

Do differences make a difference: Systems biology of human immune variation

ADVAC 2026
May 13, 2026

John Tsang

Anthony N. Brady Professor of Immunobiology and Biomedical Engineering
Director, Yale Center for Systems and Engineering Immunology (CSEI)
Investigator, Chan Zuckerberg Biohub
Co-CSO, Human Immunome Project

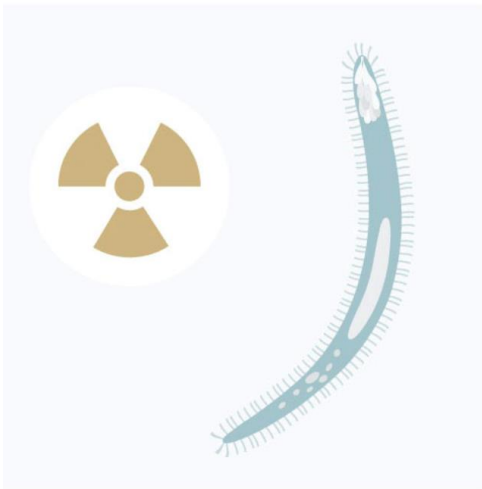
Web: www.TsangLab.org

Bluesky: [@Tsanglab.bluesky.social](https://bsky.app/profile/Tsanglab.bluesky.social)



Fight against malaria over?

Radiation-attenuated
P. falciparum sporozoites



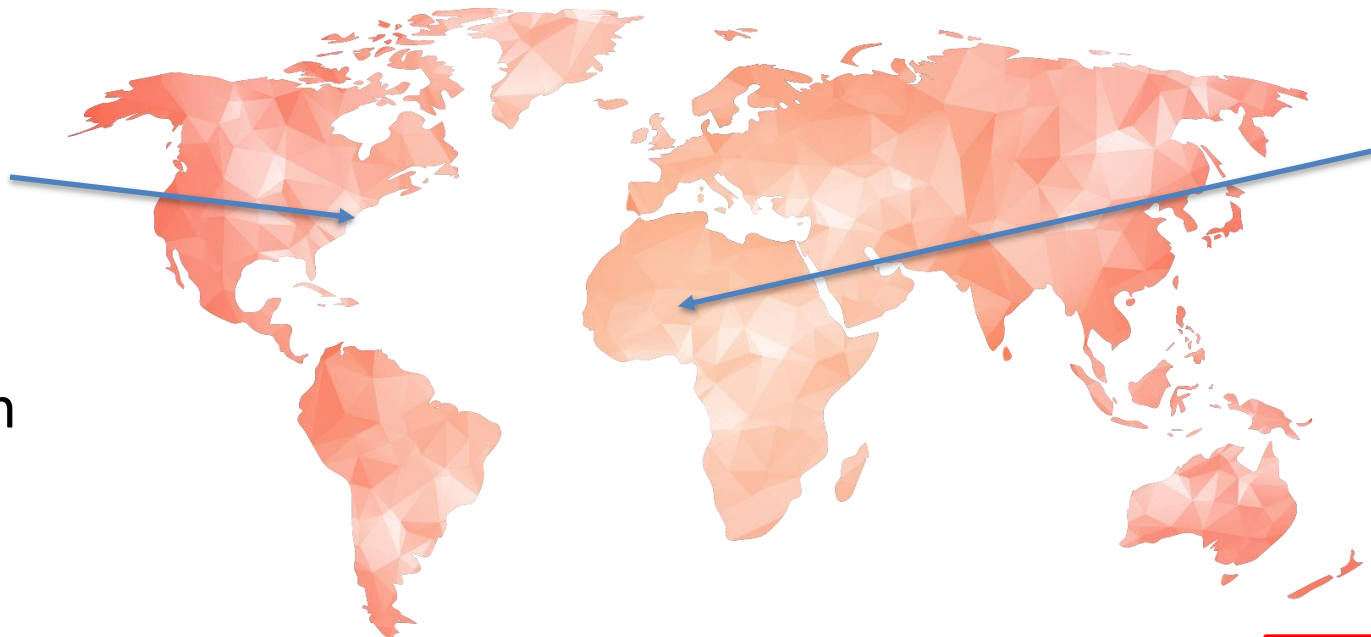
Protection Against Malaria by Intravenous Immunization with a Nonreplicating Sporozoite Vaccine

Robert A. Seder,^{1*†} Lee-Jah Chang,^{1*} Mary E. Enama,¹ Kathryn L. Zephir,¹ Uzma N. Sarwar,¹ Ingelise J. Gordon,¹ LaSonji A. Holman,¹ Eric R. James,² Peter F. Billingsley,² Anusha Gunasekera,² Adam Richman,² Sumana Chakravarty,² Anita Manoj,² Soundarapandian Velmurugan,² MingLin Li,³ Adam J. Ruben,² Tao Li,² Abraham G. Eappen,² Richard E. Stafford,^{2,3} Sarah H. Plummer,¹ Cynthia S. Hendel,¹ Laura Novik,¹ Pamela J. M. Costner,¹ Floreliz H. Mendoza,¹ Jamie G. Saunders,¹ Martha C. Nason,⁴ Jason H. Richardson,⁵ Jittawadee Murphy,⁵ Silas A. Davidson,⁵ Thomas L. Richie,⁶ Martha Sedegah,⁶ Awalludin Sutamihardja,⁶ Gary A. Fahle,⁷ Kirsten E. Lyke,⁸ Matthew B. Laurens,^{8,9} Mario Roederer,¹ Kavita Tewari,¹ Judith E. Epstein,⁶ B. Kim Lee Sim,^{2,3} Julie E. Ledgerwood,¹ Barney S. Graham,^{1‡} Stephen L. Hoffman,^{2,3‡} the VRC 312 Study Team[§]

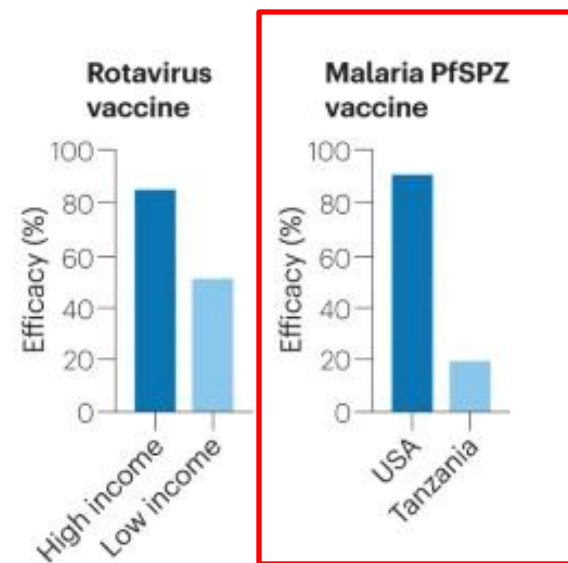
The host matters



80-100% protection



~0-30% protection



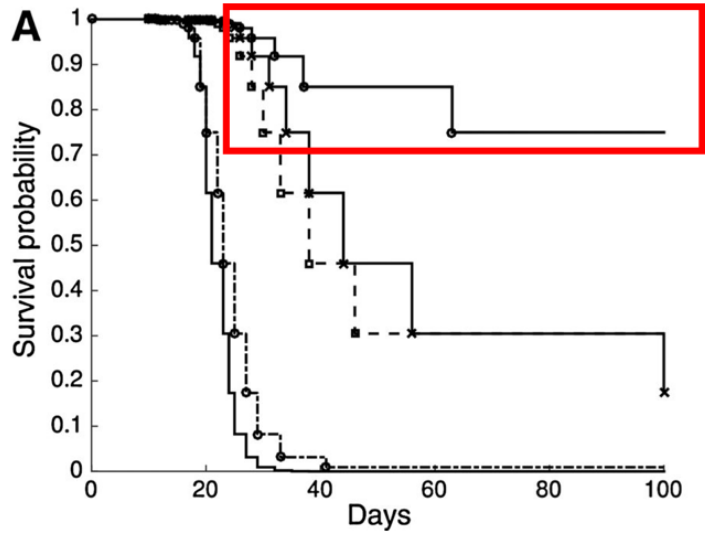
Some key questions

- Why are some individuals more protected than others?
- Why do some individuals or populations respond better?
- Can high-dimensional data and AI help identify correlates of protection (CoP) beyond antibodies and T cells?
- How important is antigen-agnostic memory? What is the interplay between antigen-agnostic and –specific memory?
- Can vaccines that work for all be developed, or do we ultimately need personalized vaccines, like in cancer?

