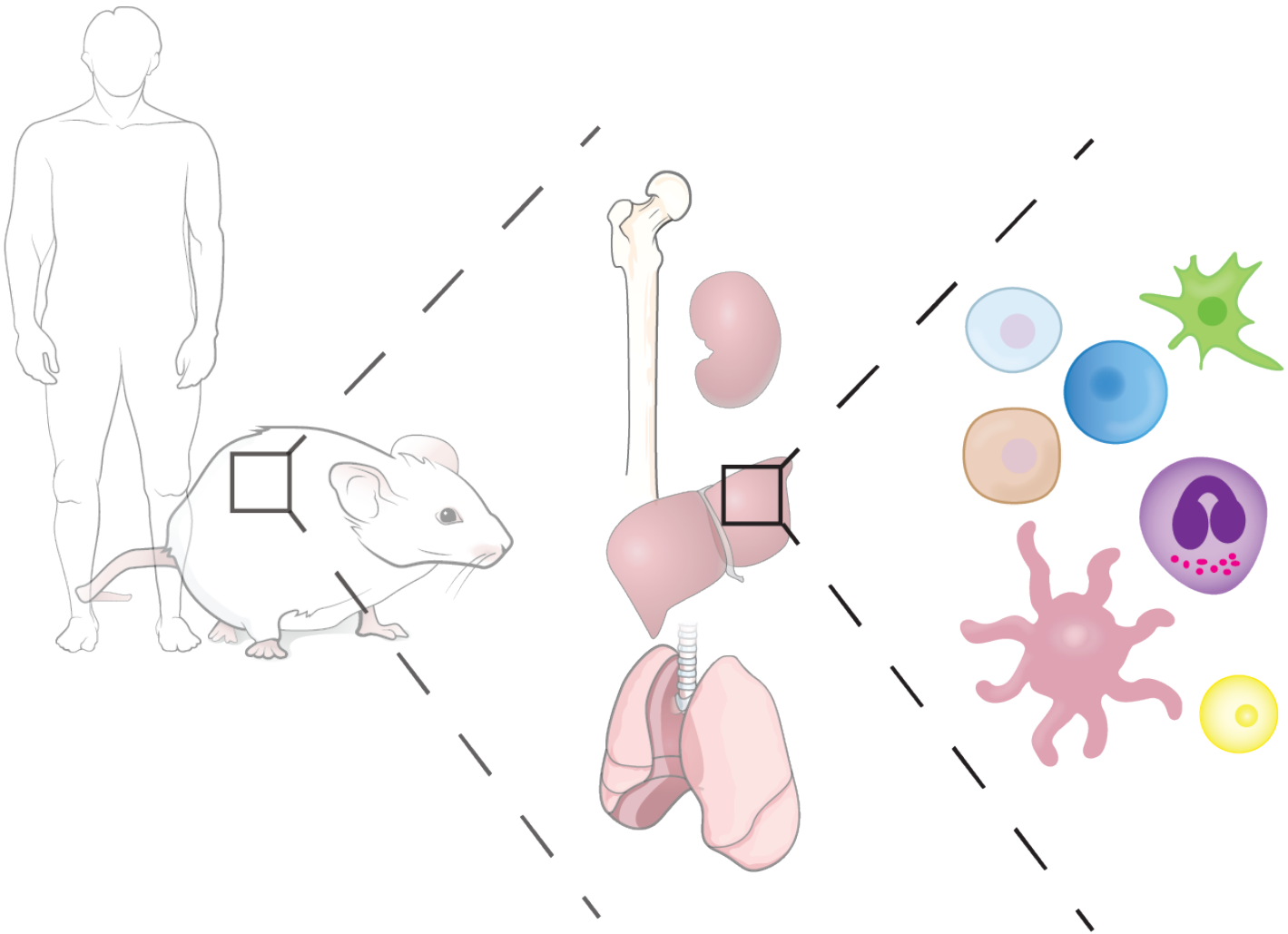
# Systems Immunology

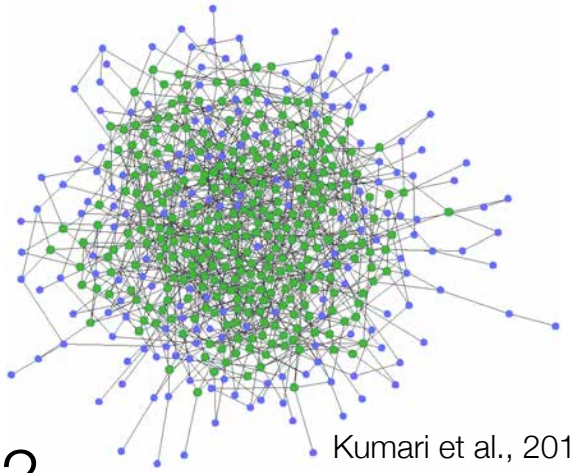


Matt Spitzer

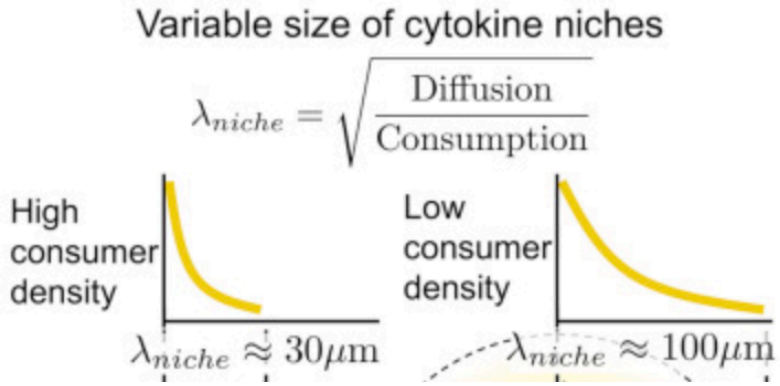
Micro 204
Nov 26, 2018

# What is “Systems Immunology”?

- Big data?
- “-omics”?
- Computation? Informatics?
- High throughput/content screens?
- Mechanistic modeling?



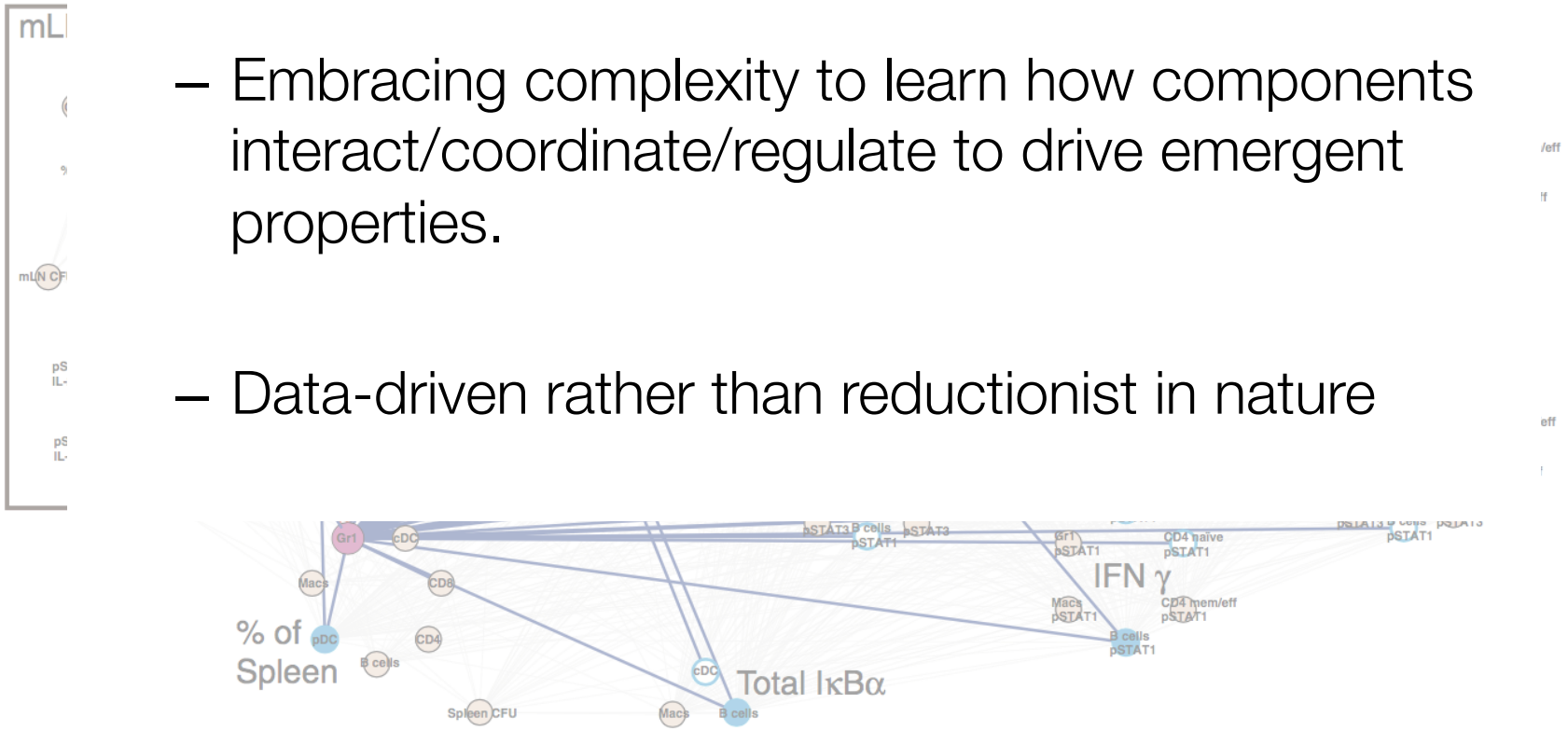
Kumari et al., 2012




Oyler-Yaniv et al., 2017

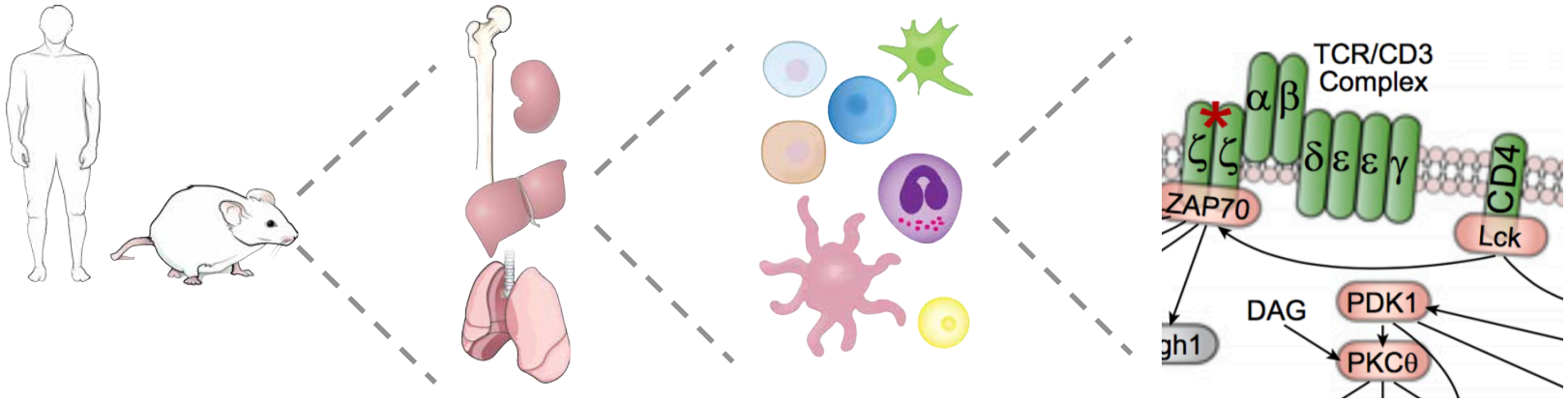

# What is “Systems Immunology”?


- A mindset rather than any single approach:
  - Embracing complexity to learn how components interact/coordinate/regulate to drive emergent properties.
  - Data-driven rather than reductionist in nature



# Systems Immunology Across Scales:

*Organismal Level* *Tissue Level* *Cellular Level* *Sub-cellular Level*




Gene expression

Single-cell analysis

Phenotype data

Shotgun proteomics

Phospho-flow

Clinical data

High-content microscopy

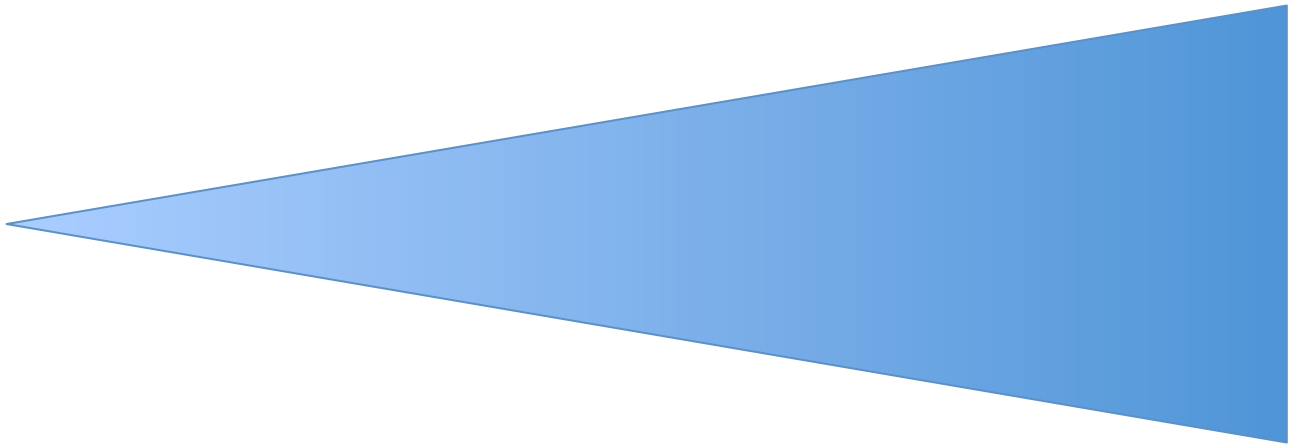
Metabolomics

Cytokine quantification

# Projects vary widely in scope:

Mechanistic Modeling

Data Mining



Goal: mathematically formalize understanding of a simple system

Goal: extract information from large data sets

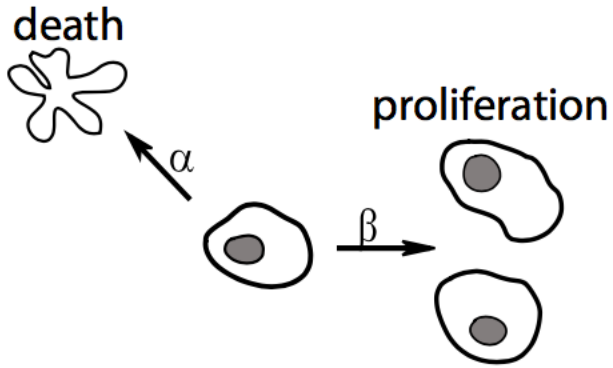
# Paradoxical Signaling by a Secreted Molecule Leads to Homeostasis of Cell Levels

Yuval Hart,[1,3] Shlomit Reich-Zeliger,[2,3] Yaron E. Antebi,[2,3] Irina Zaretsky,[2] Avraham E. Mayo,[1] Uri Alon,[1] and Nir Friedman[2,*]

Cell *158*, 1022–1032, August 28, 2014

- What parameters govern the frequency of a cell population?
  - How do T cells reach a homeostatic number without reaching their carrying capacity?
  - Why does this paradoxical effect of IL-2 (and many other signaling ligands) exist?

# Simple, first-order kinetics of cell population size are unstable

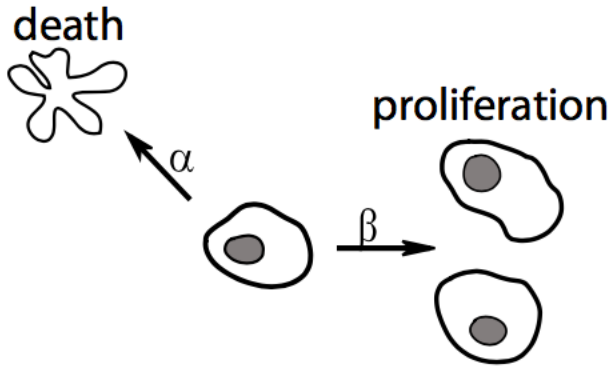



$$\frac{dX}{dt} = (\beta - \alpha)X$$

X = cell number
$\alpha$ = cell death rate
$\beta$ = cell proliferation rate

Hart et al., *Cell*, 2014

# Simple, first-order kinetics of cell population size are unstable

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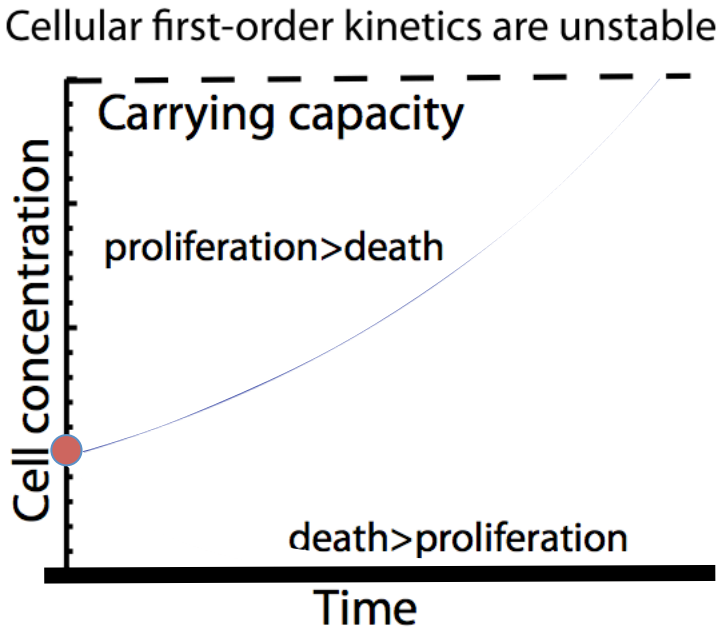


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Hart et al., *Cell*, 2014

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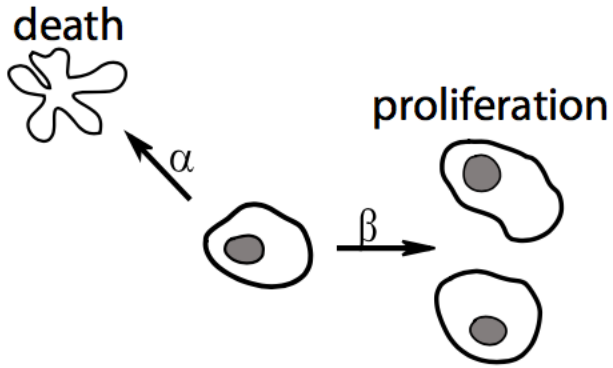


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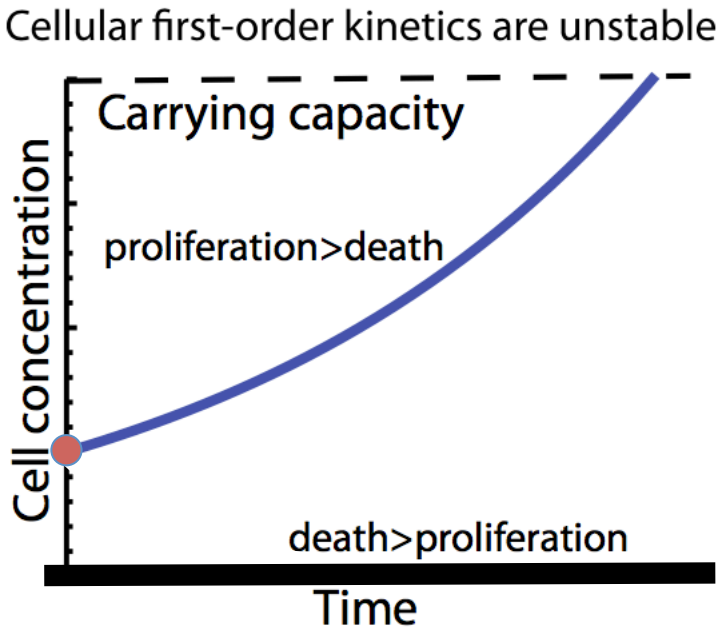


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Hart et al., *Cell*, 2014

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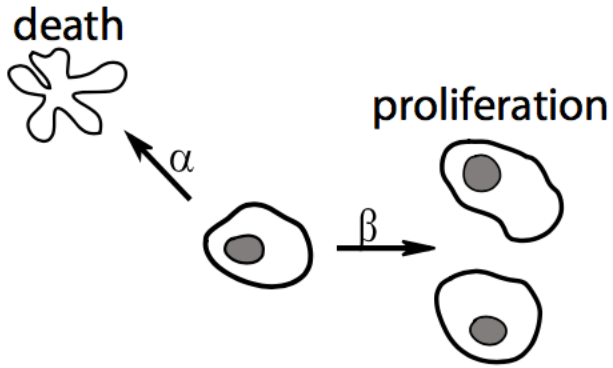


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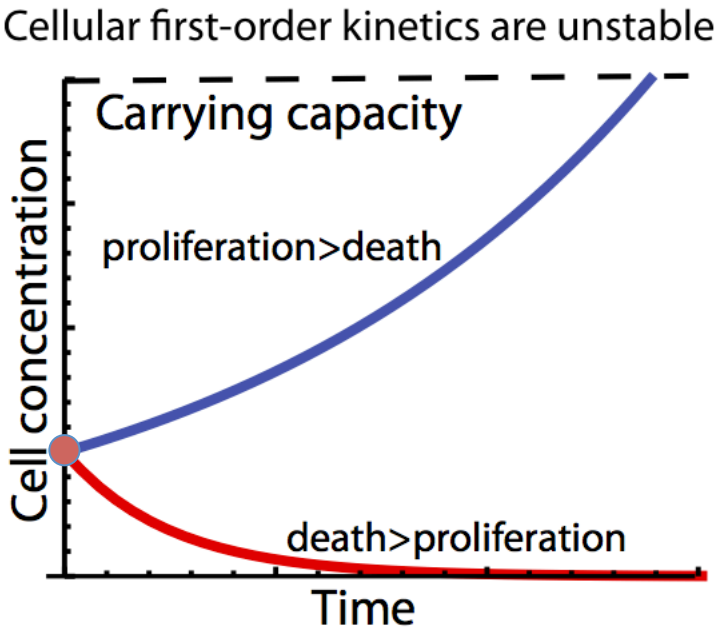
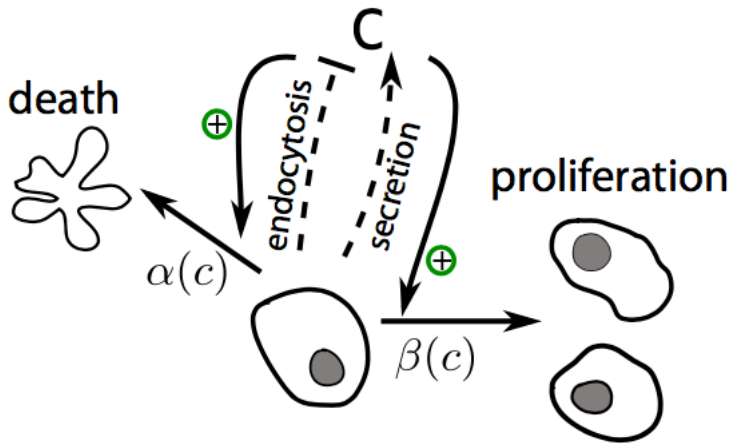



