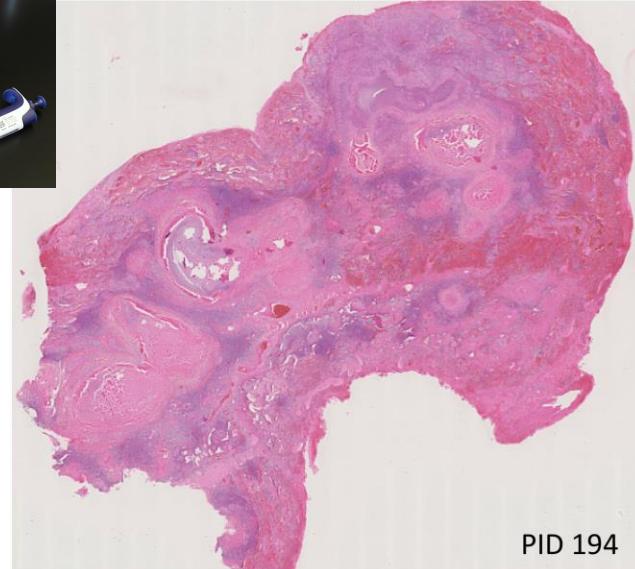


Ian
Mbano



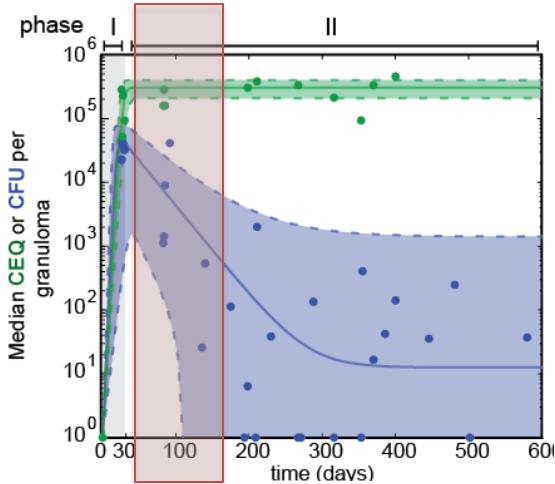
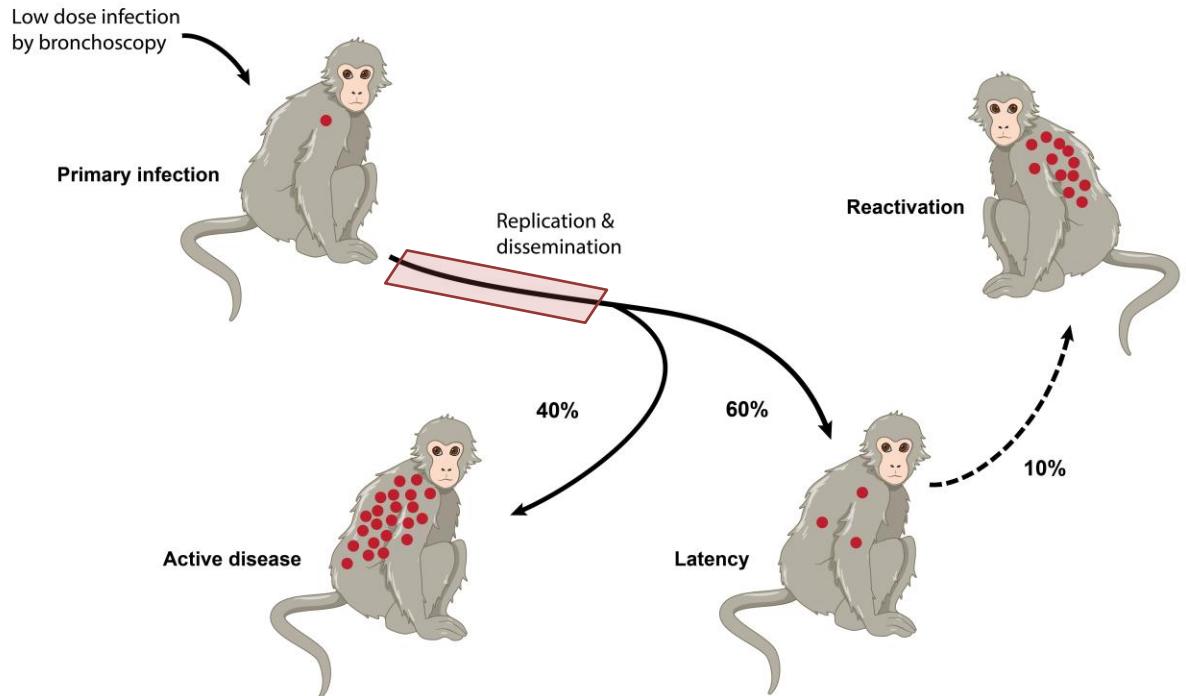
Marc
Wadsworth

Travis
Hughes

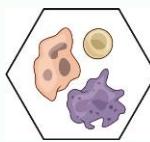


Problem: we can only study TB infection in human lung at severe active disease (and not that well).

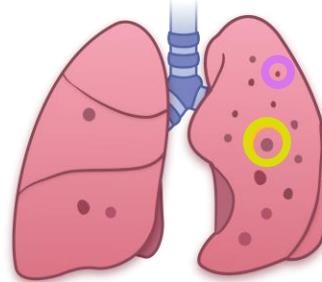
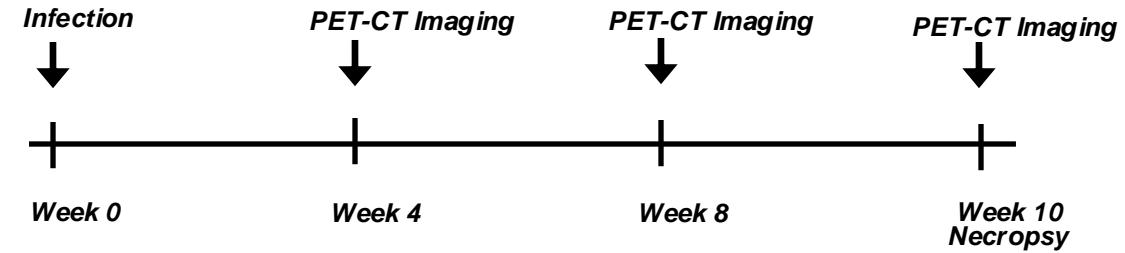
NHP Model For Successful And Failed Control OF TB



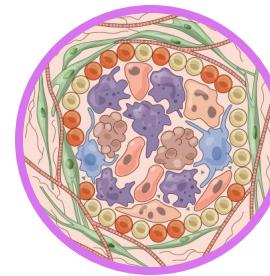
Cynomolgus macaque model by JoAnne Flynn and Ling Lin, University of Pittsburgh



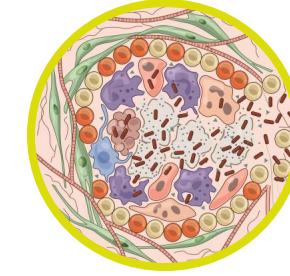
Identifying Restrictive And Permissive Features

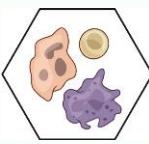


Resolving Granuloma

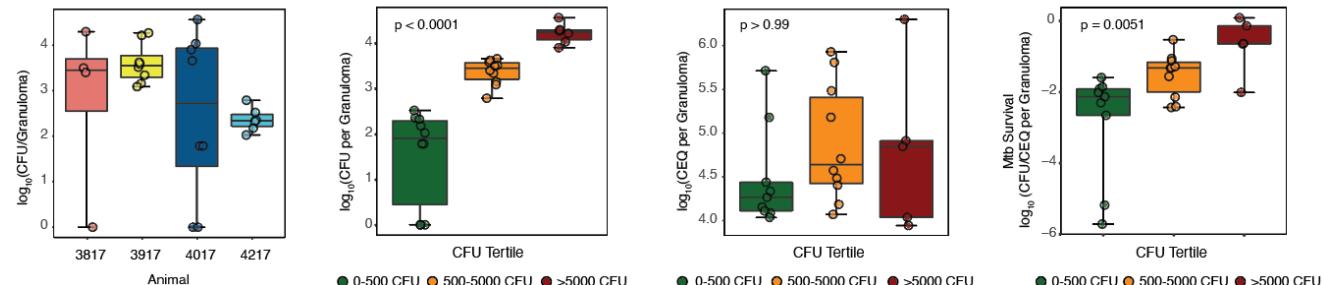
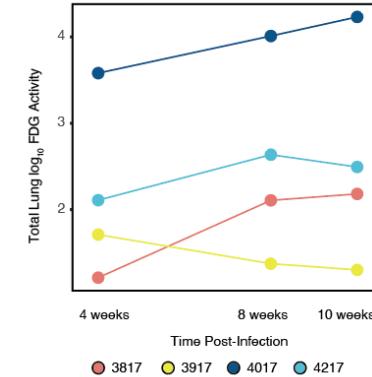
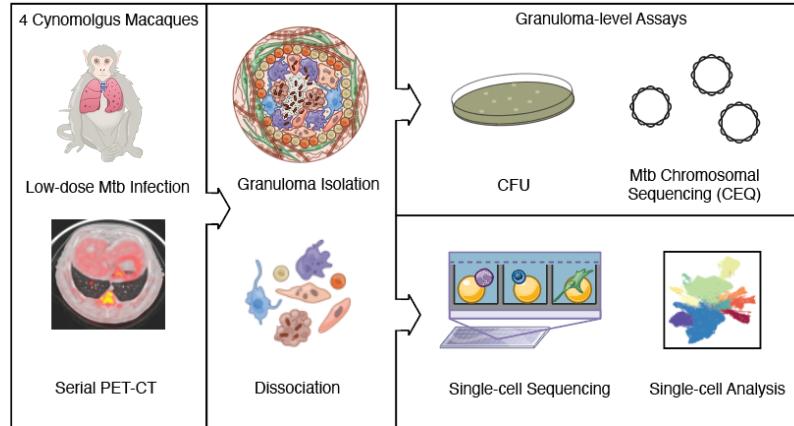


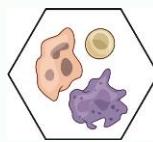
Progressing Granuloma



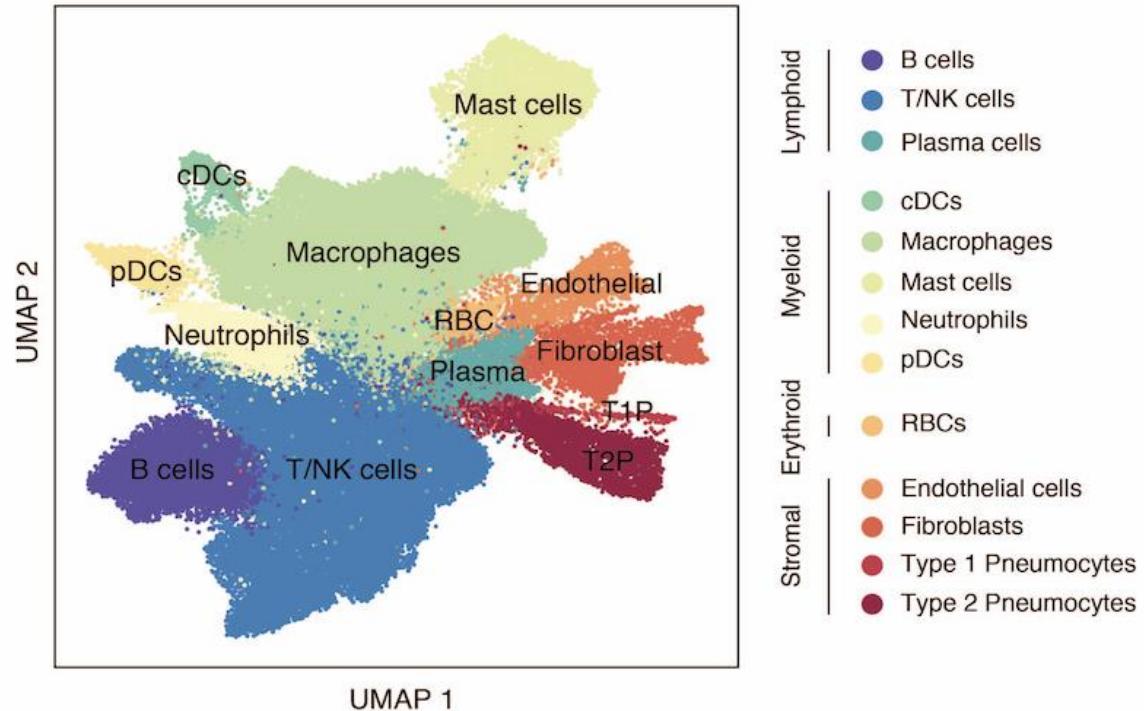
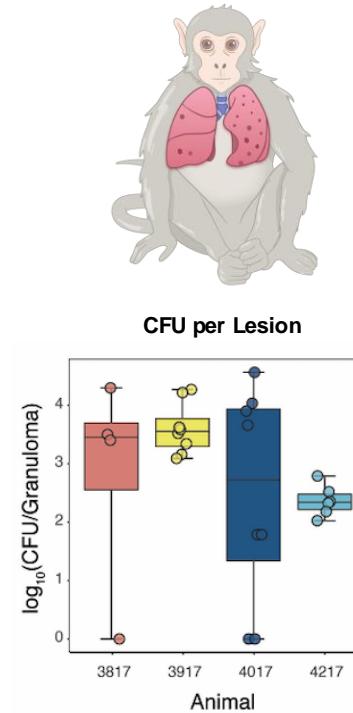


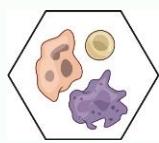
Granuloma Characteristics



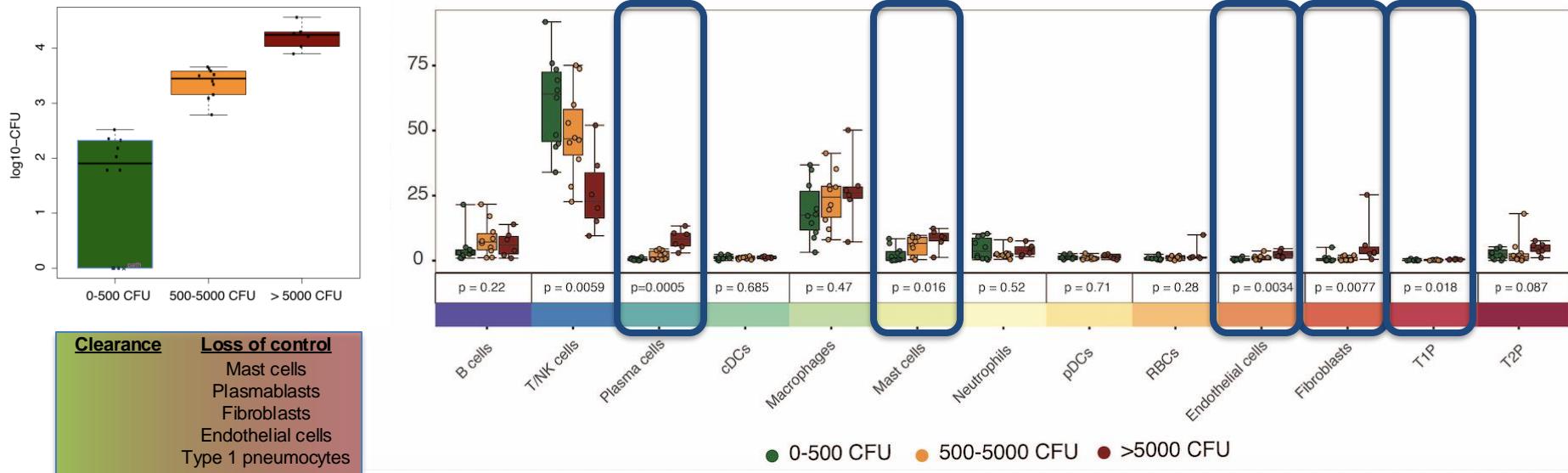


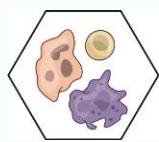
Identifying Restrictive And Permissive Features In NHP



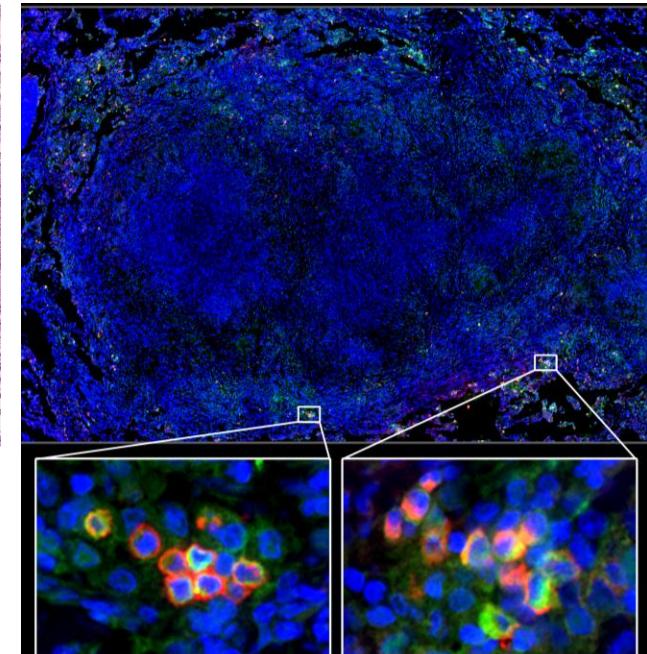
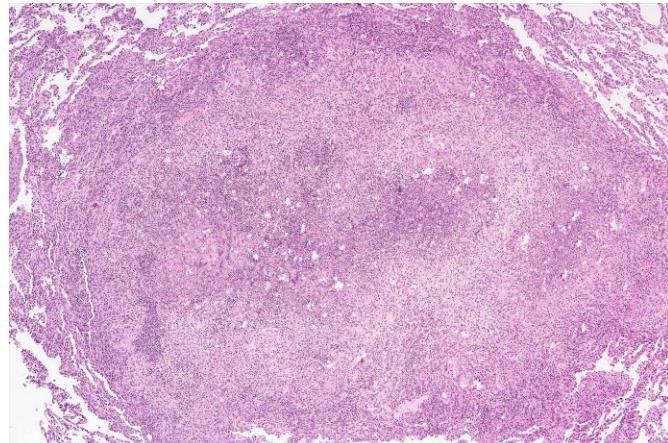
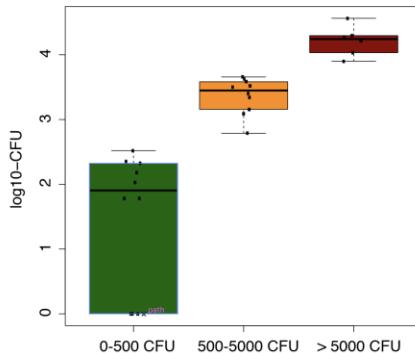