Variability is a hallmark of the human immune system

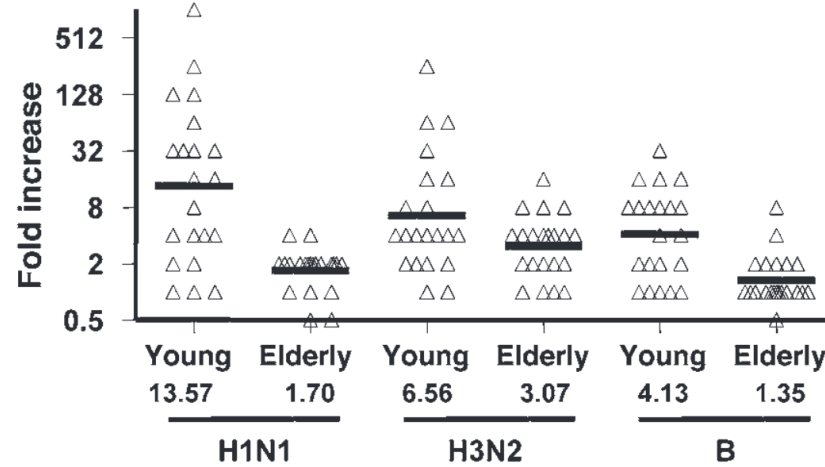
Immunotherapy

Response to cancer immunotherapy



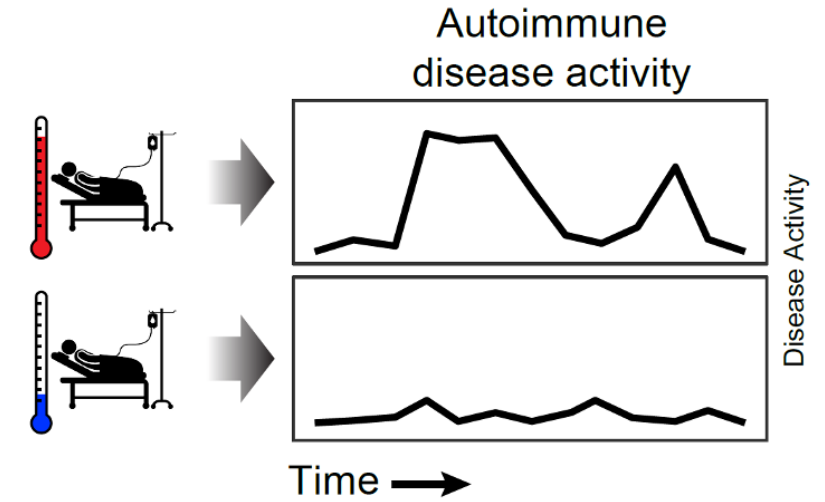
Annu. Rev. Immunol. 2009. 27:621-68

Vaccination & Infection



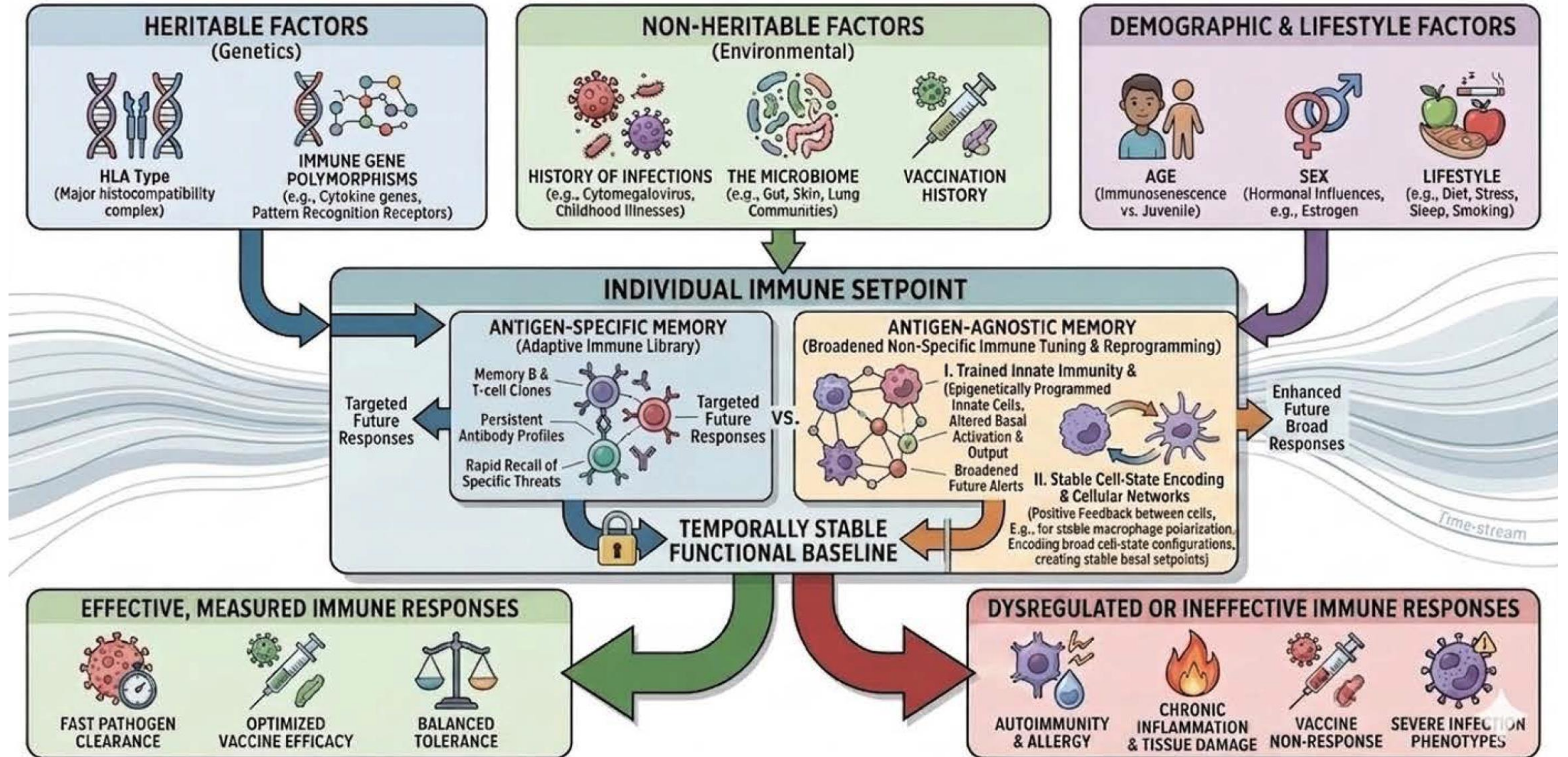
Sasaki et al. *JCI* 2011

Autoimmunity



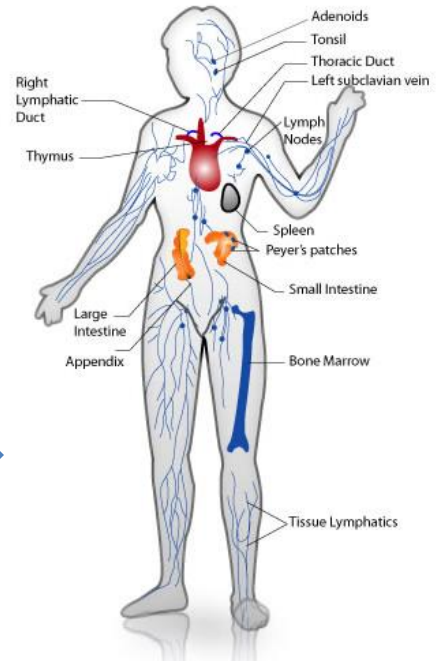
Can we predict responses?
 Can we uncover potential determinants?
 Shared predictors and mechanisms?

Why? The Immune Setpoint Hypothesis



Timescale and contributors

Evolution → Genetics



Determinants of health and disease

Vaccine response -> protection

Intervention outcomes

Health trajectories

Etc.

Lifespan → development,
environment, aging

Modern tech measures immune states comprehensively

~ $10^7 - 10^9$ parameters / timepoint / person

Tissue spatial profiling (skin, gut, nasal swabs, etc.)

Antibody profiling (pathogens and autoreactivities)

Cells:

Multimodal single cell analyses

Transcriptomics

Chromatin accessibility, etc.

TCR/BCR repertoire

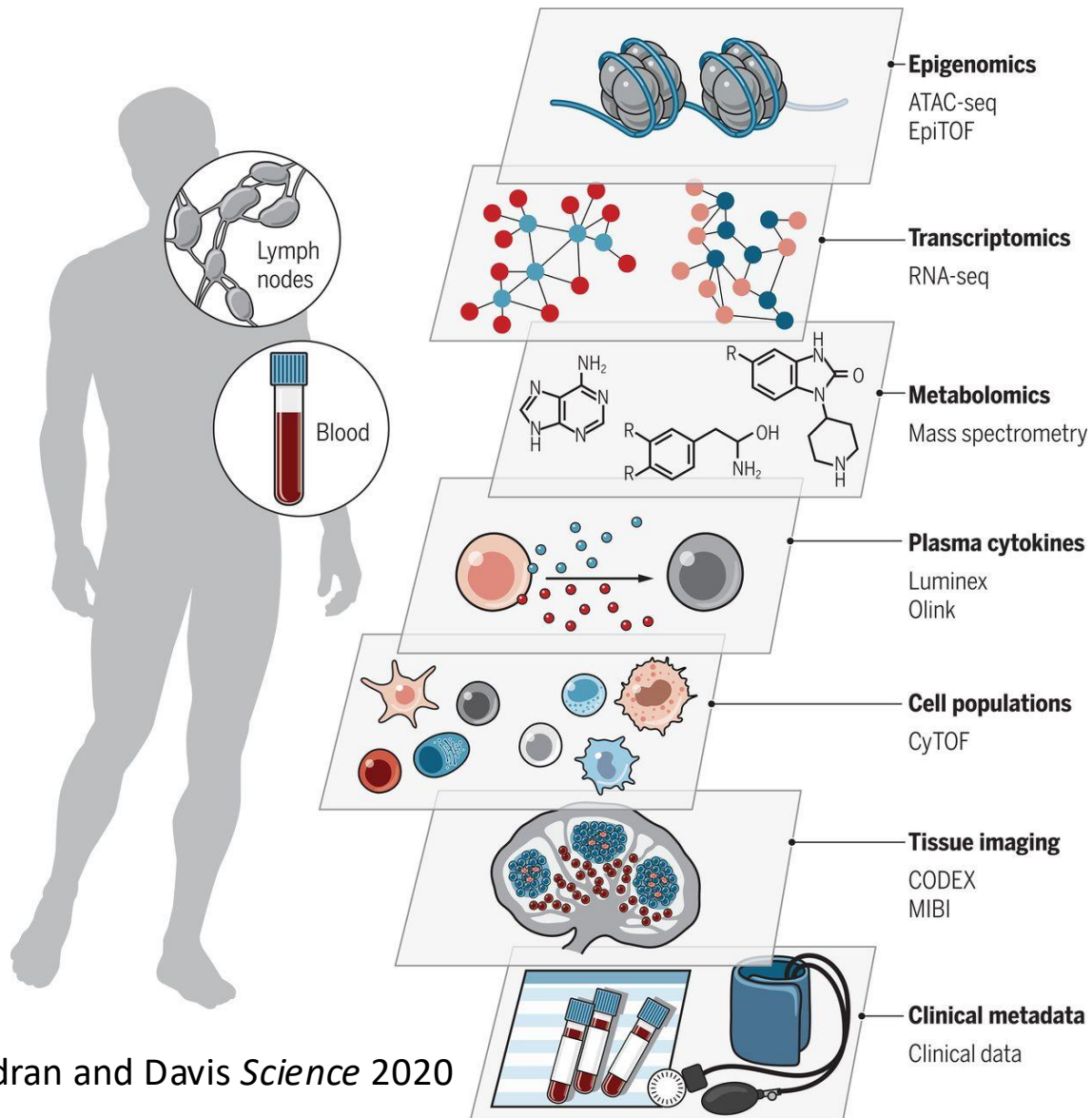
In vitro stimulation responses (signaling, RNA, etc.)

Circulating molecules:

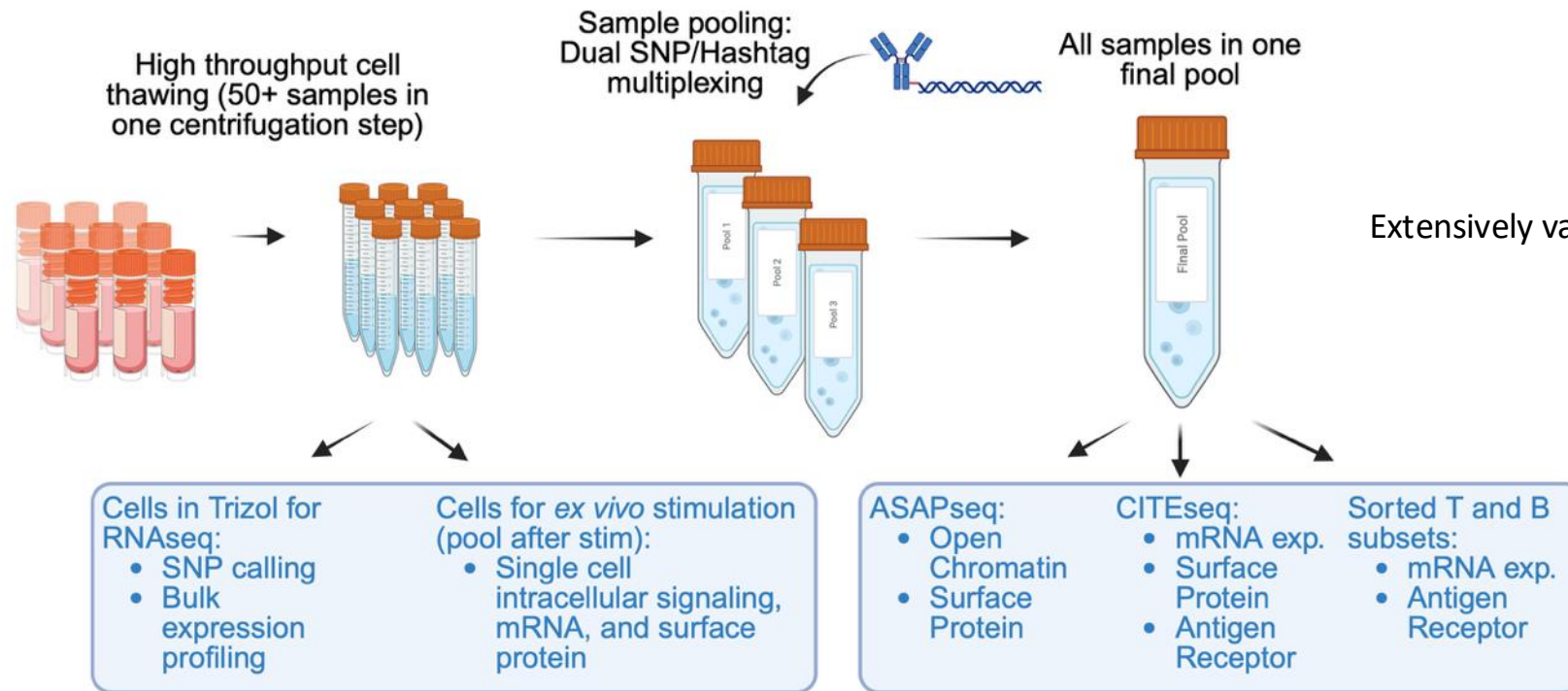
Proteomics (2,500-10,000 proteins)

Cell free DNA/RNA – cell/tissue statuses, etc.

