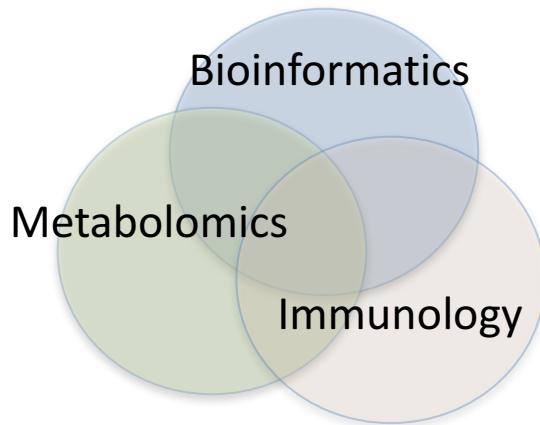
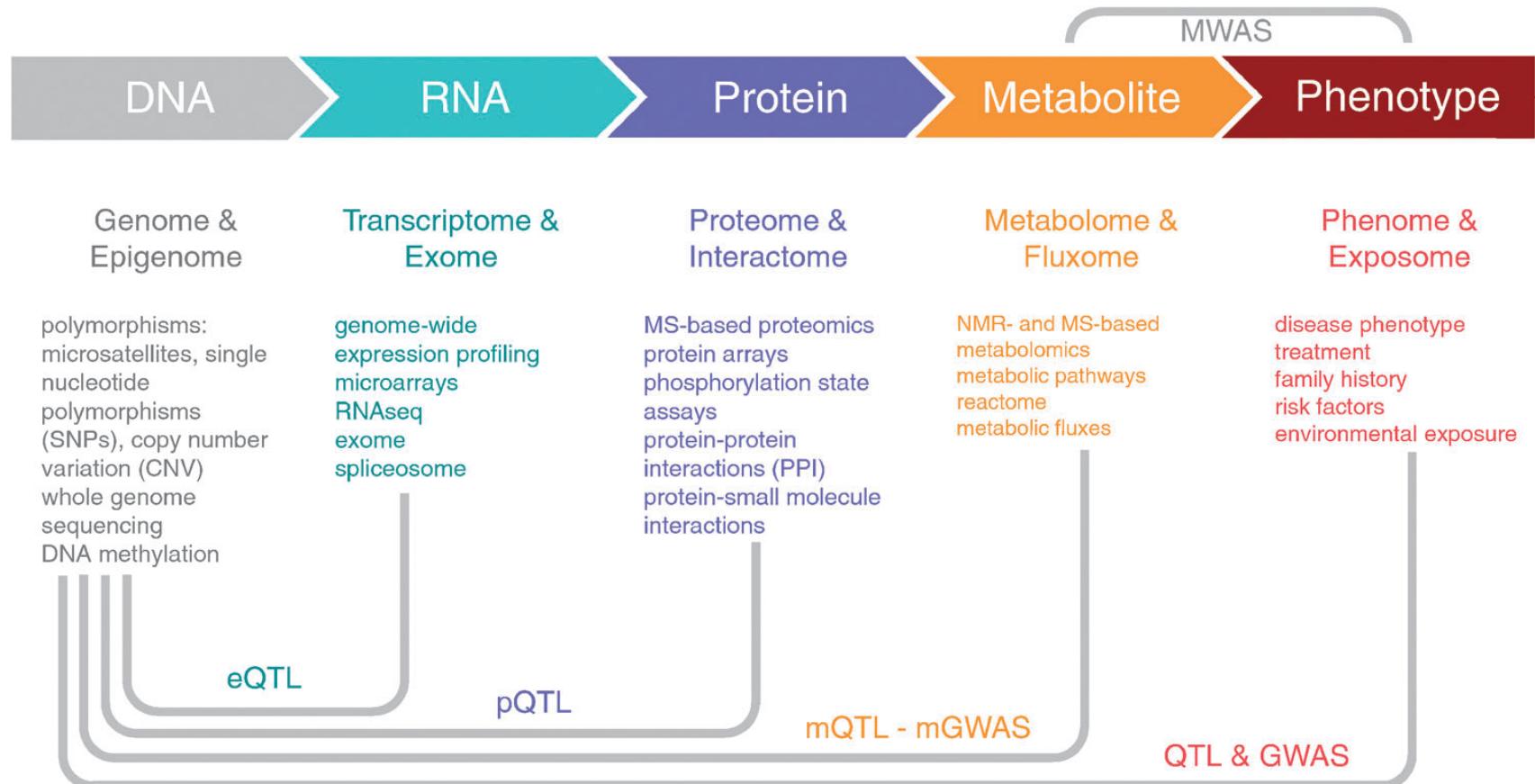