X = cell number
α = cell death rate
β = cell proliferation rate

Hart et al., *Cell*, 2014

# Adding in the effect of a secreted regulator:




$$\frac{dX}{dt} = (\beta(c) - \alpha(c))X$$

$$\frac{dc}{dt} = \mathrm{I}_0 + (\beta_1 - f(c))X - \gamma c$$

X = cell number
$\alpha$ = cell death rate
$\beta$ = cell proliferation rate
c = concentration of cytokine
$I_0$ = external cytokine supply
$\beta_1$ = cytokine production rate by cells
f(c) = cytokine consumption rate by cells
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Hart et al., *Cell*, 2014

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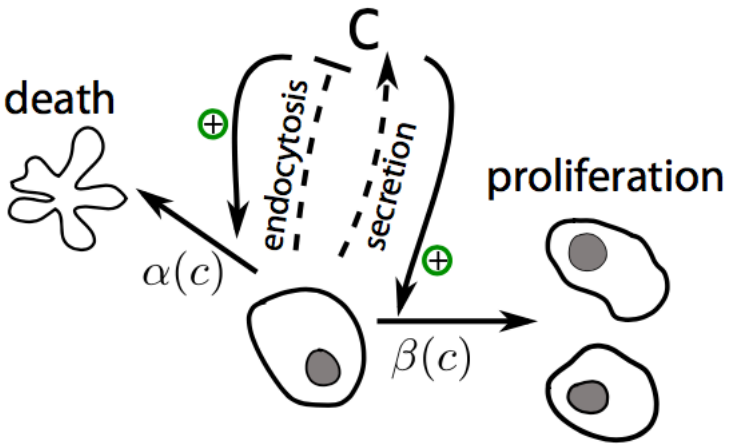


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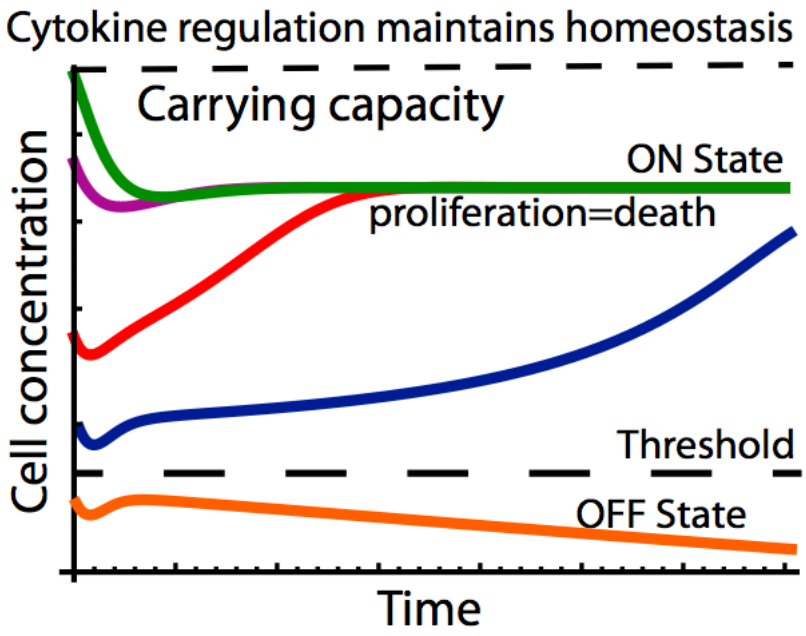


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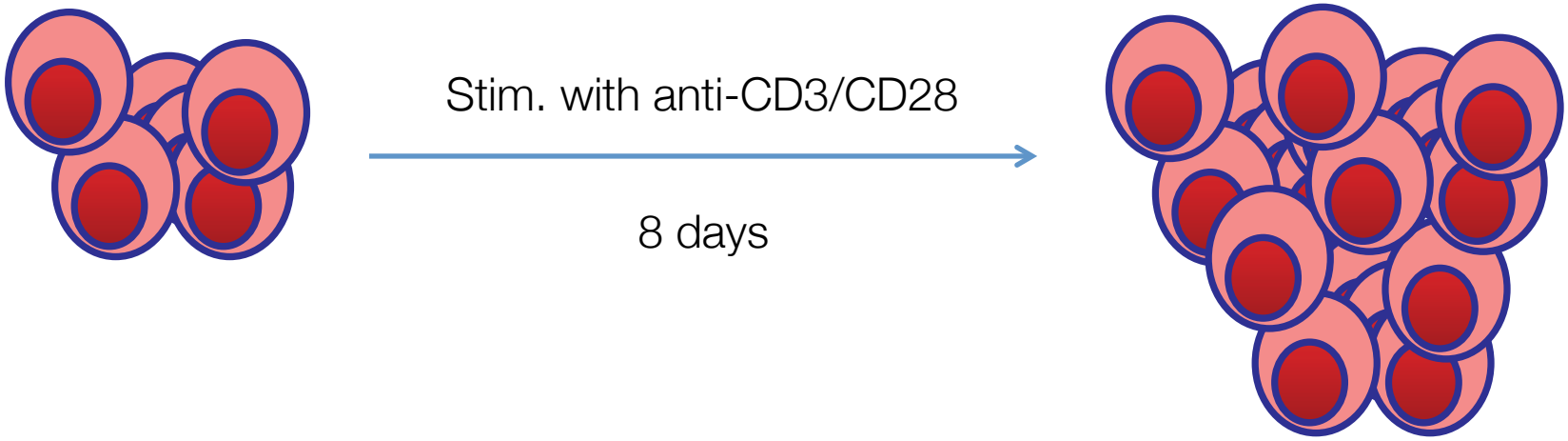
Hart et al., *Cell*, 2014

# Testing the model:
# In vitro activation of CD4 T cells




Hart et al., *Cell*, 2014

# Testing the model:
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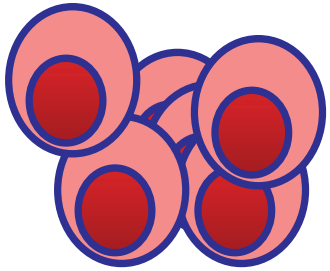
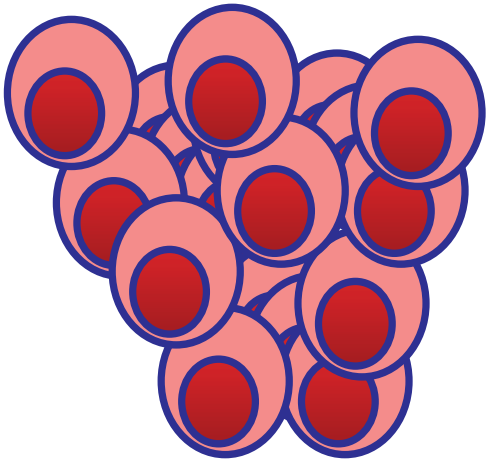
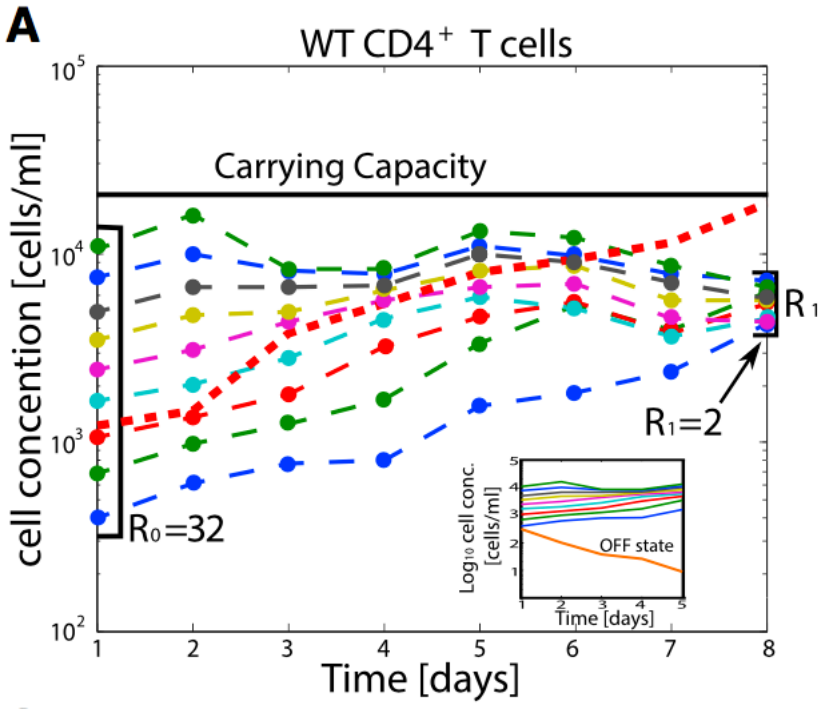


Stim. with anti-CD3/CD28

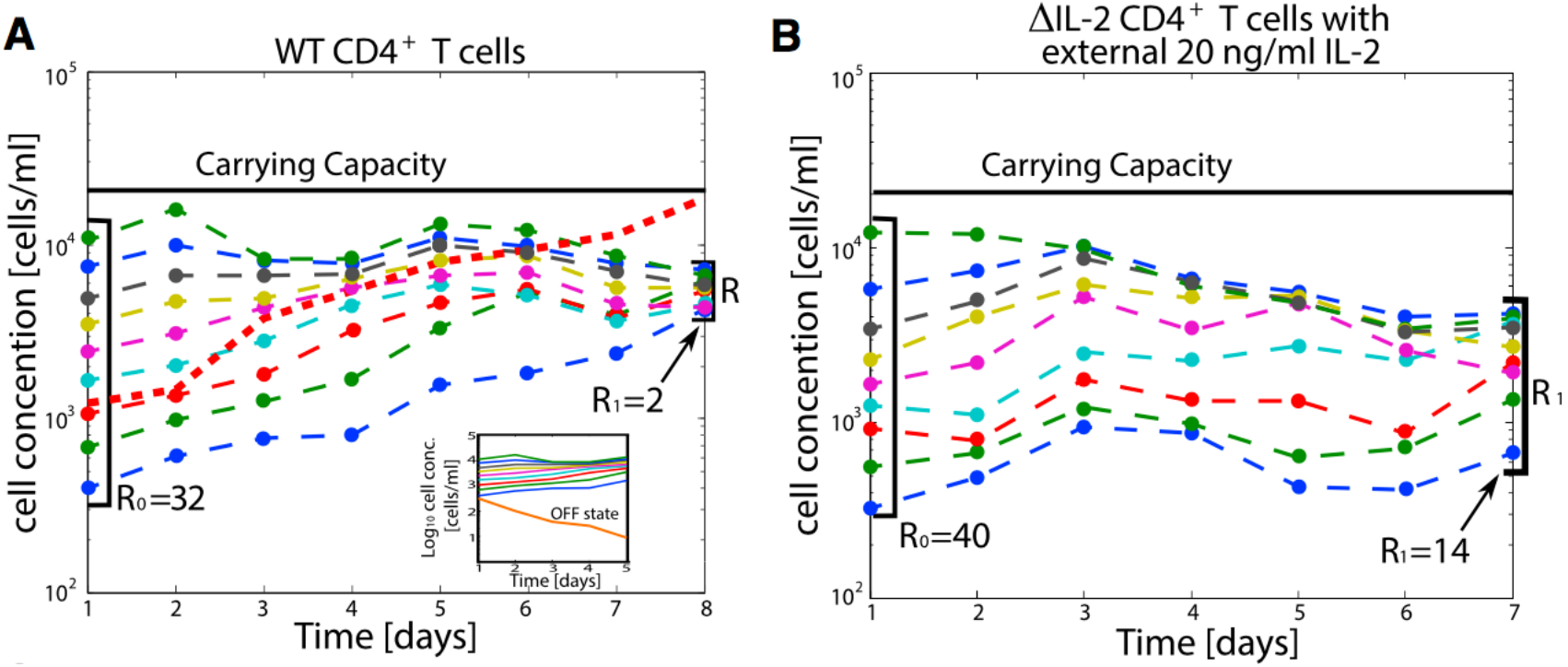
8 days





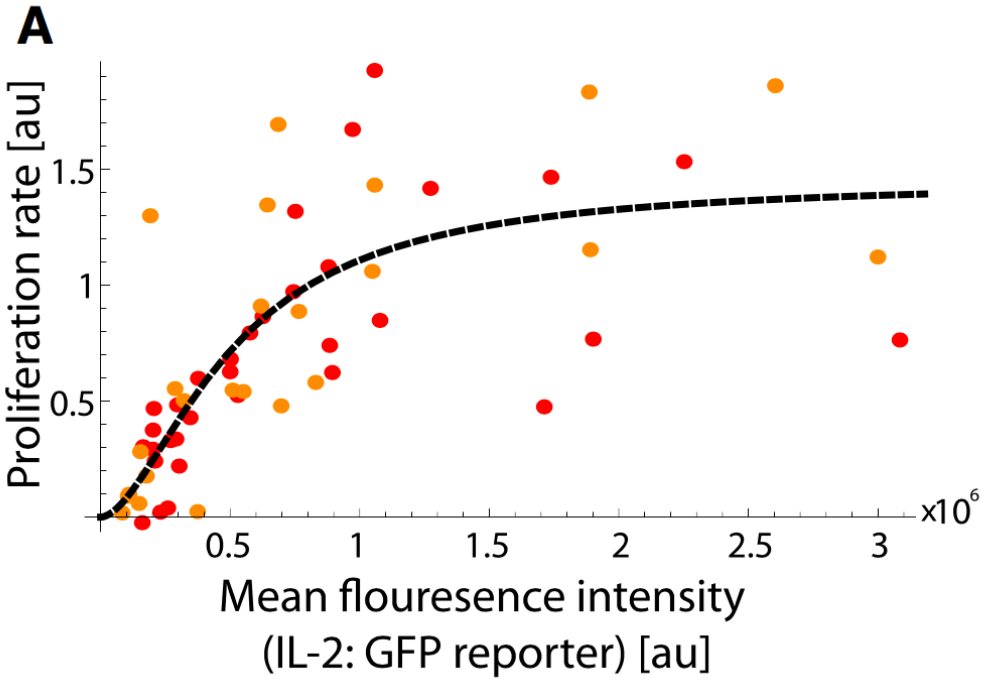

Hart et al., *Cell*, 2014

# Autocrine production of IL-2 is required for "homeostatic" behavior




Hart et al., *Cell*, 2014

# IL-2 regulates T cell proliferation and death in fundamentally different ways




Cooperative, or “ultrasensitive”
Hill coefficient = 1.7

Hart et al., *Cell*, 2014

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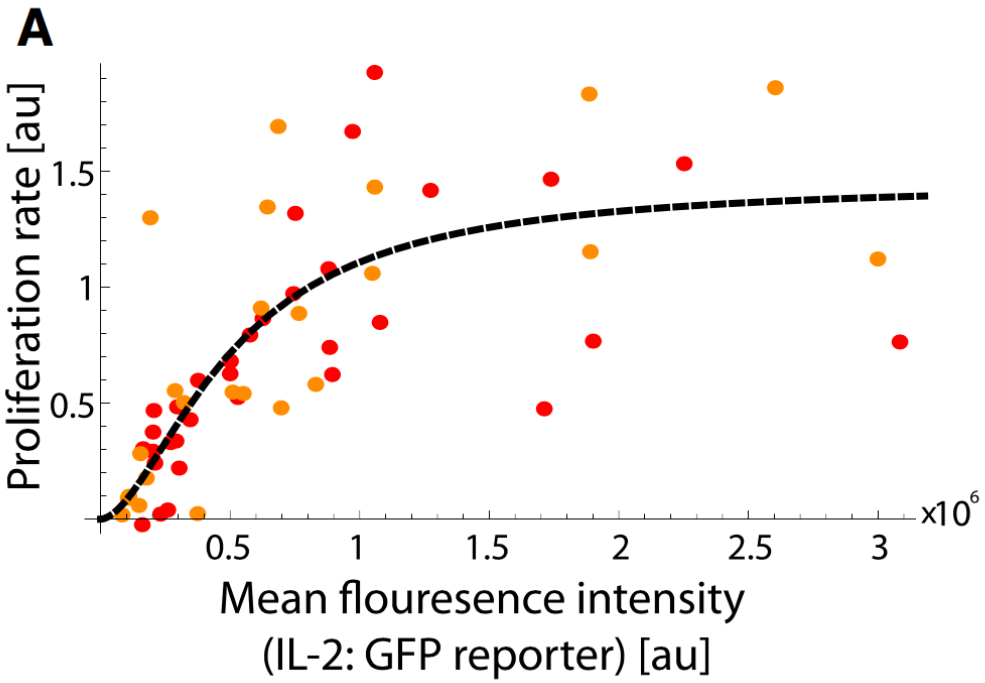


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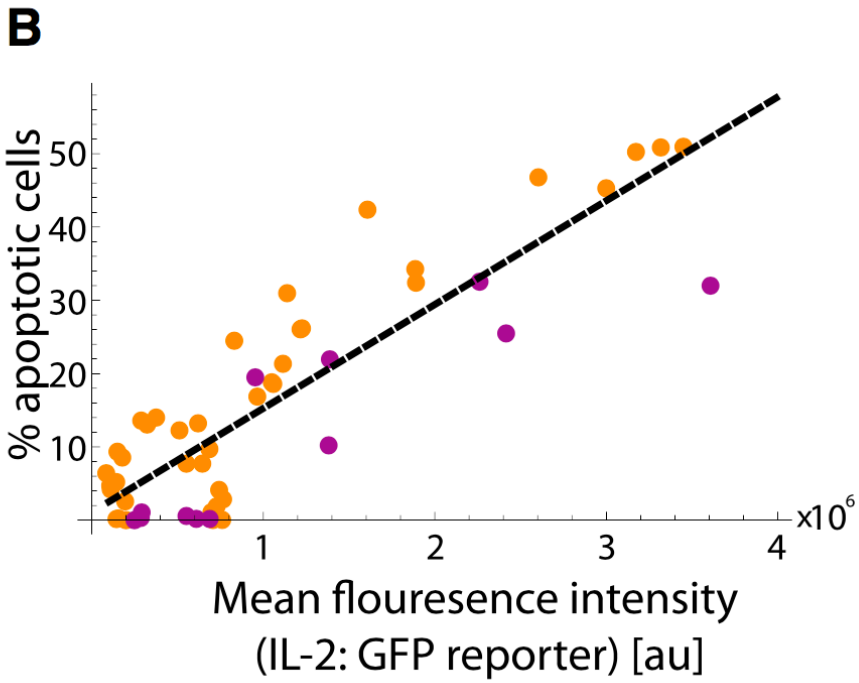
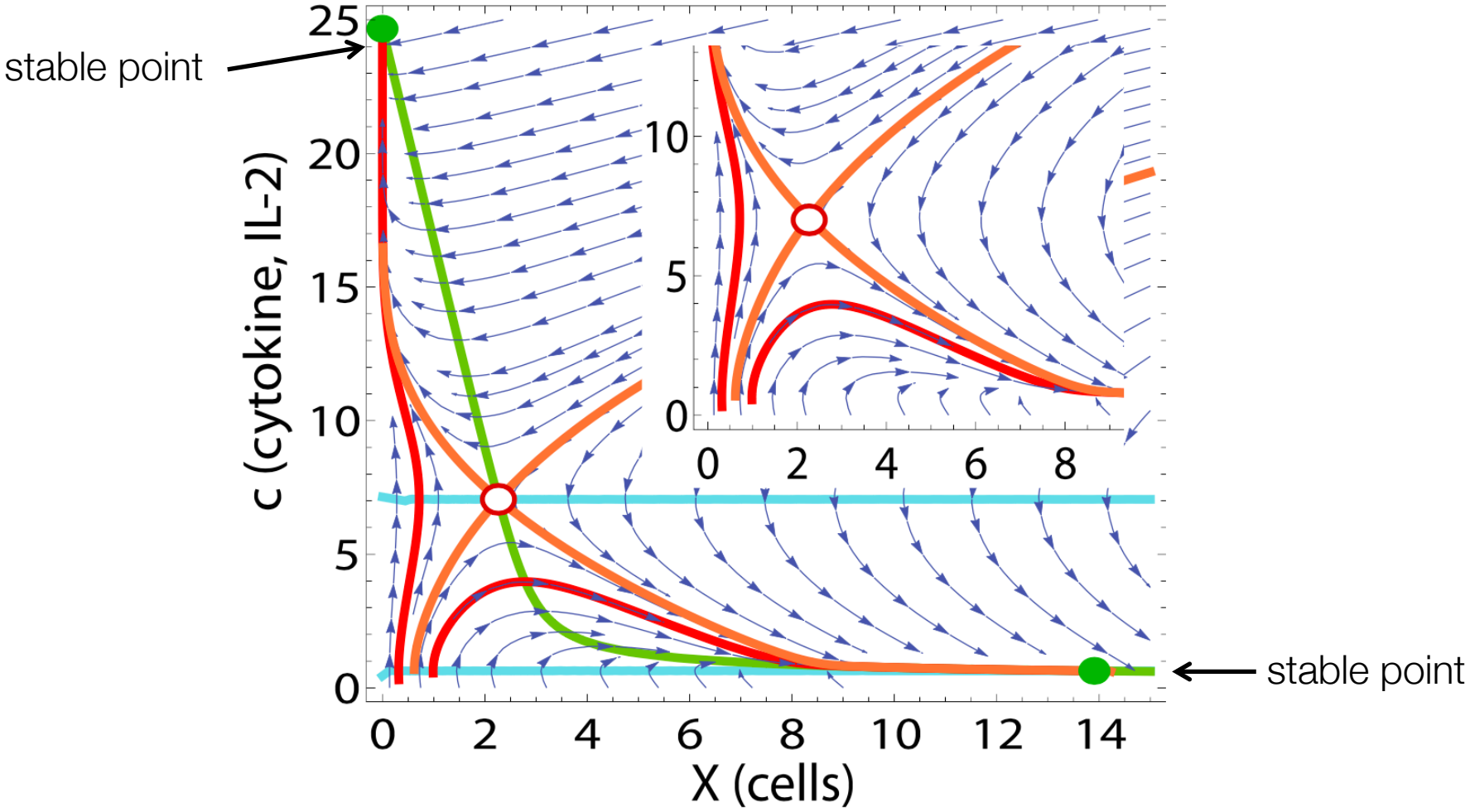



Linear
Hill coefficient = 1

Hart et al., *Cell*, 2014

# These model parameters can create a “bistable” system



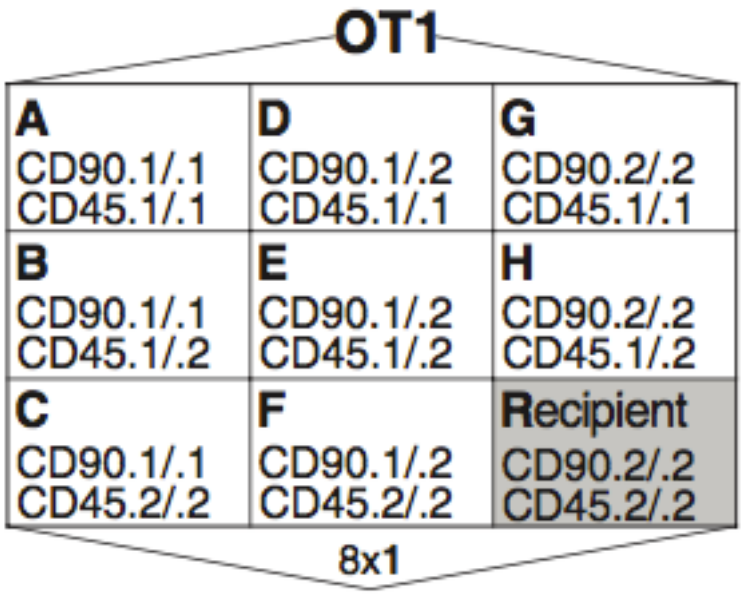

Hart et al., *Cell*, 2014

# Disparate Individual Fates Compose Robust CD8$^+$ T Cell Immunity

Veit R. Buchholz,[1]* Michael Flossdorf,[2,3]* Inge Hensel,[1] Lorenz Kretschmer,[1] Bianca Weissbrich,[1] Patricia Gräf,[1] Admar Verschoor,[1] Matthias Schiemann,[1,4] Thomas Höfer,[2,3]† Dirk H. Busch[1,4,5,6]†

3 MAY 2013 VOL 340 **SCIENCE**

- What is the differentiation pattern of CD8 T cells during an immune response?