Antibody profiling



Multiplexing single cell analysis: reducing cost, cell number, batch effects, and enabling pooled enrichment



Extensively validated and utilized workflow, e.g.:
 Liu and Martins et al. *Cell* 2021,
 Kotliarov et al. *Nat. Med* 2020,
 Mulè et al. *Immunity* 2024,
 Several ongoing projects

Cell

Article

Immunity

Article

Time-resolved systems immunology reveals a late juncture linked to fatal COVID-19

Integrating population and single-cell variations in vaccine responses identifies a naturally adjuvanted human immune setpoint

Influenza vaccination reveals sex dimorphic imprints of prior mild COVID-19

Graphical abstract

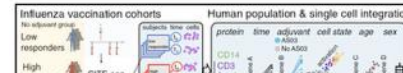
Authors

Graphical abstract

Authors



Can Liu, Andrew J. Martins, William W. Lau, ..., Jeffrey I. Cohen, Luigi D. Notarangelo, John S. Tsang



Matthew P. Mulè, Andrew J. Martins, Foo Cheung, ..., Jinguo Chen, Pamela L. Schwartzberg, John S. Tsang

<https://doi.org/10.1038/s41586-022-05670-5>

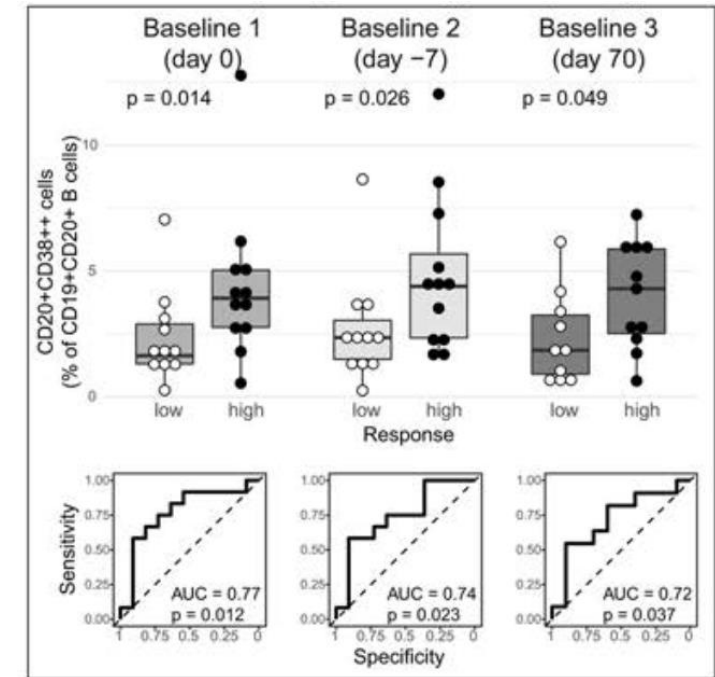
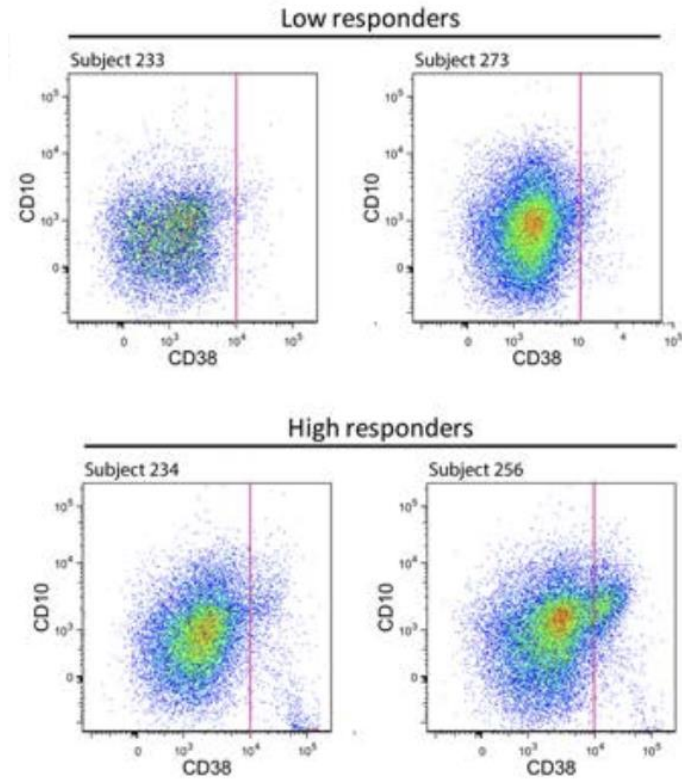
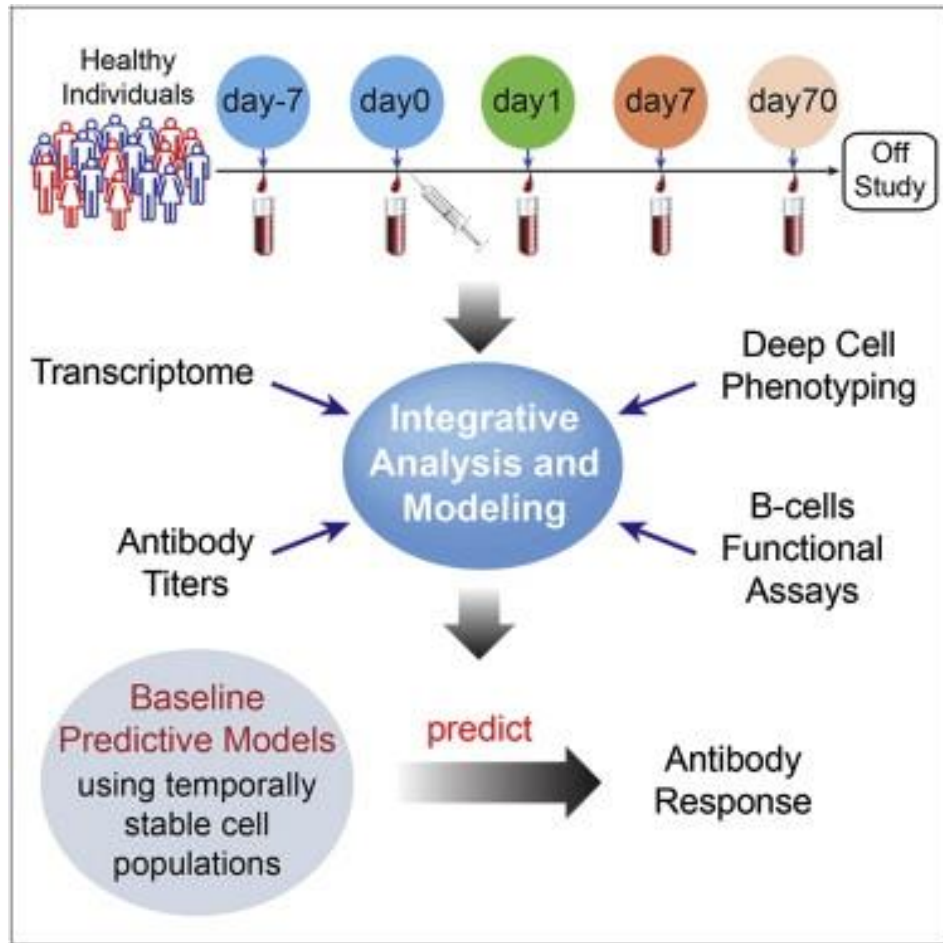
Received: 3 February 2022

Accepted: 19 December 2022

Published online: 4 January 2023

Rachel Sparks^{1,4}, William W. Lau^{1,4}, Can Liu^{1,2,4}, Kyu Lee Han¹, Kiera L. Vrindten¹, Guangping Sun^{1,4}, Milann Cox¹, Sarah F. Andrews¹, Neha Bansal¹, Laura E. Failla¹, Jody Manischewitz¹, Gabrielle Grubbs¹, Lisa R. King¹, Galina Koroleva¹, Stephanie Leimenstoll¹, LaQuita Snow^{2,3}, OP11 Clinical Staff¹, Jinguo Chen¹, Juanjie Tang¹, Amrita Mukherjee¹, Brian A. Sellers¹, Richard Apps¹, Adrian B. McDermott¹, Andrew J. Martins¹, Evan M. Bloch¹, Hana Golding¹, Surender Khurana¹ & John S. Tsang^{1,2,3,4,5}

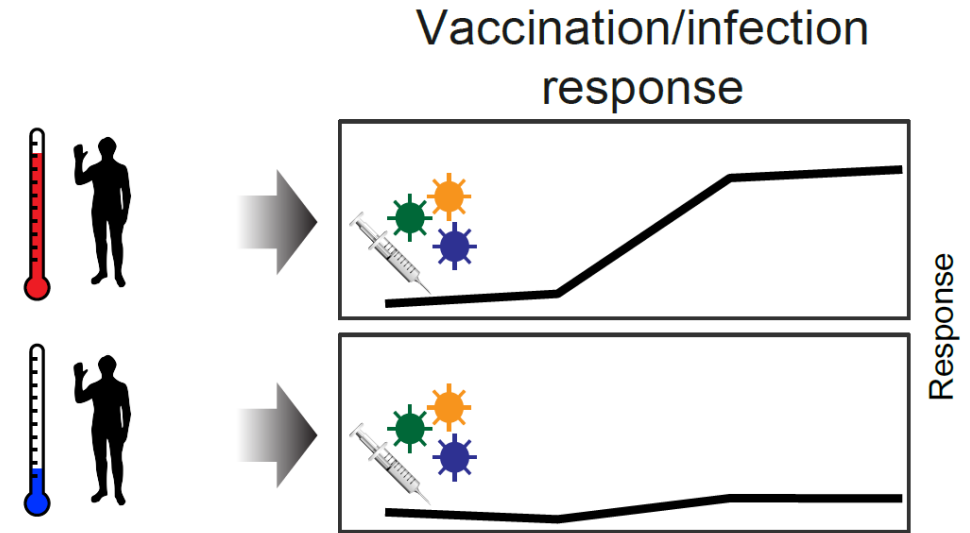
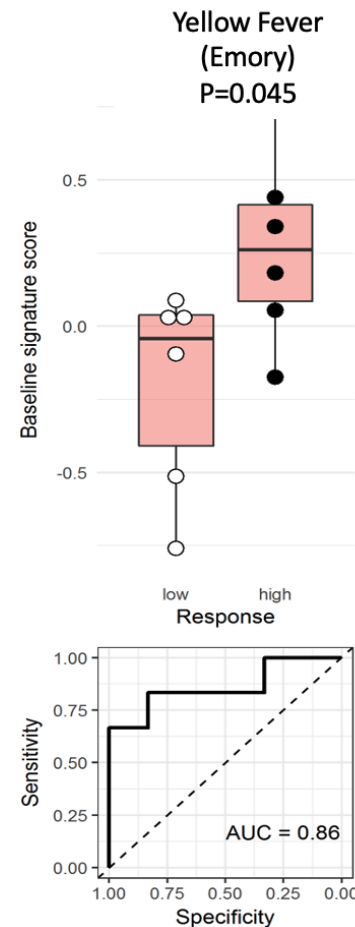
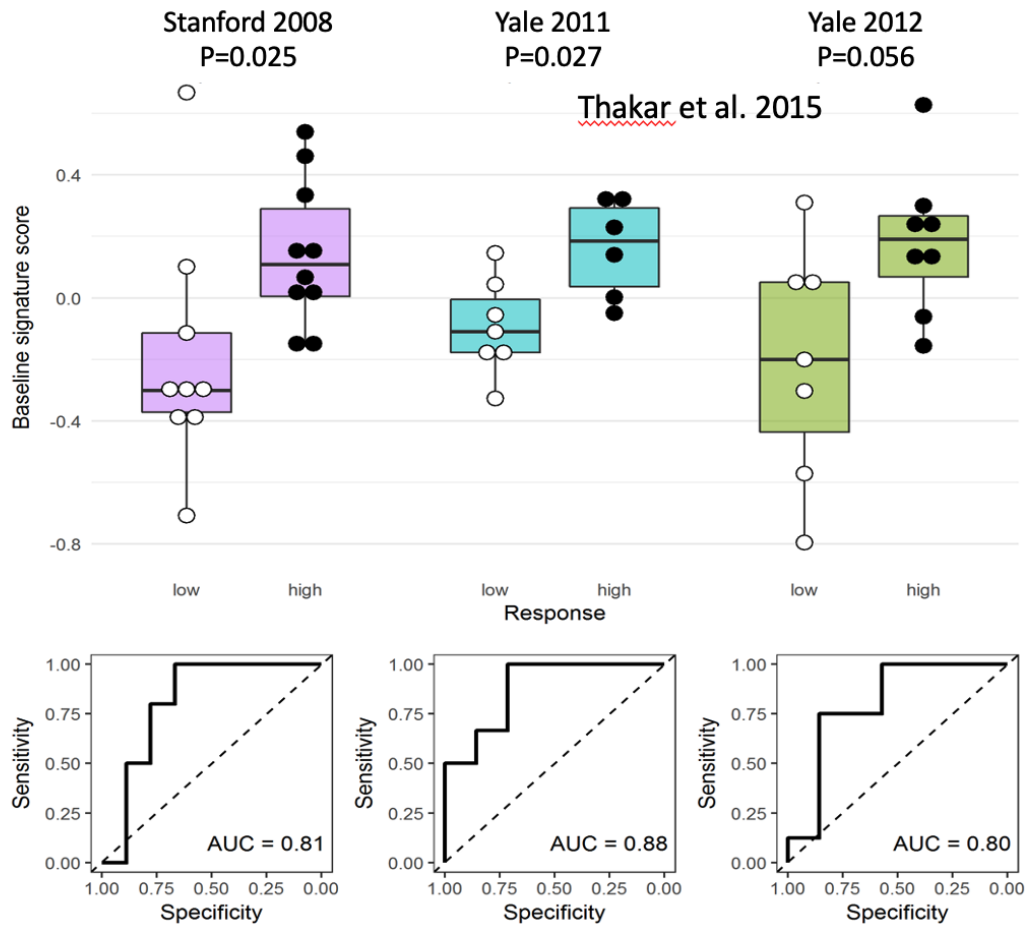
Baseline matters: **beyond** age, sex, and pre-existing immunity