CFU – Cell Type Associations



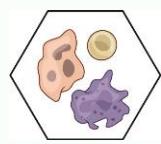


CFU – Cell Type Associations

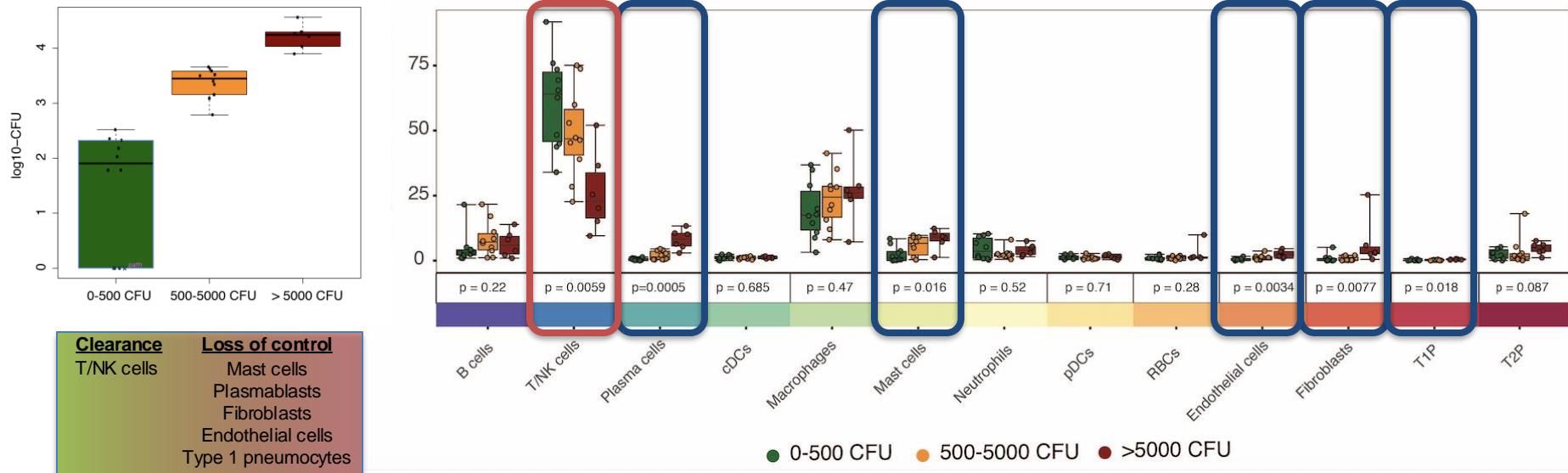


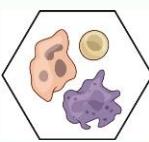
c-KIT (red), Tryptase (green)

<u>Clearance</u>	<u>Loss of control</u>
	Mast cells
	Plasmablasts
	Fibroblasts
	Endothelial cells
	Type 1 pneumocytes



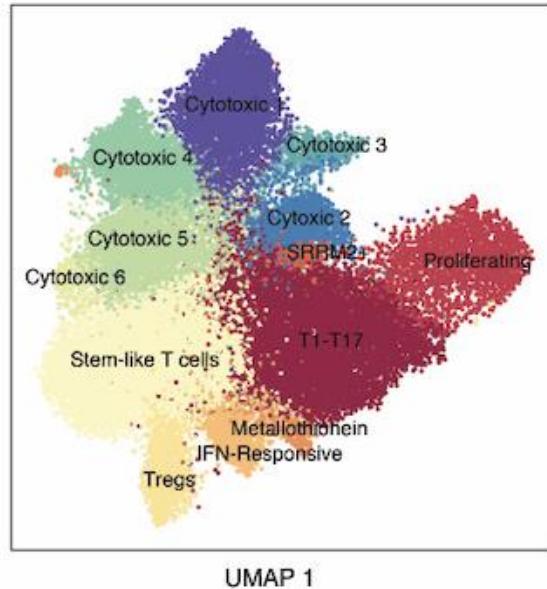
CFU – Cell Type Associations





T Cells As Likely Candidate Mediators Of Control

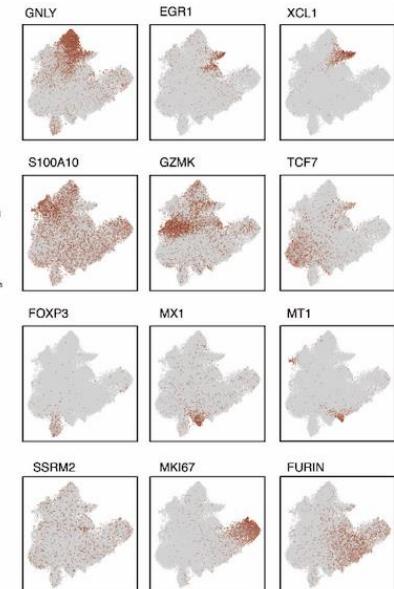
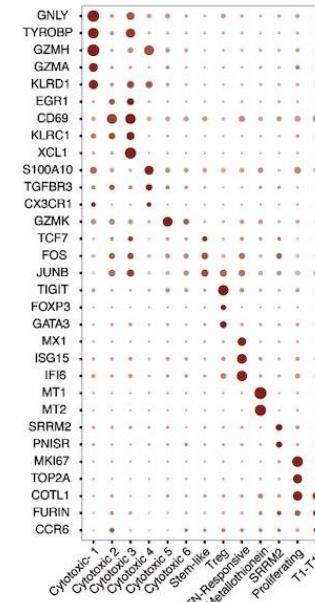
UMAP 2

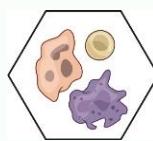


CD8+

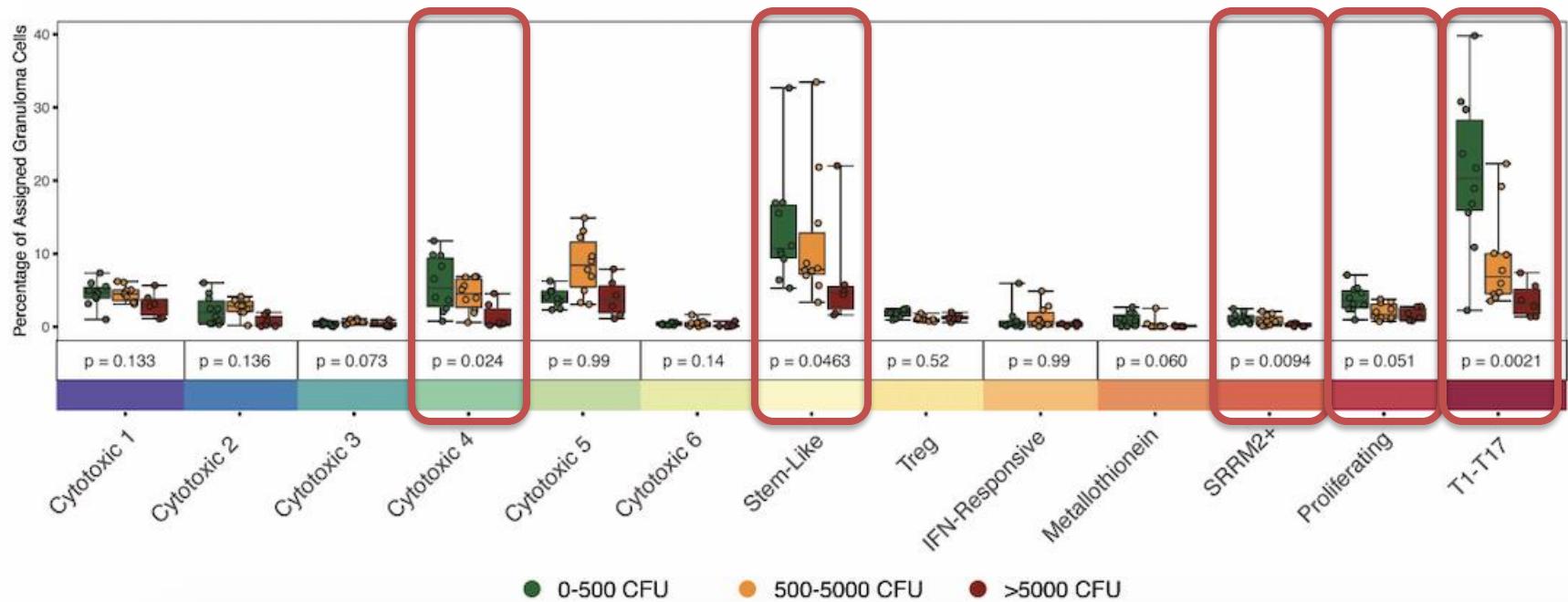
CD4+

CD4-CD8+

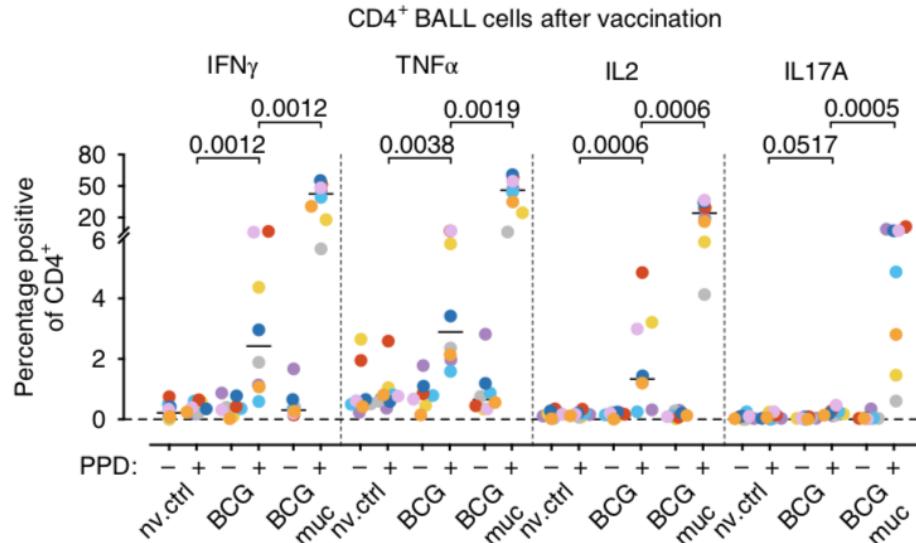
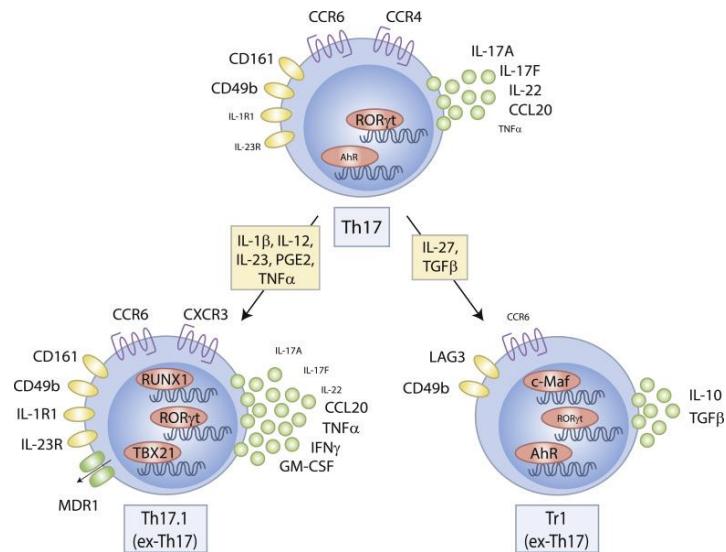




T Cell Cluster Association With Bacterial Burden

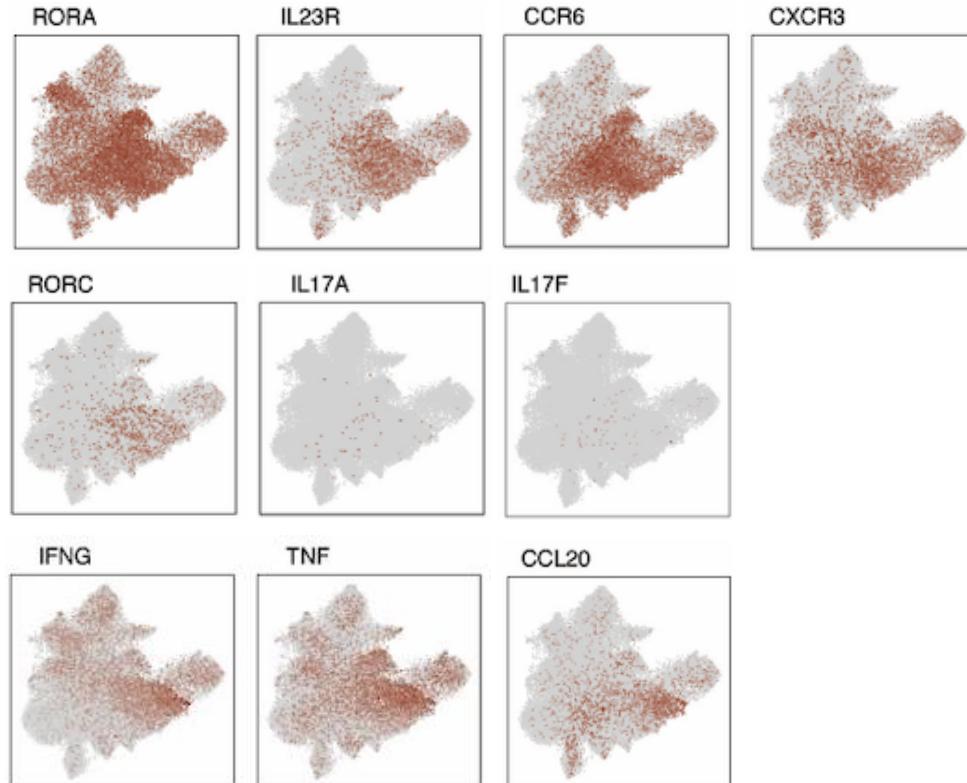
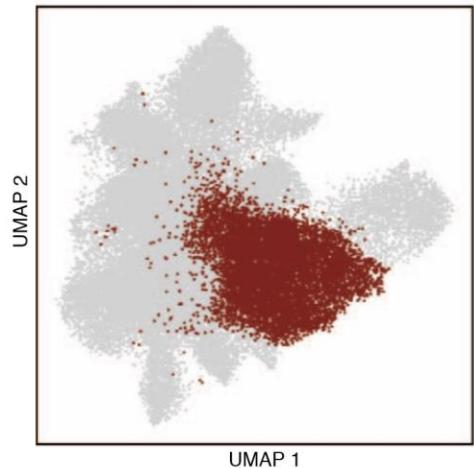


Literature Indicates Potential Role For T1-T17 Cells In TB Control In NHP



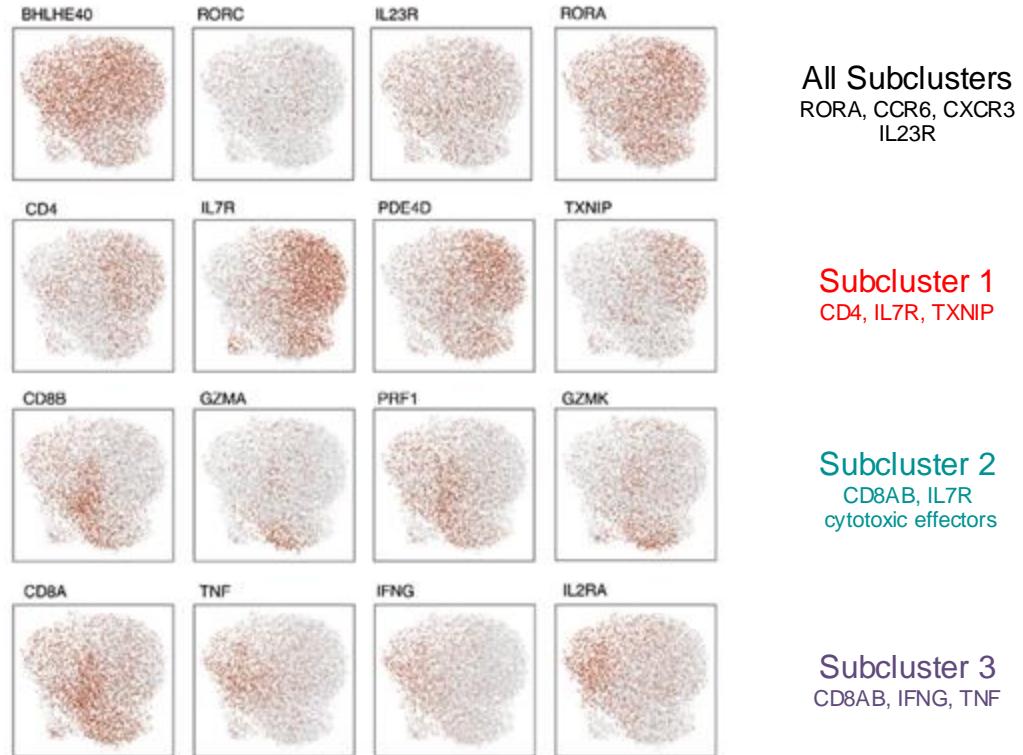
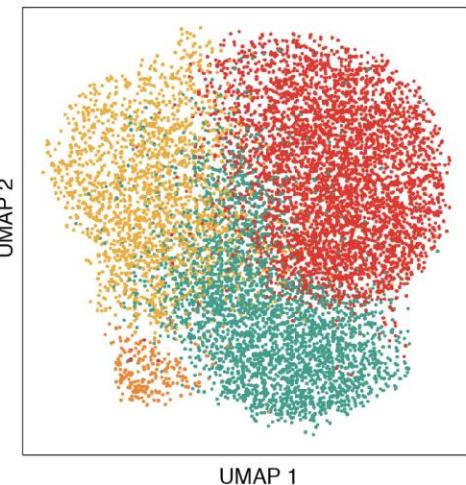
Control Associated With T Cell Cluster Defined By Expression Of Genes Indicative Of T1-T17