Metabolomics and systems biology integration



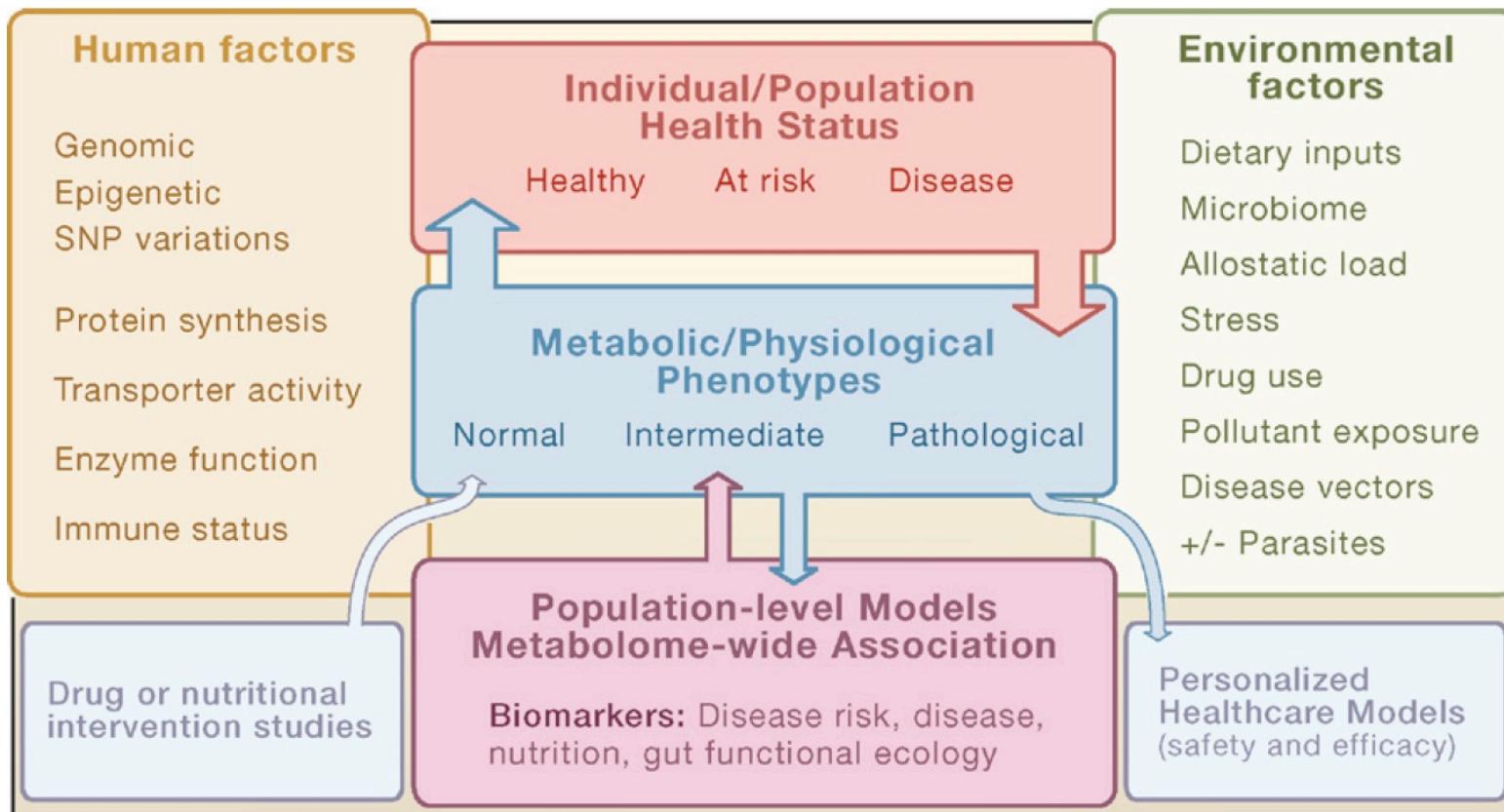
Shuzhao Li, Ph.D
Assistant Professor
Department of Medicine
Emory University
August 30, 2019

Biomedical -omics data

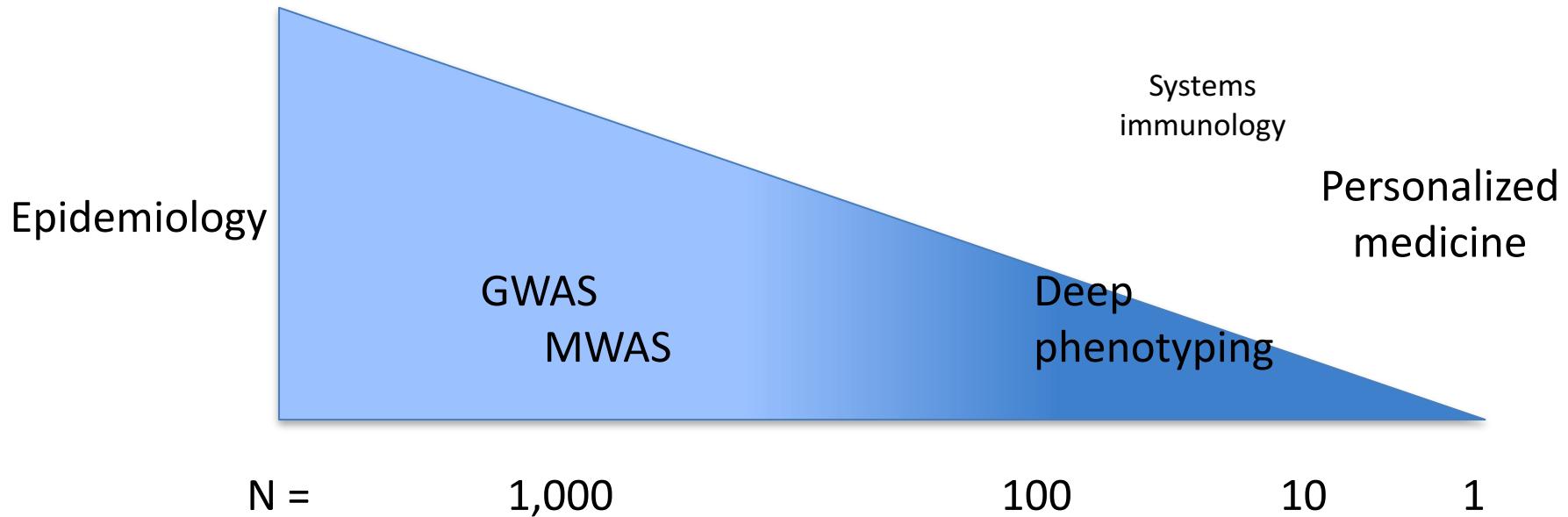


Modeling systems medicine

Holmes, Wilson, Nicholson (2008). Cell 134:714



The “N” in systems medicine



Challenges in data integration

- High-dimensional data, redundancy vs specificity
- Different variance structure from different technologies
- Systemic measurement vs localized biology
- Interpretation, connecting prior knowledge