Signature of high responders:

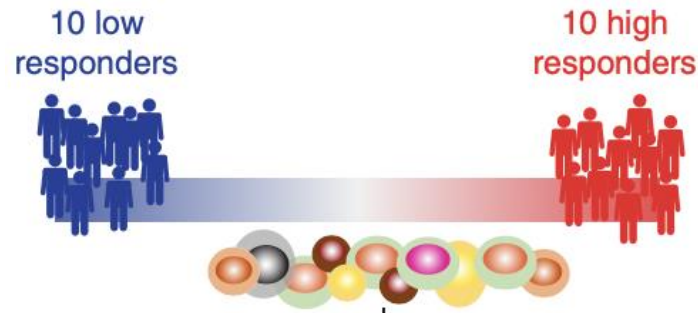
Elevated activated/switched B cells (antigen agnostic)
Increased cDCs

Personal immune setpoint predicts outcome

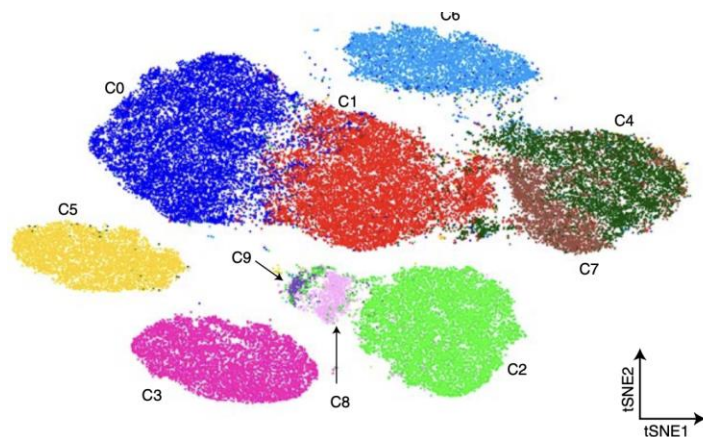


Kotliarov, Sparks, et al. Tsang *Nature Medicine* 2020
Sparks, Lau, Liu, et al. Tsang *Nature* 2023
Mule et al. Tsang *Immunity* 2024

Baseline setpoint states are encoded by correlated cell states



CITE-seq:
Profiling 82 cell surface
protein markers and
transcriptome in single cells

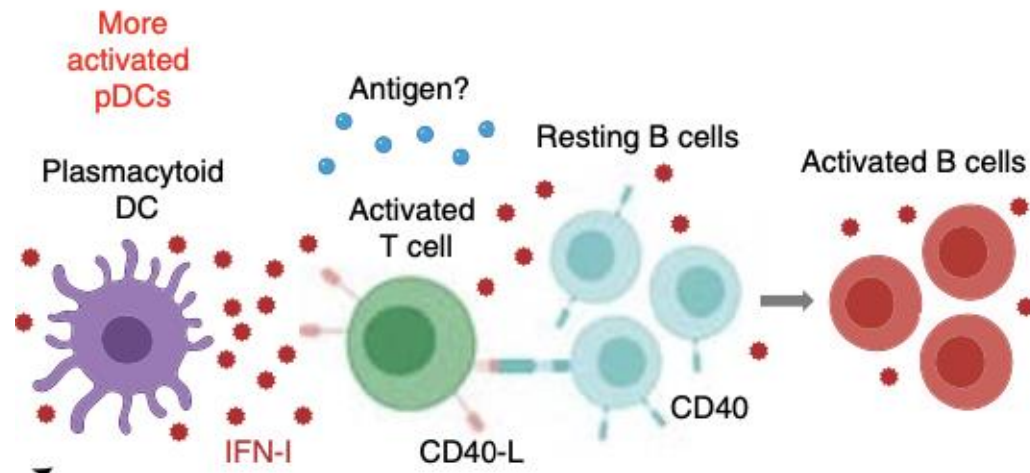


Setpoint encoded by **networks of immune cells**

- Activated pDCs
- Type I IFN signatures across cell types
- More activated T cells with CD40L signatures
- More switched B cells

Reduced Surrogate Signature: Can be captured by 10 transcripts in blood

→ General strategy for Correlate of Protection development

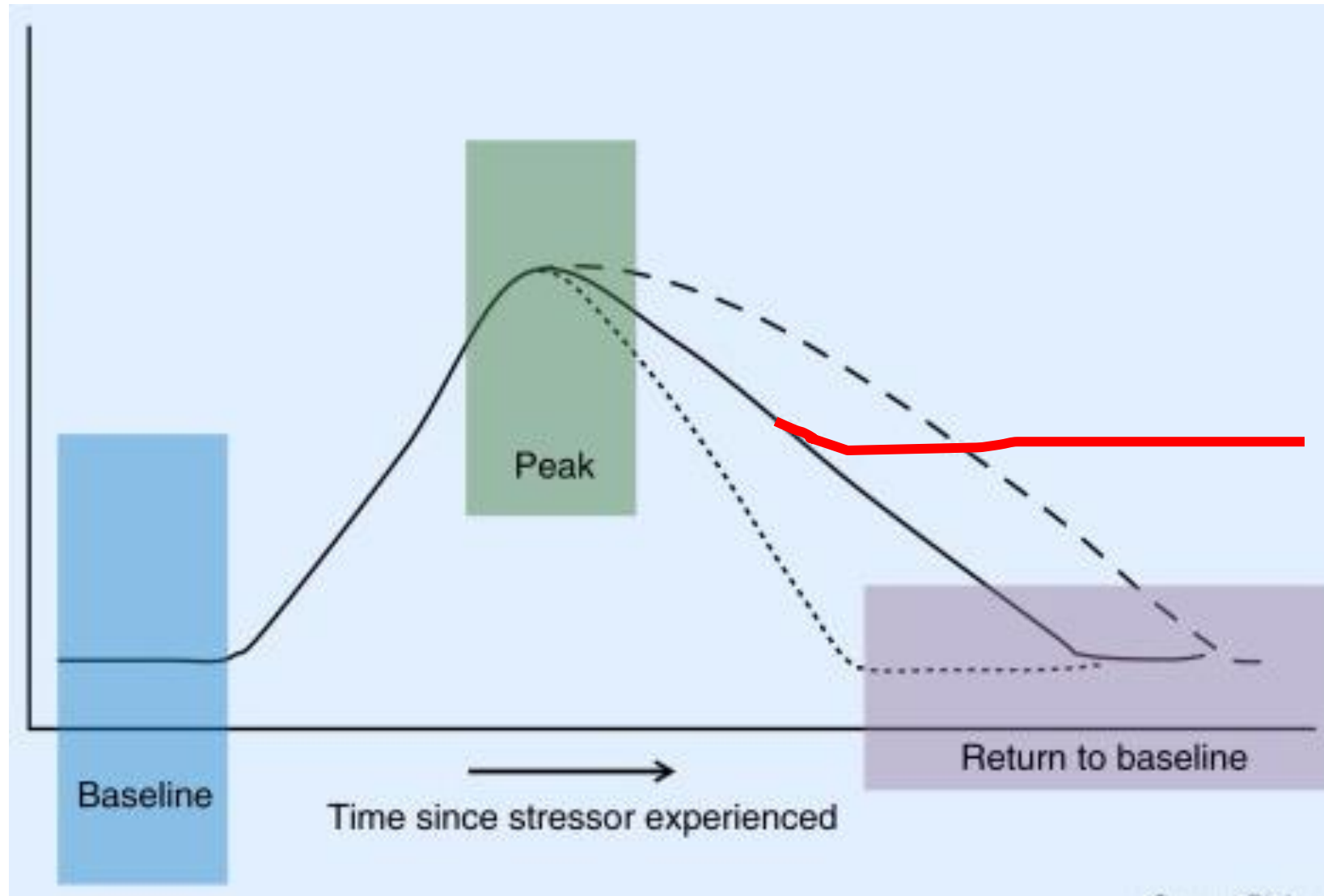


How are (antigen-agnostic)
baseline setpoint states established?

Early pediatric development

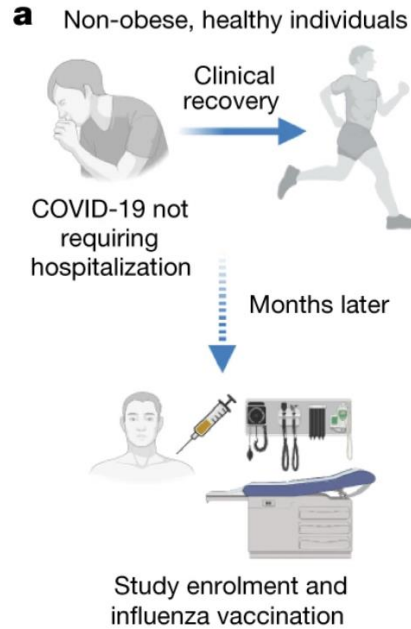
Environmental perturbations?

Beyond classic adaptive immune memory



Baseline setpoints can be shaped by inflammatory exposures in a sex dimorphic manner

Fall 2020



752 | Nature | Vol 614 | 23 February 2023

Article

Influenza vaccination reveals sex dimorphic imprints of prior mild COVID-19

<https://doi.org/10.1038/s41586-022-05670-5>

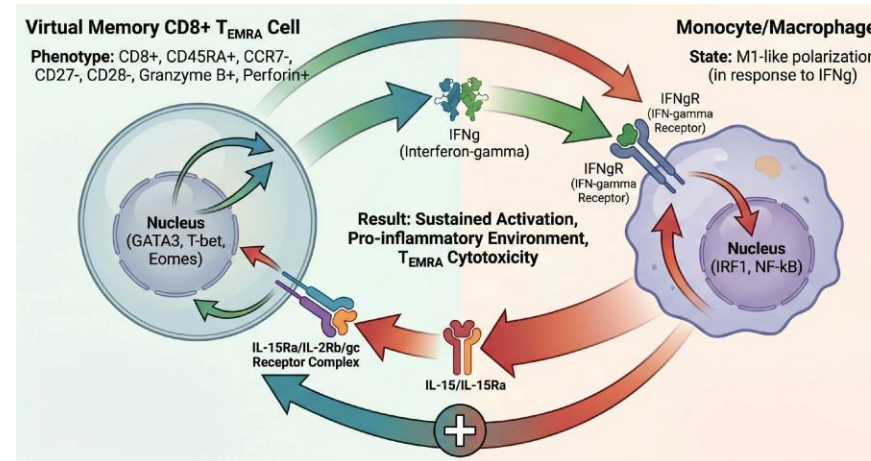
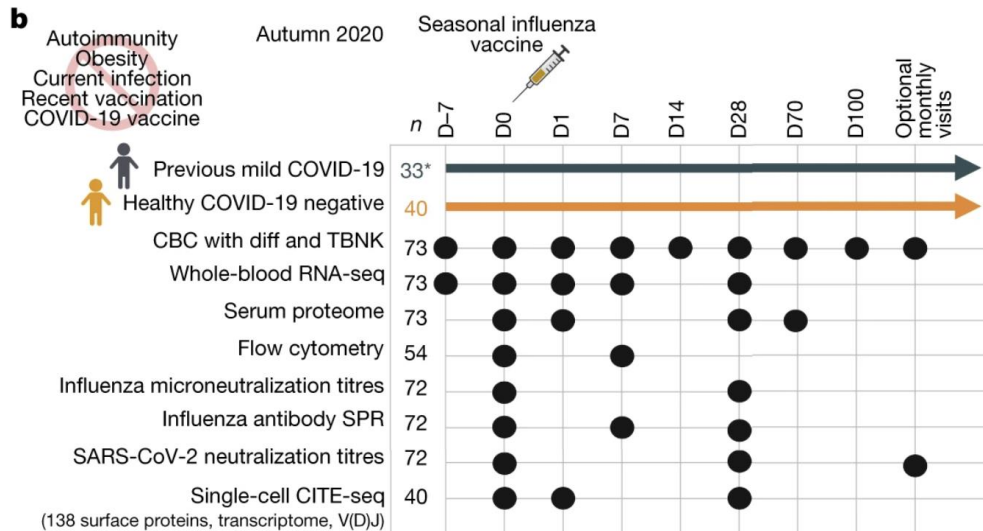
Received: 3 February 2022