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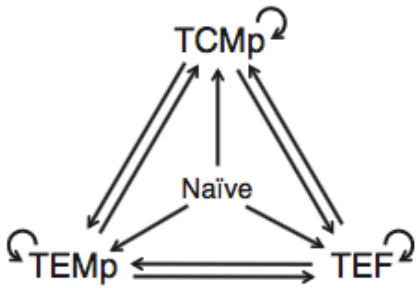
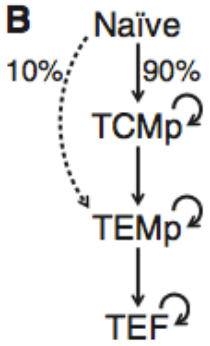
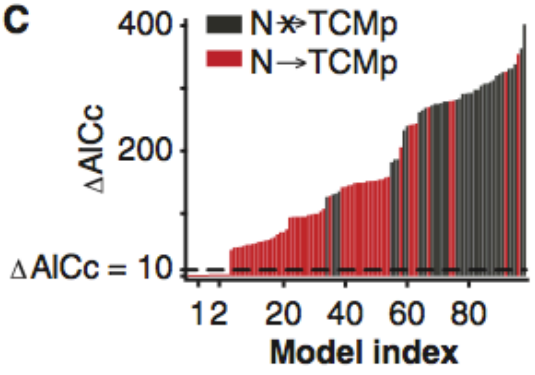
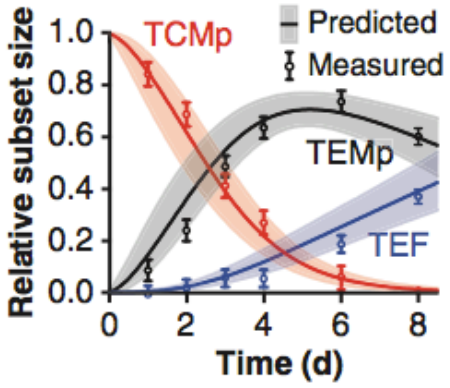


# Conditional density-based analysis of T cell signaling in single-cell data

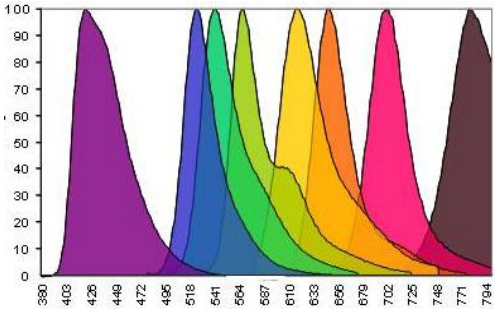
Smita Krishnaswamy, Matthew H. Spitzer, Michael Mingueneau, Sean C. Bendall, Oren Litvin, Erica Stone, Dana Pe'er,*† Garry P. Nolan†

28 NOVEMBER 2014 • VOL 346 ISSUE 6213 1079

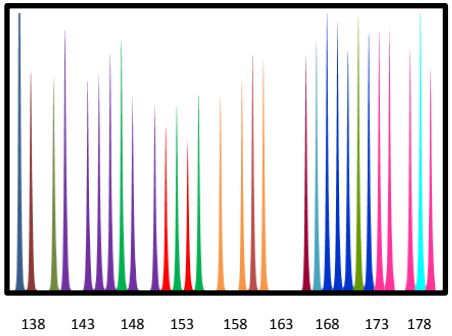
- Signaling through the T cell receptor triggers a well-defined phosphorylation cascade.
- Can we model signal transduction using single cell data?
- Is TCR signaling impacted by the state/context of the T cell?

# The diversity of immune cells has prompted development of single-cell technologies

Flow Cytometry



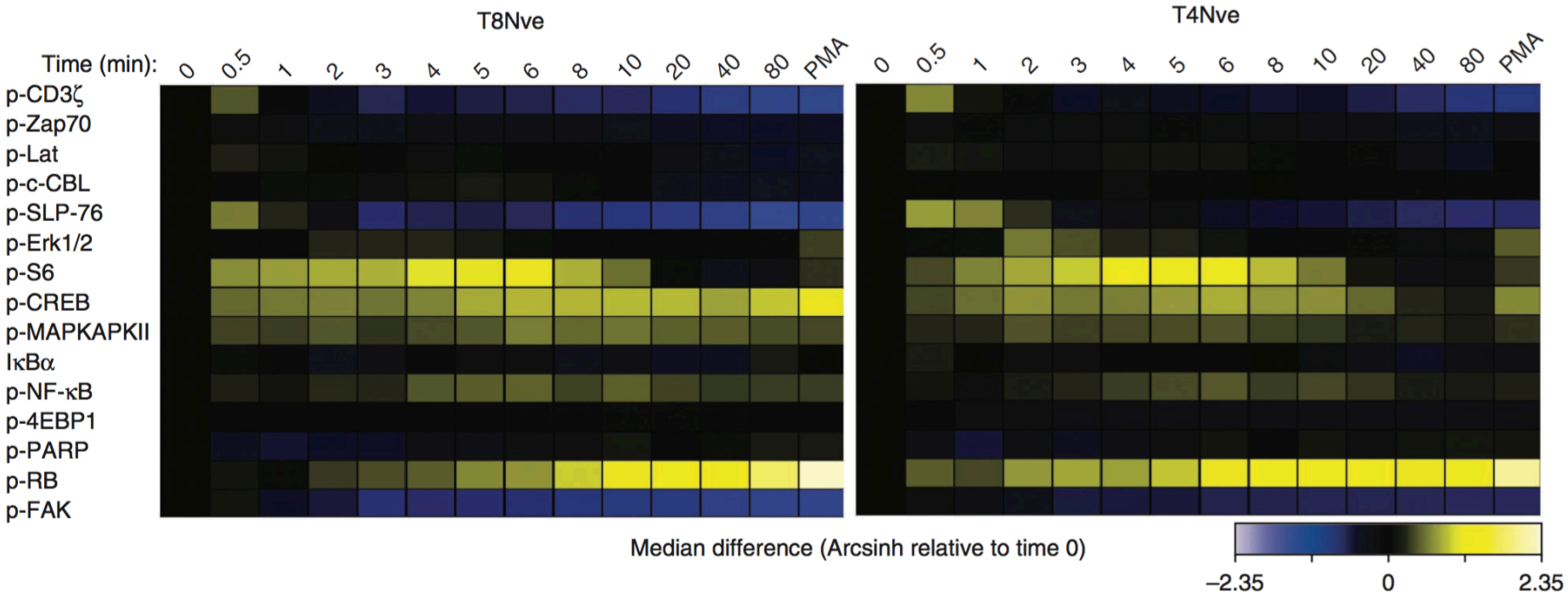

Mass Cytometry




Replacing light with mass enables significantly more multiplexing.

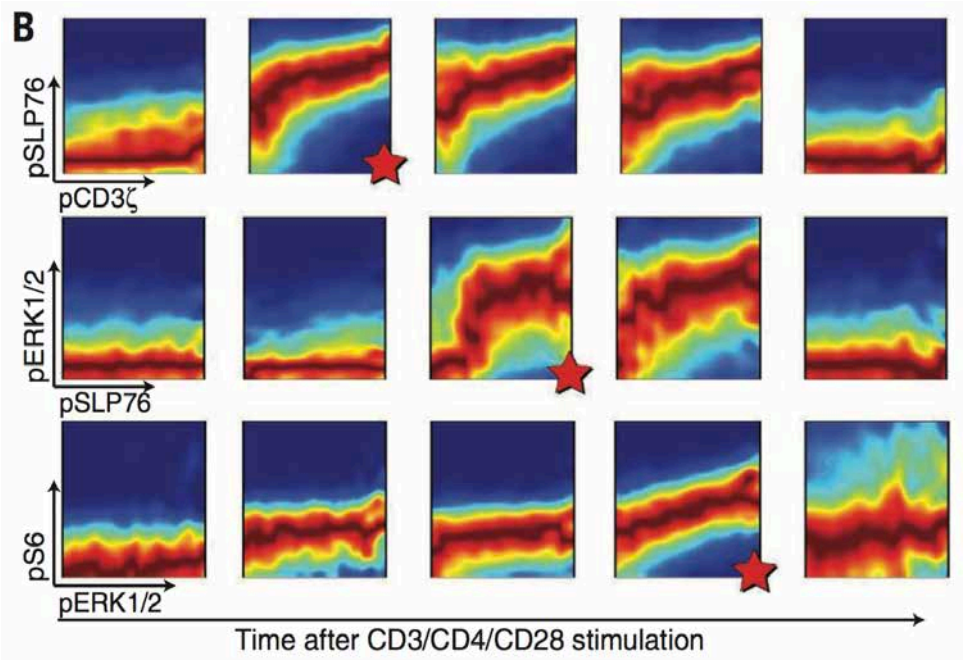
A new powerful experimental tool for “systems immunology”
*at multiple levels of molecular and cellular function.*

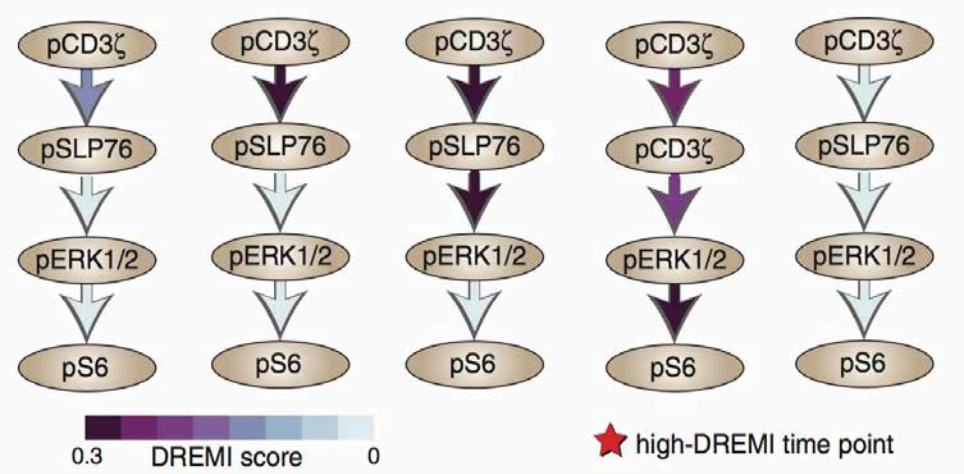
# The primary data at the population level



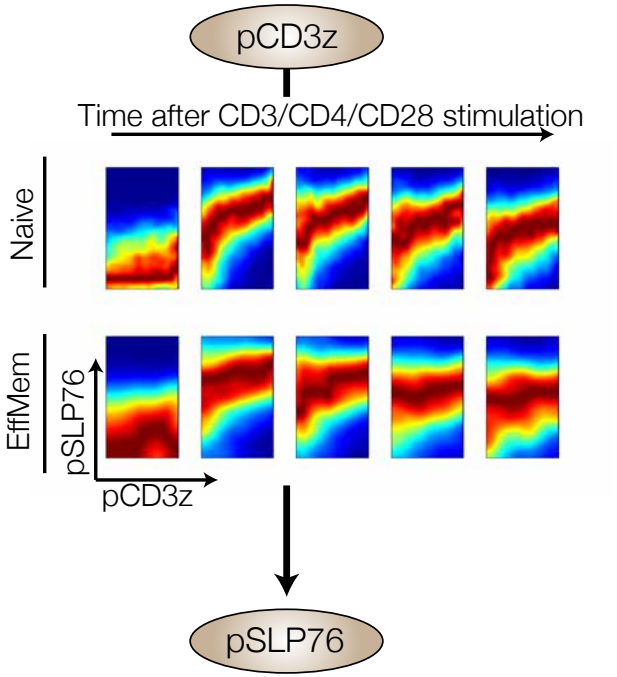

Mingueneau et al., Nat. Immunol. (2013)

# Conditional density analysis reveals information transfer through signal transduction



# Requirement for information transfer softens through CD4 T cell differentiation



Cell

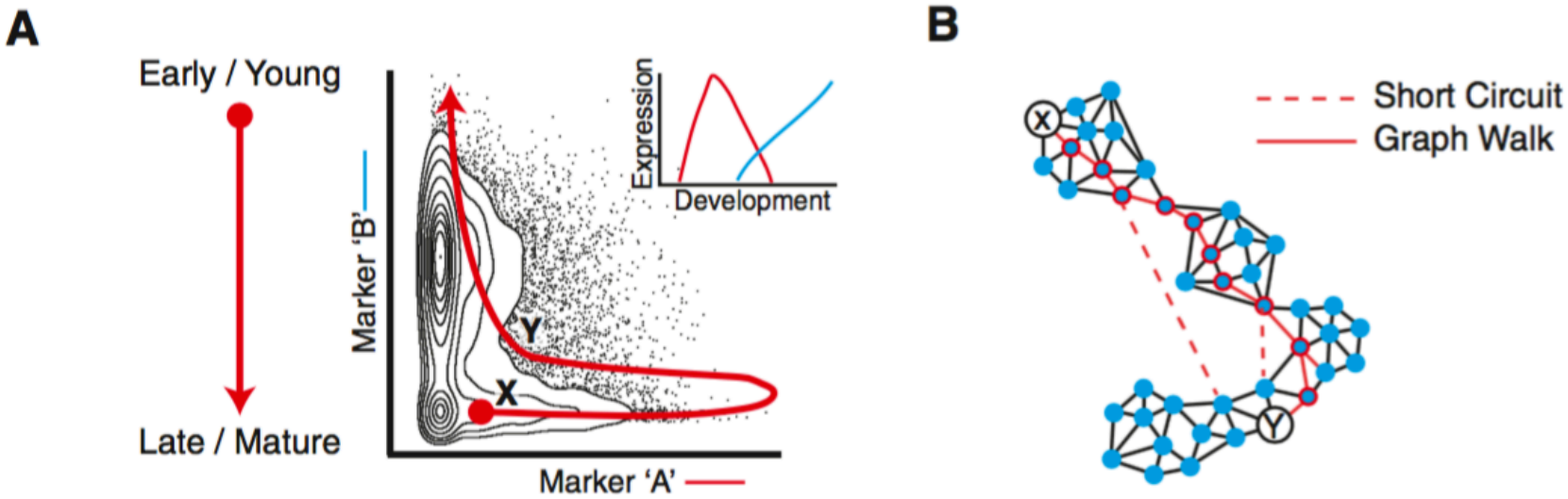


# Single-Cell Trajectory Detection Uncovers Progression and Regulatory Coordination in Human B Cell Development

Sean C. Bendall,[1,2,7] Kara L. Davis,[1,3,7] El-ad David Amir,[4,7] Michelle D. Tadmor,[4] Erin F. Simonds,[1] Tiffany J. Chen,[1,5,6] Daniel K. Shenfeld,[4] Garry P. Nolan,[1,8,*] and Dana Pe'er[4,8,*]

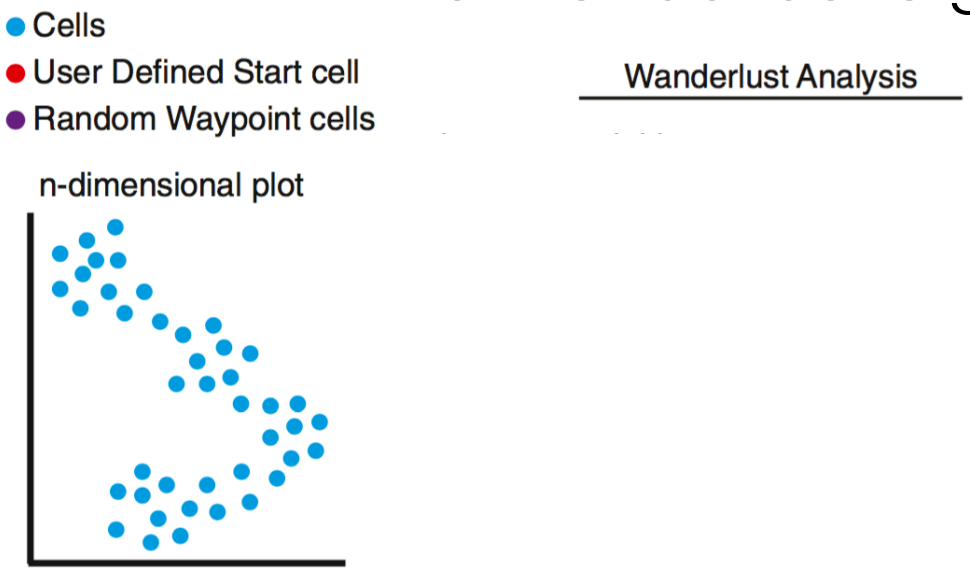
- Healthy human bone marrow contains individual cells at all stages of B cell development in a "snapshot."
- Can single-cell data help clarify this trajectory?

# Organizing individual cells according to their developmental time

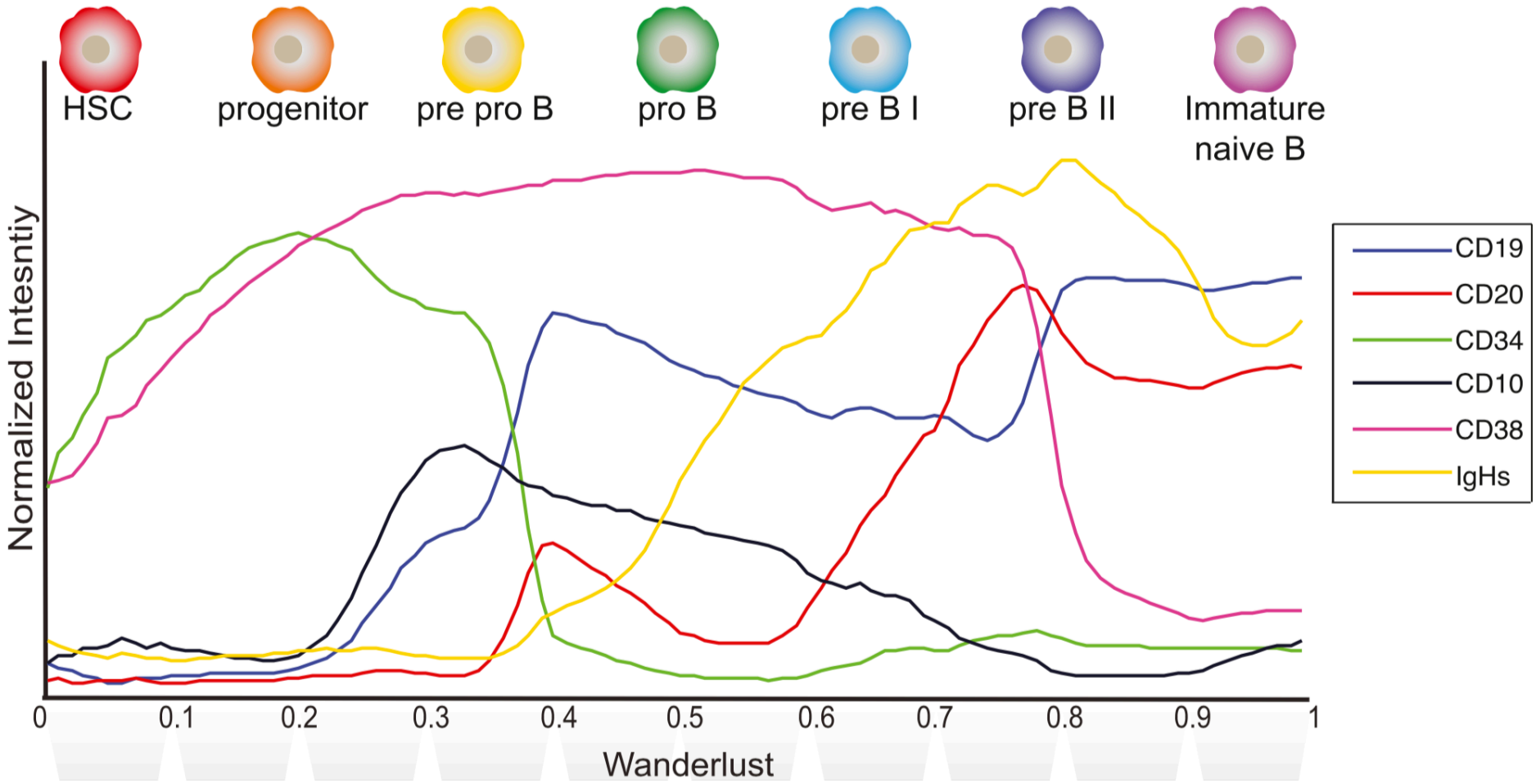



Developmental trajectories are often non-linear.