T1-T17 Cells



Gideon et al, *Immunity* (2022)

Sub-clustering Of T1-T17 Reveals Additional Substructure



All Subclusters
RORA, CCR6, CXCR3
IL23R

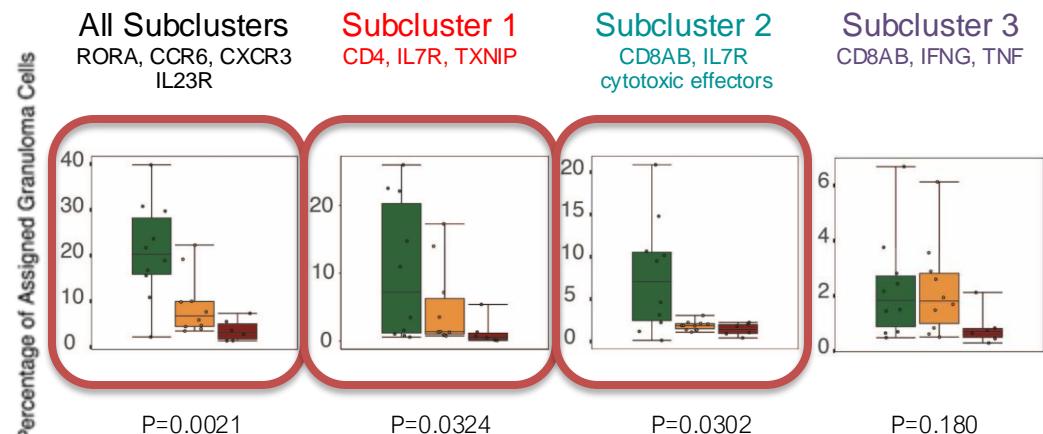
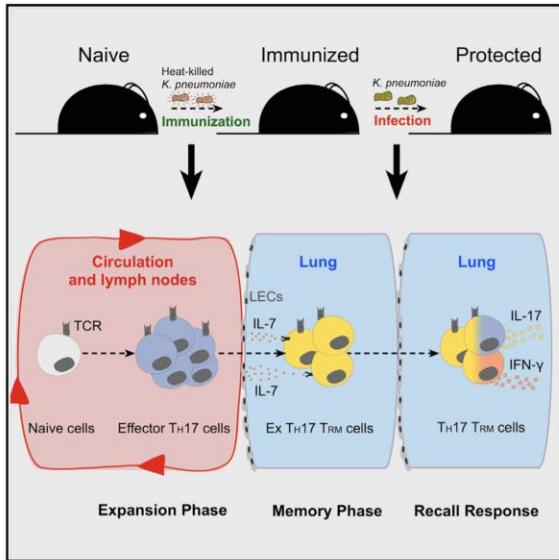
Subcluster 1
CD4, IL7R, TXNIP

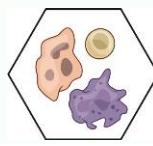
Subcluster 2
CD8AB, IL7R
cytotoxic effectors

Subcluster 3
CD8AB, IFNG, TNF

Subcluster 4
Small numbers

T1-T17 Subcluster Associations With Burden

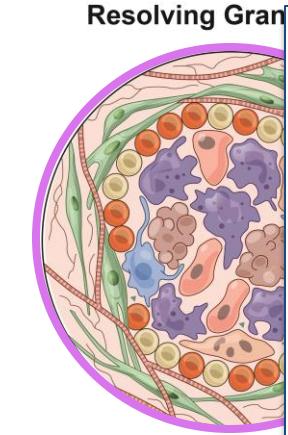




Natural Correlates Of Mtb Control

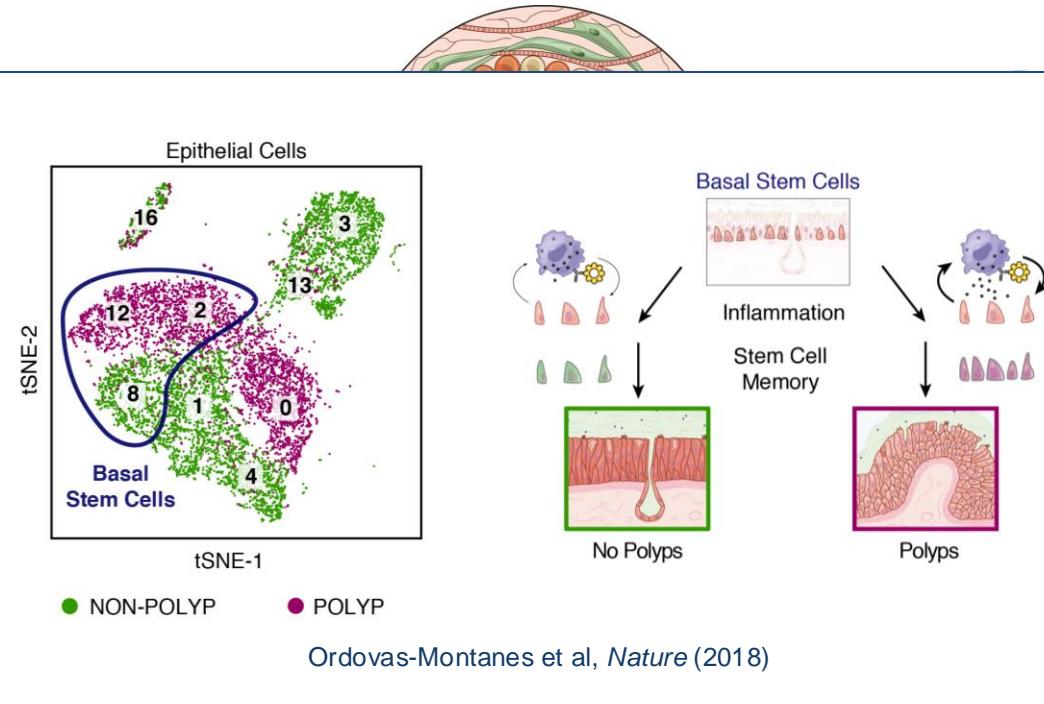


Jose
Ordovas



Type1/17 Response

- T1/T17 T cells*
- Cd8 T cells*



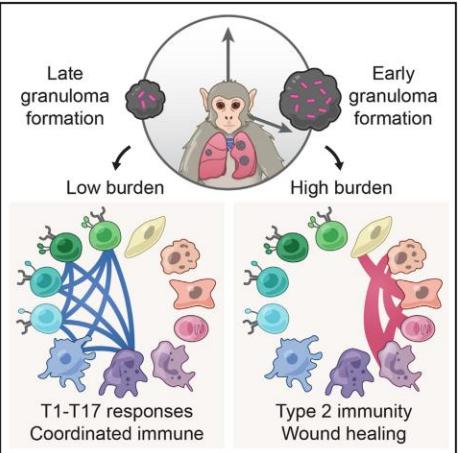
sponses (early)

- Endothelial Cells
- Type 1 pneumocytes



Testing Host Correlates *In Vivo*

Josh Bromley Sarah Nyquist



CD4 T Cell Correlates:

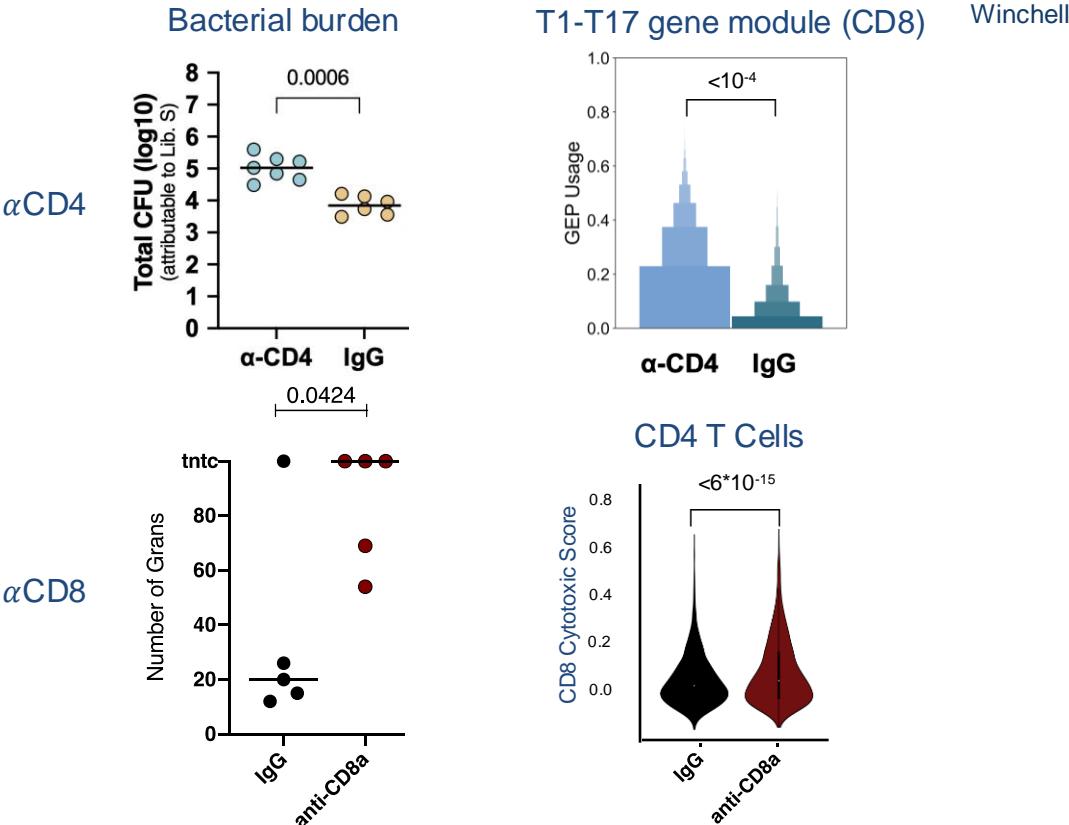
T1-T17 ($q=0.016$)

SRRM2+ ($q=0.044$)

Stem-like, Metallothionein, & Proliferating ($q=0.074$)

CD8 T Cell Correlates:

Cytotoxic 4 ($q=0.074$)



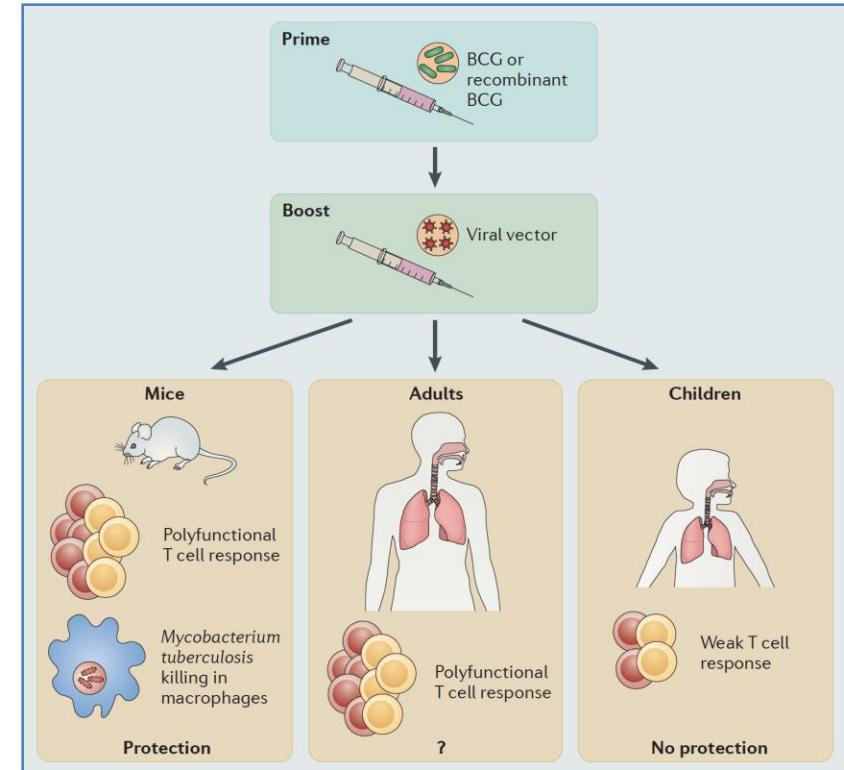
Deciphering The Cellular And Molecular Drivers Of TB Protection

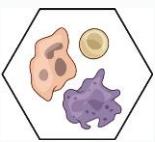
How can we identify restrictive cellular phenotypes?

1. Examining cellular correlates of immune control
2. Profiling protective vaccine responses

Vaccinating Against TB

- Bacille Calmette-Guerin (BCG), an attenuated form of *Mycobacterium bovis*, is the basis of the standard vaccine for tuberculosis (TB).
- BCG is routinely administered intradermally (ID) in countries with a high prevalence of TB primarily to prevent TB meningitis.
- The BCG vaccine is only 19% effective against pulmonary infection in children and 58% effective against progression to active disease.
- What drives response variability is unknown.





Will Altering the Route of BCG Immunization affect Protection?



Robert
Seder

Mario
Roederer

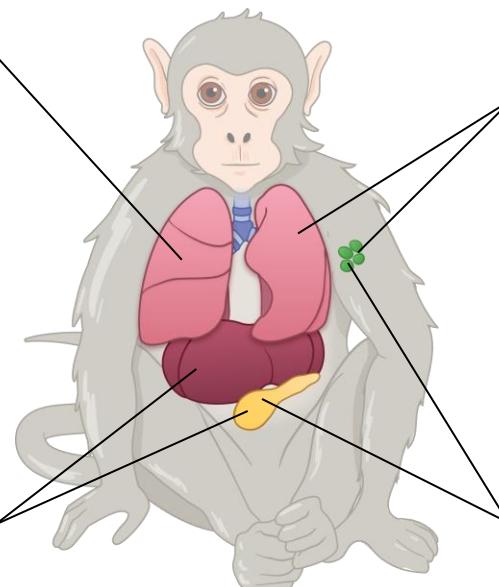
Patricia
Darrah

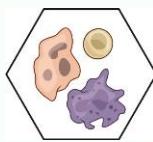
Aerosol (AE)
Lung LN
 T_{rm} cells in lung

Aerosol + ID
Lung T_{rm} +
circulating T_{mem}

Intravenous (IV)
Lung, Liver, Spleen, LN
 T_{rm} and circulating T_{mem}

Intradermal (ID)
Draining LN
Circulating T_{mem}

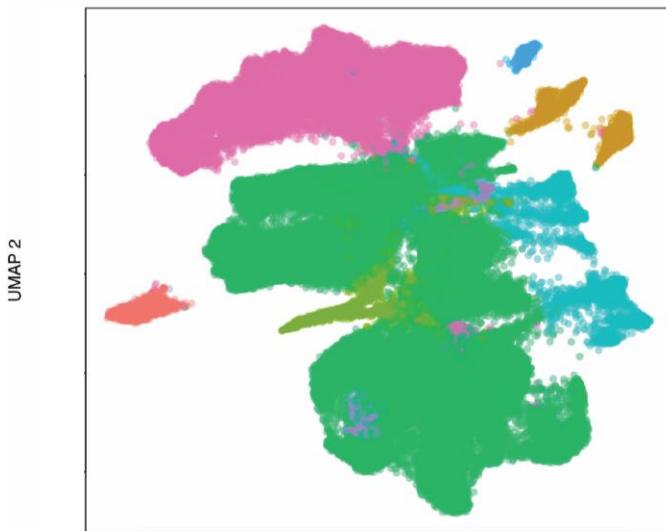




Profiling Cellular Response To Vaccination In Rhesus Bronchoalveolar Lavages (BALs)

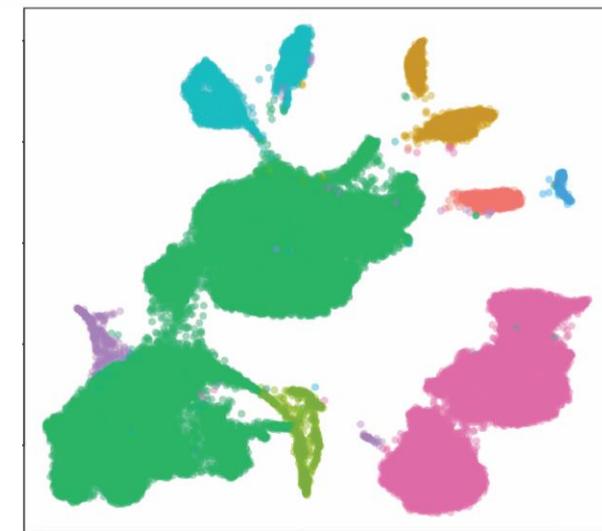
Week 13

(Peak Response; 98,993 Cells)



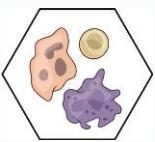
Week 25

(Memory Phase; 63,497 Cells)