Accepted: 19 December 2022

Published online: 4 January 2023

Check for updates

Rachel Sparks^{1,14}, William W. Lau^{1,14}, Can Liu^{1,2,14}, Kyu Lee Han³, Kiera L. Vrindten¹, Guangping Sun^{1,4}, Milann Cox¹, Sarah F. Andrews⁵, Neha Bansal¹, Laura E. Failla¹, Jody Manischewitz⁶, Gabrielle Grubbs⁶, Lisa R. King⁶, Galina Koroleva³, Stephanie Leimenstoll⁷, LaQuita Snow^{7,11}, OP11 Clinical Staff*, Jinguo Chen³, Juanjie Tang⁶, Amrita Mukherjee³, Brian A. Sellers³, Richard Apps³, Adrian B. McDermott⁵, Andrew J. Martins¹, Evan M. Bloch⁸, Hana Golding⁶, Surender Khurana⁶ & John S. Tsang^{1,3,12,13}✉



Rachel Sparks



William Lau

antigen-agnostic memory

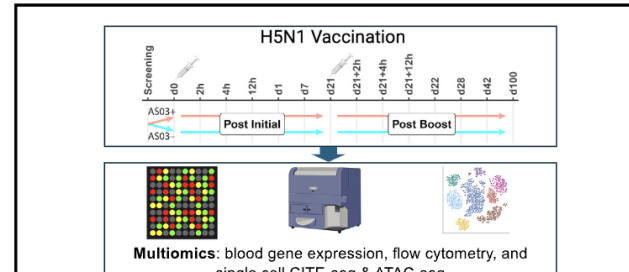
Sparks, Lau, Liu et al. *Nature* 2023

Vaccination alone (w/o adjuvants) can induce trained immune states with functional consequences

Cell Reports

Acute and persistent responses after H5N1 vaccination in humans

Graphical abstract



Authors

Richard Apps, Angélique Biancotto, Julián Candia, ..., Ronald N. Germain, Pamela L. Schwartzberg, John S. Tsang

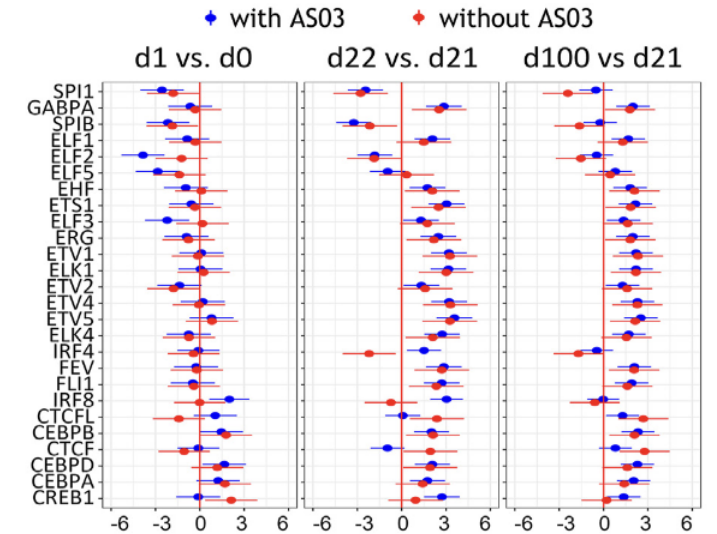
Correspondence

john.tsang@yale.edu

In brief

Apps et al. use systems immunology to

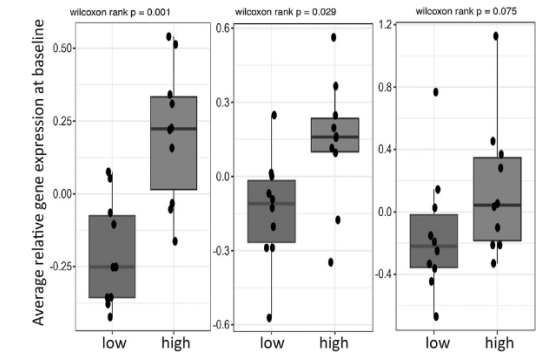
F H5N1 scATAC-seq CD14+ monocytes



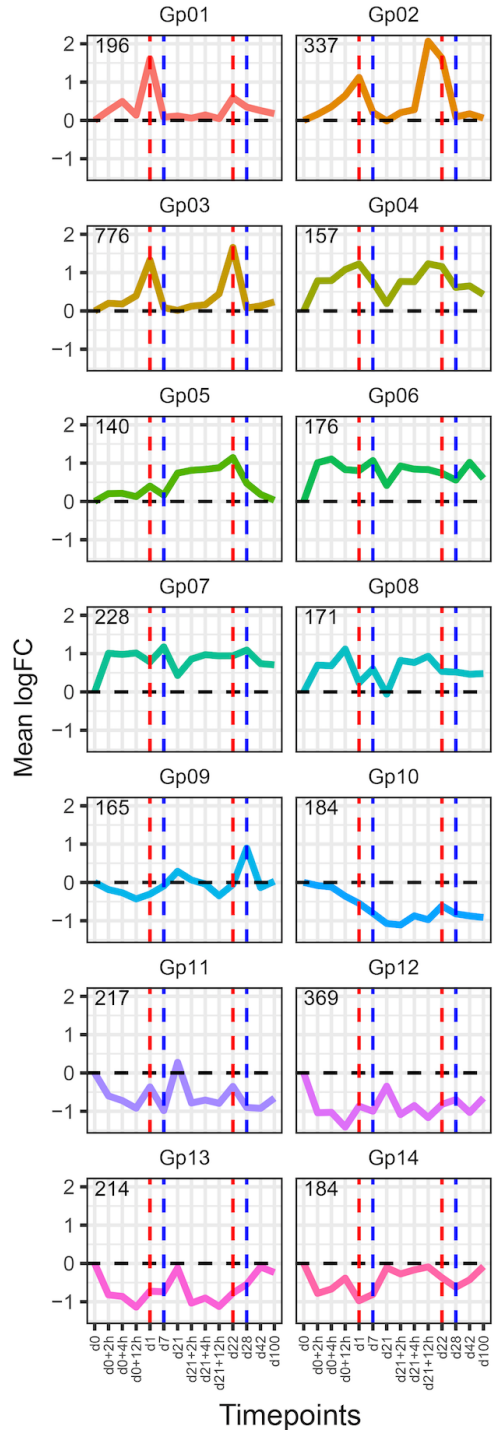
Difference in transcription factor activity estimated from ChromVar

G 2009-flu cohort baseline CITE-Seq

Gp06 CD8 naive Gp04 CD8 naive Gp04 monocyte



Category of response to vaccine based on induced anti-flu titre



Timepoints

How long do such memory last?

Positive feedback is important:
cell intrinsic mechanisms alone are likely insufficient

New Results

 [Follow this preprint](#)

Constraints and tunability of antigen-agnostic memory durability

 Shubham Tripathi, Can Liu, William W. Lau, Rachel Sparks, John S. Tsang

doi: <https://doi.org/10.1101/2025.07.18.663399>

This article is a preprint and has not been certified by peer review [[what does this mean?](#)].

Abstract

Full Text

Info/History

Metrics

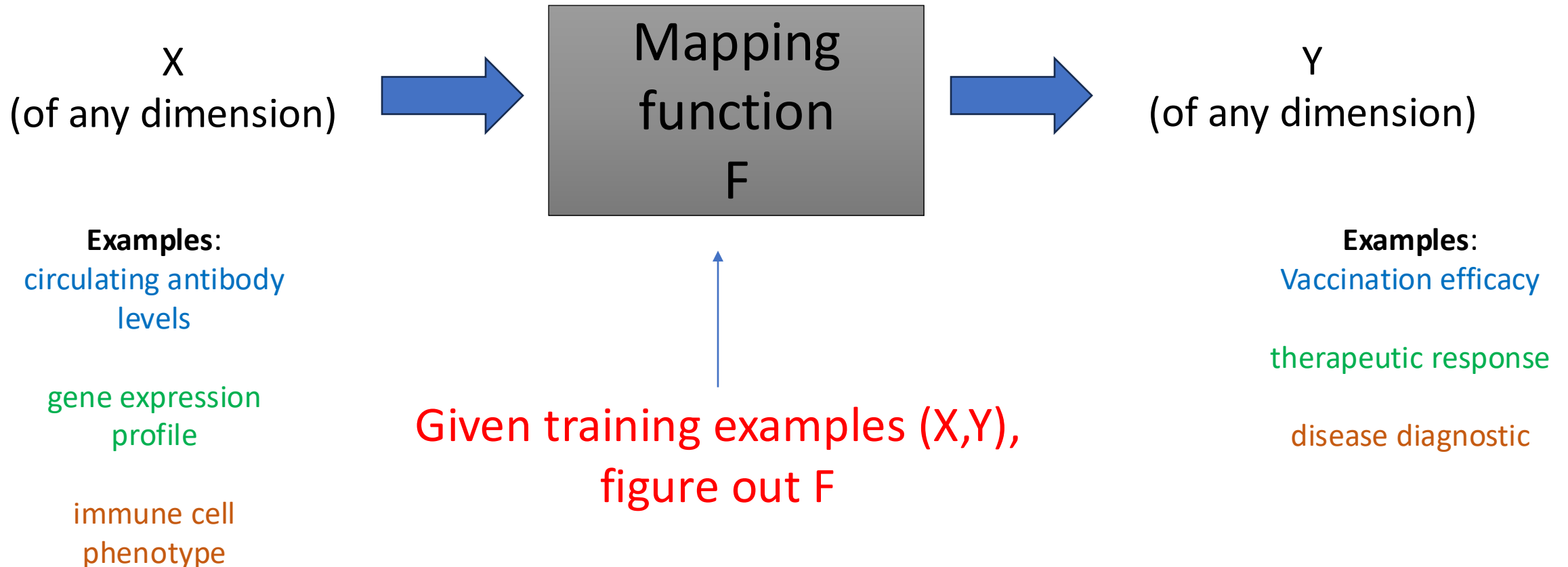
 [Preview PDF](#)

Side Note: What is AI/Machine Learning (ML)?

AI (Artificial Intelligence) refers to computer systems designed to perform tasks that typically require human intelligence.

Machine learning (ML) develops algorithms to learn "AI models" from data to perform tasks;

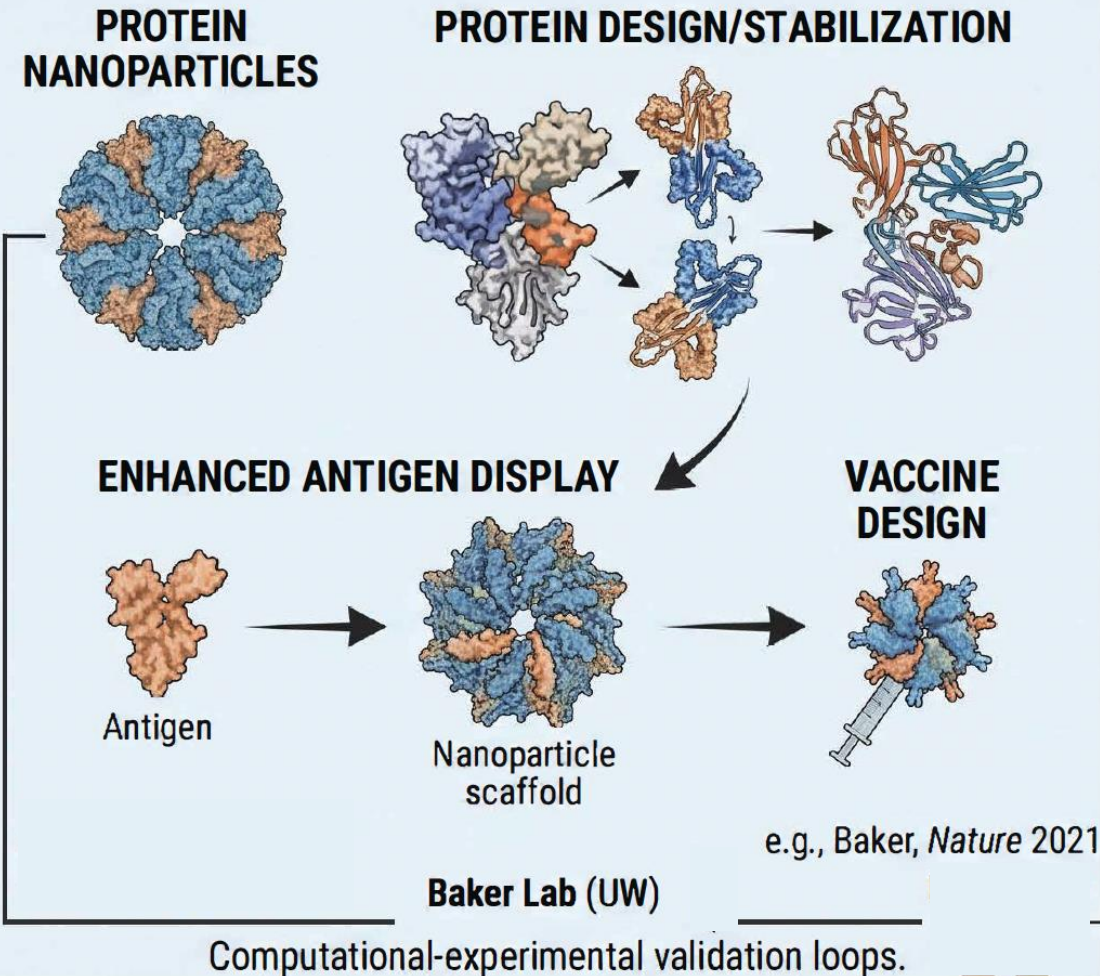
ML is currently the dominant paradigm in AI