Multi-omics integration

□ Knowledge/model driven

- Proteins and genes can be linked to metabolites via enzymatic reactions
- Multiple data types can be overlaid to same pathways, given prior pathway definition
- Prior knowledge can be coded into network statistics and topology
- MWAS still in early days

□ Data driven

- Statistical association via CCA, PLS, etc
- Evidence propagation in various forms
- Machine learning and artificial intelligence

❑ Knowledge/model driven

XCMS Online overlaps multiomics data to the same pathways

nature methods

Techniques for life scientists and chemists

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home ▶ current issue ▶ correspondence ▶ abstract

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NATURE METHODS | CORRESPONDENCE

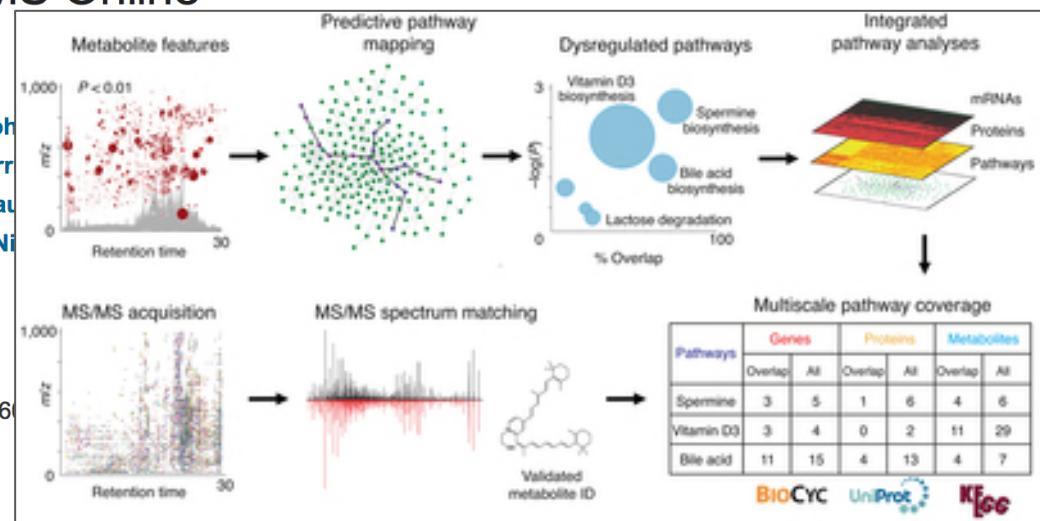


Systems biology guided by XCMS Online metabolomics

Tao Huan, Erica M Forsberg, Duane Rinehart, Caroline H John Benton, Mingliang Fang, Aries Aisporna, Brian Hilmers, Farr Michael W W Adams, Gregory Krantz, Matthew W Fields, Paul Niedernhofer, Trey Ideker, Erica L Majumder, Judy D Wall, Nicholas Goodacre, Luke L Lairson & Gary Siuzdak

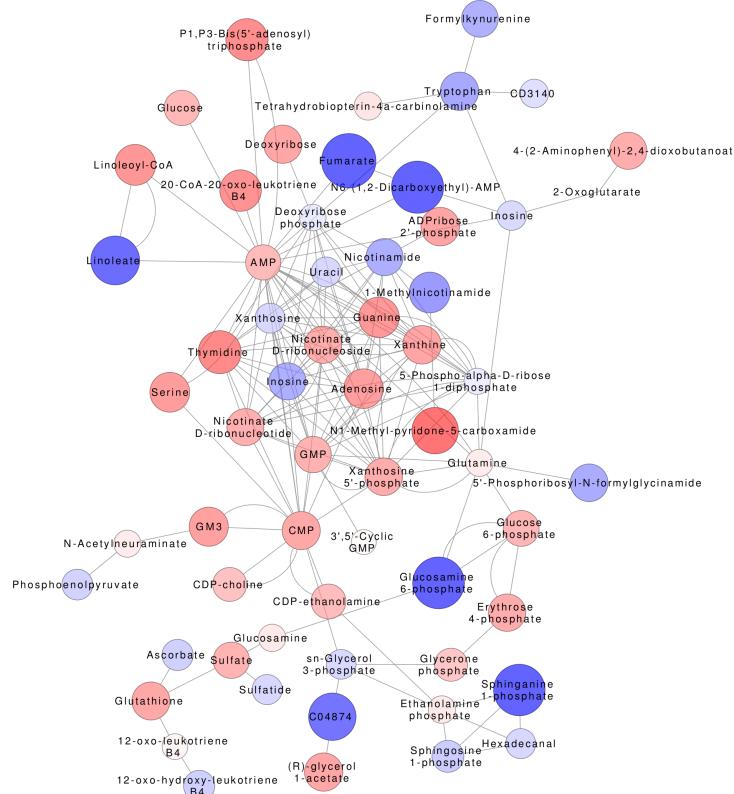
[Affiliations](#) | [Corresponding author](#)