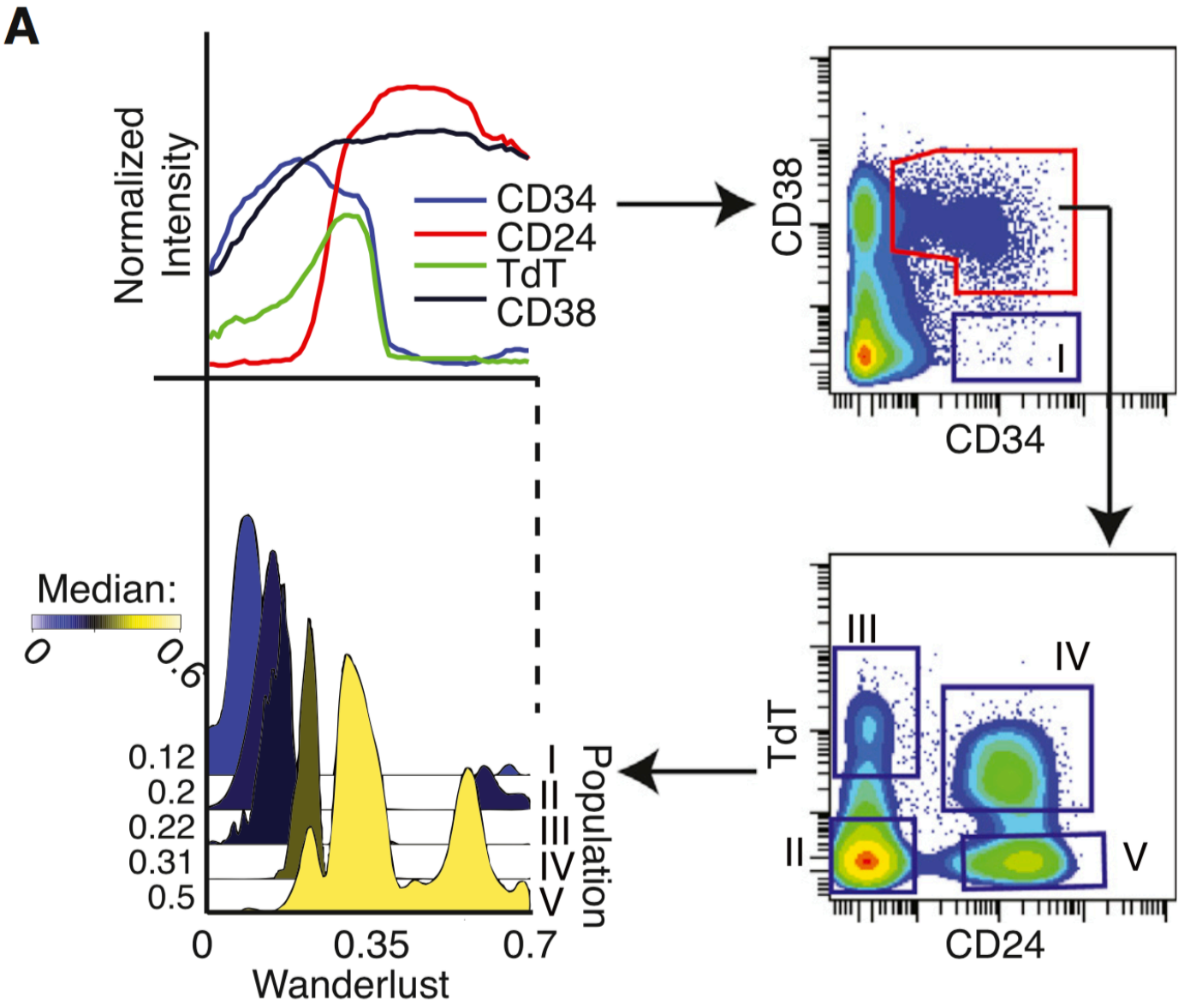
# Organizing individual cells according to their developmental time: The Wanderlust algorithm



# Applying the method to human bone marrow B cells



# Identification of early B cell progenitor subsets



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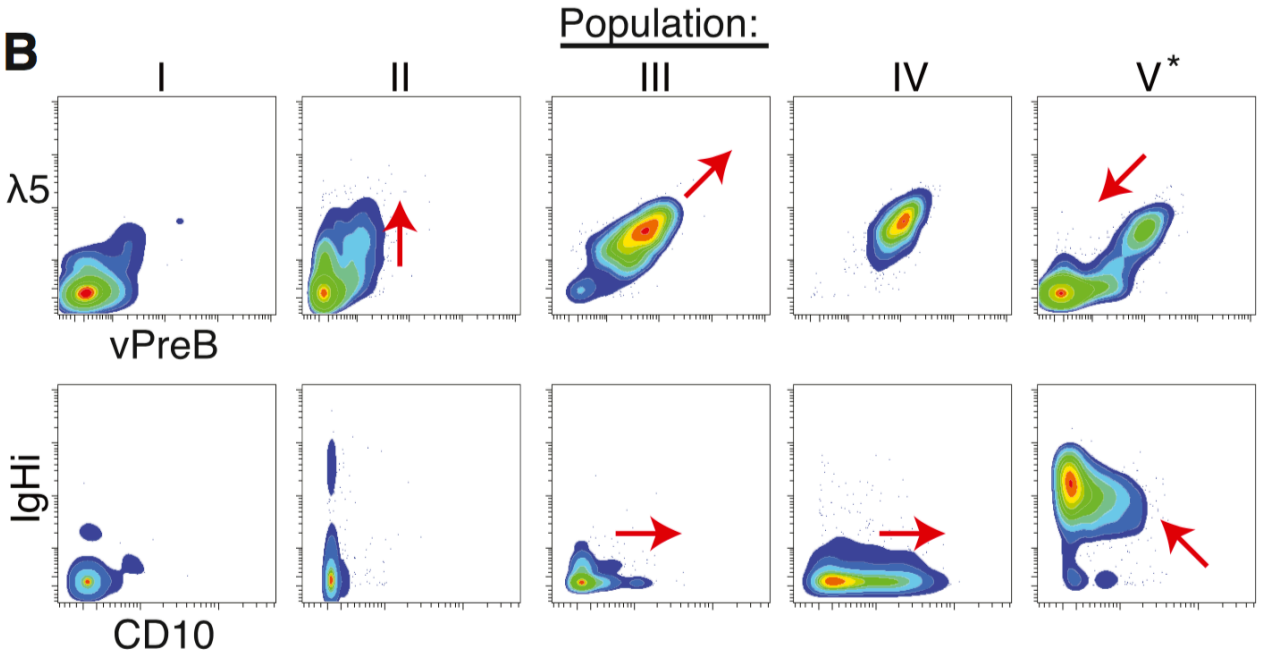


# IL-7 requirement in mice vs. humans

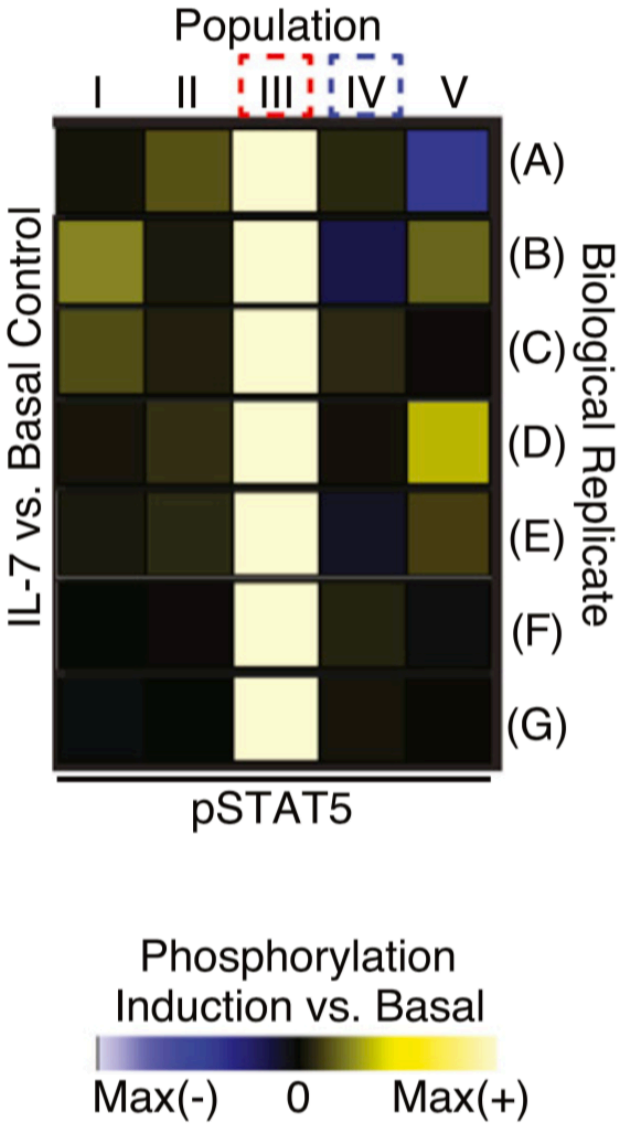
J. Exp. Med. (1980)

**Early Lymphocyte Expansion Is Severely Impaired in Interleukin 7 Receptor–deficient Mice**

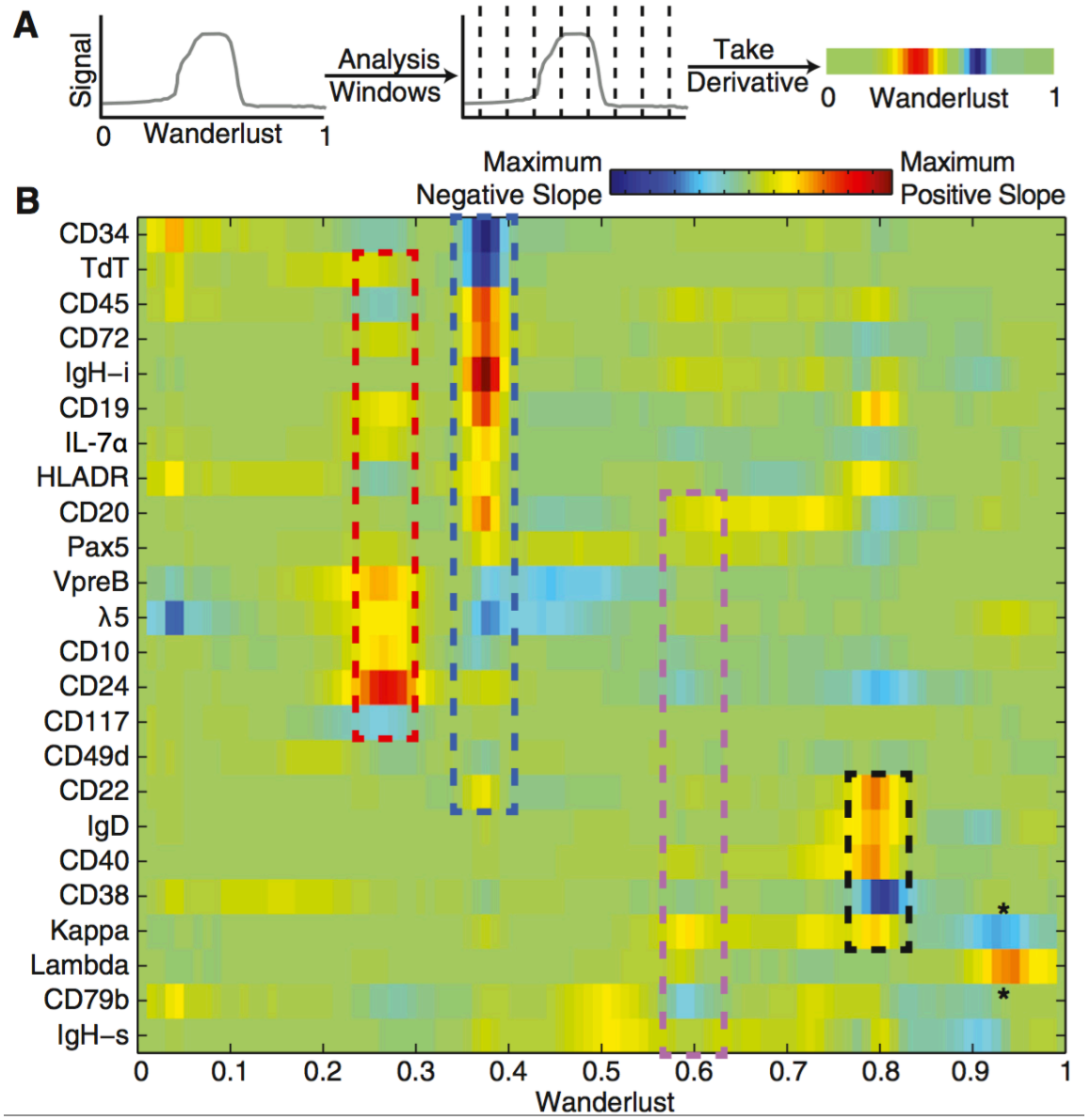
Imm. Rev. (2005)

| | | | Circulating lymphocytes | | |
|---|---|---|---|---|---|
| $T^-B^+$ SCID | Gene defective | Defective pathway | T | B | NK |
| X-linked SCID | IL2RG | Multiple cytokine mediated signaling | ↓↓ | Normal | ↓↓ |
| Jak3 deficiency | Jak3 | Multiple cytokine mediated signaling | ↓↓ | Normal | ↓↓ |
| IL-7R deficiency | IL7RA | IL-7-mediated signaling | ↓↓ | Normal | Normal |

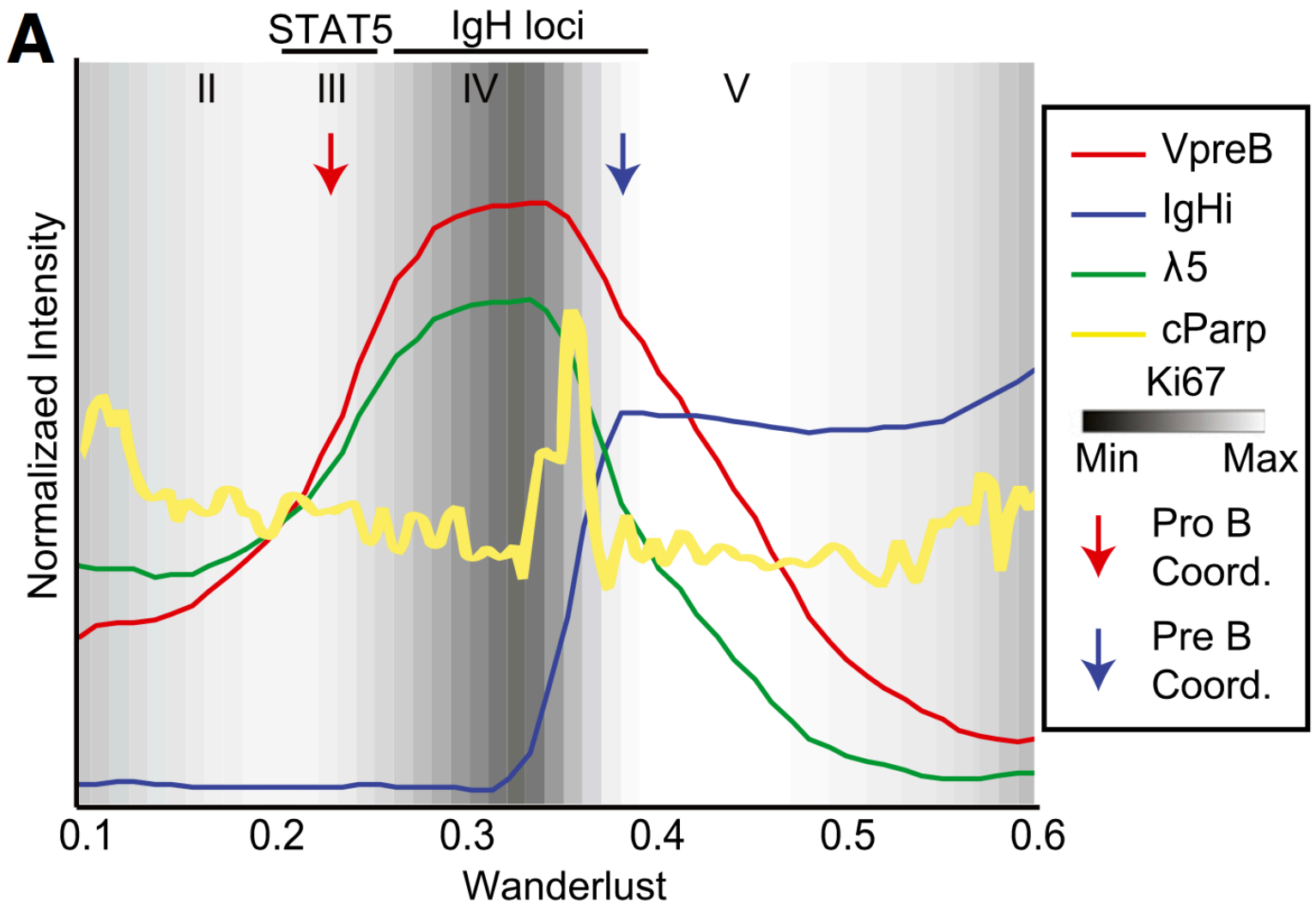
# Which B cell subset responds to IL-7?



# Derivative analysis reveals B cell checkpoints



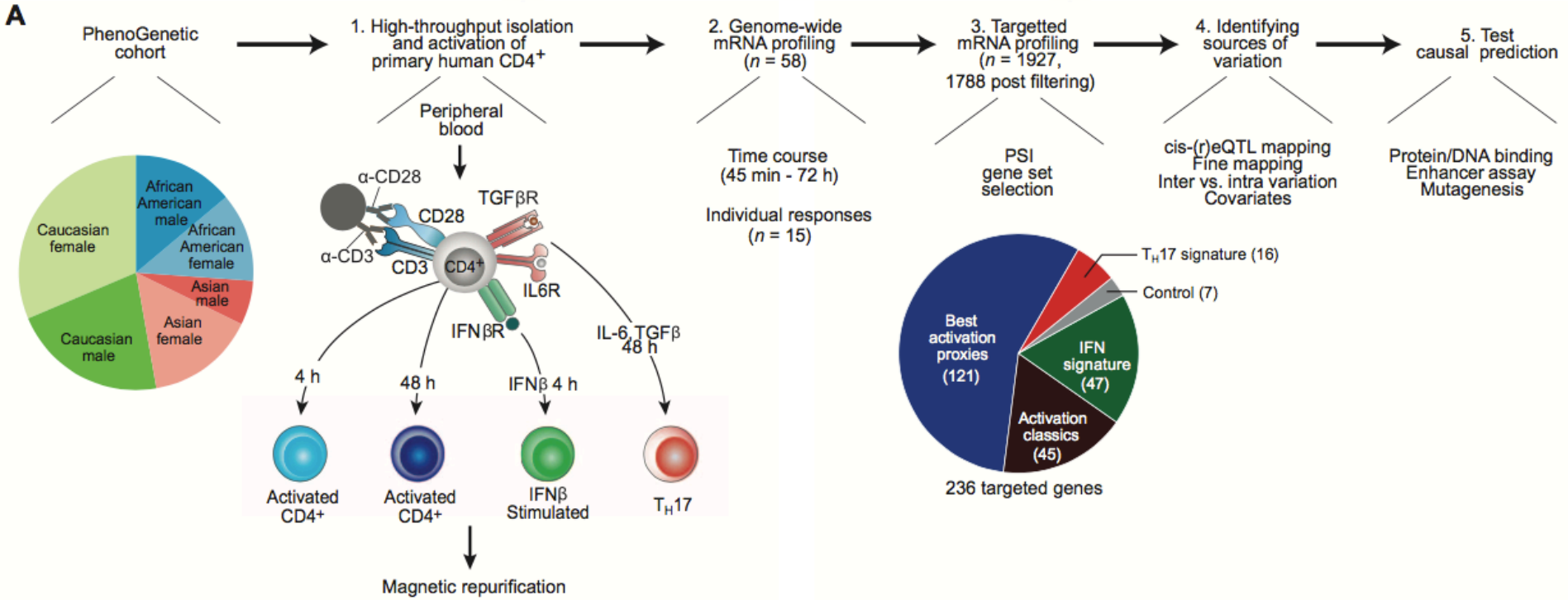
# Derivative coordination points represent pro- and pre-B cell transition points



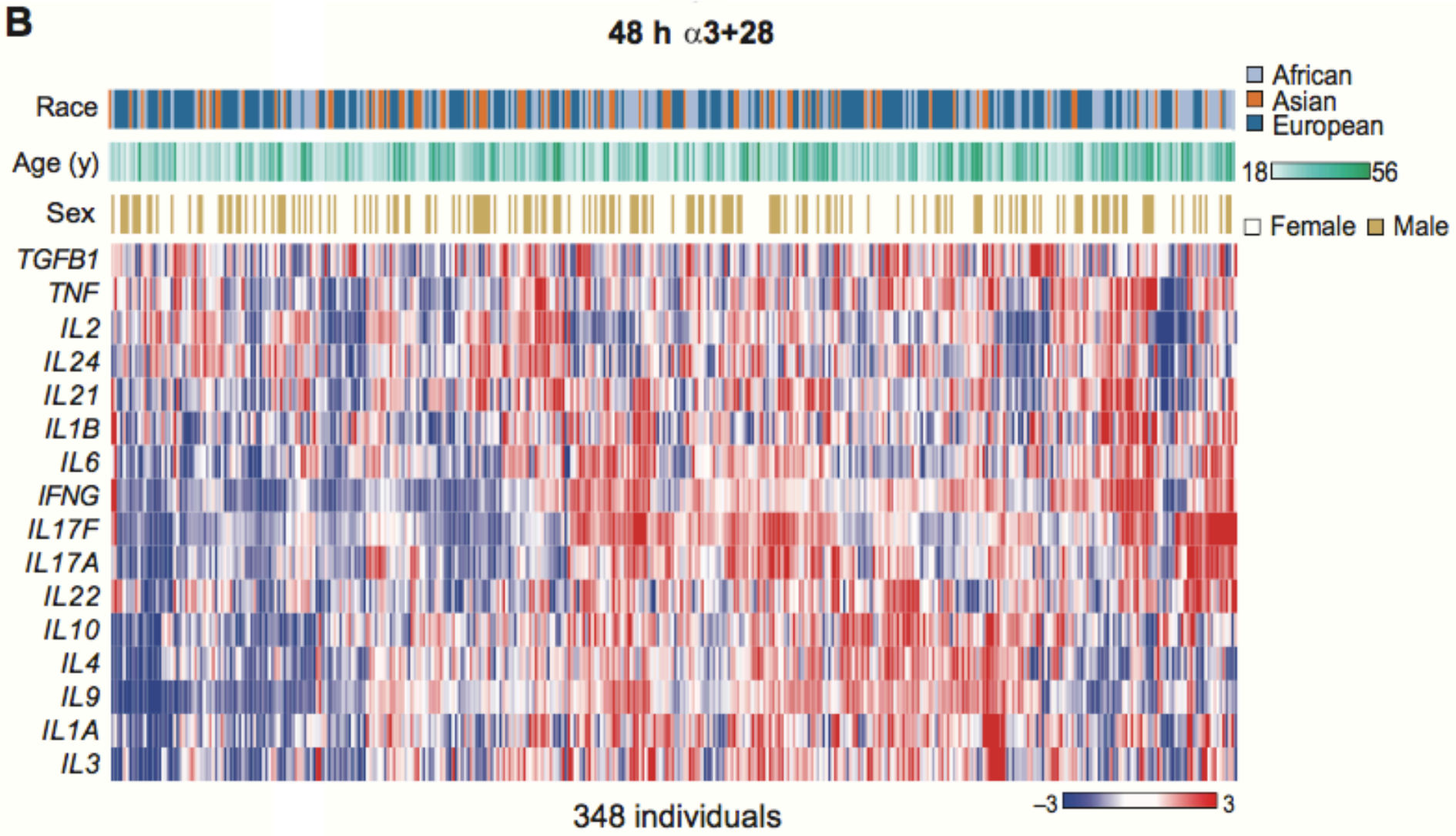
IMMUNOGENETICS SCIENCE 12 SEPTEMBER 2014 • VOL 345 ISSUE 6202