AI in vaccine research and development

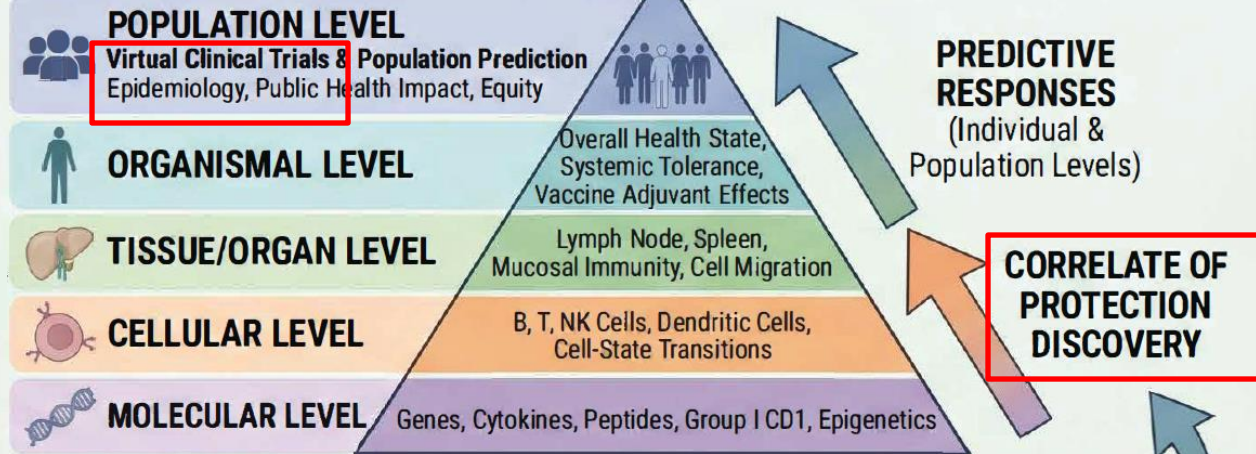
PILLAR 1: IMMUNOGEN & VACCINE PLATFORM

AI-Driven Immunogen Design (Current Substantial Advances)

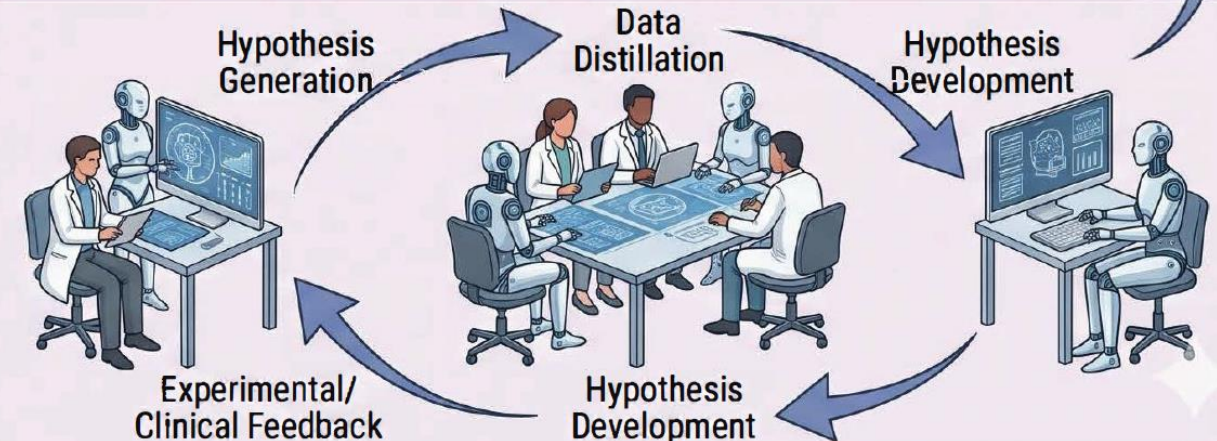


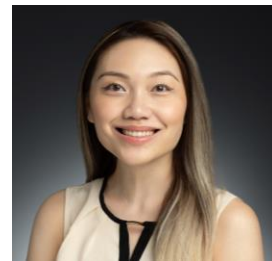
PILLAR 2: UNDERSTANDING HUMAN IMMUNE VARIATION AND RESPONSES

THE FRONTIER - MULTI-SCALE IMMUNE SYSTEM MODELS



AI AGENT - HUMAN TEAMS FOR DATA AND SCIENTIFIC INSIGHTS

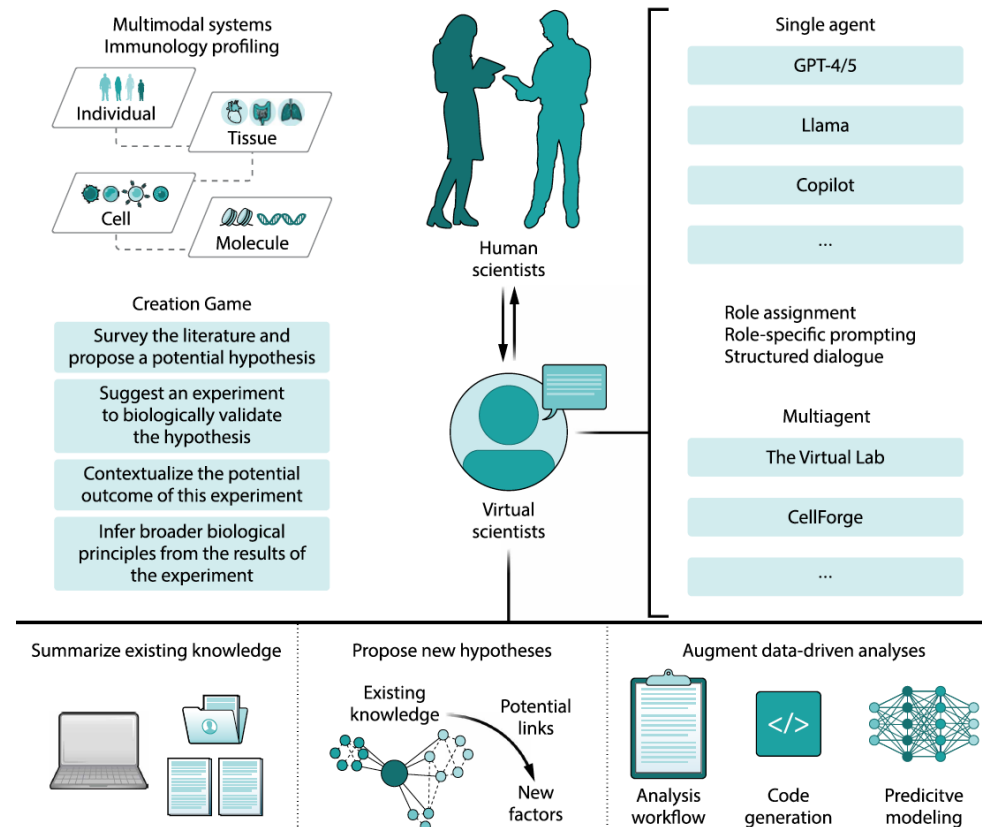


*Annual Review of Immunology*Systems Human Immunology
and AI: Immune Setpoint and
Immune HealthYona Lei¹ and John S. Tsang^{1,2,3}¹Yale Center for Systems and Engineering Immunology and Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut, USA; email: john.tsang@yale.edu²Department of Biomedical Engineering, Yale University, New Haven, Connecticut, USA³Chan Zuckerberg Biohub NY, New Haven, Connecticut, USAYona Lei
MSTP MD PhD student

SYSTEMS IMMUNOLOGY

AI immunologists are here: Are they ready for
prime time?Jacob Kim^{1†}, Ao Huang^{1,2†}, John S. Tsang^{1,2,3,4*}

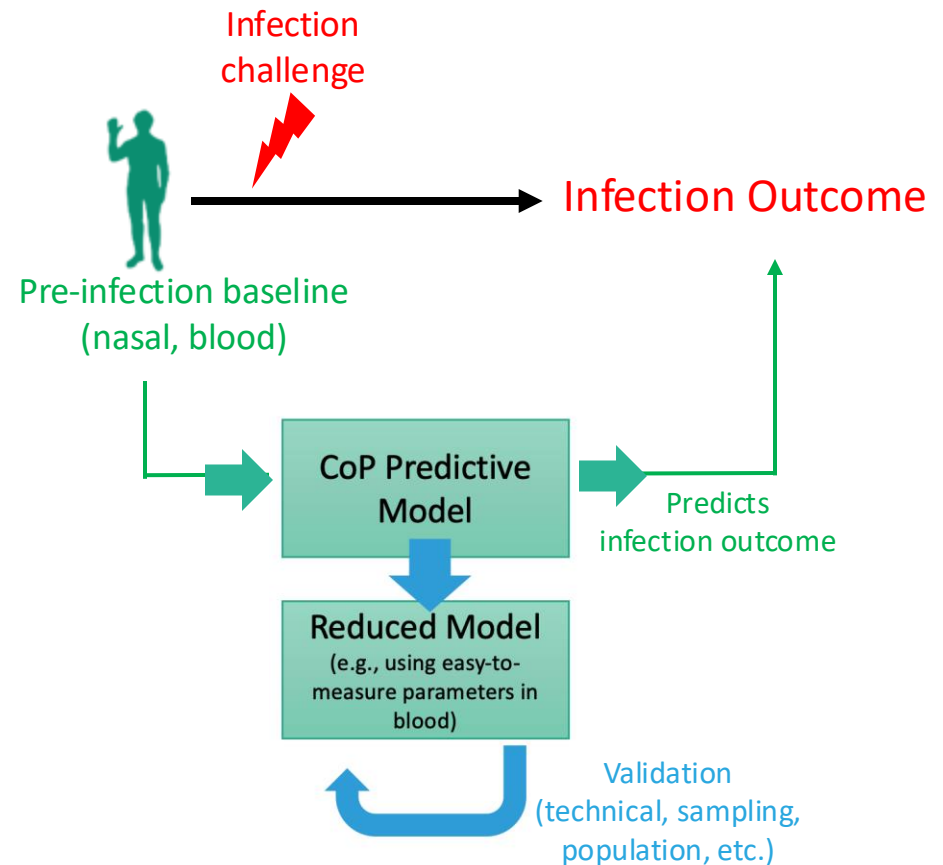
Large language model (LLM)-based artificial intelligence (AI) agents are powerful tools that can help researchers automate complex tasks such as literature review, data mining, computational code generation, and summarization of existing knowledge, but they can still fall short in developing original biological hypotheses and insights (see related Research Article by Rodriguez-Coffinet *et al.* in this issue). Emerging advances in multiagent systems and human-agent collaborative frameworks offer promising steps forward.