Nature Methods 14, 461–462 (2017) | doi:10.1038/nmeth.4260
Published online 27 April 2017

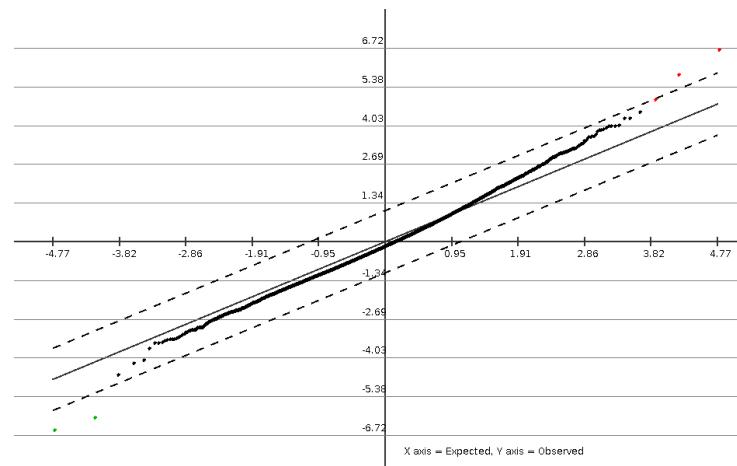


Autophagy is essential for effector CD8⁺ T cell survival and memory formation

Xiaojin Xu^{1,5}, Koichi Araki^{1,5}, Shuzhao Li², Jin-Hwan Han¹, Lilin Ye¹, Wendy G Tan¹, Bogumila T Konieczny¹, Monique W Bruinsma³, Jennifer Martinez⁴, Erika L Pearce³, Douglas R Green⁴, Dean P Jones², Herbert W Virgin³ & Rafi Ahmed¹