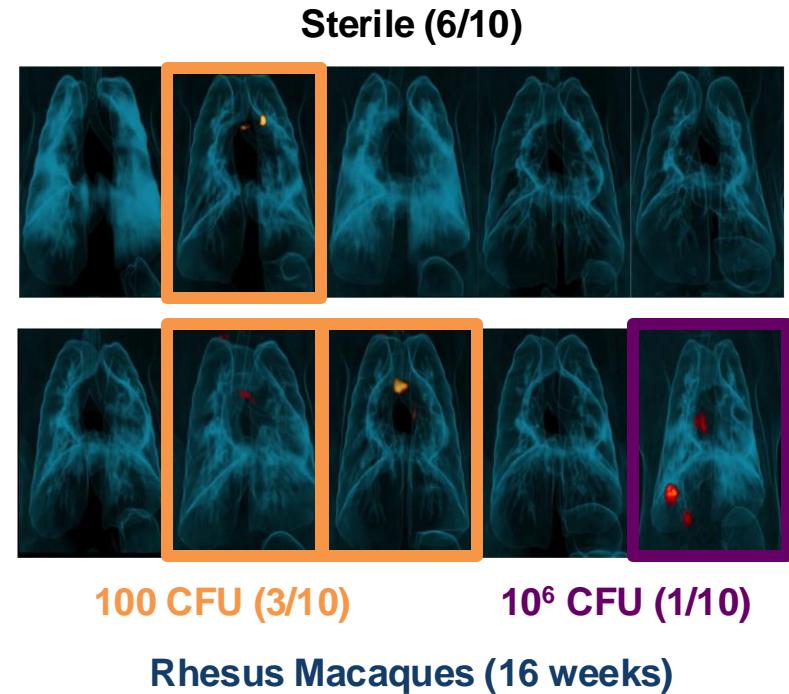
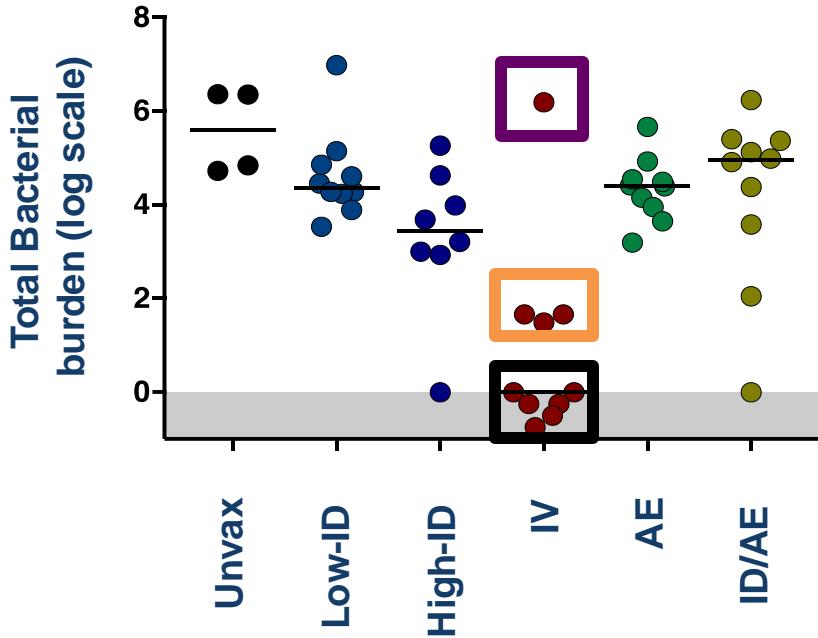


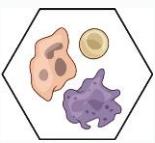
15 NHP (3 per route) +/- Stimulation

Darrah et al, *Nature* (2020)

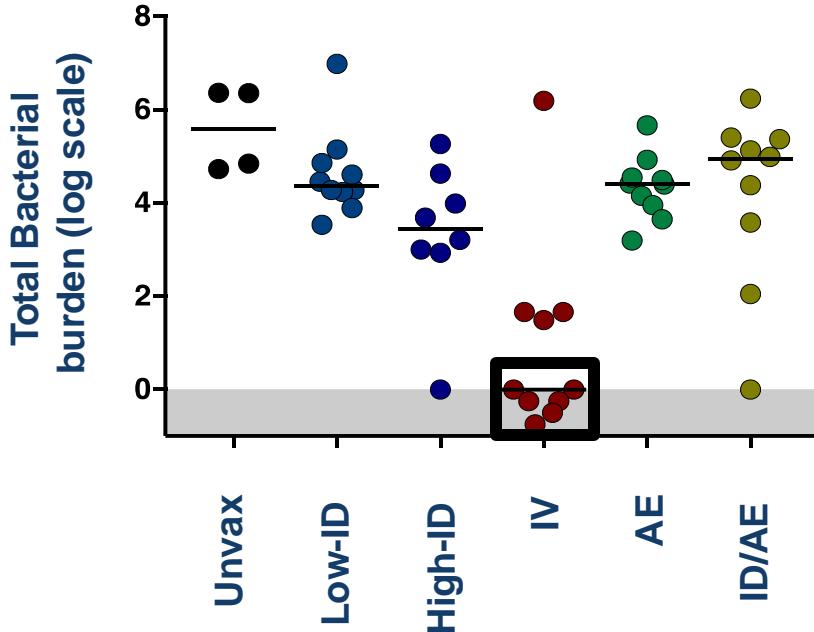


IV BCG Vaccination In Rhesus Can Elicit *Sterilizing Immunity*





IV-BCG Induced Vaccine Correlates



IV BCG Control

Type 1 responses!

- Th1/Th17 Cd4 T cells
- M1 Macrophages

Note: ID vaccination yields Type I IFN



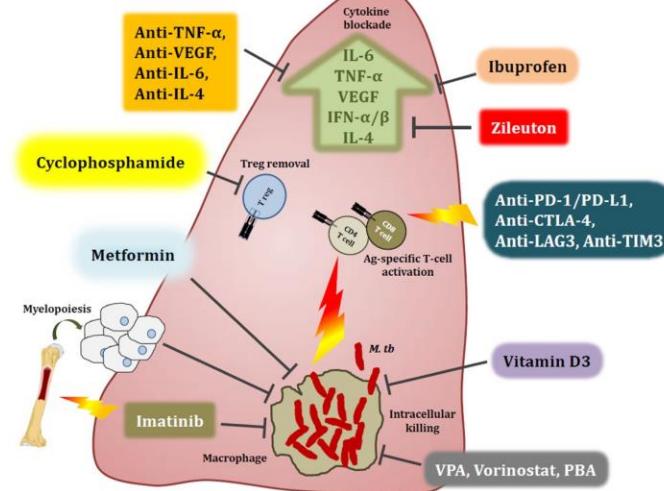
What Can We Do With These Cellular Signatures?

How can we leverage these features to improve therapeutics and prophylactic interventions?

Can We Utilize Immunotherapy-Inspired Approaches?



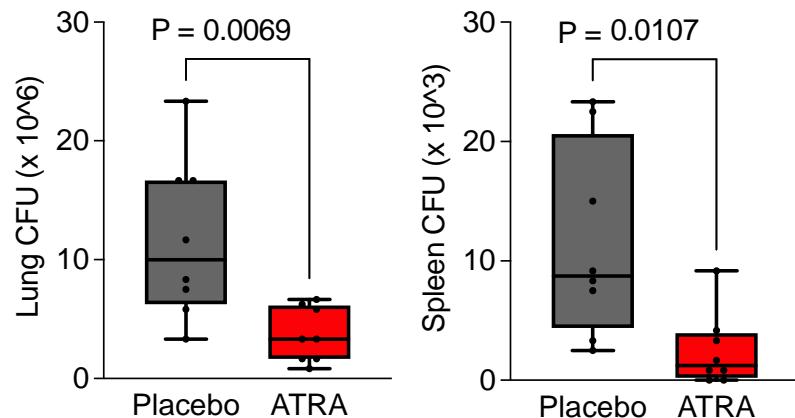
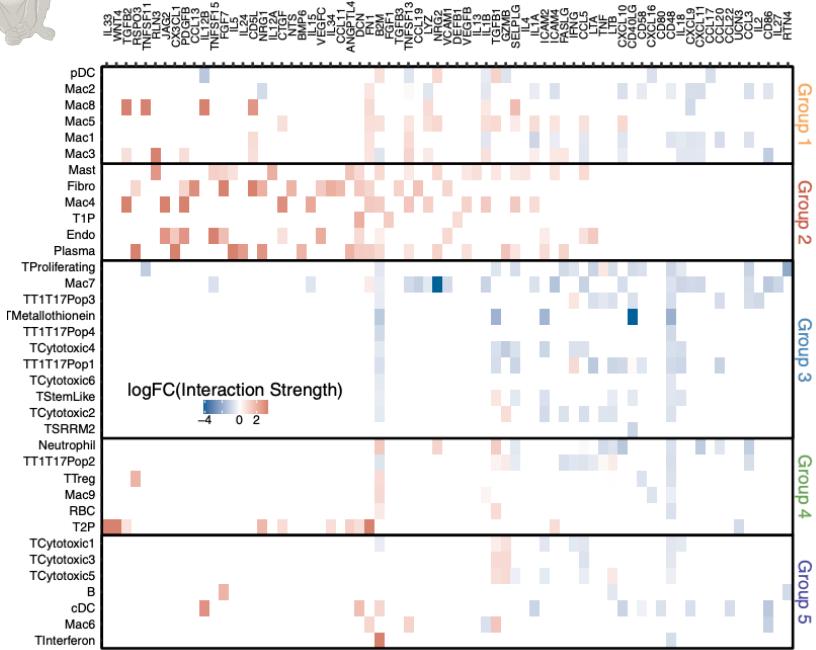
Nobel Prize in Medicine, 2018



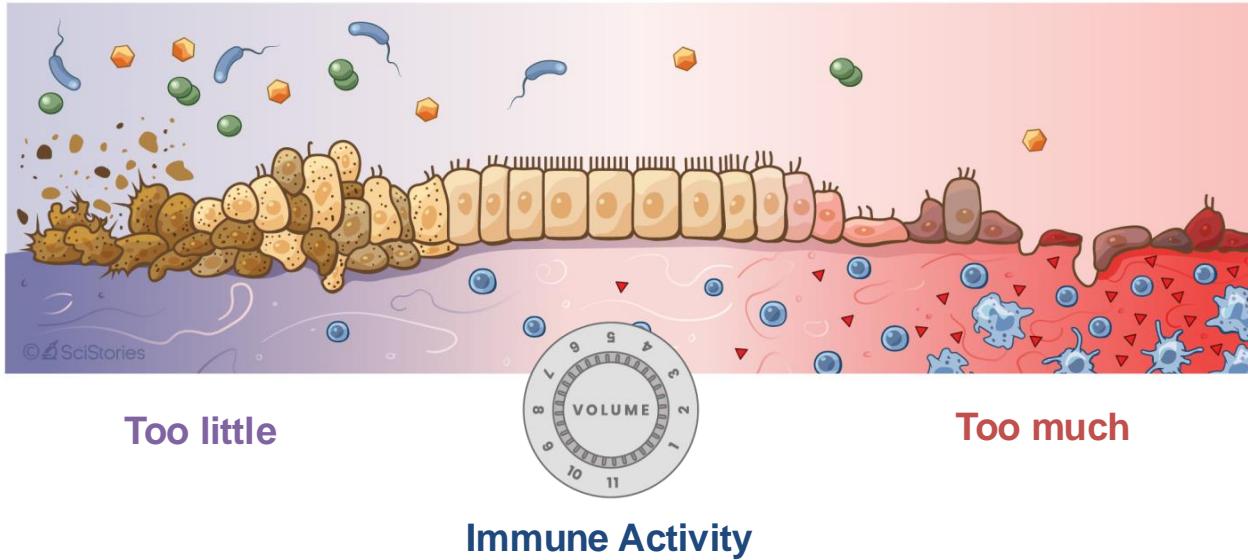
Can we use single-cell data to rationally engineer preferred immune cell responses by modulating restrictive and permissive cellular pathways?



Jake
Rosenberg



Identifying and Testing Cellular Correlates Of TB Protection



- The outcomes of TB infection are heterogeneous, both between and within hosts.
- NHP models recapitulate different critical features of human success and failure.
- Single-cell profiling suggests macrophage and T cell states correlated with control and protection.
- Models (*if carefully selected) enable functional testing to accelerate translation back to humans.

Scaling And Integrating

HI-IMPAcTB: Harmonized Investigation of Immune Mechanisms of Protection Against TB

Human cohorts

Acute Mtb exposure (+ PET-CT)

Resisters / RSTRs

Reverters / RVRTs

Non-human primates

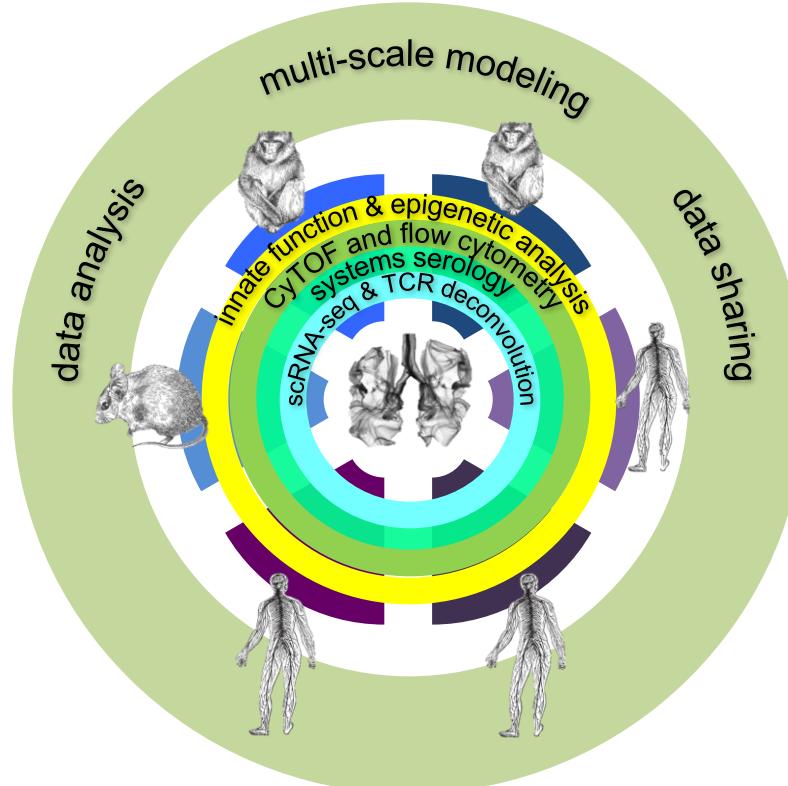
Natural infection

IV-BCG vaccination

Mouse models

IFN γ independent responses

Validation of therapeutic candidates



High-dimensional profiling platforms

Systems serology and mechanistic analysis

Single-cell sequencing

CyTOF and flow cytometry

T cell receptor analyses

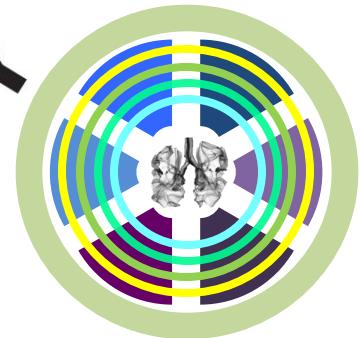
Innate myeloid responses and epigenetics

Integration

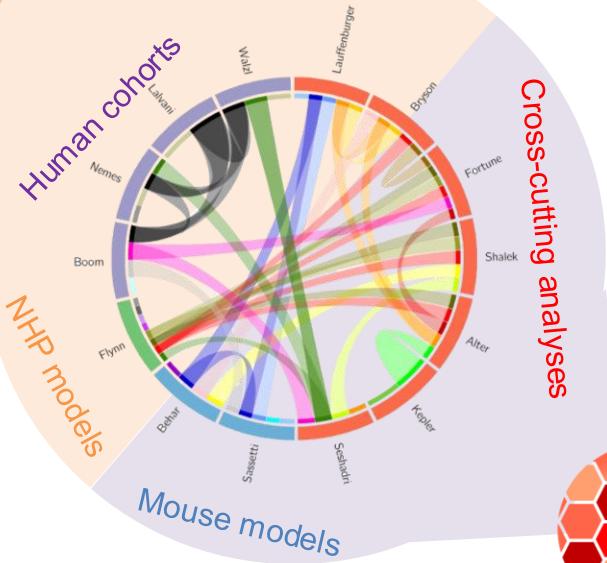
Computational modeling
(Meta)data sharing

International Collaboration And Scientific Integration

HI-IMPAcTB
(Fortune/Flynn/Bloom)



VRC/NIH
(Darrah/Reoderer/Seder)



Cross-cutting analyses

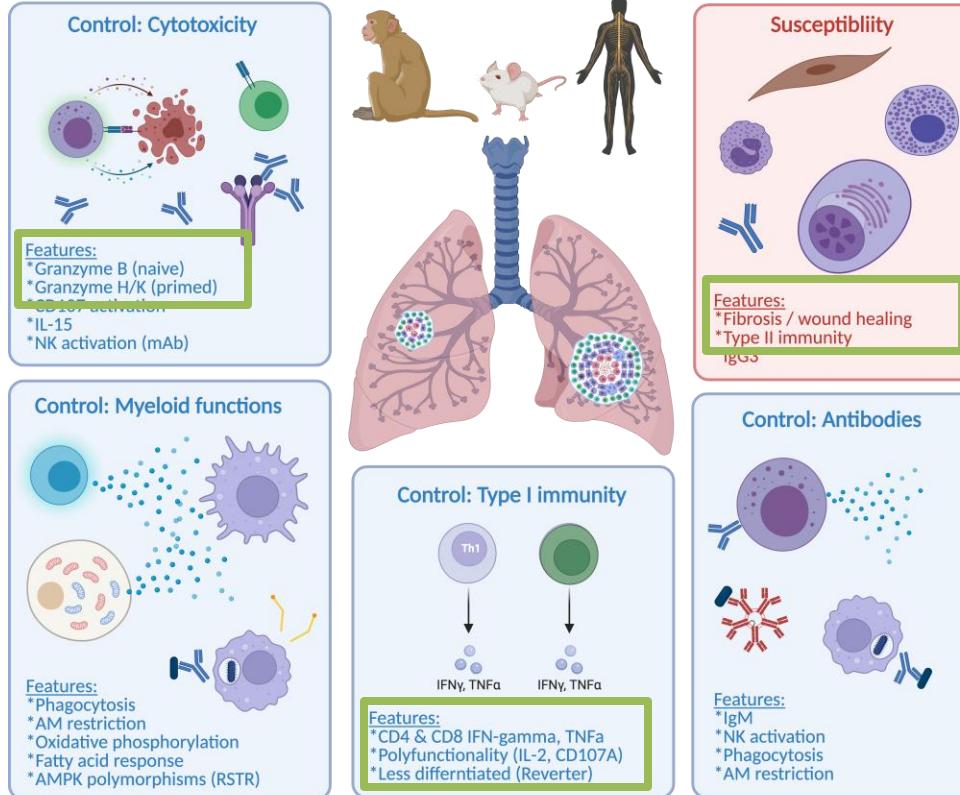


CASCADE

Wellcome Δ Tissue
(Rozot)



Emerging Concepts



Thank You!!!