# Intersection of population variation and autoimmunity genetics in human T cell activation

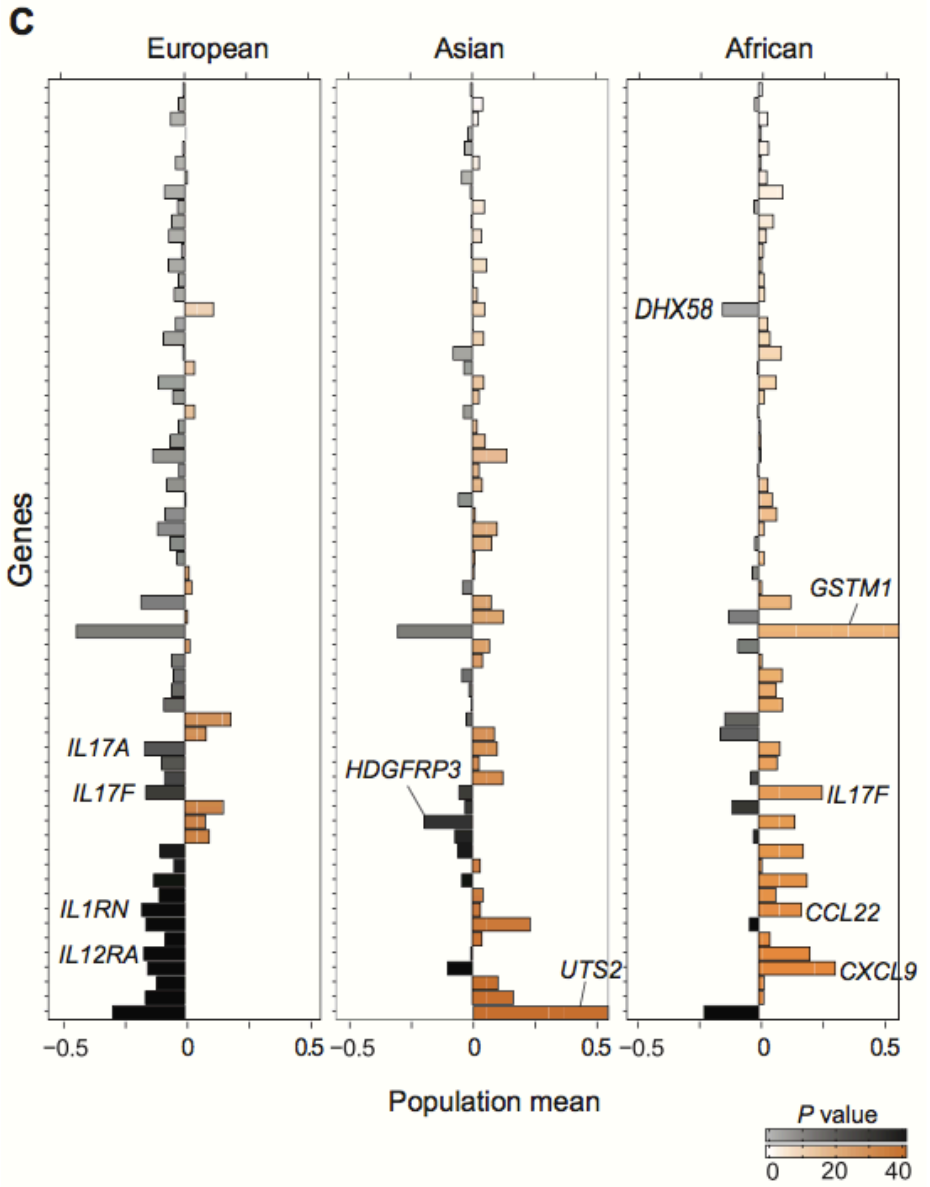
Chun Jimmie Ye,[1] Ting Feng,[2] Ho-Keun Kwon,[2] Towfique Raj,[1,3] Michael T. Wilson,[2] Natasha Asinovski,[2] Cristin McCabe,[1,3] Michelle H. Lee,[3] Irene Frohlich,[3] Hyun-il Paik,[2] Noah Zaitlen,[4] Nir Hacohen,[2] Barbara Stranger,[5] Philip De Jager,[1,3] Diane Mathis,[1,2] Aviv Regev,[1,6]* Christophe Benoist[1,2]*



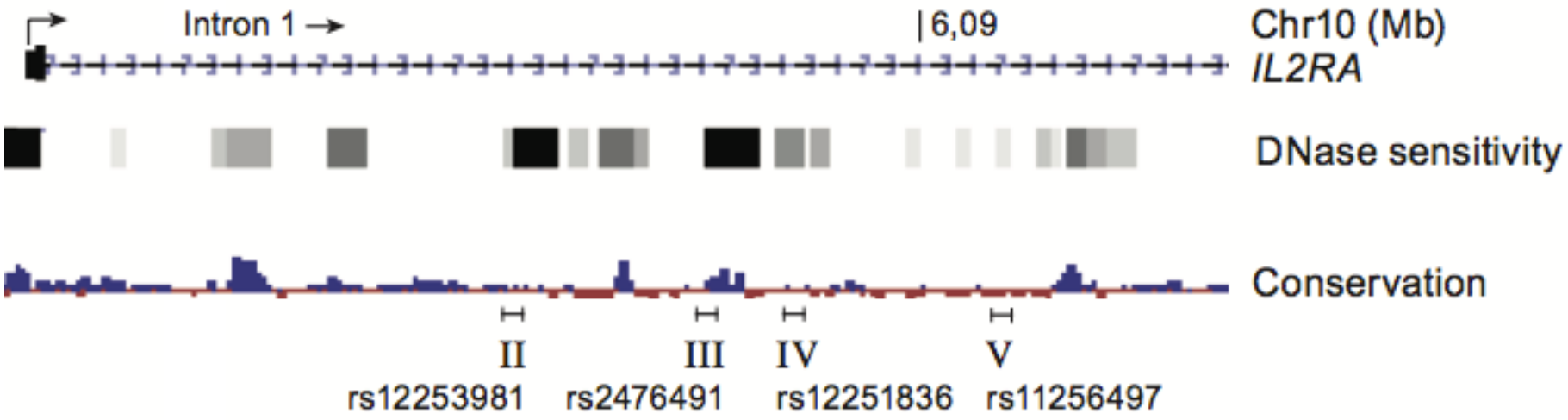
# Significant variability across individuals in cytokine gene transcript levels



# Specific gene expression patters correlated with ethnicity



# Identifying a SNP in an enhancer of IL-2 that regulates expression upon TCR stimulation



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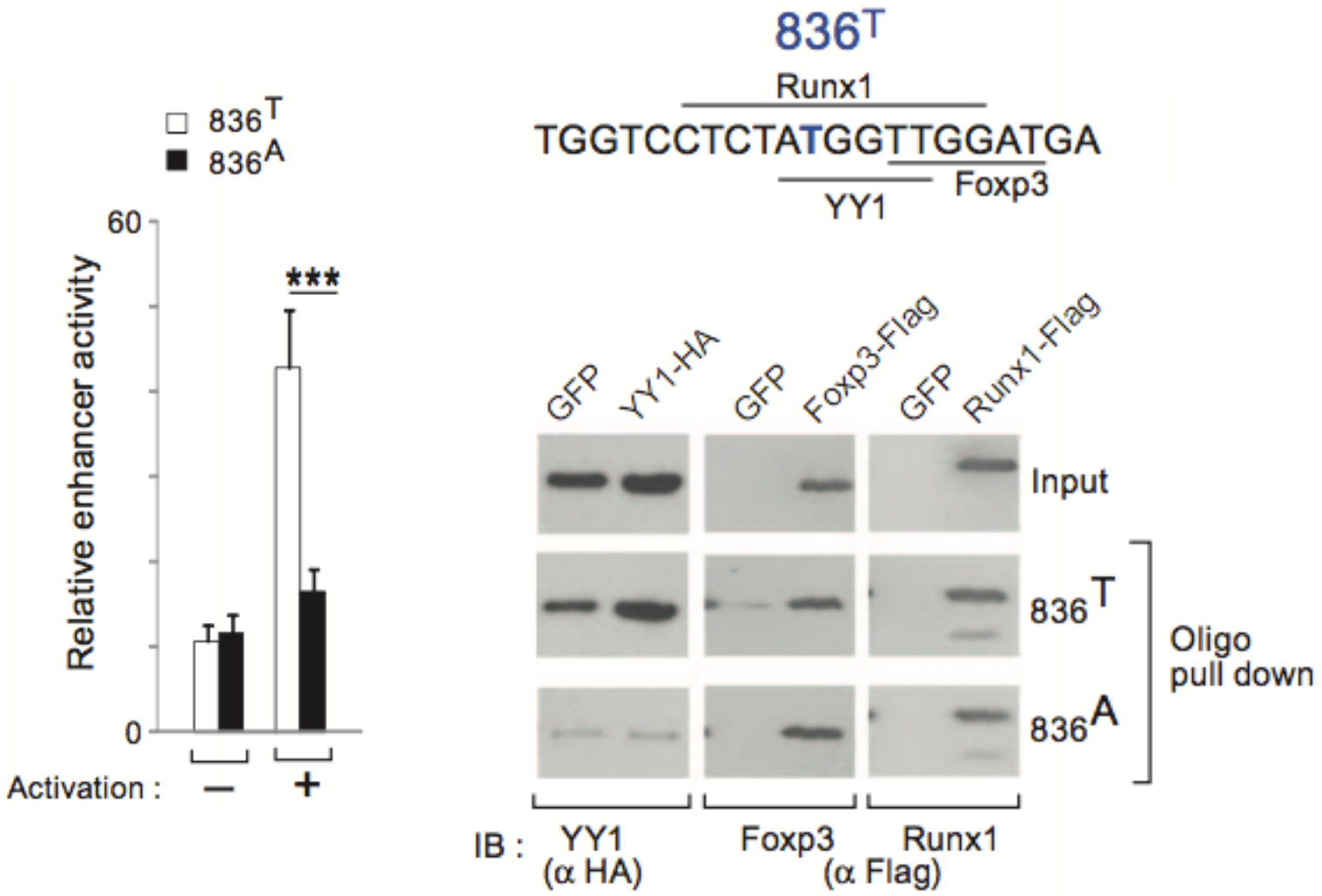
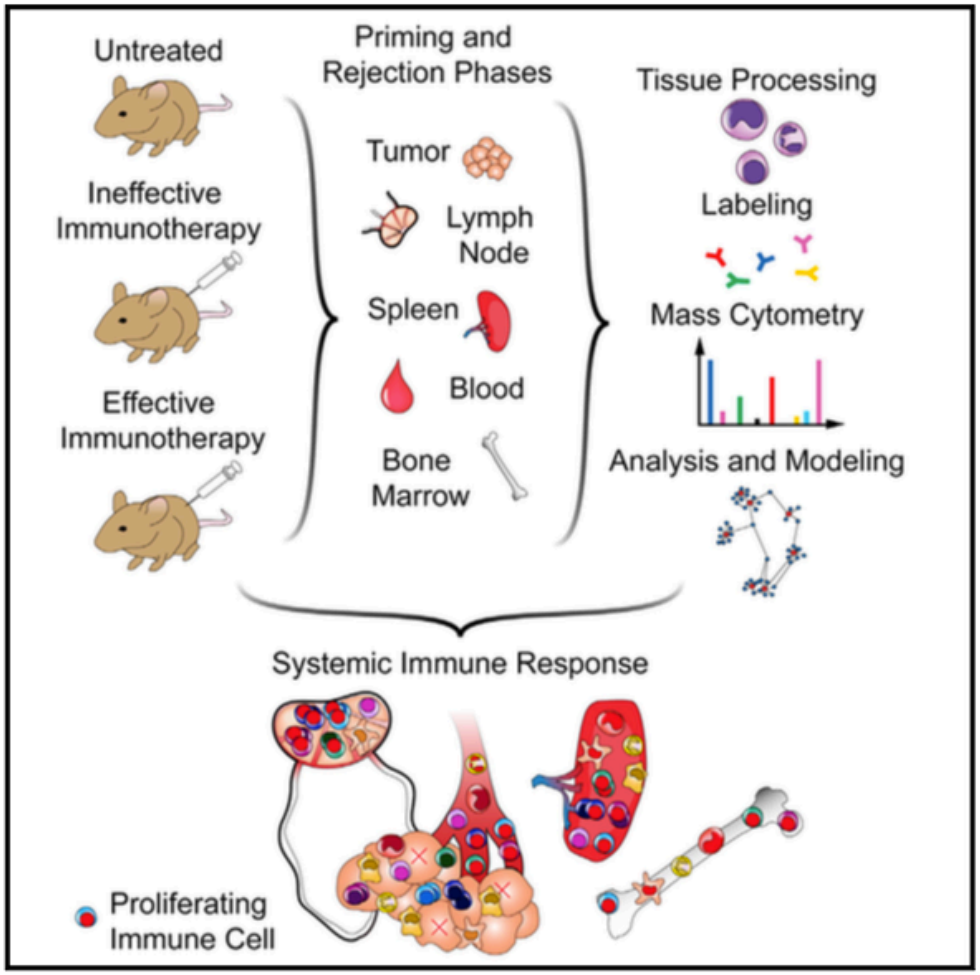


# Systemic Immunity Is Required for Effective Cancer Immunotherapy

Matthew H. Spitzer,[1,2,3,4,6,8,9,*] Yaron Carmi,[1,7,8] Nathan E. Reticker-Flynn,[1,8] Serena S. Kwek,[5] Deepthi Madhireddy,[2] Maria M. Martins,[1] Pier Federico Gherardini,[2] Tyler R. Prestwood,[1] Jonathan Chabon,[1] Sean C. Bendall,[1] Lawrence Fong,[5,6] Garry P. Nolan,[2,3,*] and Edgar G. Engleman[1,3,*]

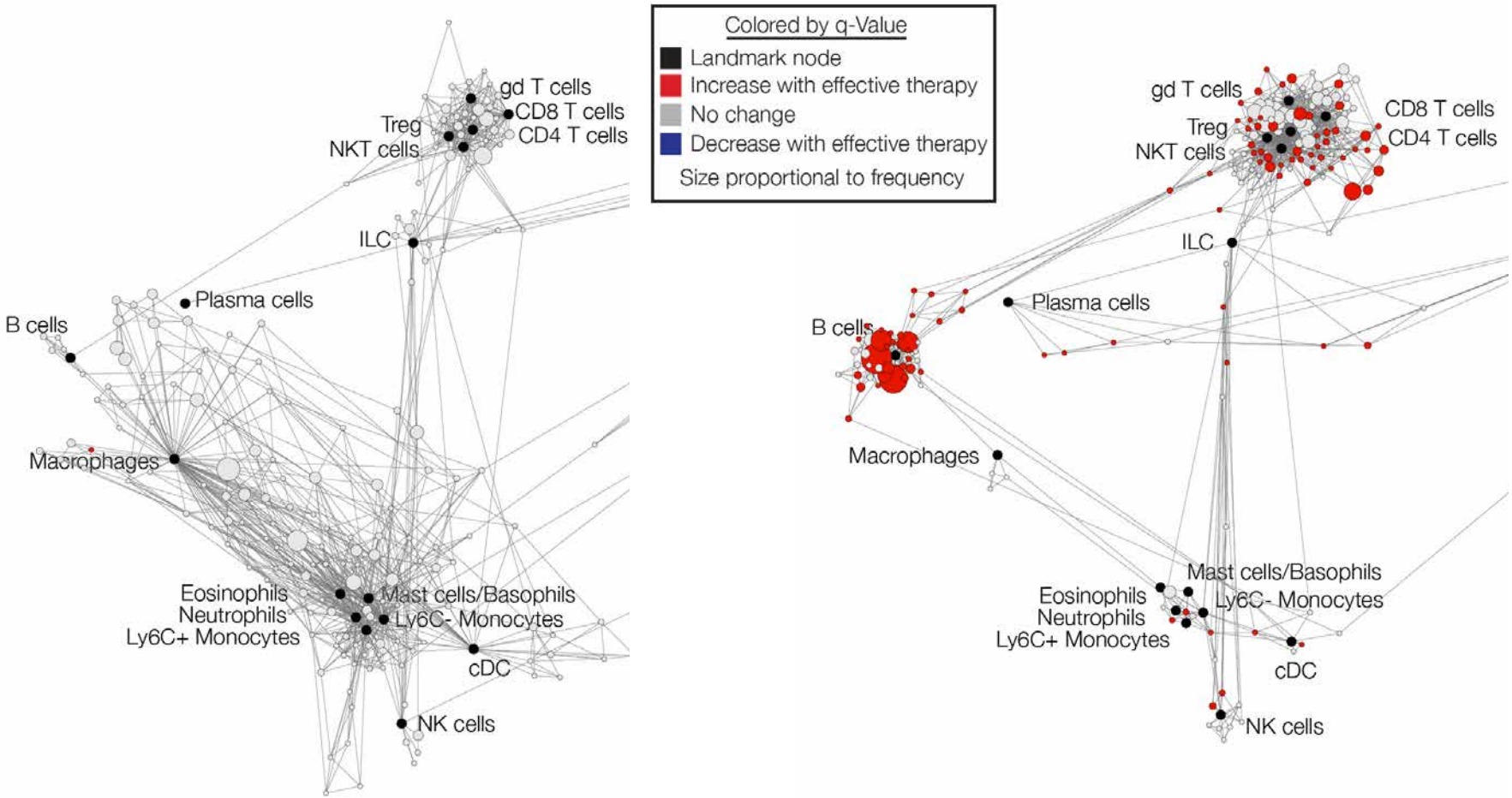
Cell *168*, 487–502, January 26, 2017 © 2016



# Immune cell proliferation is sustained from outside the tumor during effective immunotherapy

Tumor Microenvironment

Draining Lymph Node

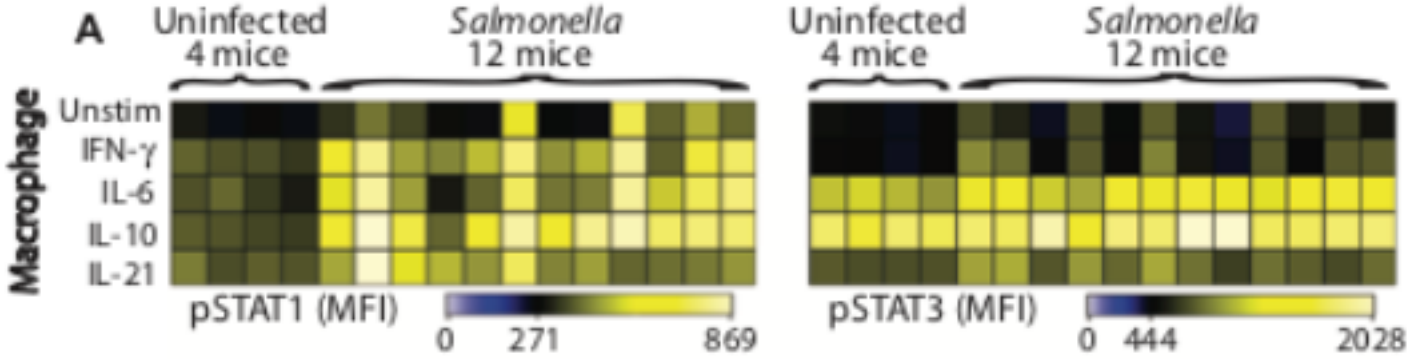



Red nodes are subsets with increased proliferation after therapy.