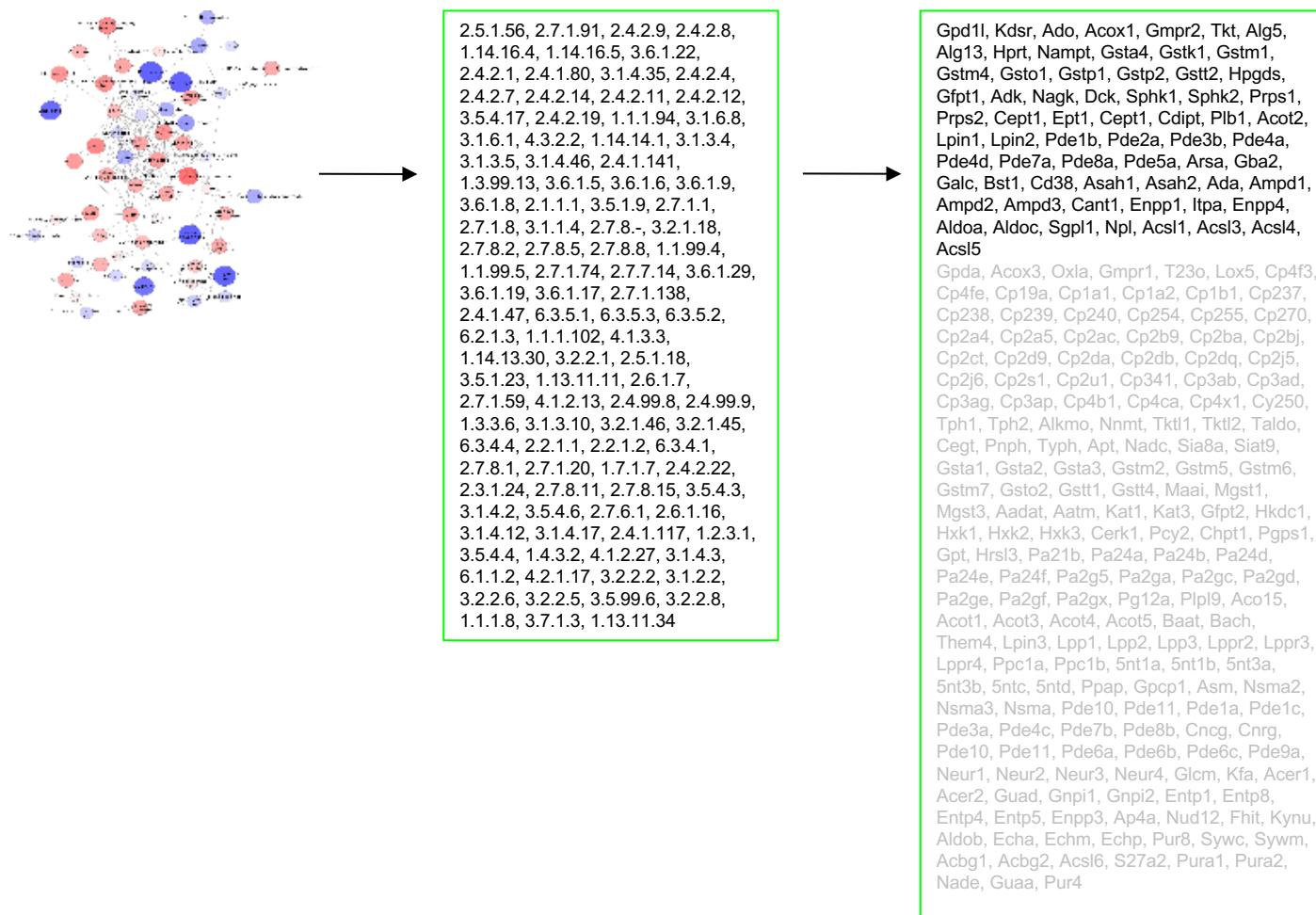


metabolomics

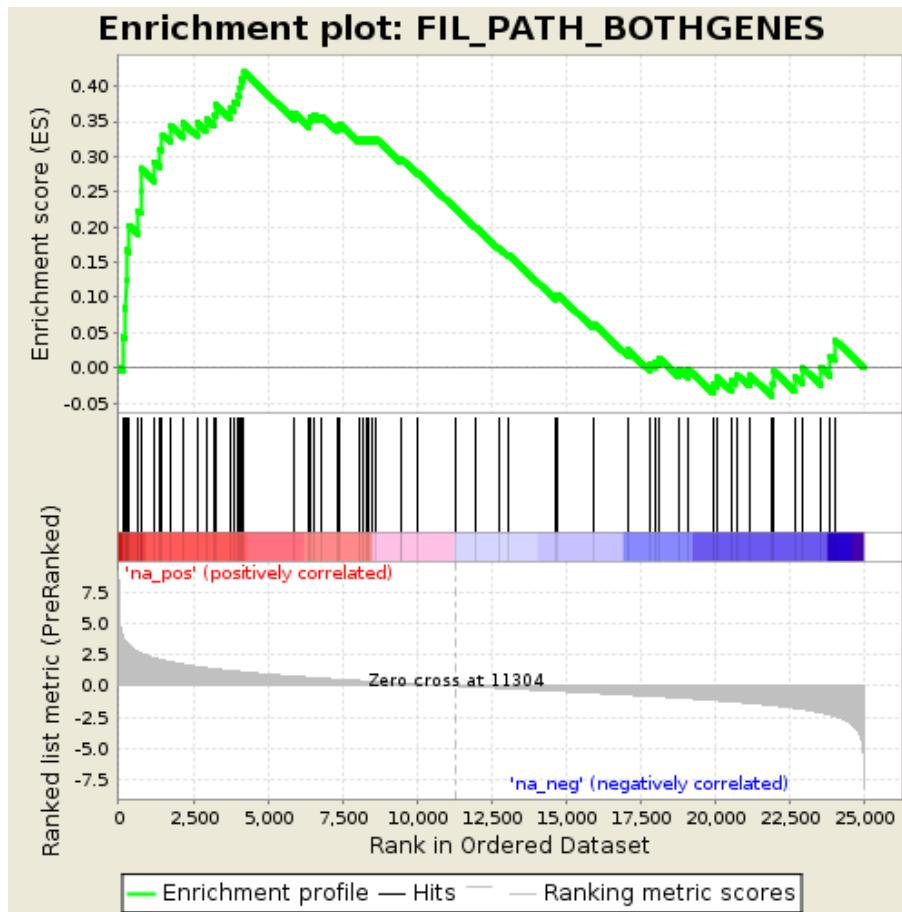


transcriptomics

Enzymes associated with significant metabolites



Enzyme genes significantly enriched towards KO



Expression of genes corresponding to related enzymes are enriched for KO cells, DNA microarray data, GSEA (Gene Set Enrichment Analysis). Nominal p = 0, FWER p = 0.024.