Acknowledgements



HI IMPAcTB



Sarah Fortune
Harvard



Henry Boom
CWRU



JoAnne Flynn
Pitt

Administration



Mike Chao
Program Manager



BlakeLee Kaiser
Program Admin



Kristine Guinn
Grants and contracts



Julia Nelson
Contract
management

Cross cutting technologies/Data



Alex K. Shalek
Seq-Well



Galit Alter
Systems Serology



Sam Behar
T cell Ag ID



Bryan Bryson
Epigenetic
profiling



Chetan Seshadri
CyTOF



Chris Sassetti
CC Mice



Doug Lauffenburger
Data analysis/Model



Stuart Levine
Data Sharing



Elisa Nemes
RVRTR



Gerhard Walzl
RVRTR



Cathy Stein
RSTR



Ajit Lalvani
Acute Exposure



Human studies

NHP studies



Bob Seder
BCG IV



Mario Roederer
BCG IV



Chuck Scanga
BCG IV/SIV



Tricia Darrah
BCG IV



Acknowledgements

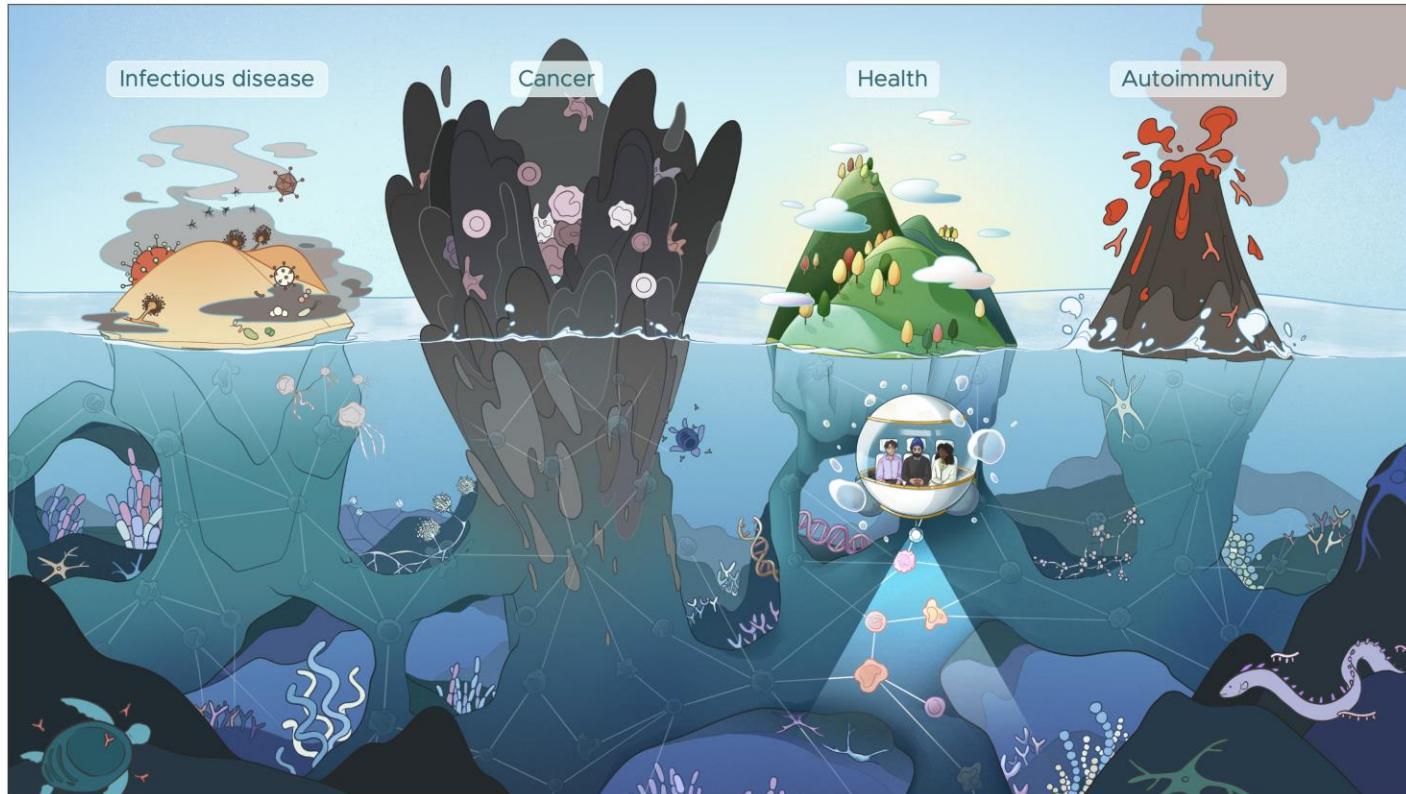
Chris Love (MIT)
Todd Gierahn (MIT)
AI Leslie (AHRI)
Ian Mbano (AHRI)
JoAnne Flynn (Pitt)
Hannah Gideon (Pitt)
Bryan Bryson (MIT)
Sarah Fortune (HSPH)
Sam Behar (UMass)
Ling Lin (Pitt)
Tom Scriba (Cape Town)
Virginie Rozot (Cape Town)

Mario Roederer (NIHVRC)
Bob Seder (NIHVRC)
Patricia Darrah (NIHVRC)
Tim Tickle (Broad)
Nir Yosef (UC Berkeley)
Bruce Walker (Ragon)
Doug Kwon (Ragon)
Facundo Batista (Ragon)
Henrik Kloverpris (AHRI)
Alex Sigal (AHRI)
Thumbi N'dungu (AHRI)
Doug Lauffenburger (MIT)

Leslie Kean (BCH)
Sangeeta Bhatia (MIT)
Uli Von Andrian (HMS)
Nir Hacohen (MGH)
Ramnik Xavier (MGH)
Scott Manalis (MIT)
Bill Hahn (DFCI)
Andy Aguirre (DFCI)
David Weinstock (DFCI)
Priscilla Brastianos (MGH)
Scott Carter (DFCI)
Aviv Regev (Genetech)
Eric Lander (Broad)

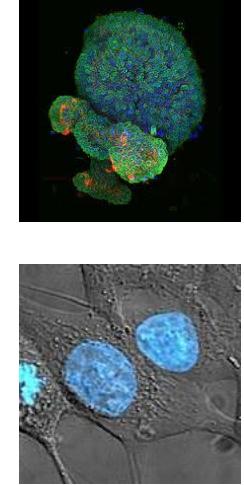
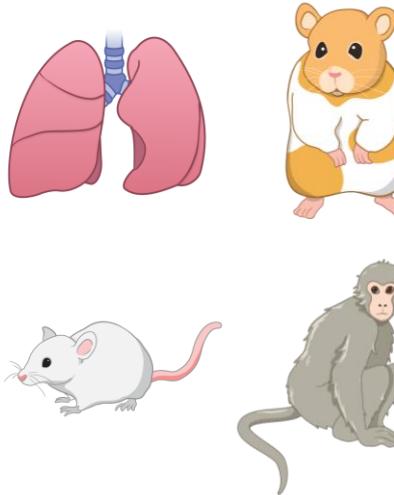
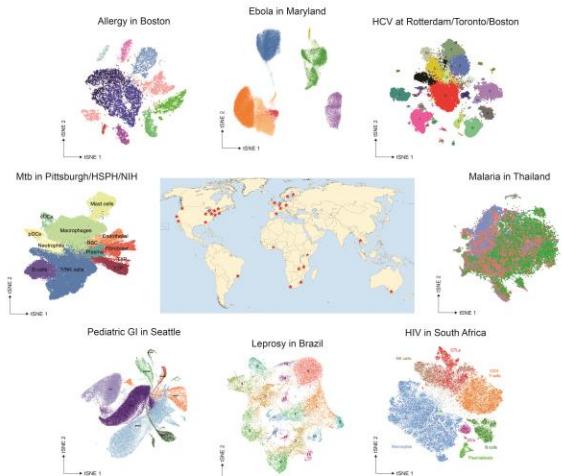
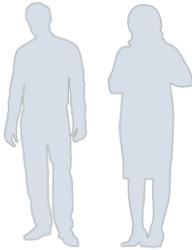


Questions?



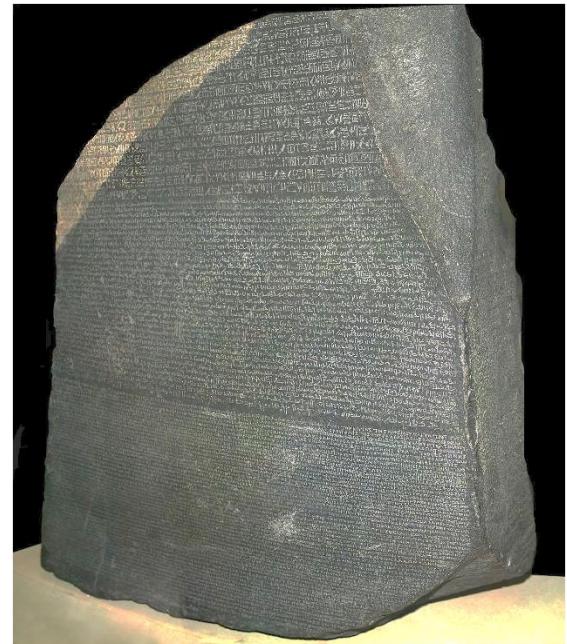
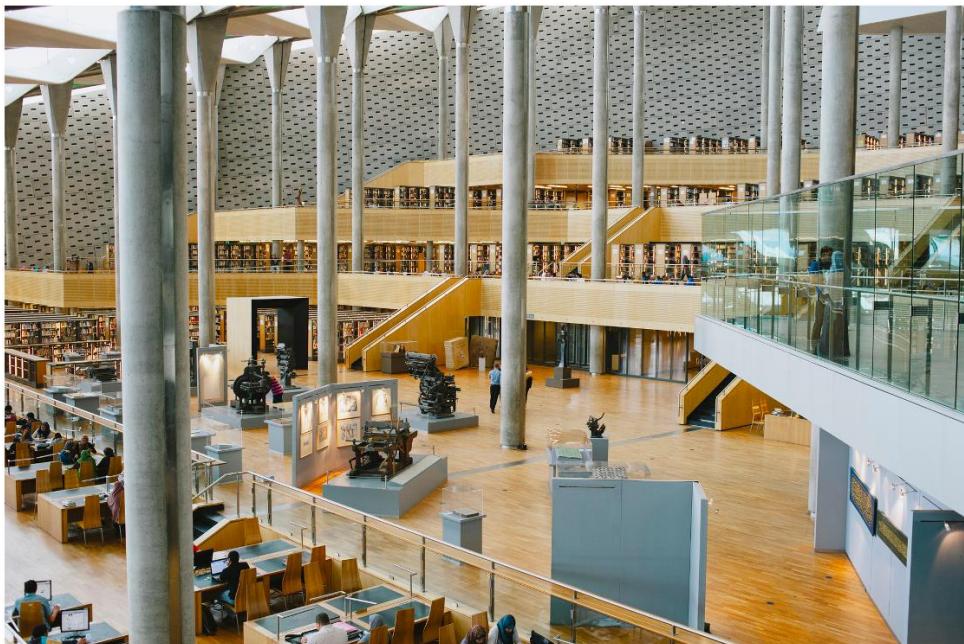


More Generally: From Human Biology To Models And Back



Top (clockwise): P. Sabeti (Broad) & L. Hensley (NIH); G. Lauer (MGH) & J. Aerssens (Janssen); S. Bhatia (MIT) & J. Prachumsri (Mahidol); B. Walker (Ragon) & T. Ndung'u (AHRF); R. Modlin (UCLA); L. Kean (Seattle Childrens); J. Flynn (Pitt), S. Fortune (HSPH),& B. Seder (NIH); N. Barrett & J. Boyce (BWH).

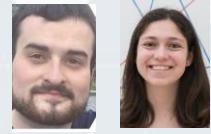
Next Steps: Scaling To Enabling Rapid Translation



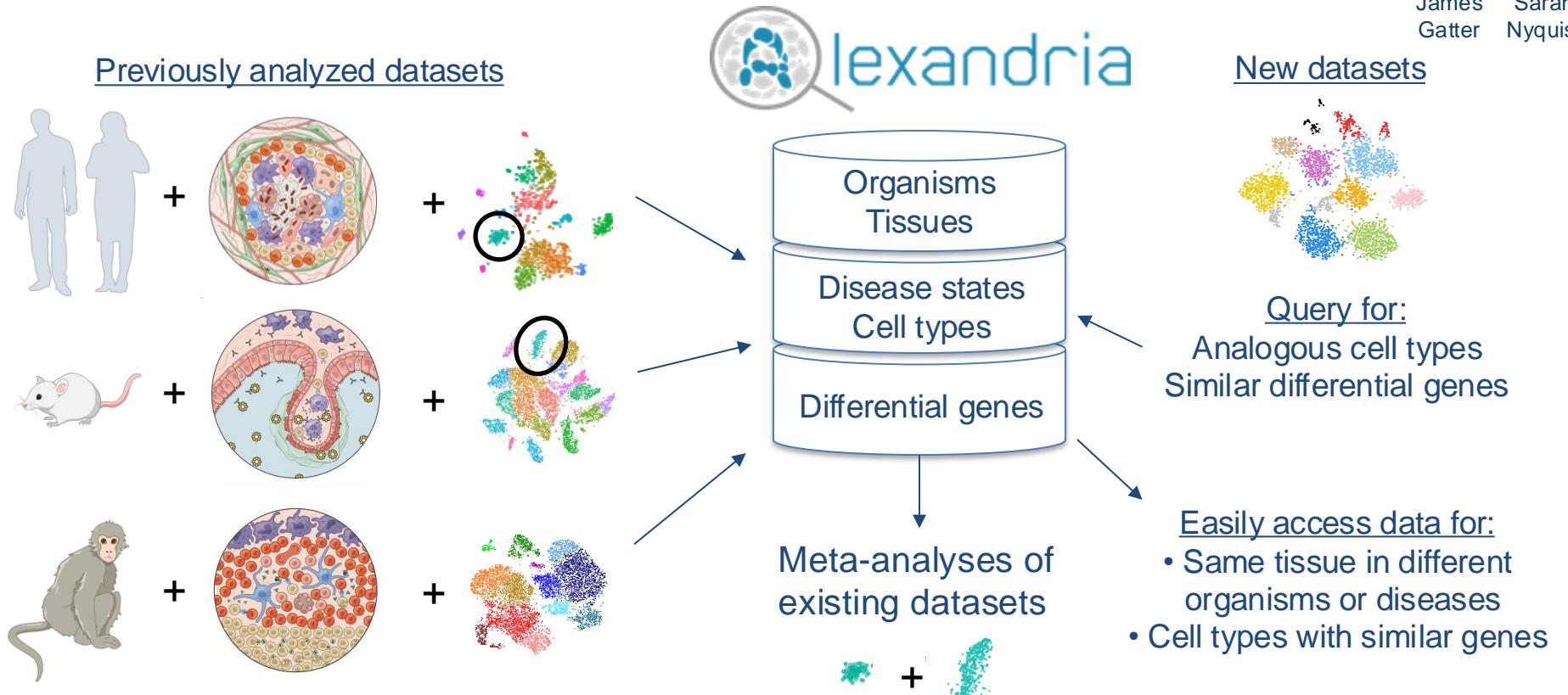
Large queryable libraries and signature sets

Left: www.businessinsider.com; Right: www.wikipedia.com

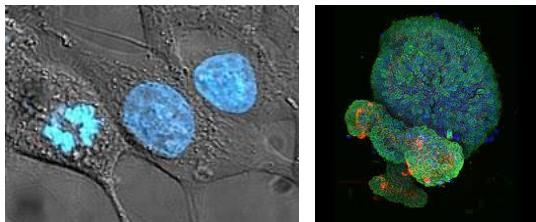
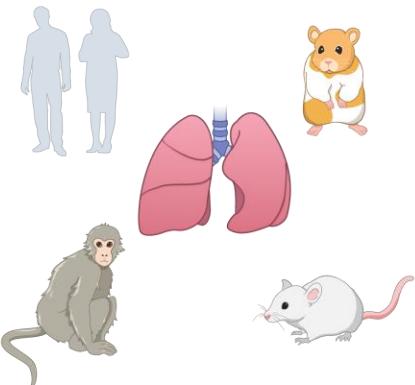
A Queryable Multi-Species Library Empowers New Analyses



James Gatter
Sarah Nyquist



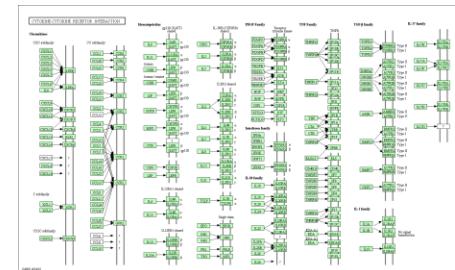
Ensuring Interpretability: Making “Rosetta Stones”



DATA!!!
scRNA-Seq
RNA-Seq
ATAC-Seq
Imaging
Your Favorite Assay Here



Discovery!