SYSTEMS IMMUNOLOGY

# Coordinate actions of innate immune responses oppose those of the adaptive immune system during *Salmonella* infection of mice

Andrew N. Hotson,[1,2*] Smita Gopinath,[2*] Monica Nicolau,[1] Anna Khasanova,[1] Rachel Finck,[1,2] Denise Monack,[2] Garry P. Nolan[1,2†]



SYSTEMS IMMUNOLOGY

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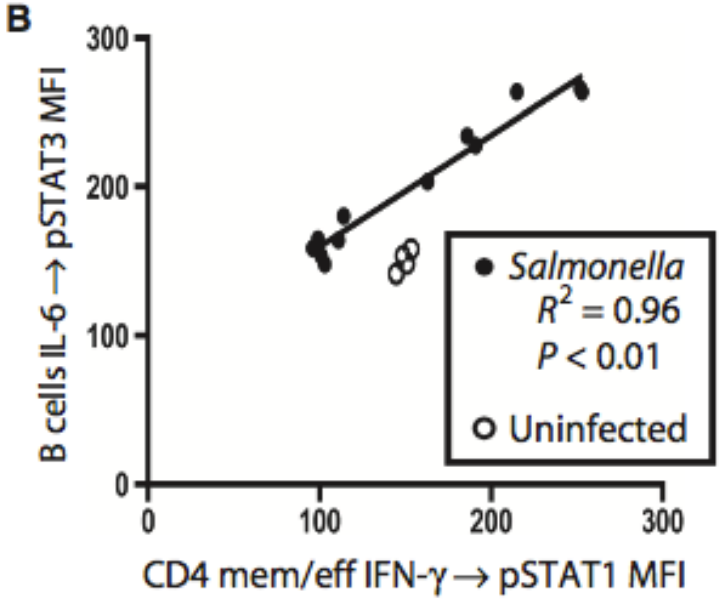
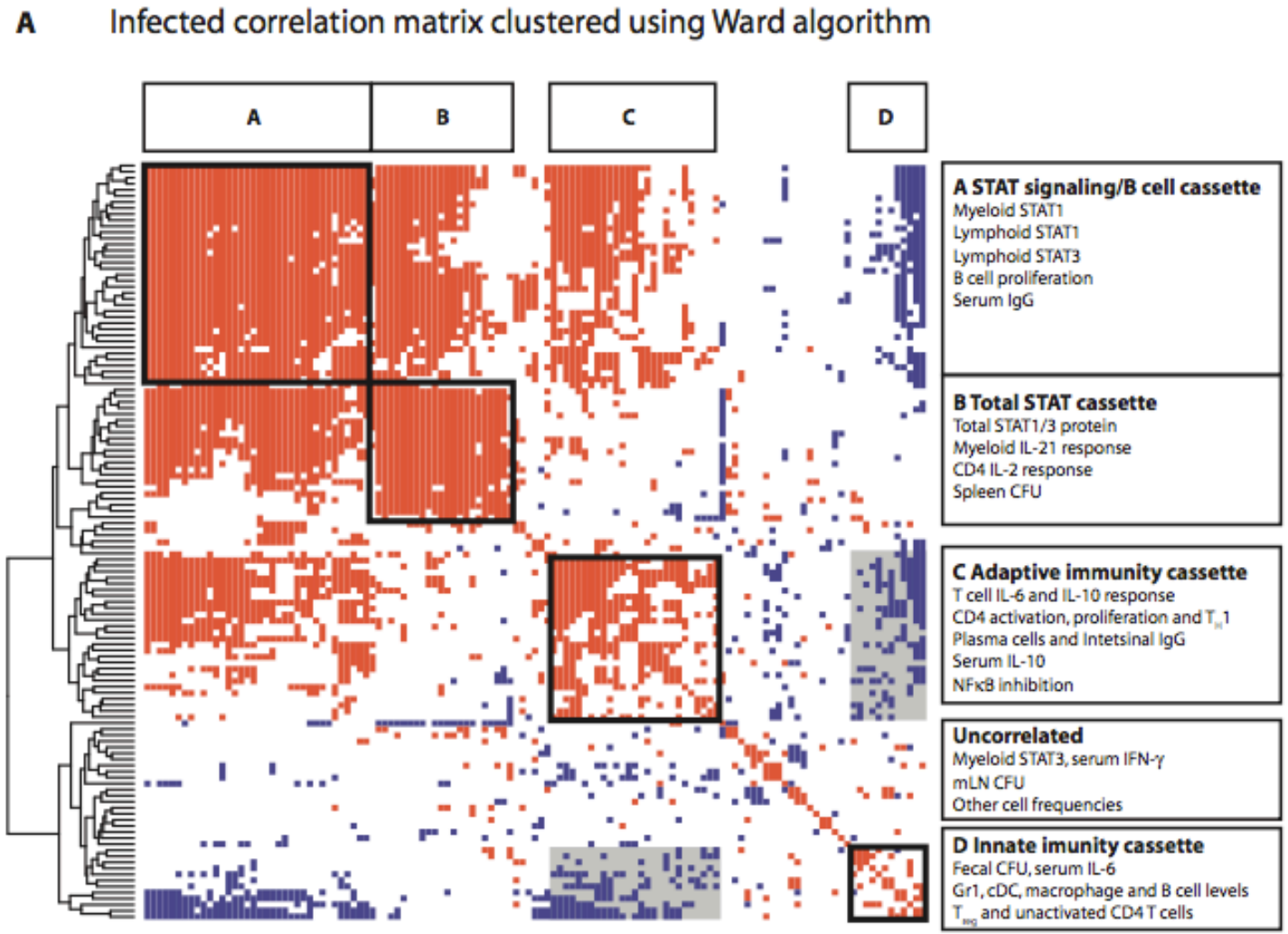
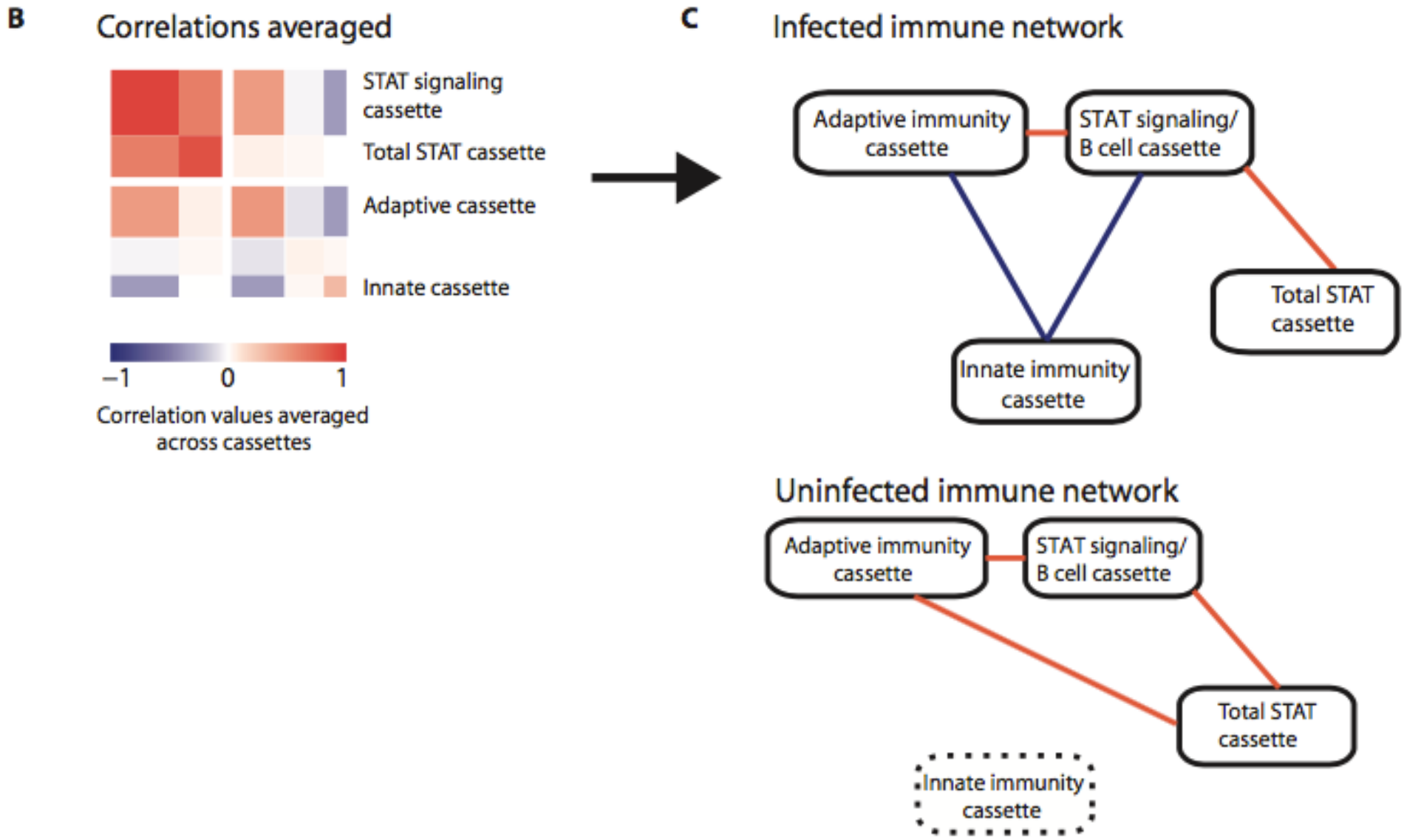


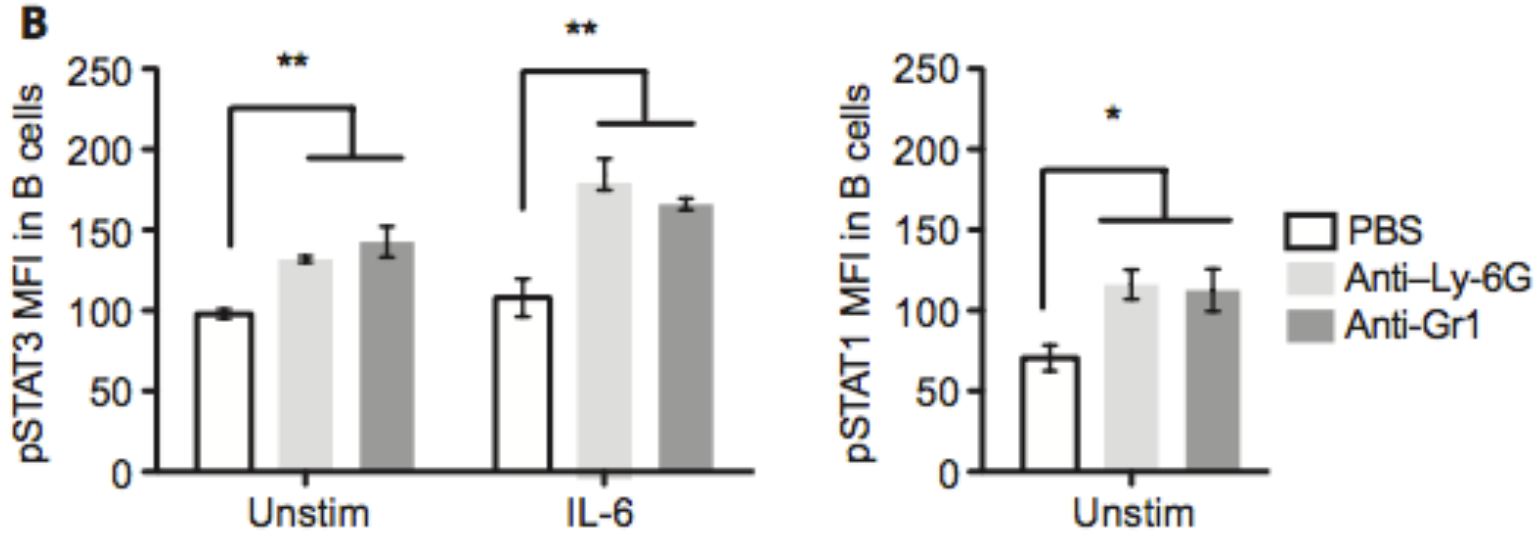
# Immune cell signaling is highly correlated across animals after infection



# These relationships can be simplified into a model that changes during infection



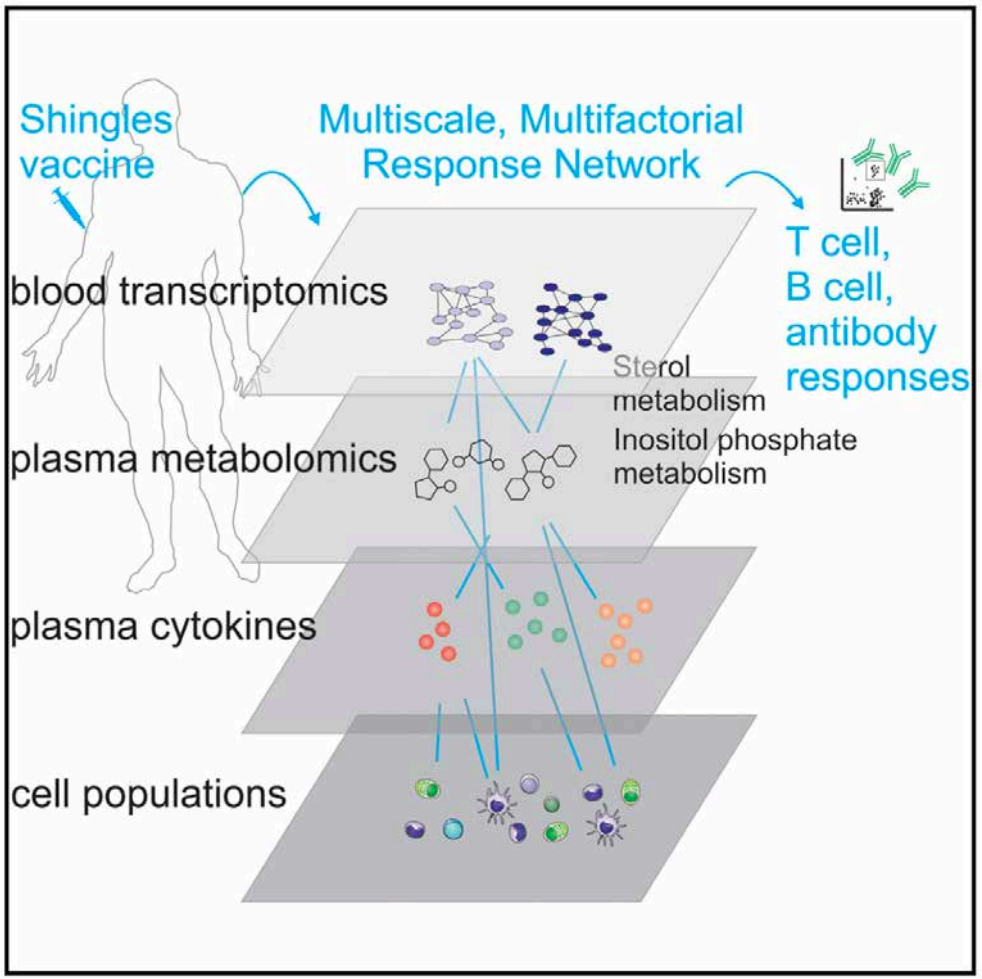
# Depleting neutrophils augments B cell signaling during *Salmonella* infection



# Metabolic Phenotypes of Response to Vaccination in Humans

Cell *169*, 862–877, May 18, 2017

Shuzhao Li,[1,12] Nicole L. Sullivan,[2,12,14] Nadine Rouphael,[1,3] Tianwei Yu,[4] Sophia Banton,[1] Mohan S. Maddur,[2] Megan McCausland,[2] Christopher Chiu,[2] Jennifer Canniff,[5] Sheri Dubey,[6] Ken Liu,[1] ViLinh Tran,[1] Thomas Hagan,[2] Sai Duraisingham,[2] Andreas Wieland,[2] Aneesh K. Mehta,[1] Jennifer A. Whitaker,[1,13] Shankar Subramaniam,[7] Dean P. Jones,[1] Alessandro Sette,[8] Kalpit Vora,[6] Adriana Weinberg,[5] Mark J. Mulligan,[1,3] Helder I. Nakaya,[9,10] Myron Levin,[5] Rafi Ahmed,[2,11] and Bali Pulendran[2,10,15,*]



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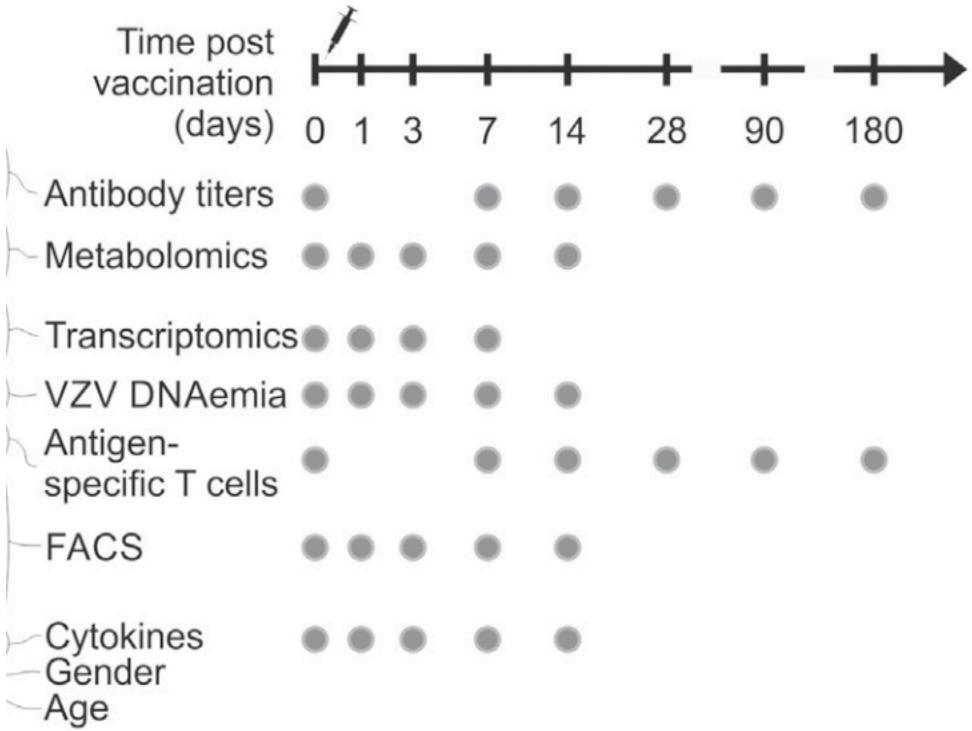
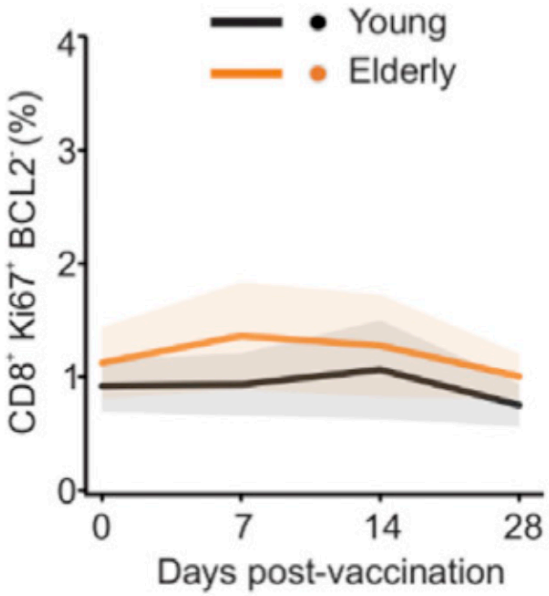
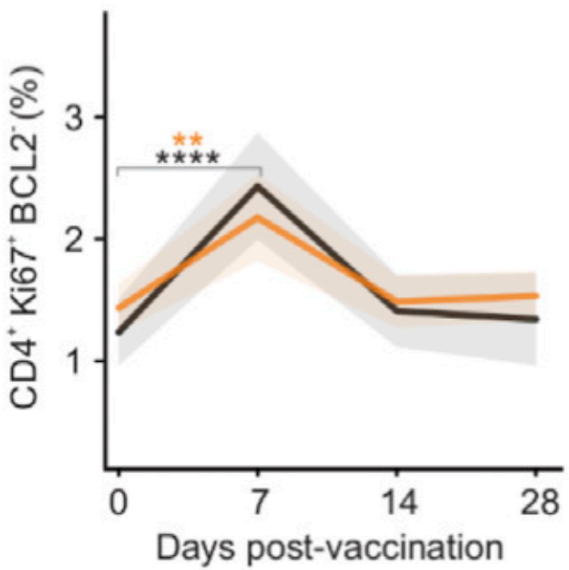
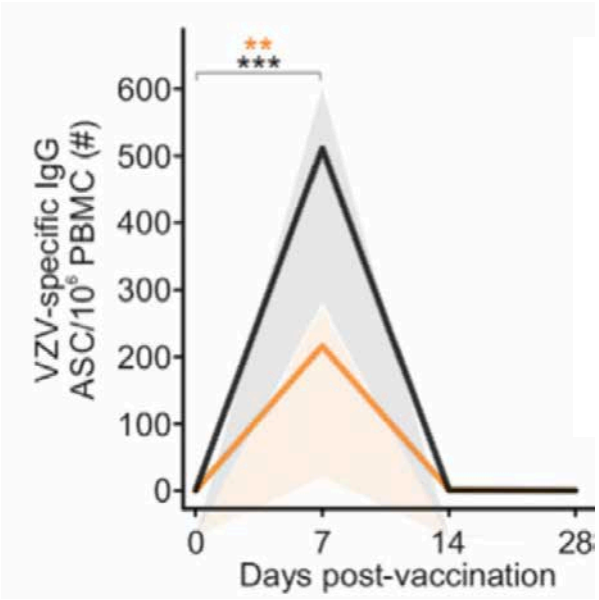


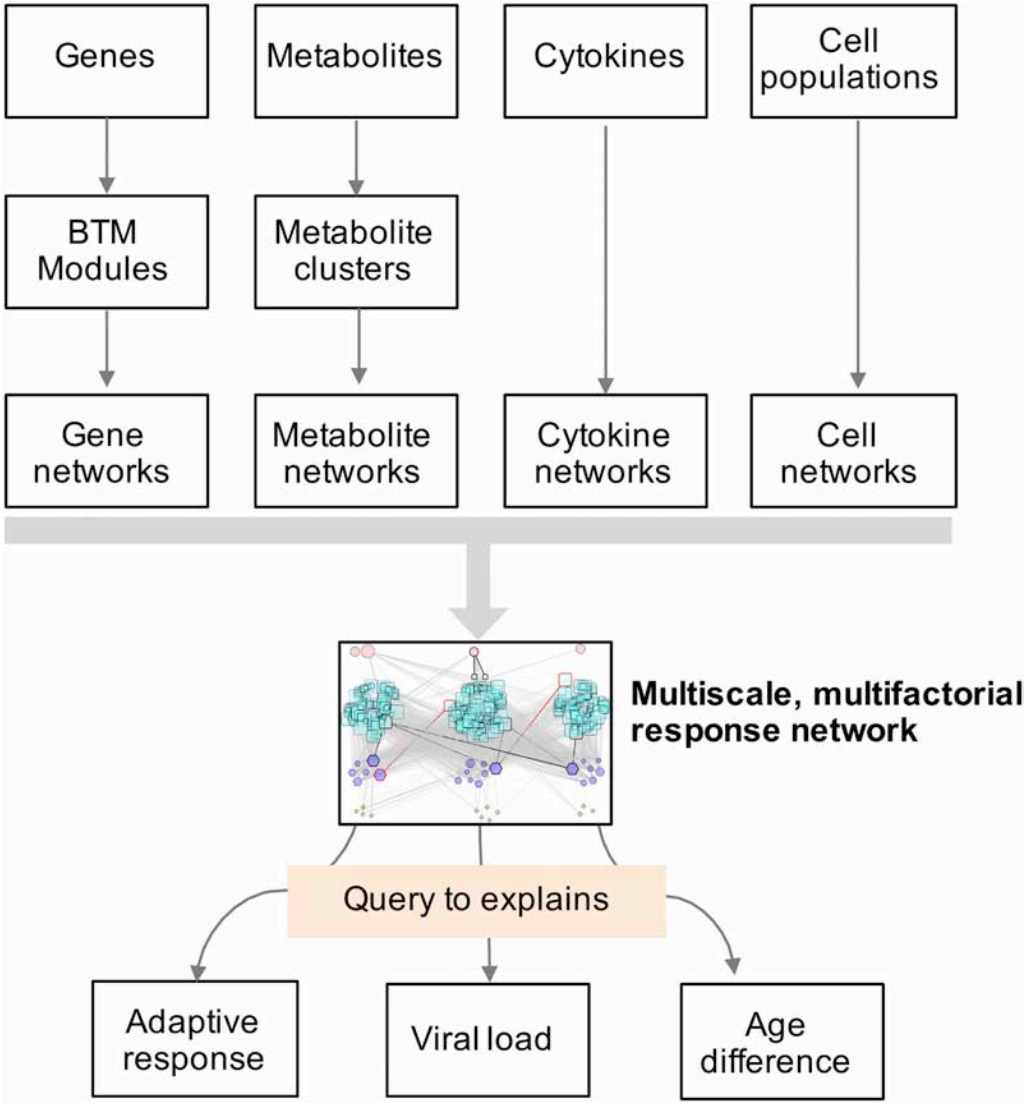
# T cells and B cells become activated after vaccination