❑ Data driven

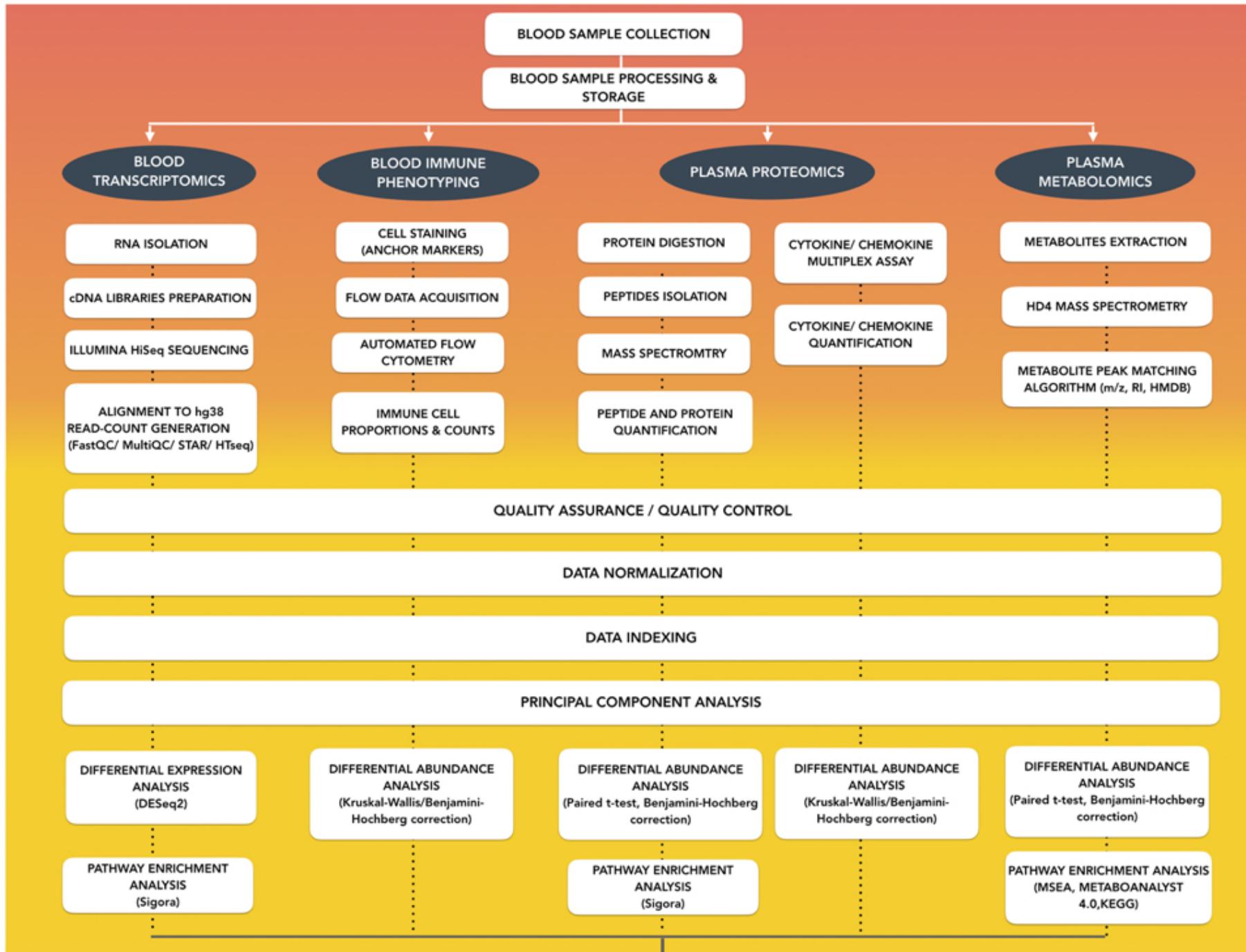
ARTICLE

<https://doi.org/10.1038/s41467-019-108794-x>

OPEN

Dynamic molecular changes during the first week of human life follow a robust developmental trajectory

Amy H. Lee¹, Casey P. Shannon¹, Nelly Amenyogbe^{3,25}, Tue B. Bennike^{4,5,6}, Joann Diray-Arce^{5,6}, Olubukola T. Idoko^{7,8}, Erin E. Gill¹, Rym Ben-Othman⁹, William S. Pomat¹⁰, Simon D. van Haren^{5,6}, Kim-Anh Lê Cao¹¹, Momoudou Cox⁷, Alansana Darboe¹², Reza Falsafi¹, Davide Ferrari¹¹, Daniel J. Harbeson³, Daniel He¹², Cai Bing⁹, Samuel J. Hinshaw^{1,12}, Jorjoh Ndure⁷, Jainaba Njie-Jobe⁷, Matthew A. Pettengill⁵, Peter C. Richmond^{13,14}, Rebecca Ford¹⁰, Gerard Saleu¹⁰, Geraldine Masiria¹⁰, John Paul Matlam¹⁰, Wendy Kirarock¹⁰, Elishia Roberts⁷, Mehrnoush Malek¹⁵, Guzmán Sanchez-Schmitz^{5,6}, Amrit Singh¹⁶, Asimenia Angelidou^{5,6,17}, Kinga K. Smolen^{5,6}, The EPIC Consortium[#], Ryan R. Brinkman^{15,18}, Al Ozonoff^{5,6,19}, Robert E.W. Hancock¹, Anita H.J. van den Biggelaar¹⁴, Hanno Steen^{4,5,7}, Scott J. Tebbutt^{2,20,21}, Beate Kampmann^{7,22}, Ofer Levy^{5,6,23} & Tobias R. Kollmann¹ 3,9,25