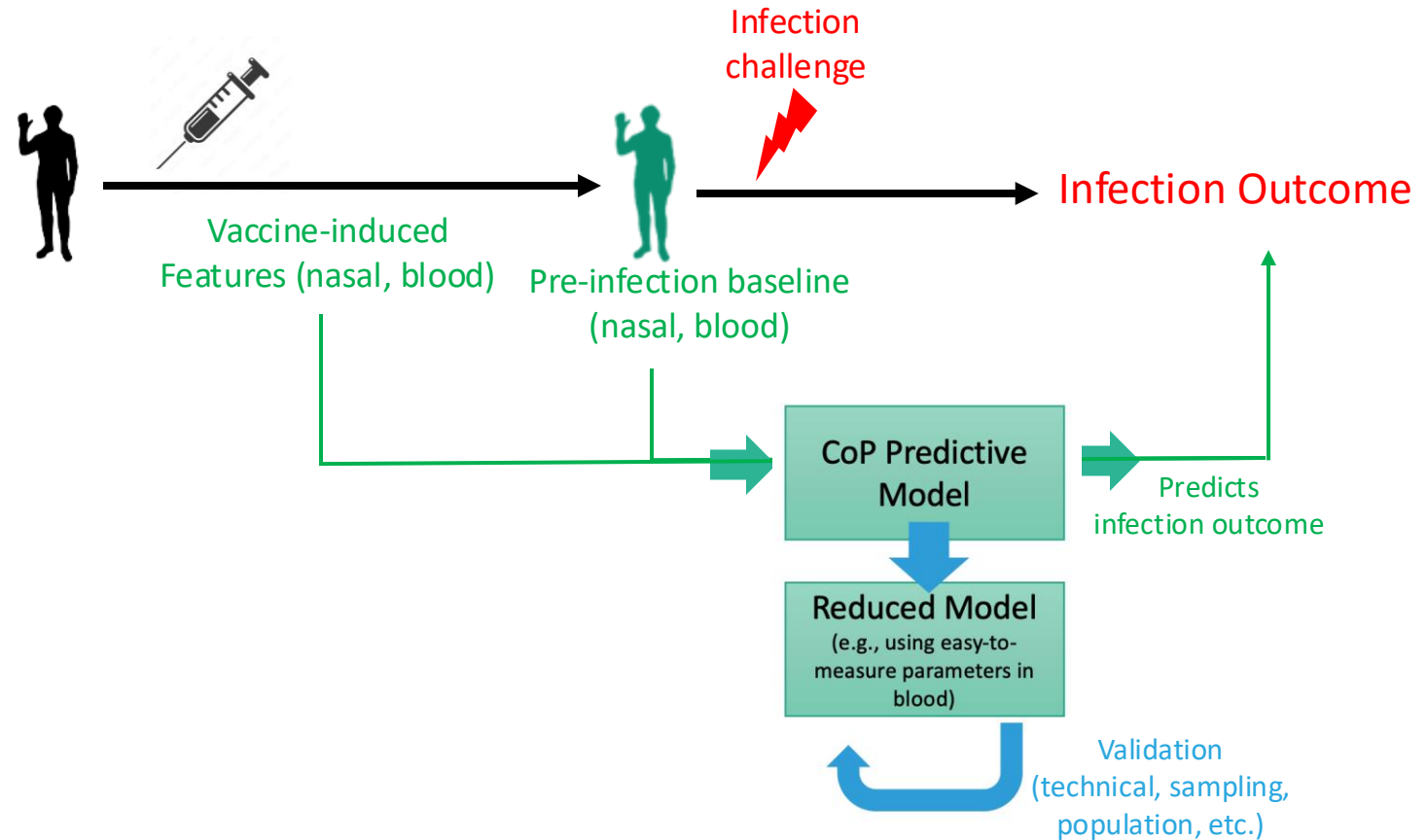
How to apply baseline setpoint concepts and tools to vaccine R&D? Baseline matters.

Predict who is protected based on their baseline immune profiles – protective profiles could originate from many sources including previous infections and vaccinations, personal immune setpoints, etc.

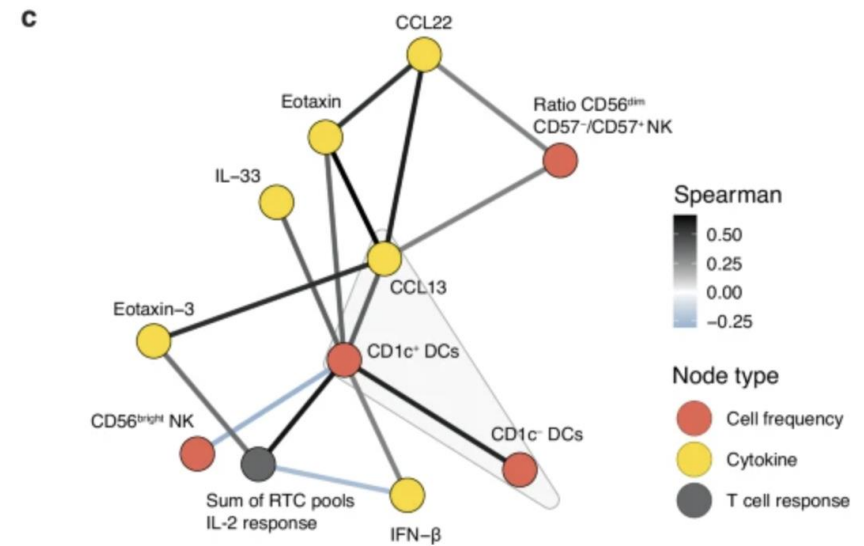
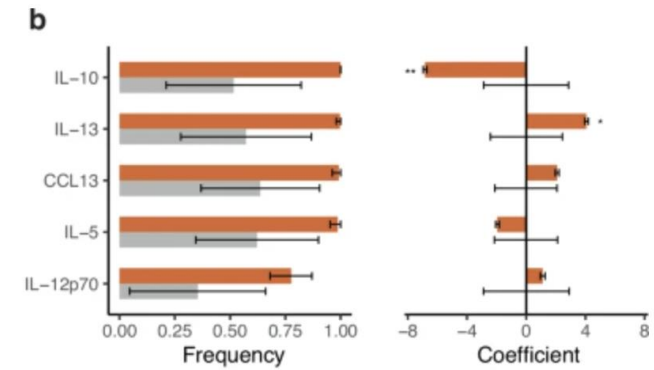
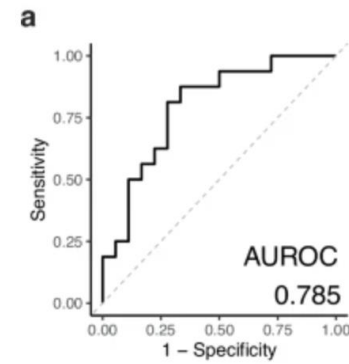
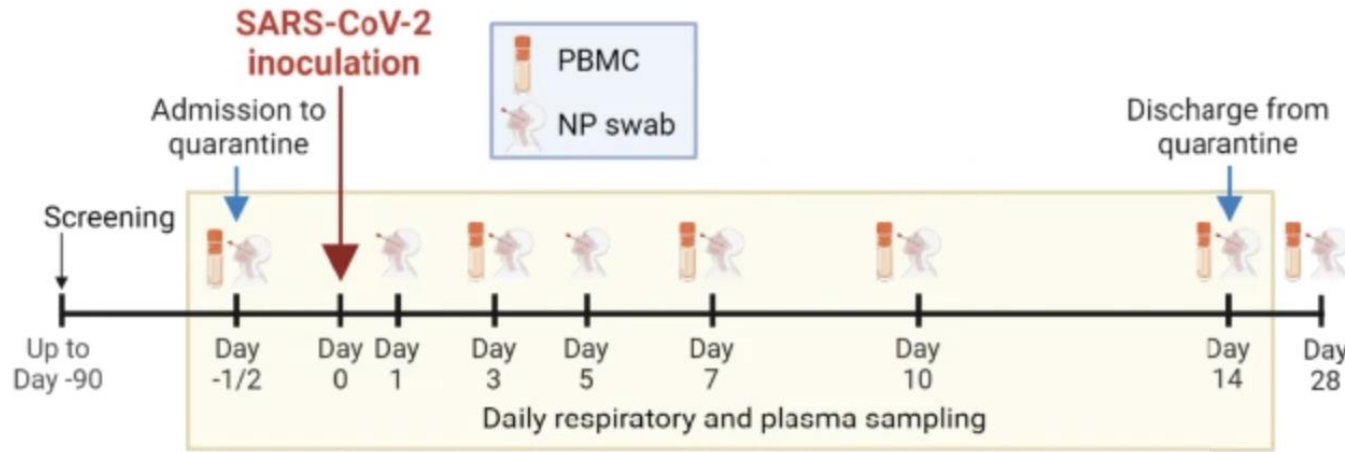
Do CoPs operate at the individual or population levels?



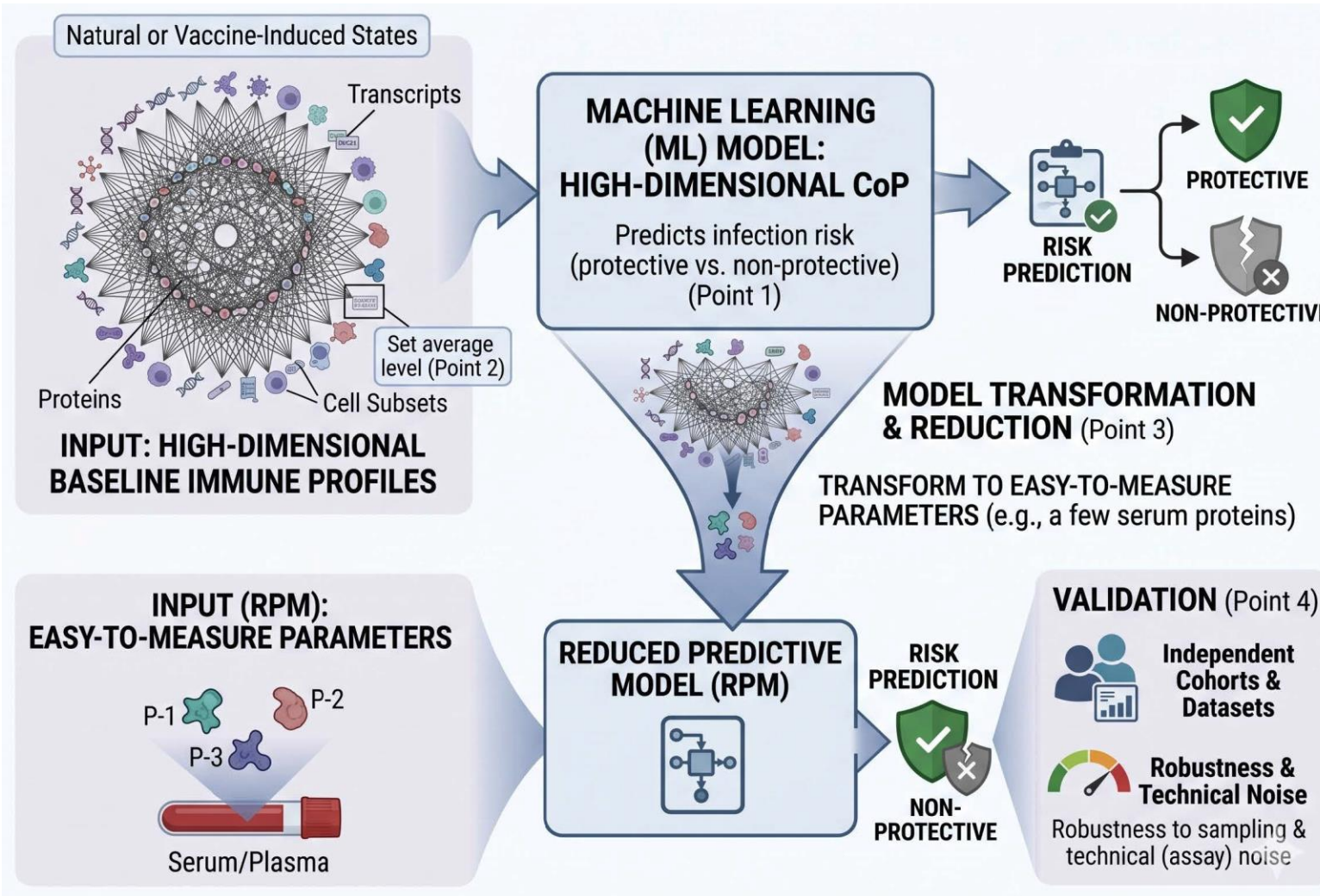
How to apply baseline setpoint concepts and tools to vaccine R&D? Baseline matters.