# Development of a multiscale model incorporating different data types



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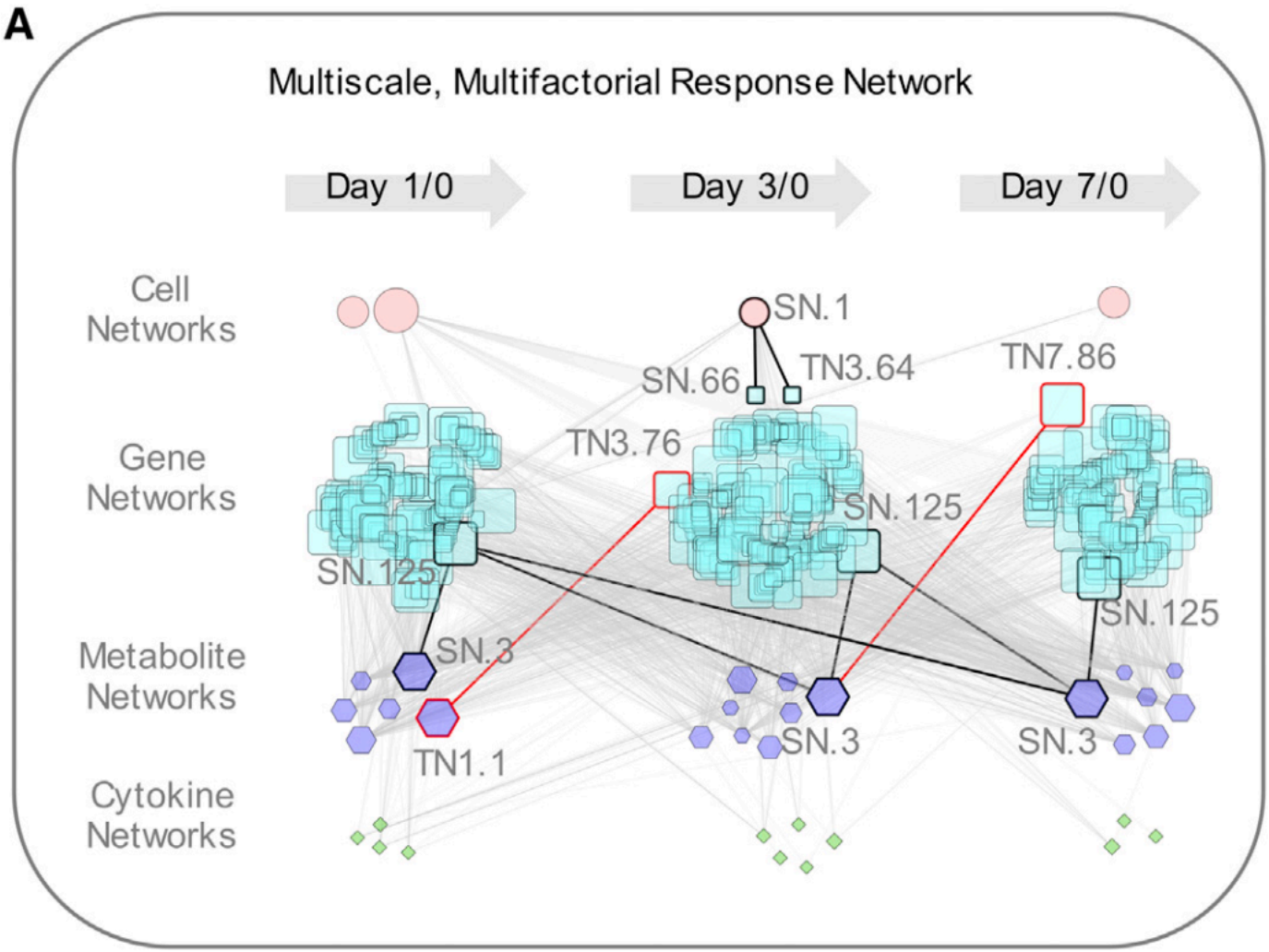
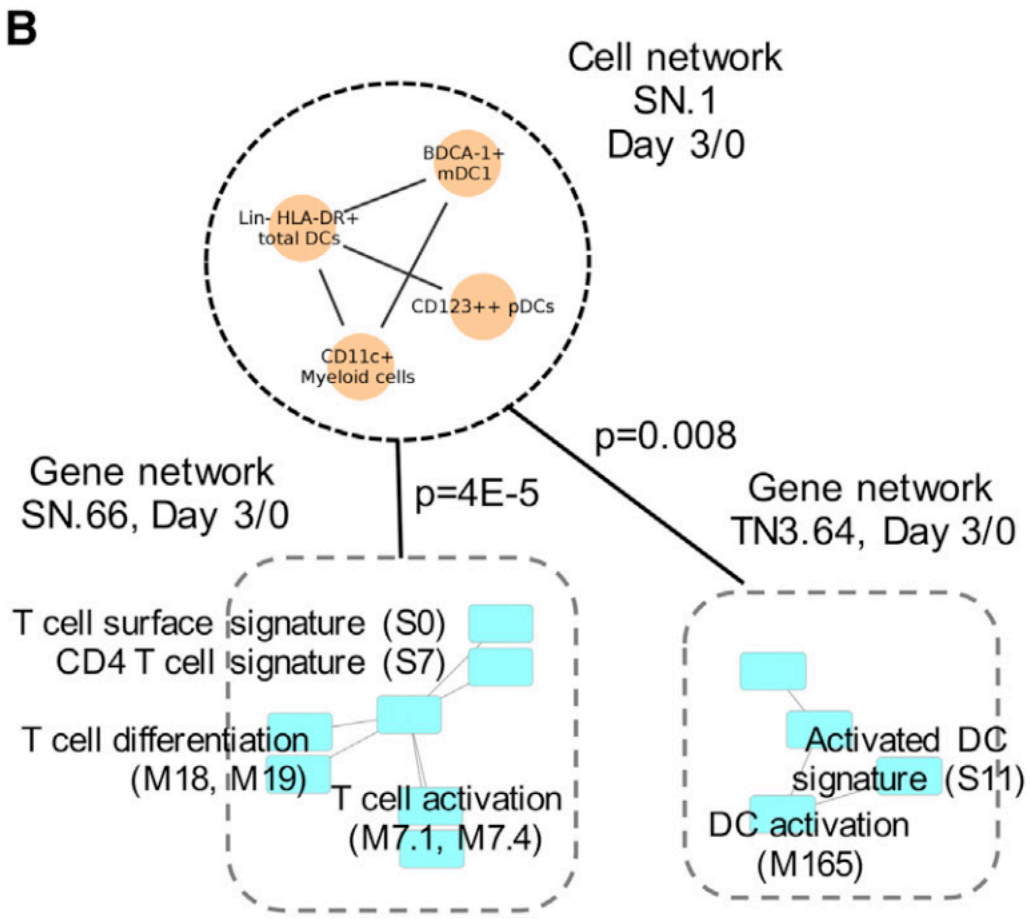
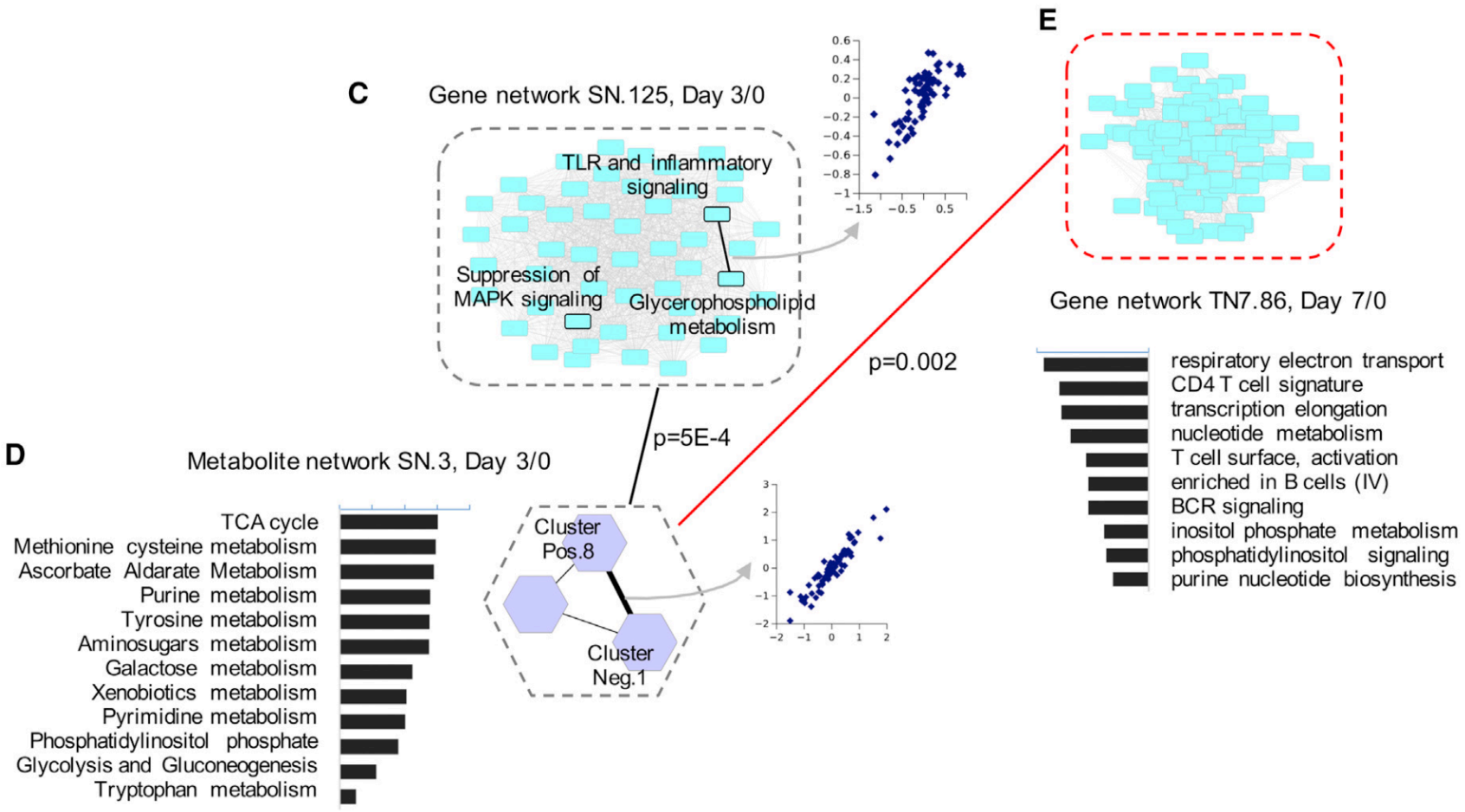


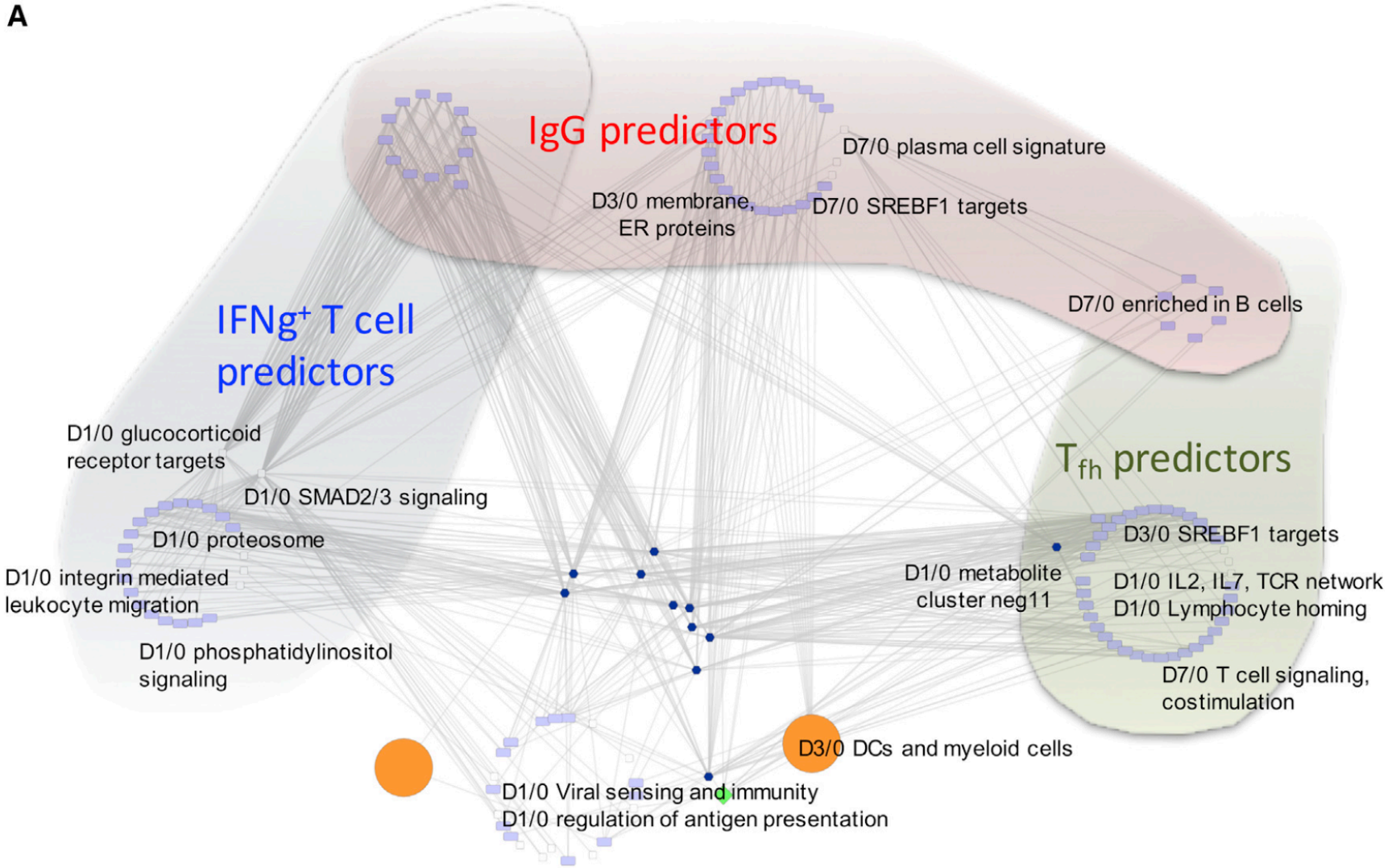
# A DC activation network associates with a T cell activation network



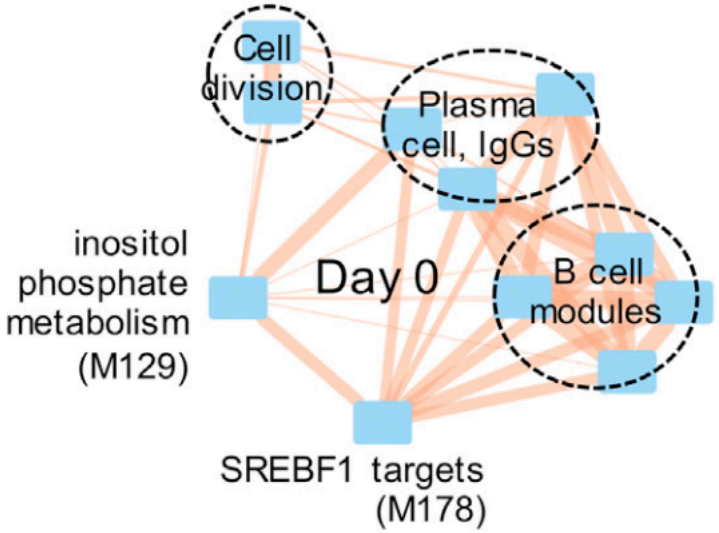
# Associations of TCA, nucleotide and phosphatidylinositol metabolism across data types

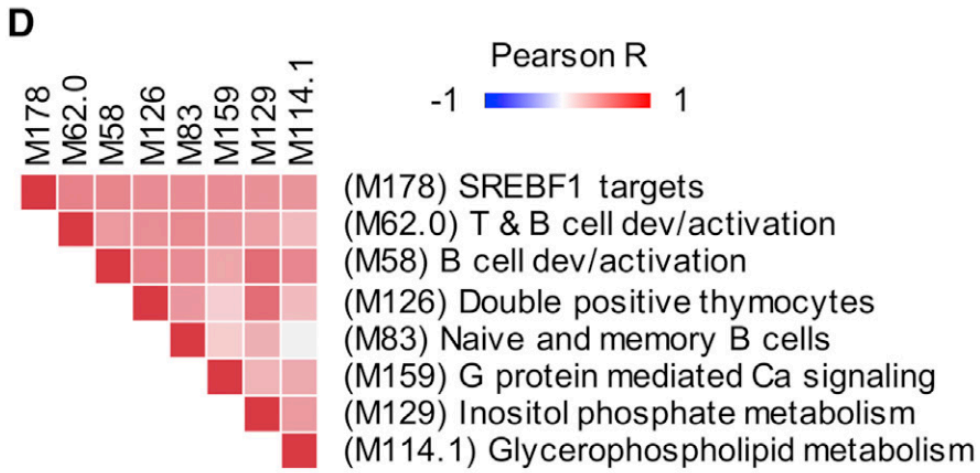


# Predictors of adaptive immune response strength



# Sterol metabolism as a central hub of immune coordination



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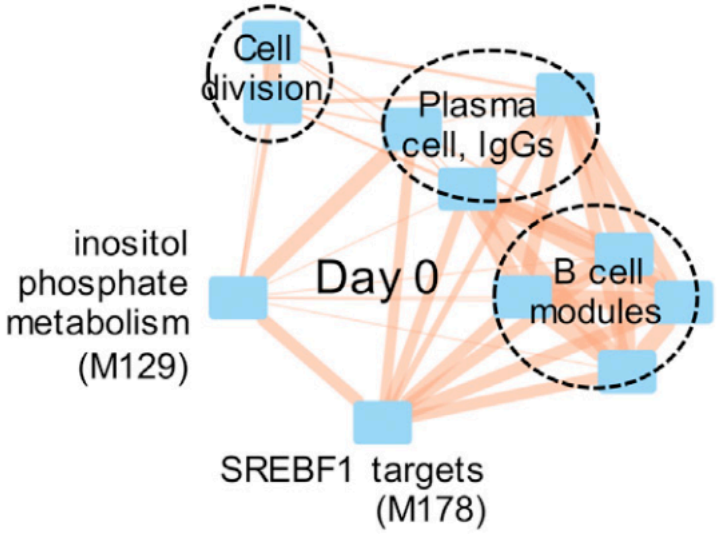
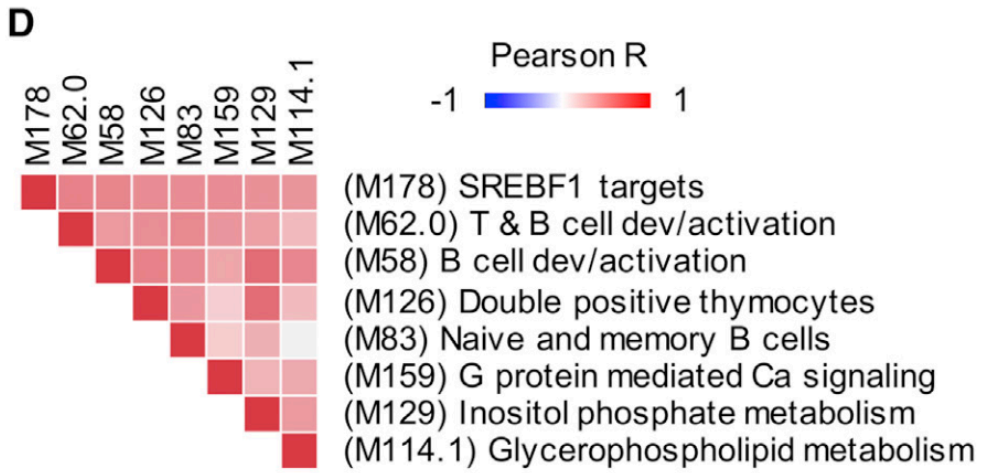
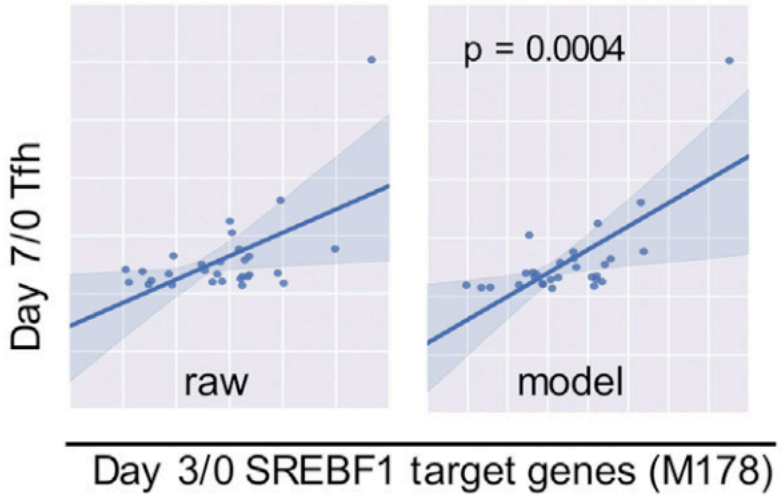
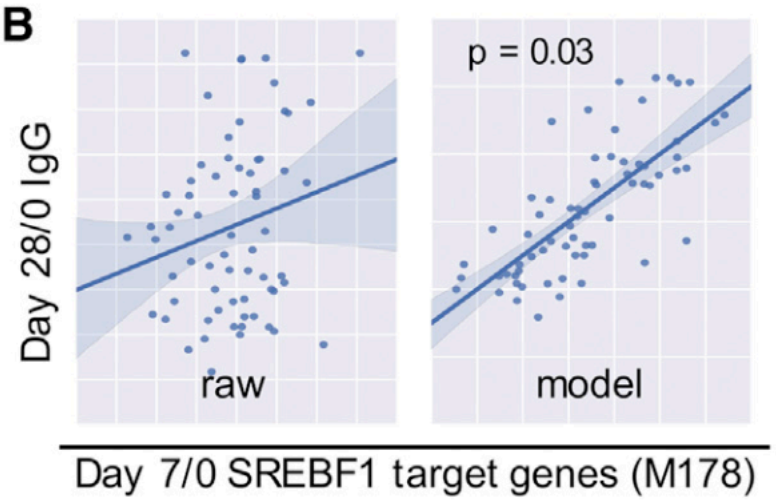
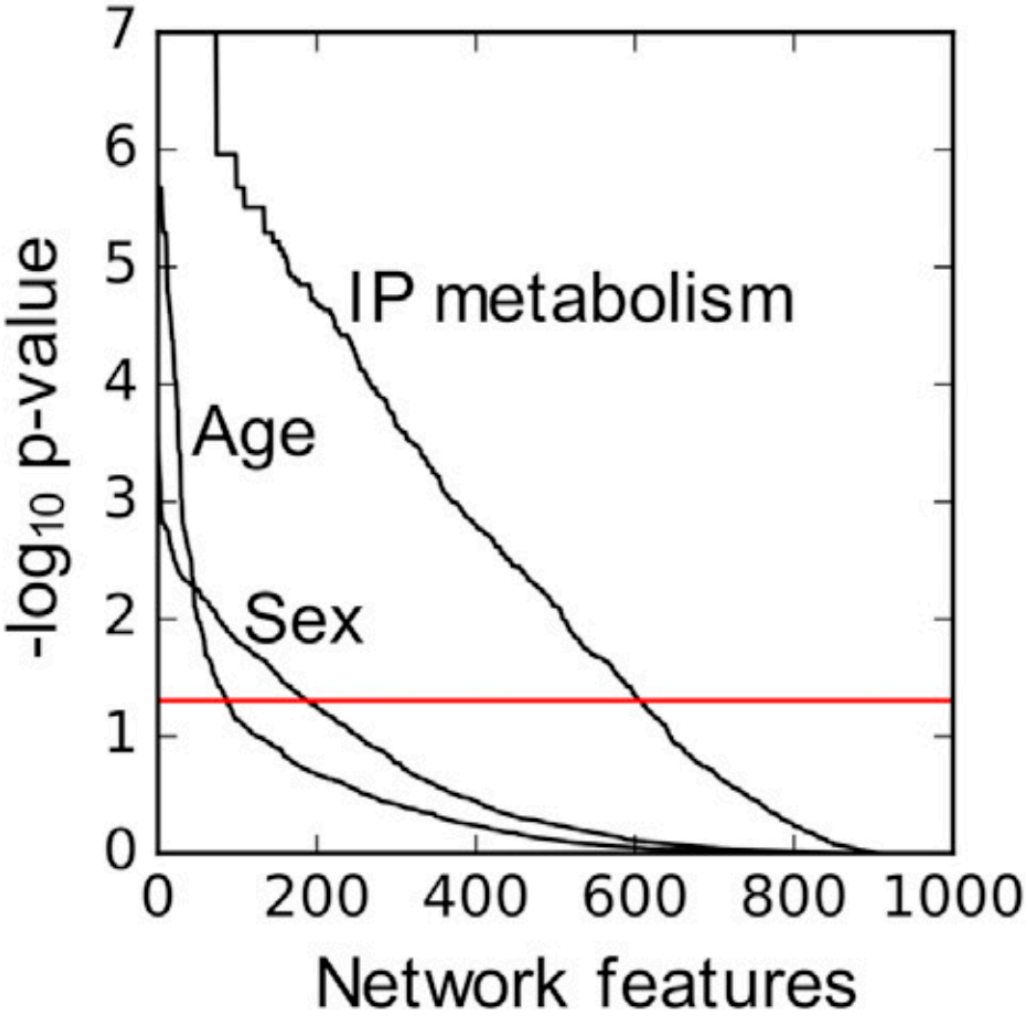