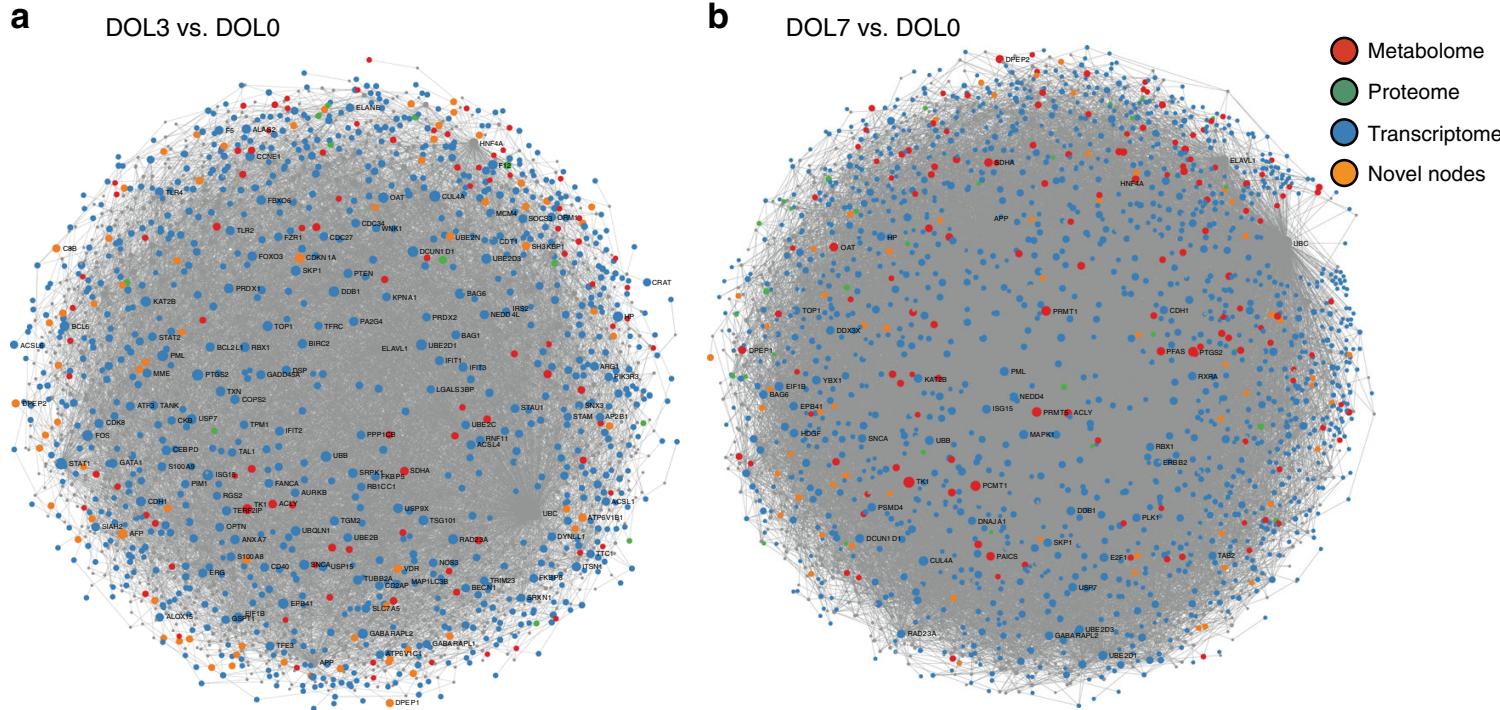
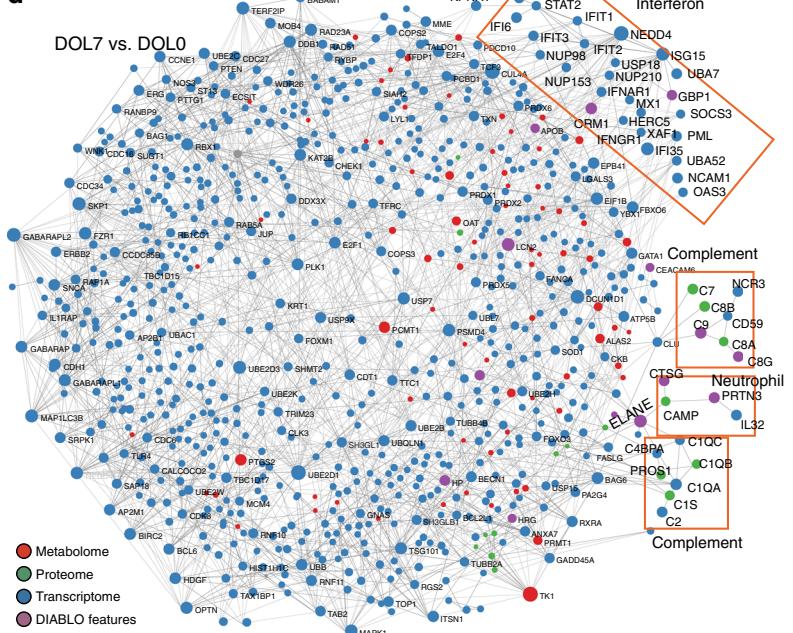
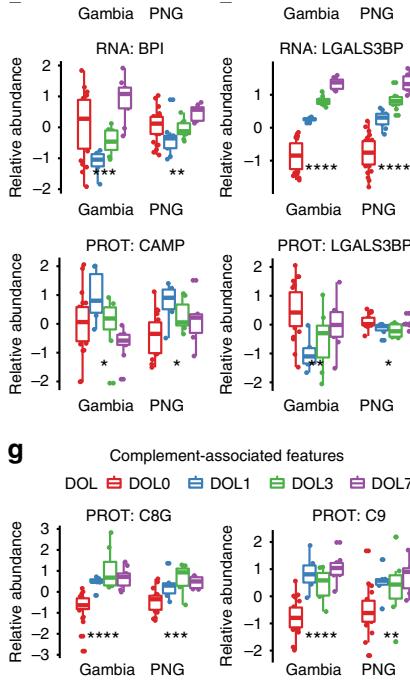
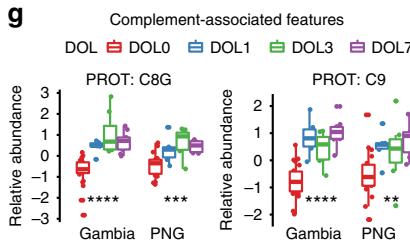
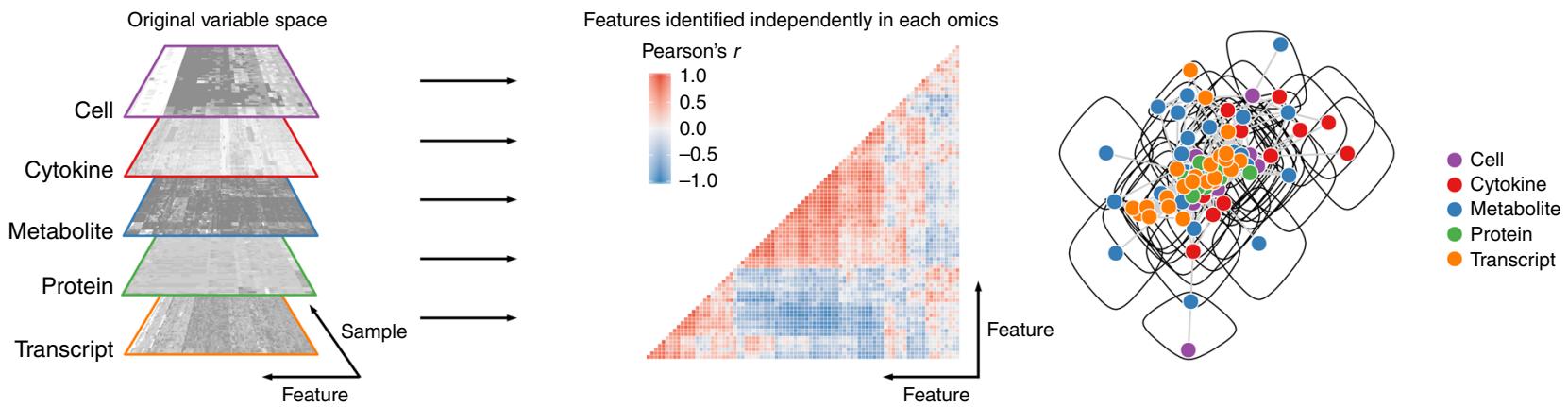