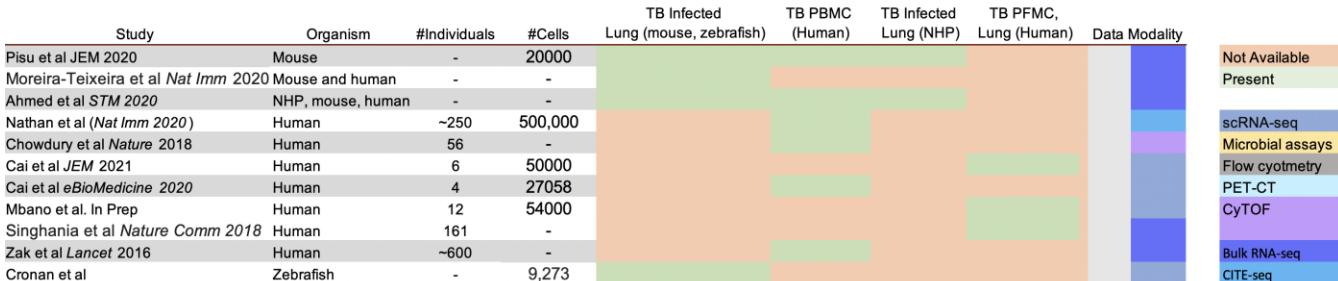
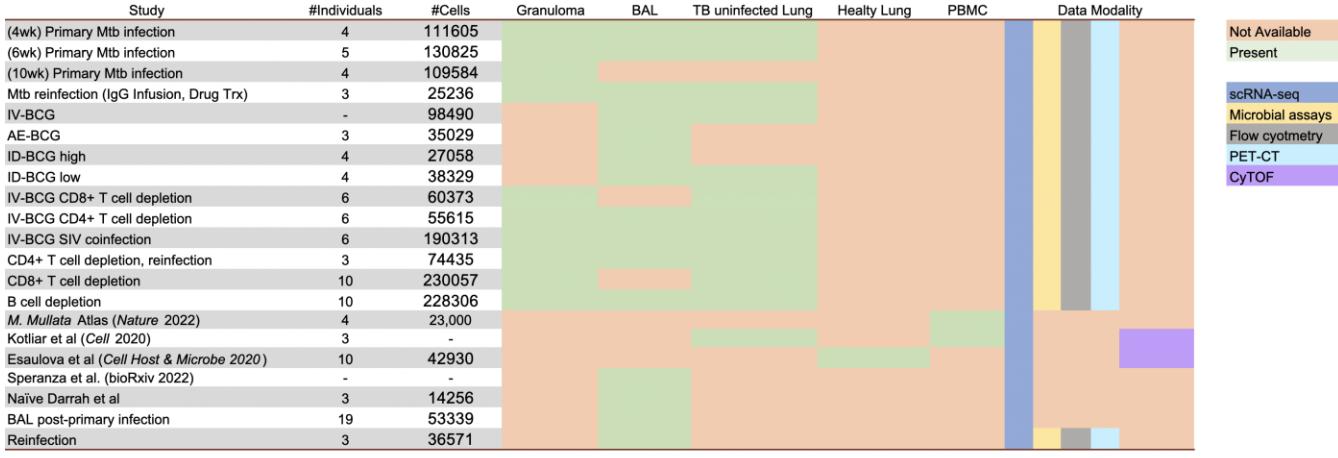


Multiple Data Sets For TB Across Species

NHP

Human
Mouse
Zebrafish

...





The Challenge: Linking Biology Across Scales, Compartments, and Models

Josh Bromley Sarah Nyquist Carly Ziegler Zoë Steier

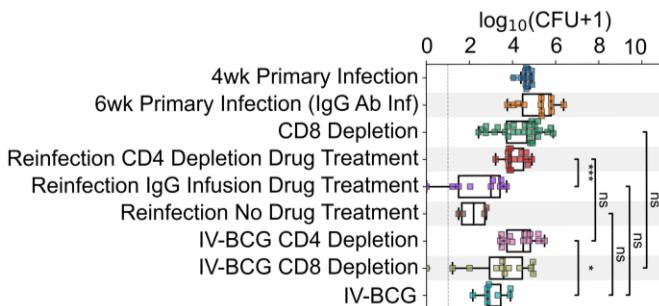


Table 1. Macaque Cohort Composition and Sample Types

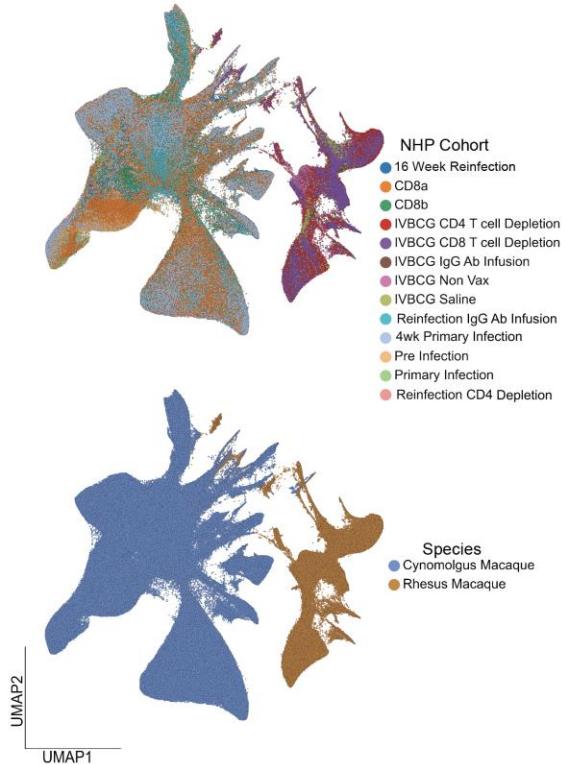
NHP Cohort	Number of NHPs	Number of Granulomas	Number of Uninvolved Lung Samples	Number of BAL Samples
4wk Primary Infection	5	10	5	5
6wk Primary Infection (IgG Ab Infusion)	5	12	5	0
CD8 Depletion (anti-CD8 α and anti-CD8 β)	10 anti-CD8 α (n=5) anti-CD8 β (n=5)	27 anti-CD8 α (n=16) anti-CD8 β (n=11)	10 anti-CD8 α (n=5) anti-CD8 β (n=5)	0
Reinfection CD4 Depletion (Drug T _x)	7	13	7	14
Reinfection IgG Ab Infusion (Drug T _x)	6	8	6	12
Reinfection (No Drug T _x)	5	4	8	10
IV-BCG CD4 Depletion	6	12	6	12
IV-BCG CD8 Depletion	6	9	13	12
IV-BCG	9	13	11	18

Overview

- 13 NHP Cohorts
 - 65 *Mtb* infected NHPs
- 2 NHP species
- 3 compartments
 - Bronchoalveolar lavage (BAL)
 - Uninvolved lung tissue
 - Granuloma
- 811,197 high-quality cells



The Challenge: Linking Biology Across Scales, Compartments, and Models



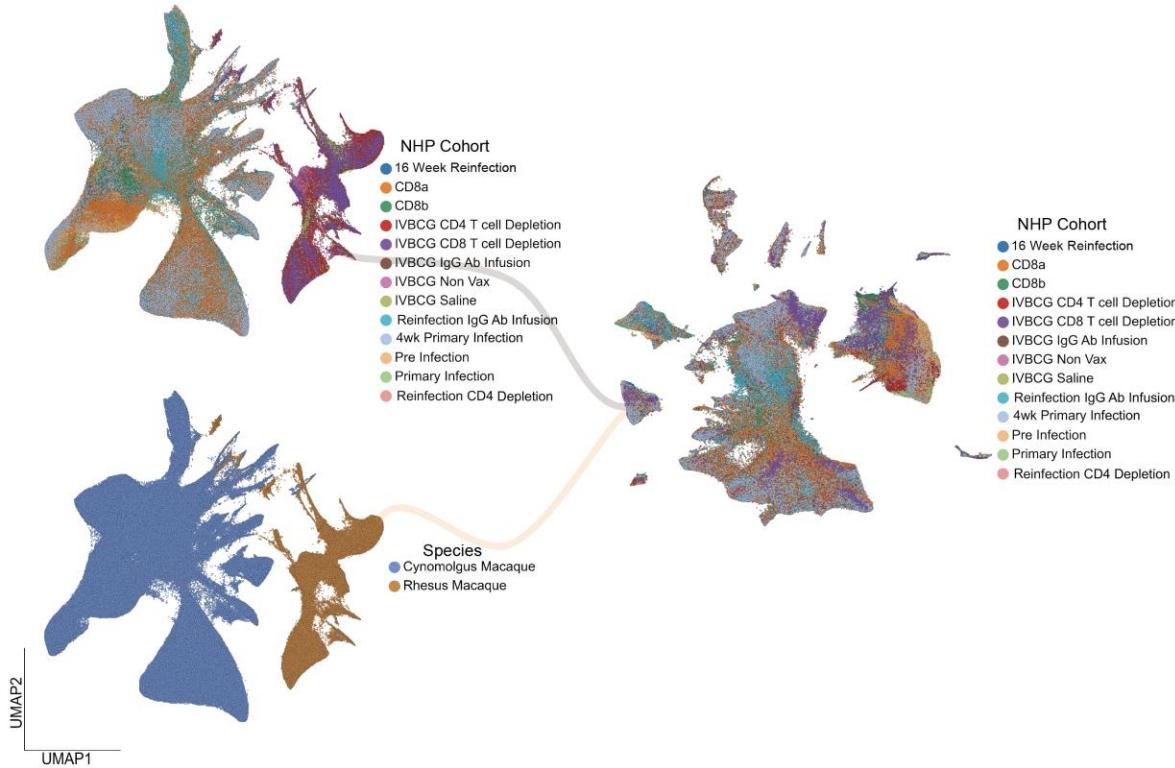
Challenge(s)

- Technical batch effects
- Biological covariates
 - Granuloma heterogeneity
 - Perturbation (e.g., T cell depletion)
 - Vaccination
 - Infection time point
 - Sample compartment

Solution

- Integrate?

The Challenge: Linking Biology Across Scales, Compartments, and Models



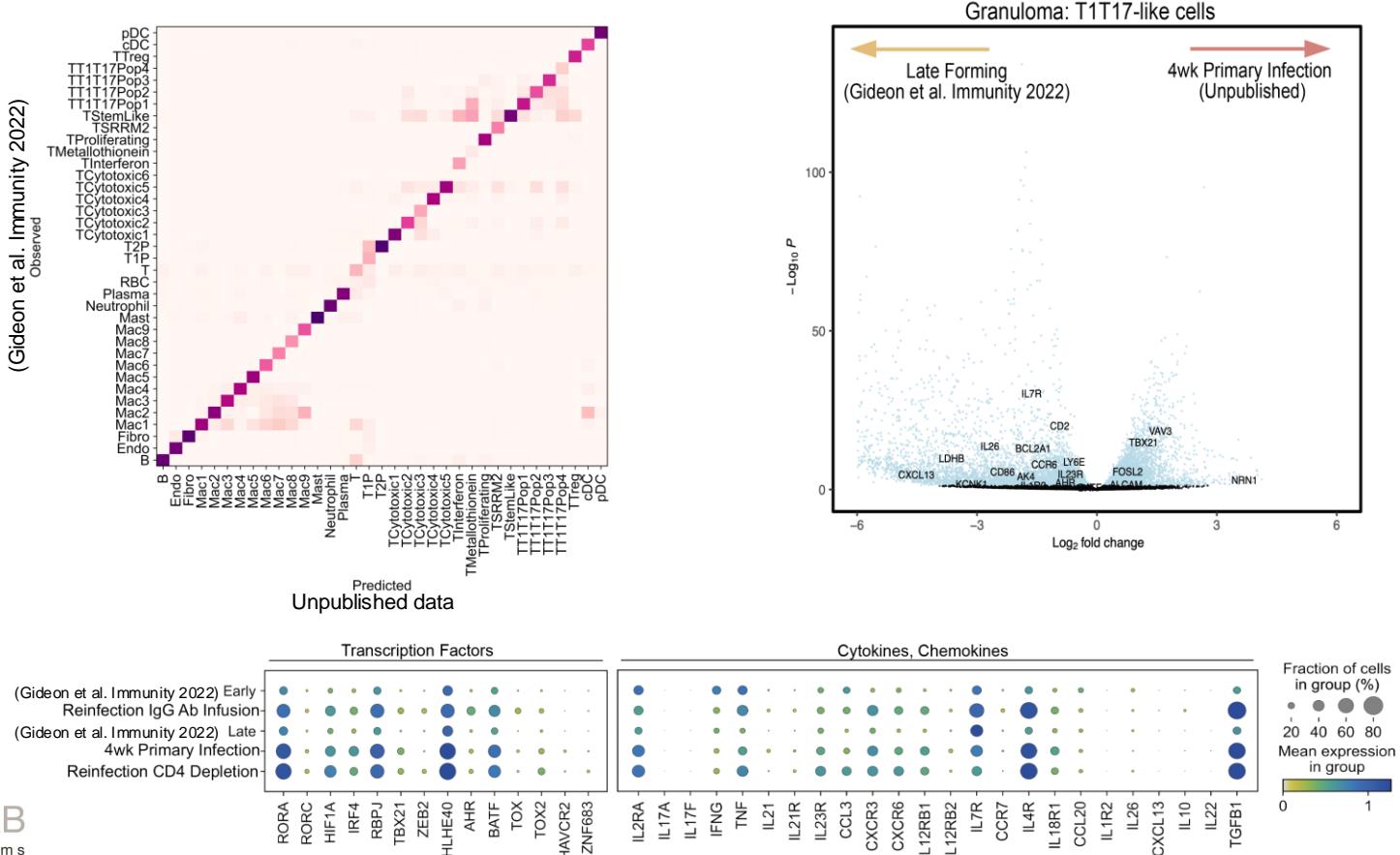
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 - Infection time point
 - Sample compartment

Solution

- Integrate?

The Challenge: Linking Biology Across Scales, Compartments, and Models



Fundamental, From Where Does This Problem Come?

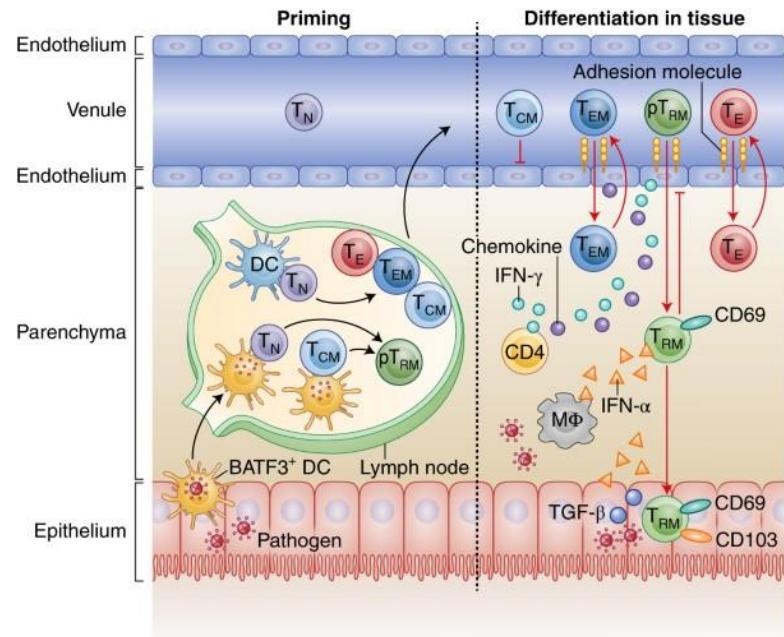
Why the mismatch?

Cell identity depends on spatiotemporal context:

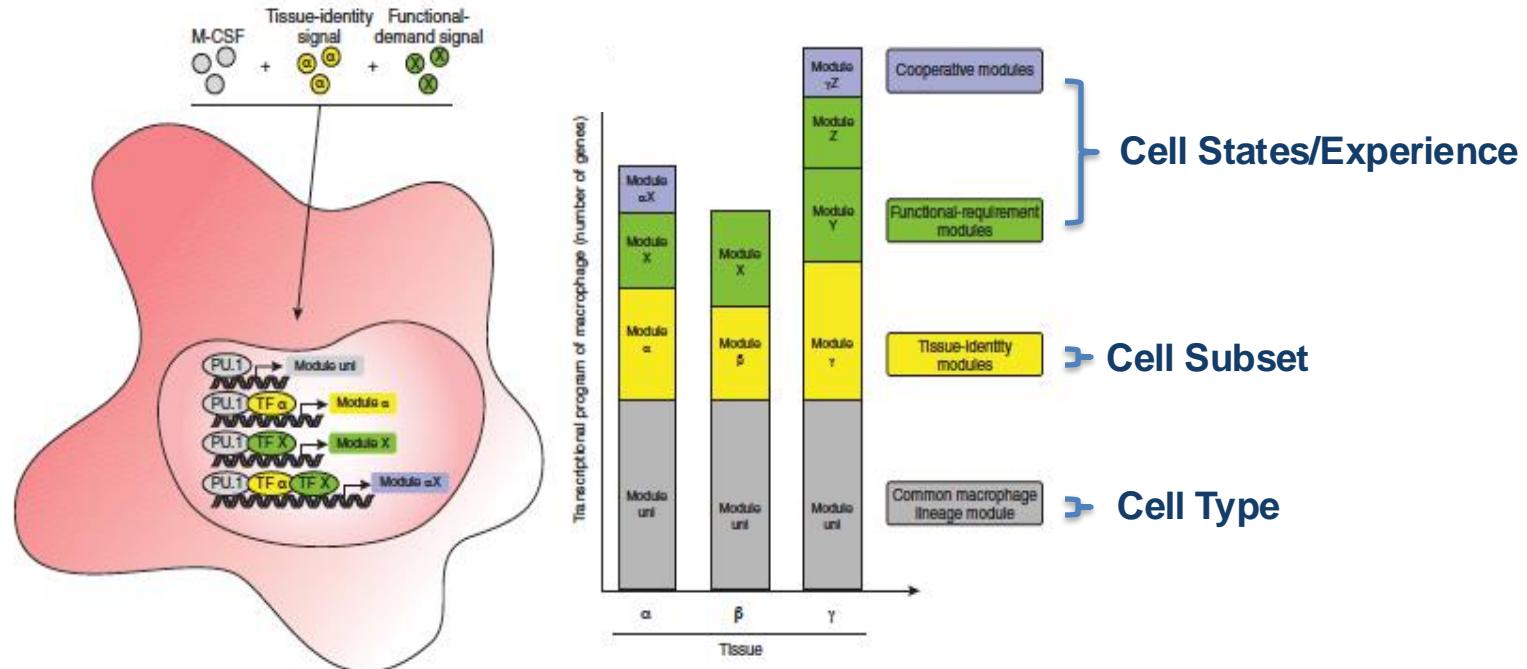
- Developmental stage
- Exposure history
- Spatial context
- Etc