# Inositol phosphate metabolism is highly associated with numerous aspects of the immune response



RESOURCE

nature immunology

JANUARY 2009 NATURE IMMUNOLOGY

# Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans

Troy D Querec[1,8], Rama S Akondy[1,8], Eva K Lee[2], Weiping Cao[1], Helder I Nakaya[1], Dirk Teuwen[3], Ali Pirani[4], Kim Gernert[4], Jiusheng Deng[1], Bruz Marzolf[5], Kathleen Kennedy[5], Haiyan Wu[5], Soumaya Bennouna[1], Herold Oluoch[1], Joseph Miller[1], Ricardo Z Vencio[5], Mark Mulligan[1,6], Alan Aderem[5], Rafi Ahmed[1] & Bali Pulendran[1,7]

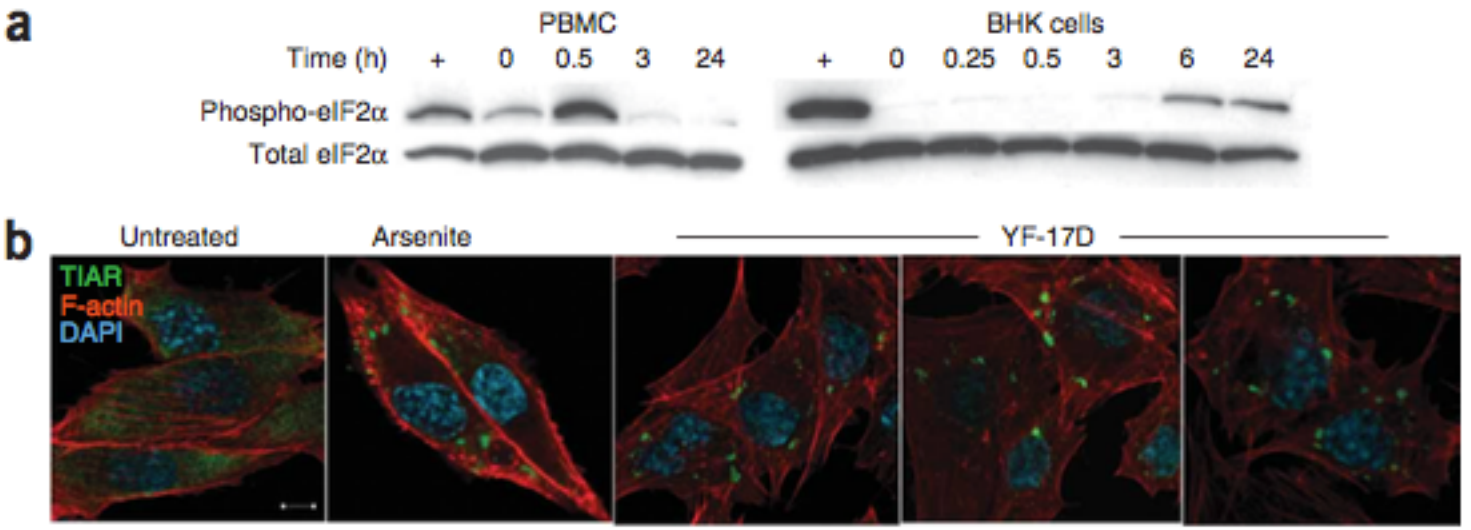
25 healthy humans vaccinated with yellow fever vaccine

Luminex, flow cytometry and gene expression longitudinally

# EIF2AK4 (GCN1), regulator of the integrated stress response, is a strong predictor of CD8 T cell responses

**Table 2 Genomic signatures that predict the magnitude of the CD8$^+$ T cell responses using the DAMIP model**

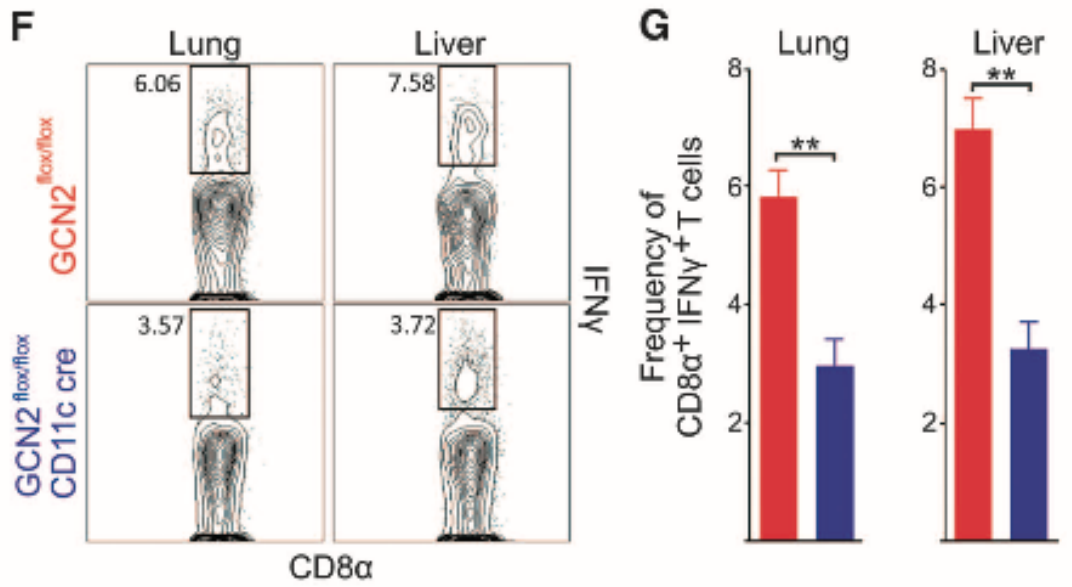
| | | | DAMIP model predictive signatures | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Train on trial 1, test on trial 2 | | | | | | | | Train on trial 2, test on trial 1 | | | | | | | | | | | | | |
| Gene name | Gene symbol | Gene ID | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Solute carrier family 2 (facilitated glucose transporter), member 6 | *SLC2A6* | Hs.244378 Day 7 | X | | X | X | X | X | X | X | X | X | X | | X | | X | | | X | X | X | X | |
| Eukaryotic translation initiation factor 2 alpha kinase 4 | *EIF2AK4* | Hs.412102 Day 7 | X | X | X | | X | | X | X | | | | | | | | X | | X | | | | X |



# Vaccine Activation of the Nutrient Sensor GCN2 in Dendritic Cells Enhances Antigen Presentation

Rajesh Ravindran,[1]* Nooruddin Khan,[1,2]* Helder I. Nakaya,[1,3] Shuzhao Li,[1] Jens Loebbermann,[1] Mohan S. Maddur,[1] Youngja Park,[4] Dean P. Jones,[5] Pascal Chappert,[6,7] Jean Davoust,[6,7] David S. Weiss,[8] Herbert W. Virgin,[9] David Ron,[10] Bali Pulendran[1,3]†

SCIENCE VOL 343 17 JANUARY 2014

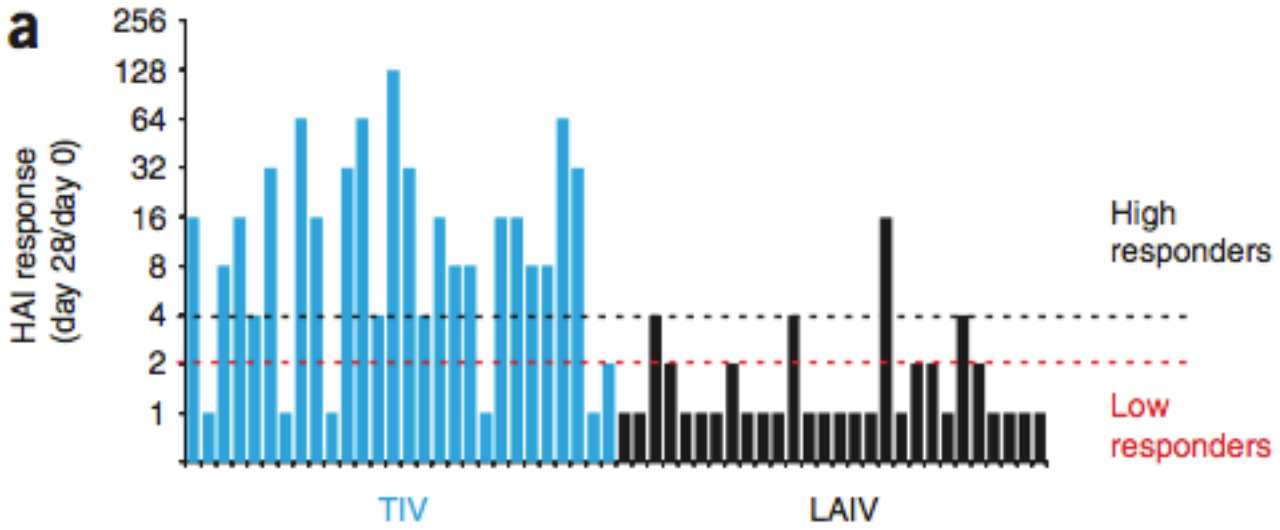



GCN2 regulates autophagy in DC, which promotes cross-presentation to CD8 T cells.

# Systems biology of vaccination for seasonal influenza in humans

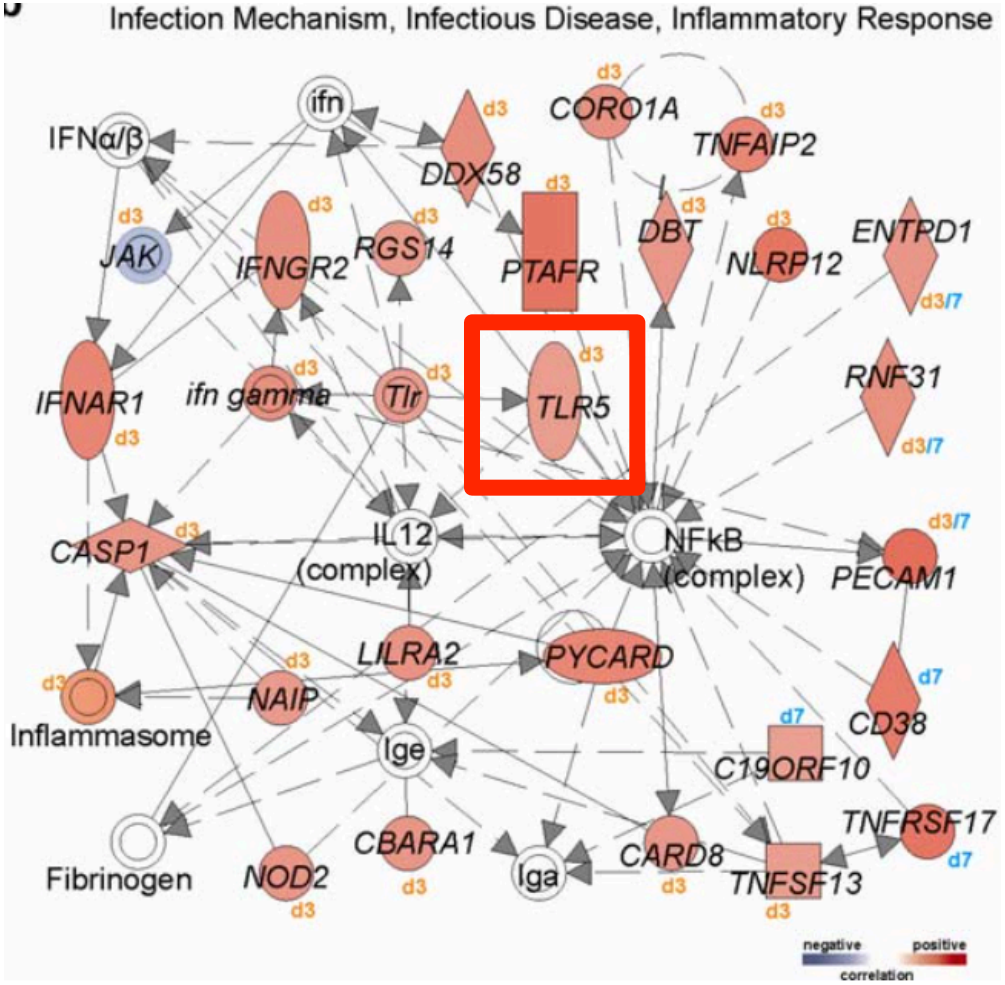
Helder I Nakaya[1,2], Jens Wrammert[1,3], Eva K Lee[4], Luigi Racioppi[5,6], Stephanie Marie-Kunze[1,2], W Nicholas Haining[7], Anthony R Means[6], Sudhir P Kasturi[1,2], Nooruddin Khan[1,2], Gui-Mei Li[1,3], Megan McCausland[1,3], Vibhu Kanchan[1,3], Kenneth E Kokko[8], Shuzhao Li[1,2], Rivka Elbein[9], Aneesh K Mehta[9], Alan Aderem[10], Kanta Subbarao[11], Rafi Ahmed[1,3] & Bali Pulendran[1,2,12]

VOLUME 12 NUMBER 8 AUGUST 2011 NATURE IMMUNOLOGY




Healthy individuals vaccinated with trivalent inactivated or live-attenuated influenza vaccine

# TLR5 induction is correlate with strong responses to the vaccine



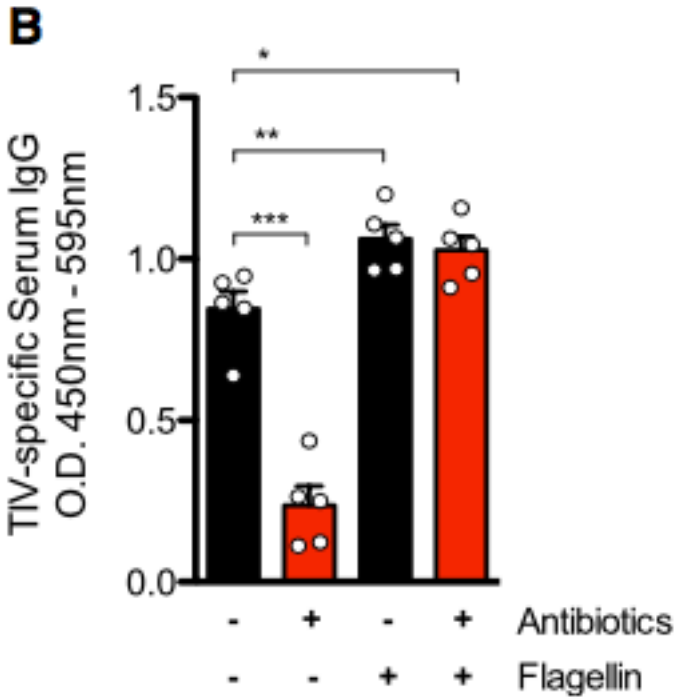
CellPress

Immunity
Article

Immunity *41*, 478–492, September 18, 2014 ©2014

# TLR5-Mediated Sensing of Gut Microbiota Is Necessary for Antibody Responses to Seasonal Influenza Vaccination

Jason Z. Oh,[1,2] Rajesh Ravindran,[1,2] Benoit Chassaing,[4] Frederic A. Carvalho,[4,5] Mohan S. Maddur,[1,2] Maureen Bower,[6] Paul Hakimpour,[2] Kiran P. Gill,[1,2] Helder I. Nakaya,[3,7] Felix Yarovinsky,[8] R. Balfour Sartor,[6] Andrew T. Gewirtz,[4] and Bali Pulendran[1,2,3,*]



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Not Adjuvanted

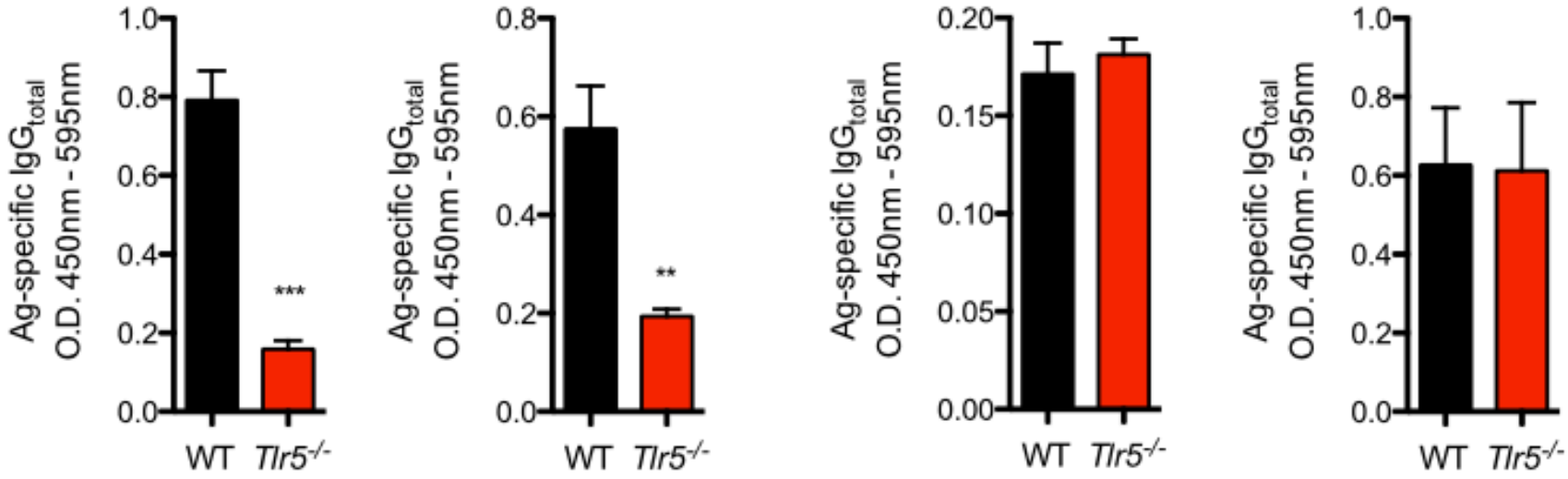
Adjuvanted

TIV

IPOL

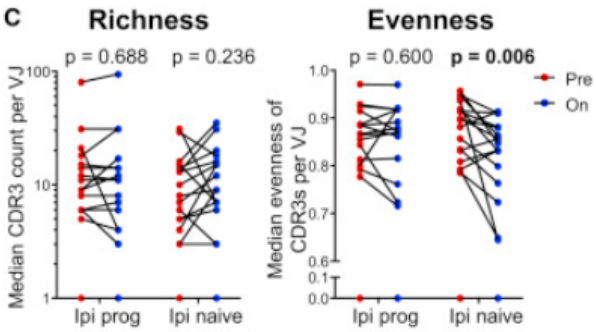
Recombivax HB (+Alum)

YF-17D



# Additional Topics of Current Interest

- Single-cell genomics
- T and B cell repertoire analysis
- MHC (neo)epitope prediction
- Deconvolution of gene expression data
- Mining public datasets




Riaz et al., *Cell*, 2017

xCell
Cell types enrichment analysis

CIBERSORT

# Challenges with Systems Immunology

- Large data sets require (a) simplification or (b) lots of time
- Integrative models of immune function don't exist (yet…)
- Complexity is exciting but intellectually daunting
- Some observations are difficult to study mechanistically
- New technologies may not have a "gold standard" for comparison or analysis
- New experimental designs or data combinations often require new analytical strategies

# Questions?

Email: Matthew.Spitzer@ucsf.edu

UCSF
University of California
San Francisco