Example: High-dimensional CoP discovery



Summary: High-dimensional CoP discovery



Concept: Tsang; Image generation: Gemini

Building on top of larger, pre-trained models that captured broader human immune variation (age, geography, sex, disease, etc.)

nature medicine

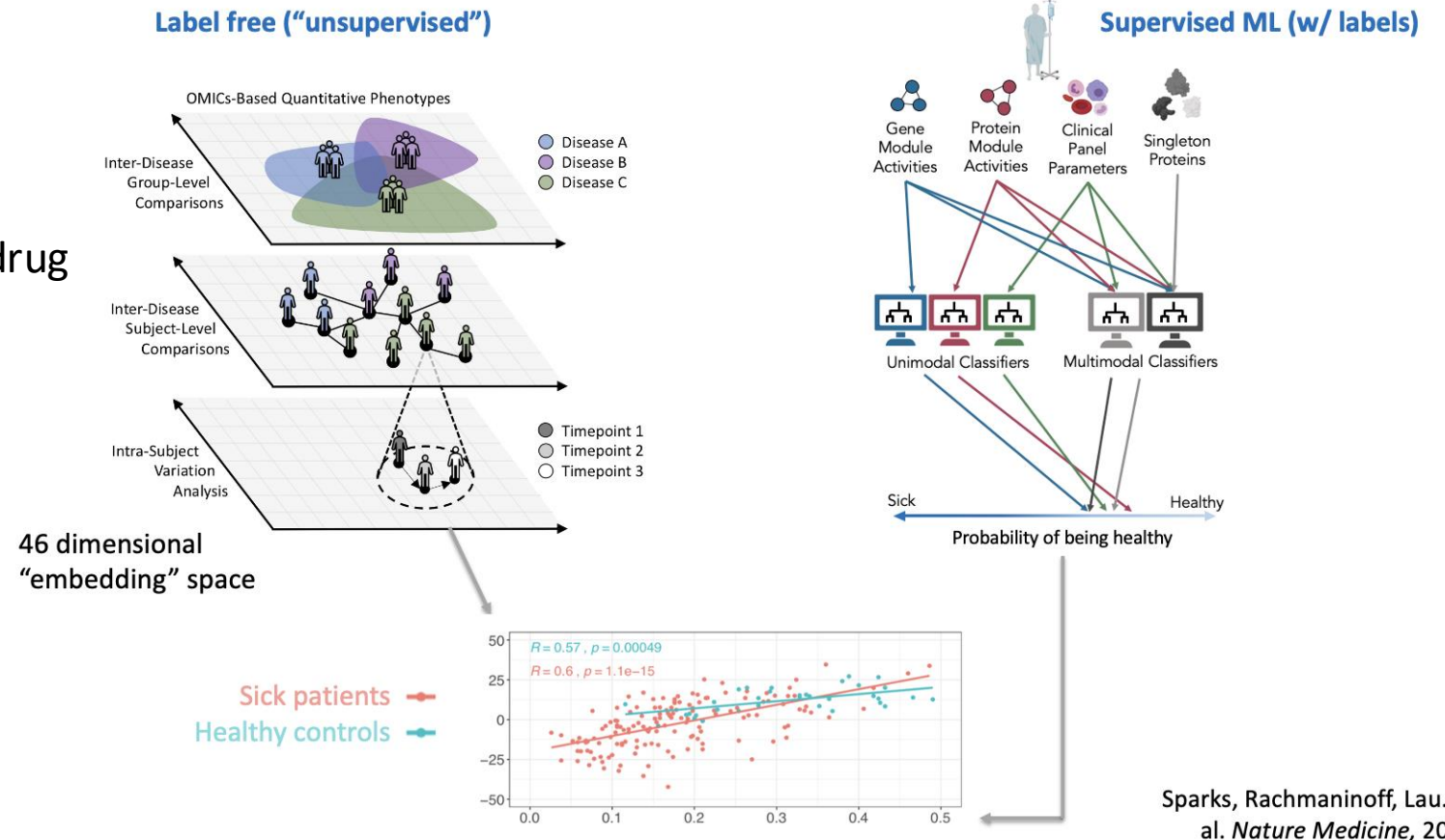
Article

<https://doi.org/10.1038/s41591-024-03092-6>

A unified metric of human immune health

Pre-trained models capturing diverse human immune states

Example model can generalize to aging, drug responses, and different diseases



But, we face a "tiny data" problem: much more DATA needed

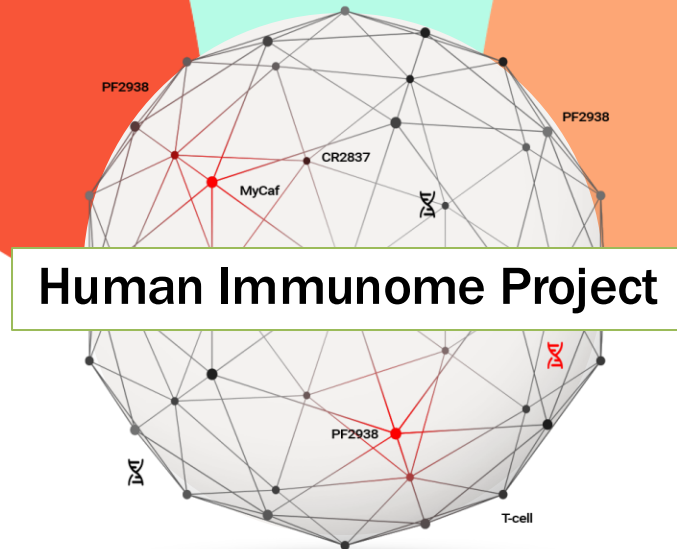
High resolution
immune
measurement
tools matured

Public health
importance
realized via
COVID

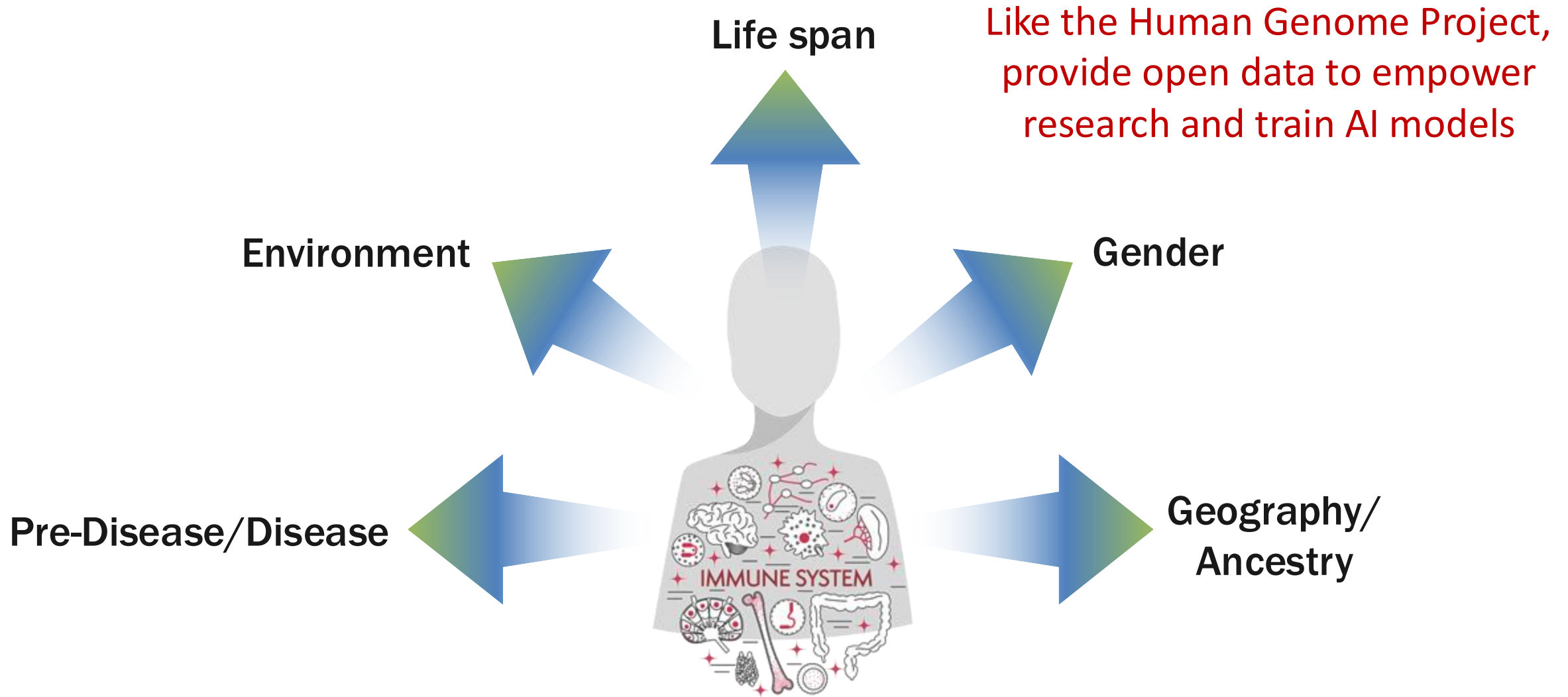
AI
revolution



Shai Shen-Orr



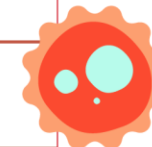
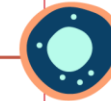
Map immune states along major axes of variation to predict responses to perturbations including vaccines



Iterative IMK development will empower scale

Immune Monitoring Kit (IMK)

Test	Measures and What They Tell Us
Clinical, e.g., CBC, CRP, TBNK	Overall health of an individual, standardized clinical lab tests.
Immune cell phenotyping	Characterize single immune cells using cytometry.
Gene expression and cell state	Global measure of expressed genes. (Bulk RNA-seq, scRNAseq, Cite-seq, scATAC multiomic)
Immune cell repertoire	Identify cell clonality in cells most responsive to a perturbation and to discover new cell states. (Bulk BCR/TCR, scTCR, scBCR.)
Whole genome sequencing	Full genetic information.
Serum proteomics and cfDNA	Immune communication, tissue state.
Functional cell assays	Test cell ability to respond to different stimulations in-vitro.
Microbiome & metabolomics	Blood metabolomics and paired microbiome/metabolomics



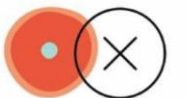
HIP global effort has begun

Phase 1 Sites



HIP Scientific Partner Network – Banbury Meeting

Cold Spring Harbor Laboratories, November 2025



**Human
Immunome
Project**

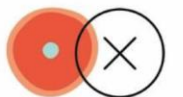
Standing on the shoulders of giants: The Human Genome Project

- 1989 meeting at the Banbury
- Generated a reference genome, tools, data infrastructure and **mindset** that catalyzed genomics advances.

1 Charles R. Cantor	9 Diane Pabst	17 Anthony V. Carrano
2 Shirley M. Tilghman	10 Elke Jordan	18 Maynard V. Olson
3 Mary-Lou Pardue	11 Uta Francke	19 Raymond L. White
4 C. Thomas Caskey	12 Mark S. Guyer	20 Sheldon Wolff
5 Benjamin J. Barnhart	13 Francis S. Collins	21 David J. Lippman
6 Eric S. Lander	14 Robert K. Moyzis	22 Mark L. Pearson
7 Norton D. Zinder	15 Jaime Carbonell	23 David Botstein
8 Leonard S. Lerman	16 James D. Watson	



- Slow to impact outcomes
- “Unexpected” limited impact on explained variation
- Unintended consequences on global inequity



**Human
Immunome
Project**

Thank You

Tsang Lab

Can Liu
Meirav Sela
Ao Huang
Shubham Tripathi
Yona Lei
Anis Barmada
Shoham Benmelech
Leon Bichmann
Andrew Johnston
Jacob Kim
Christine Dien
Annika Mordelt
Allysia Matthews
Ed Schrom
Daniel Wendisch
Max Spurrell

Alumni

William Lau
Andrew Martins
Rachel Sparks
Nick Rachmaninoff
Neha Bansal
Dylan Hirsch
Mani Narayanan
Yong Lu
Bethany Fixsen
Naisha Shah
Kate Wendelsdorf
Kyemyung Park
Matt Mule
Laura Failla
John Kim
Yuri Kotliarov
Foo Cheung
Richard Apps
Rohit Farmer
Betsy Painter

Collaborators

Steve Holland, NIAID
Dan Kastner, NHGRI
Neal Young, NHLBI
Pam Schwartzberg, NIAID
Ron Germain, NIAID
Eva Harris, UC Berkeley
Stephen Popper, UC Berkeley
Bali Pulendran, Stanford
Surender Khurana, FDA
Hana Golding, FDA
Arnaud Marchant, ULB
Margie Ackerman, Dartmouth
Marcela Pasetti, U of Maryland
Zhao Chen, NCI
Jason Guo

IVP

Bil Clemens, CZI
Jamie Friedman, CZI
Garabet Yeretssian, CZI
Steve Quake, CZI
Michele Webster, CZI
Allysia Matthews, CSEI

HIP

Shai Shen-Orr, Technion
Jane Metcalf, HIP
Lisa Goldman, HIP