Thus, gene programs vary greatly & are not stable:

- Across animals
- Across conditions
- Across experiments
- Across techniques



A Potential Solution: Describing Cells As Sums Of Gene Modules

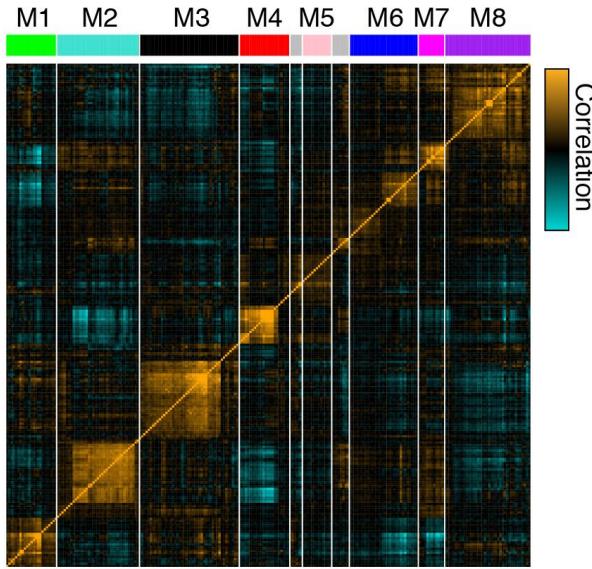


Impacted by developmental stage, exposure history, spatial context, etc
(Biologically, this means differences in epigenetics, TFs, etc)

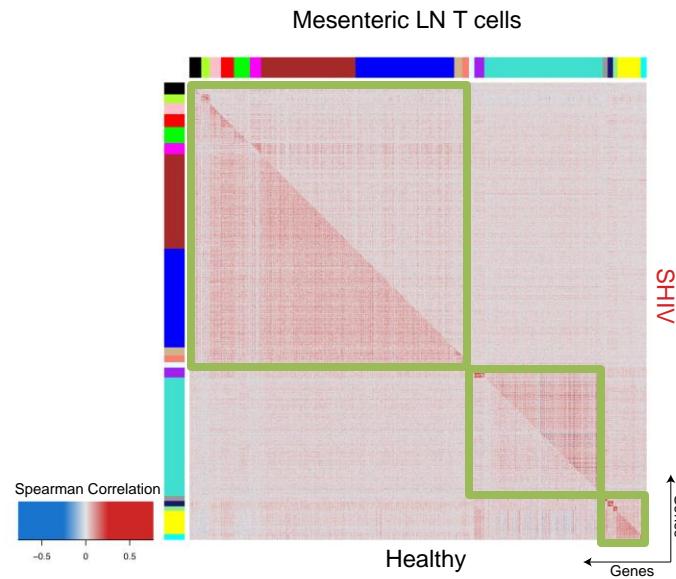
Arendt et al, *Nature Reviews Genetics* (2016); Okabe et al, *Nature Immunology* (2016)

Module Identities And Their Stability

Calculating Modules

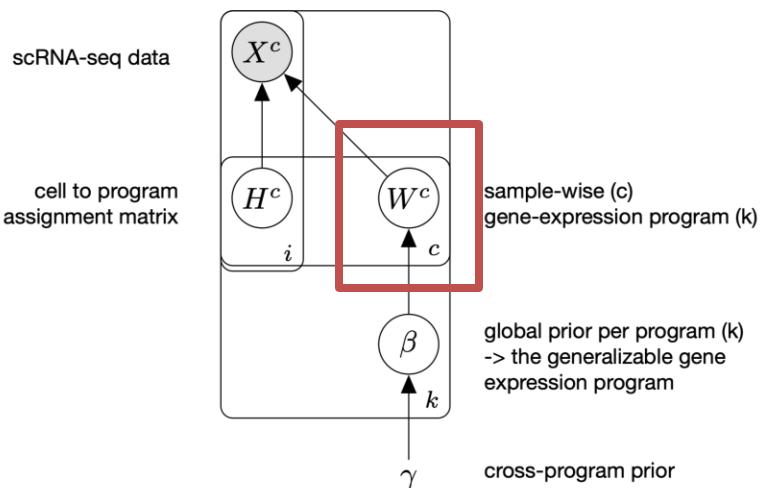


Shifting Module Membership

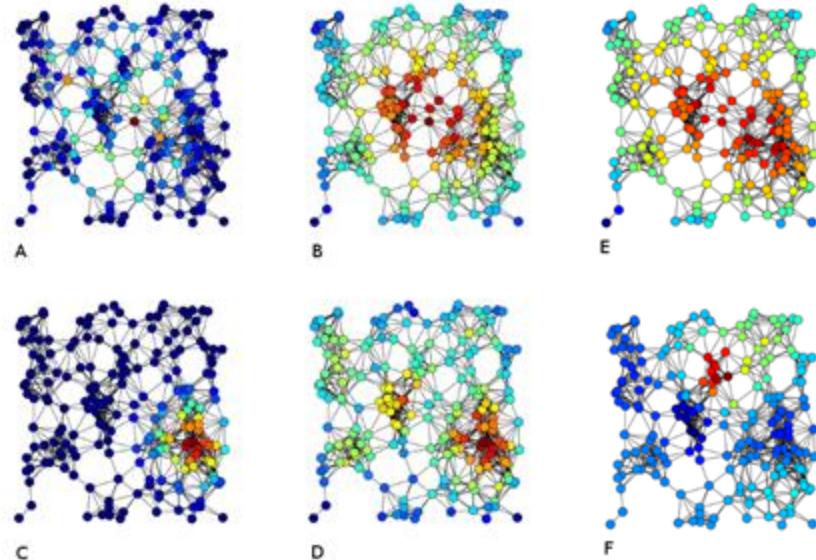


Identifying Core Modules

Parameter Inference



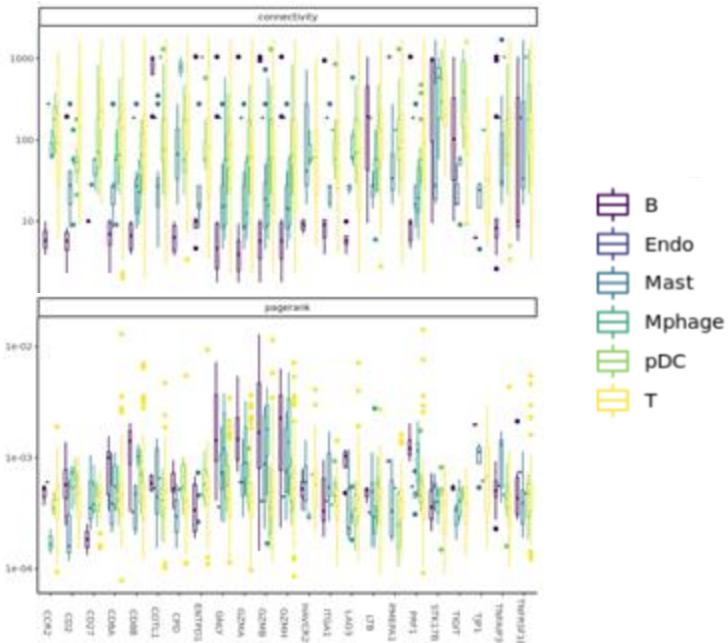
Network Centrality



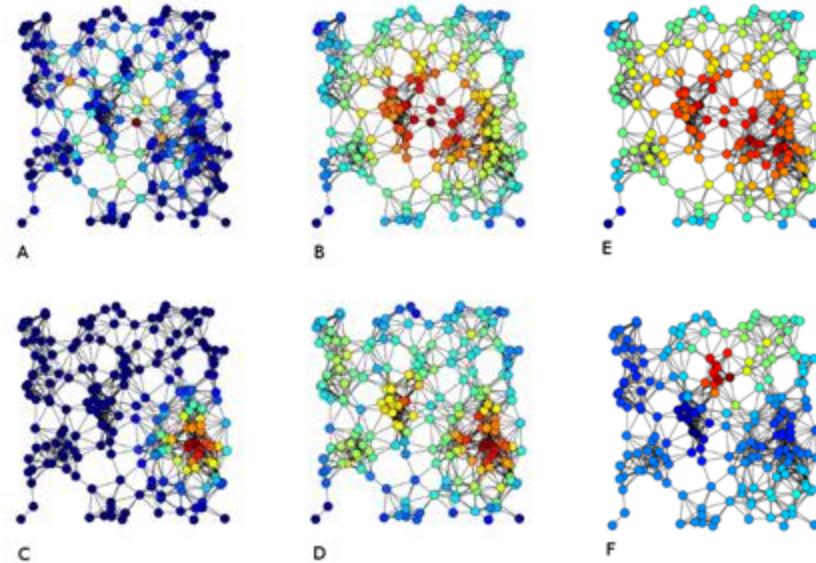
A. Betweenness; B. Closeness; C. Eigenvector;
D. Degree; E. Harmonic; F. Katz

Identifying Core Modules

Stratify network attributes per gene per cluster/state



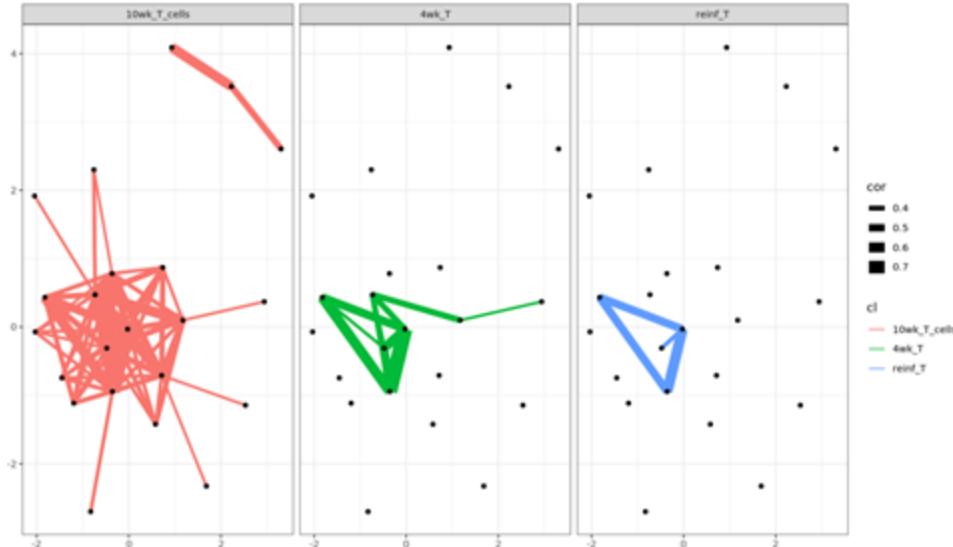
Network Centrality



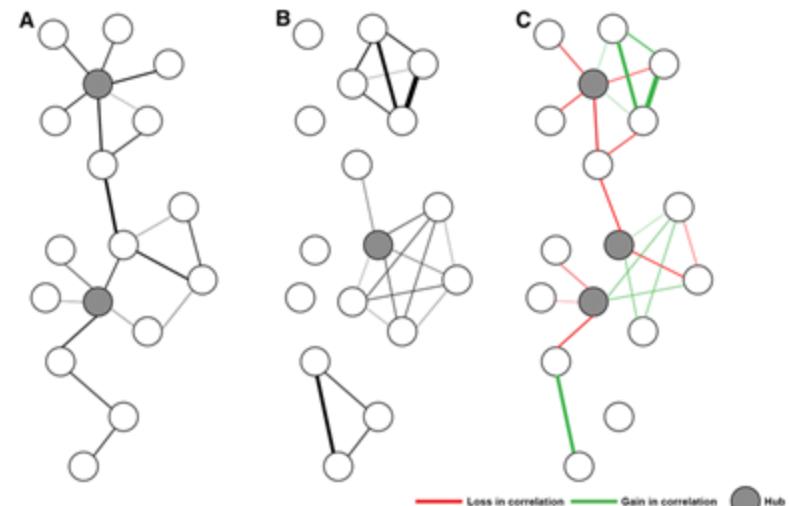
A. Betweenness; B. Closeness; C. Eigenvector;
D. Degree; E. Harmonic; F. Katz

Examining Modules & Their Variation

Shifting network structure

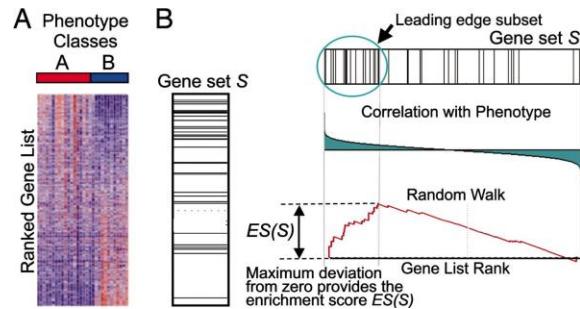


Differential networks studies, animals, samples, clusters



Linking Variation to Biology & Targetability

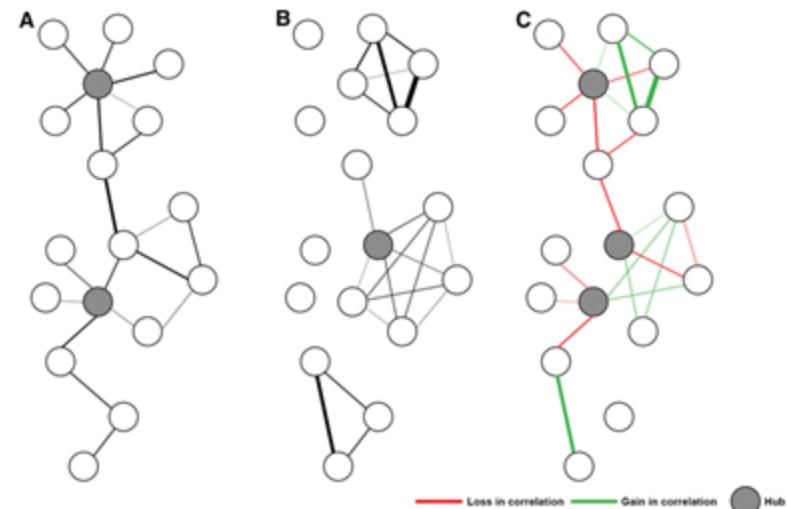
Enrichment over topological differences to nominate drivers



Explicitly model role

Model W^c using metadata
e.g., cell type, vaccination status, infection history,
model, tissue, burden, etc

Differential networks studies, animals, samples, clusters



This is step one.

Subramanian et al, PNAS (2005)

From Cellular Networks To Tissue Niches

Step Two: Define multicellular programs that govern tissue response to guide prognostics and therapeutics.

Rationale:

- TB infection impacts tissue niches (e.g., lung) not cell types
- Tissue responses (e.g., granulomas) influence the efficacy of therapies.
- Cellular interdependencies may drive unexpected, exploitable side effects.

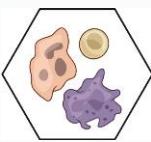
Approach:

- Explicitly model network co-dependence (networks of networks) using dissociated and spatial single-cell data

Goal:

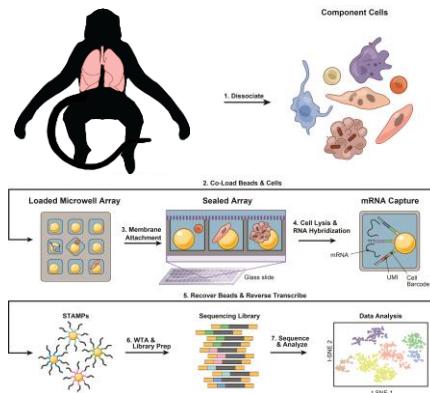
- Understand variation in TB tissue responses and codependence across scales and relate to differences in patient outcomes.
- Rationally select cellular therapeutic targets that target & modify tissue niches.
- Predict latent tissue responses (e.g., lung) from observed tissues (e.g., blood).





IV-BCG Induced Vaccine Correlates

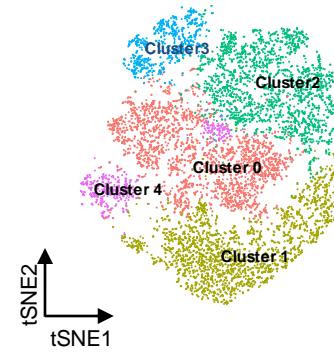
Seq-Well on NHP BALs



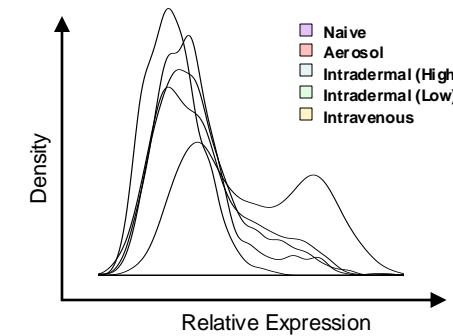
Seq-Well Set-Up



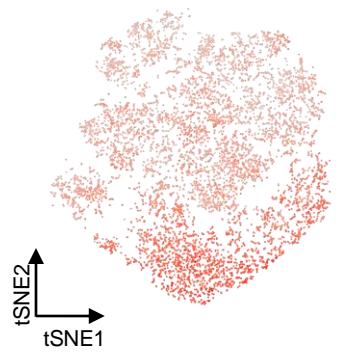
Cell Type Clustering



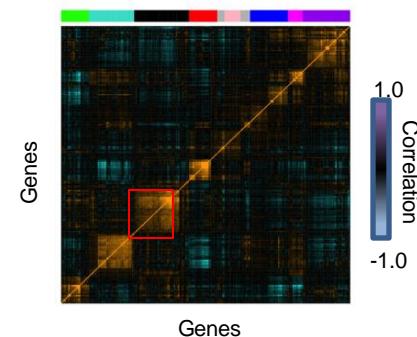
IV-BCG Induced Module



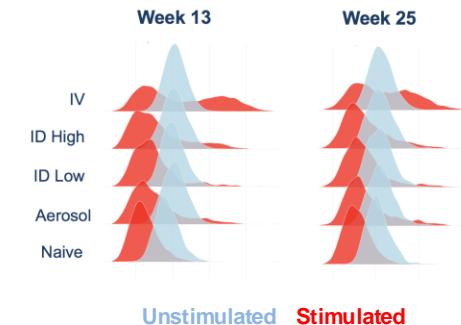
Module Expression



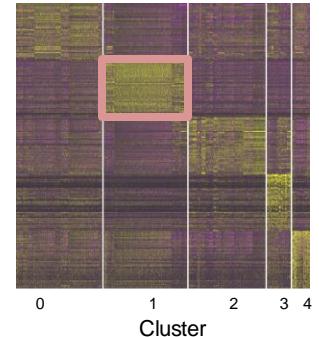
Module Identification



Expression at Peak & Memory



Cellular Identities





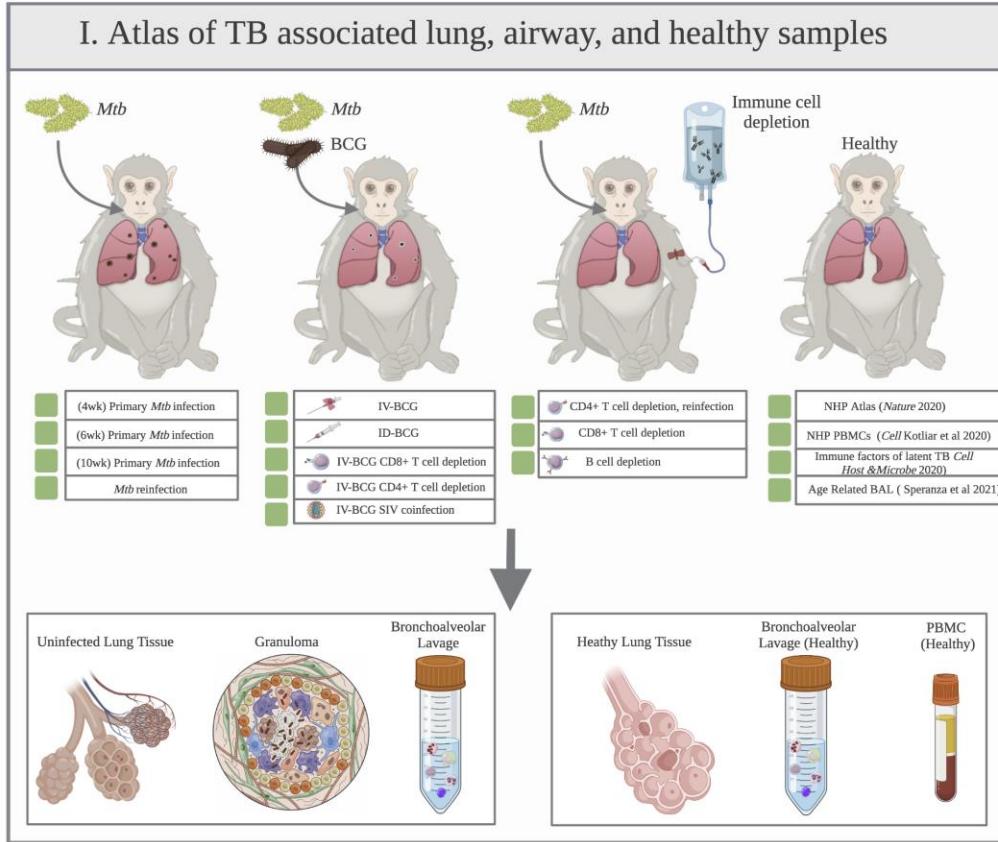
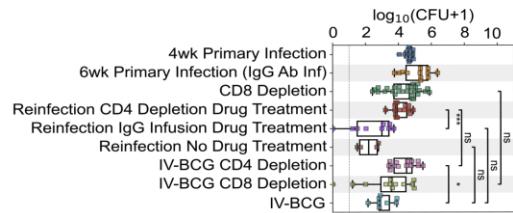


Table 1. Macaque Cohort Composition and Sample Types

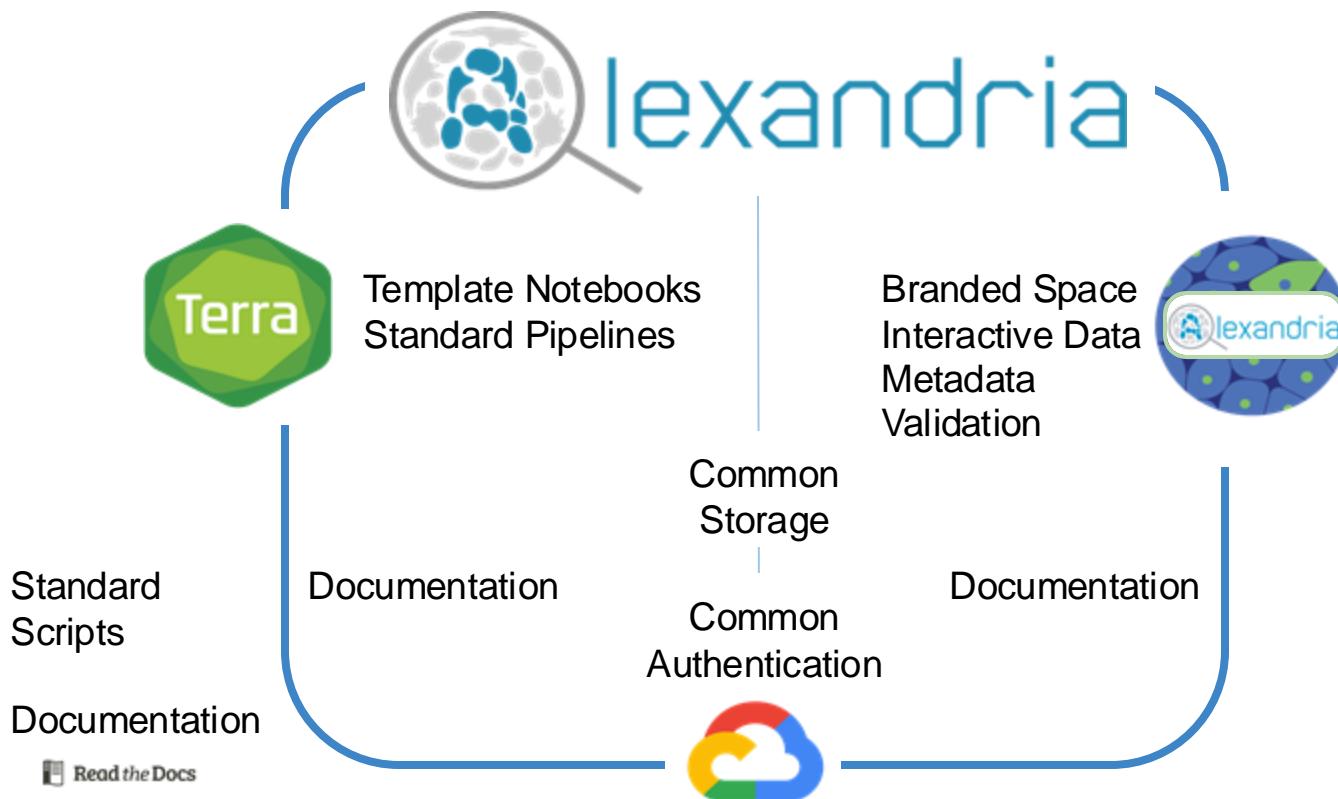
NHP Cohort	Number of NHPs	Number of Granulomas	Number of Uninvolved Lung Samples	Number of BAL Samples
4wk Primary Infection	5	10	5	5
6wk Primary Infection (IgG Ab Infusion)	5	12	5	0
CD8 Depletion (anti-CD8α and anti-CD8β)	10 (n=5) anti-CD8α (n=16) anti-CD8β (n=11)	27 anti-CD8α anti-CD8β	10 (n=5) anti-CD8α (n=5) anti-CD8β (n=5)	0
Reinfection CD4 Depletion (Drug T _h)	7	13	7	14
Reinfection IgG Ab Infusion (Drug T _h)	6	8	6	12
Reinfection (No Drug T _h)	5	4	8	10
IV-BCG CD4 Depletion	6	12	6	12
IV-BCG CD8 Depletion	6	9	13	12
IV-BCG	9	13	11	18



- ~2,000,000 cells
- Single-cell data has microbiologic, clinical, and immunologic metadata from more than 80 NHPs.
- >100 granulomas.



What is Alexandria?



Alexandria & The SCP Ecosystem

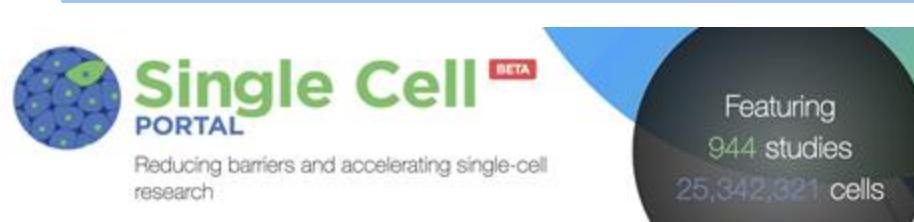
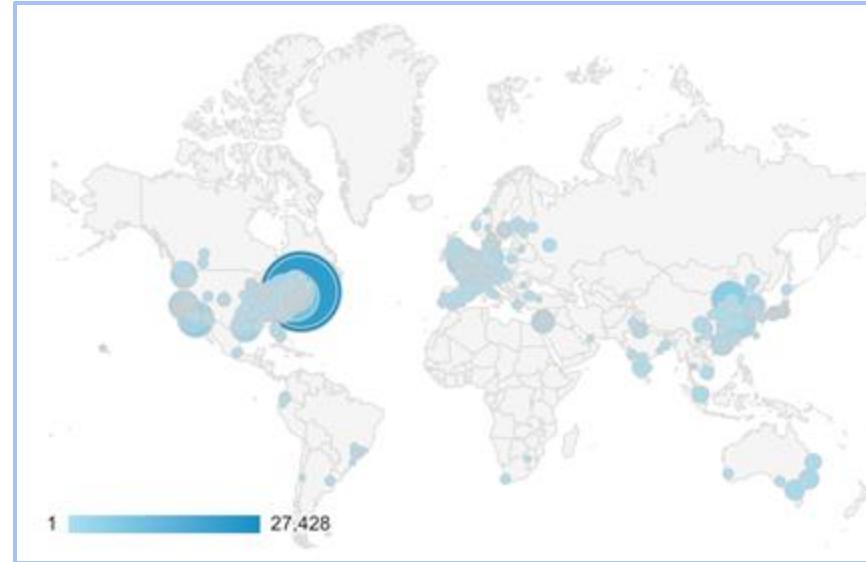
The Alexandria Project



The Alexandria Project



BICCN Anatomy and Morphology Project



Alexandria Documentation

The screenshot shows a documentation page for the Alexandria Project. The URL in the address bar is alexandria-scrna-data-library.readthedocs.io/en/latest/introduction.html. The page features a sidebar on the left with a search bar and navigation links for Introduction, Workflows, Notebooks, and Appendix. The main content area includes a large logo with a magnifying glass over a cell cluster, a status bar indicating "build passing", and a brief introduction followed by a "Background" section.

alexandria-scrna-data-library.readthedocs.io/en/latest/introduction.html

Docs » The Alexandria Project [Edit on GitHub](#)

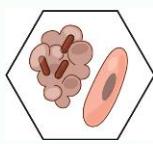
The Alexandria Project

A Single-Cell RNA-Seq and Analytics Platform for Global Health

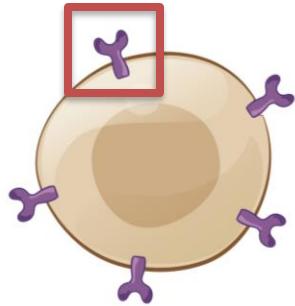
This is the work-in-progress documentation for the Alexandria platform and all associated tool workflows and notebooks.

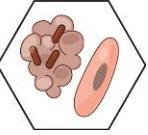
Background

Alexandria is a single-cell portal and data resource for the global health community. Alexandria will use unified pipelines to preprocess, store, and visualize datasets of interest to the global health community, enabling rapid realization of transformative insights and the prioritization of follow-ups. To maximize impact and utility, Alexandria will build upon existing efforts at the Broad, Single Cell Portal (SCP), but will be further enhanced to enable queries across gene sets, cell types, and models as inspired by the types of data collected by the global health community. This will power vital cross-comparisons while simultaneously providing novel analytic capabilities for the community at large. Moreover, Alexandria will similarly empower the broader global research community—from



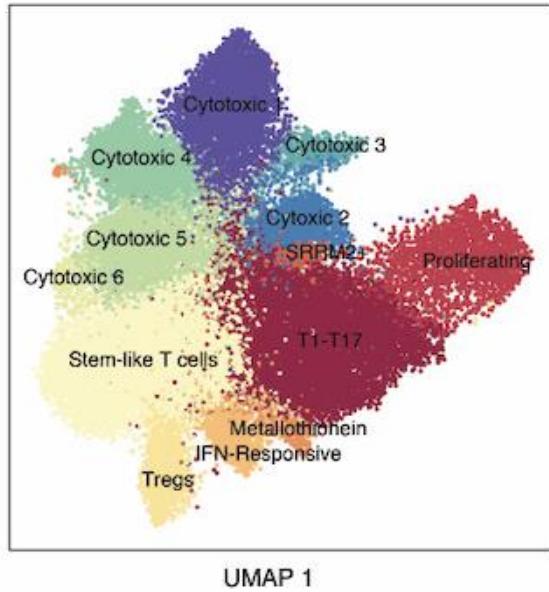
Single-Cell TCR-Seq To Dissect Immune Control And Failure At The Lesional Level



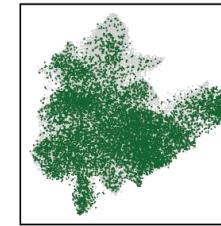


Enriched Clones Overview

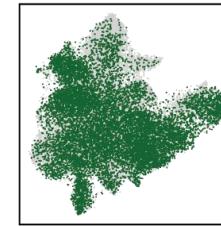
UMAP 2



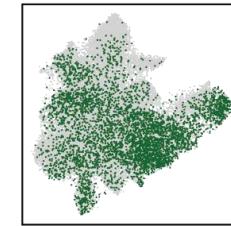
TCR Alpha Detection



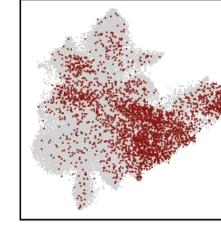
TCR Beta Detection



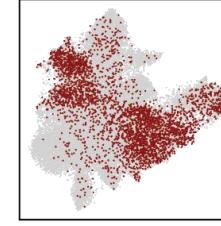
TCR Alpha-Beta Detection



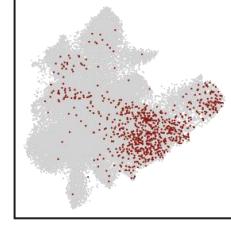
TCR Alpha Enrichment

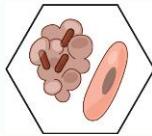


TCR Beta Enrichment



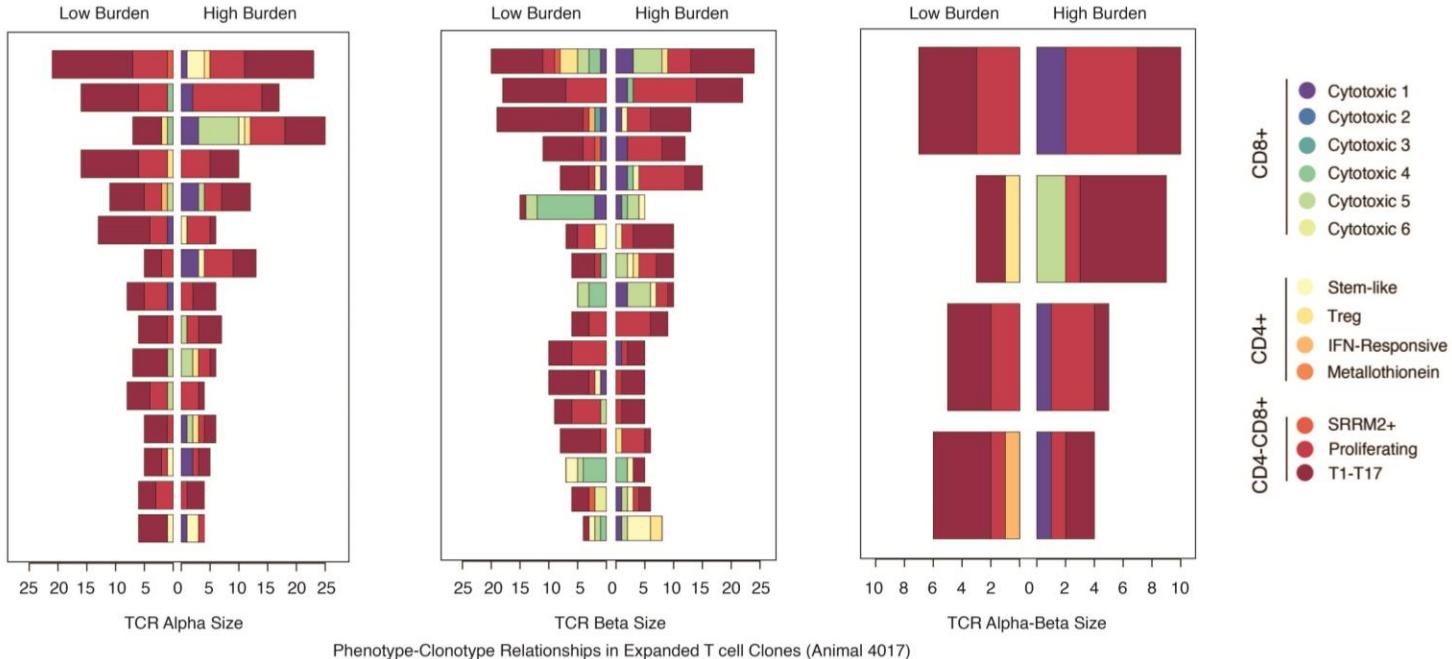
TCR Alpha-Beta Enrichment





TCR Enrichment And Sharing

TCR clones
(by abundance)



There is sharing of the most abundant CDR3s between high and low-burden lesions