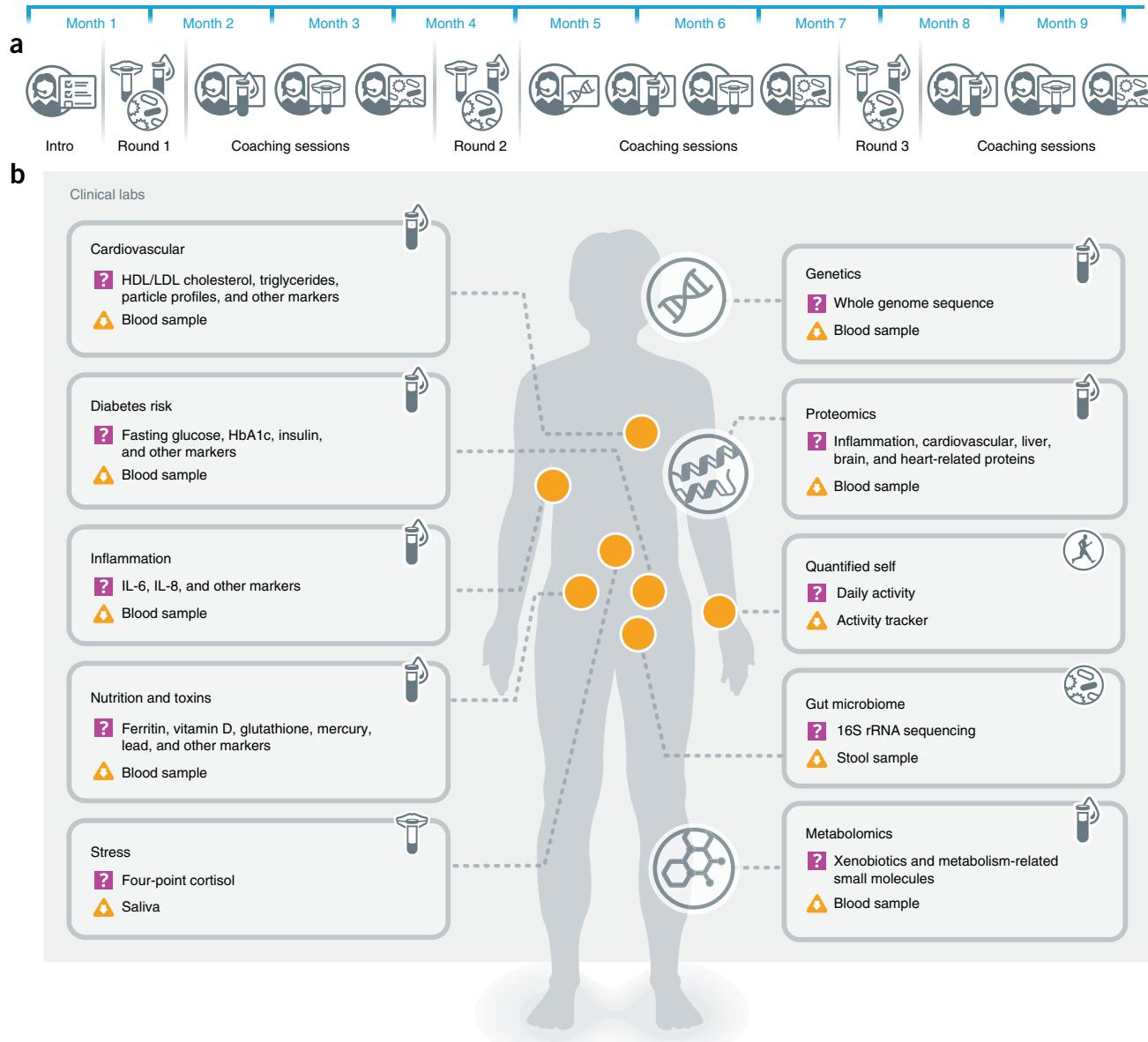
Fig. 4 Integration of multiple data types via NetworkAnalyst molecular interaction networks provided novel biological insights. Minimum-connected networks for DOL3 vs. DOL0 (**a**) and DOL7 vs. DOL0 (**b**), respectively, containing all three individual data types, where nodes derived from the transcriptome are shown in blue, nodes from the metabolome in red, and nodes from the proteome in green. Novel nodes, which are nodes that only appeared after integrating the three data types but are not present in the individual minimum network, are shown in orange. DOL: day of life

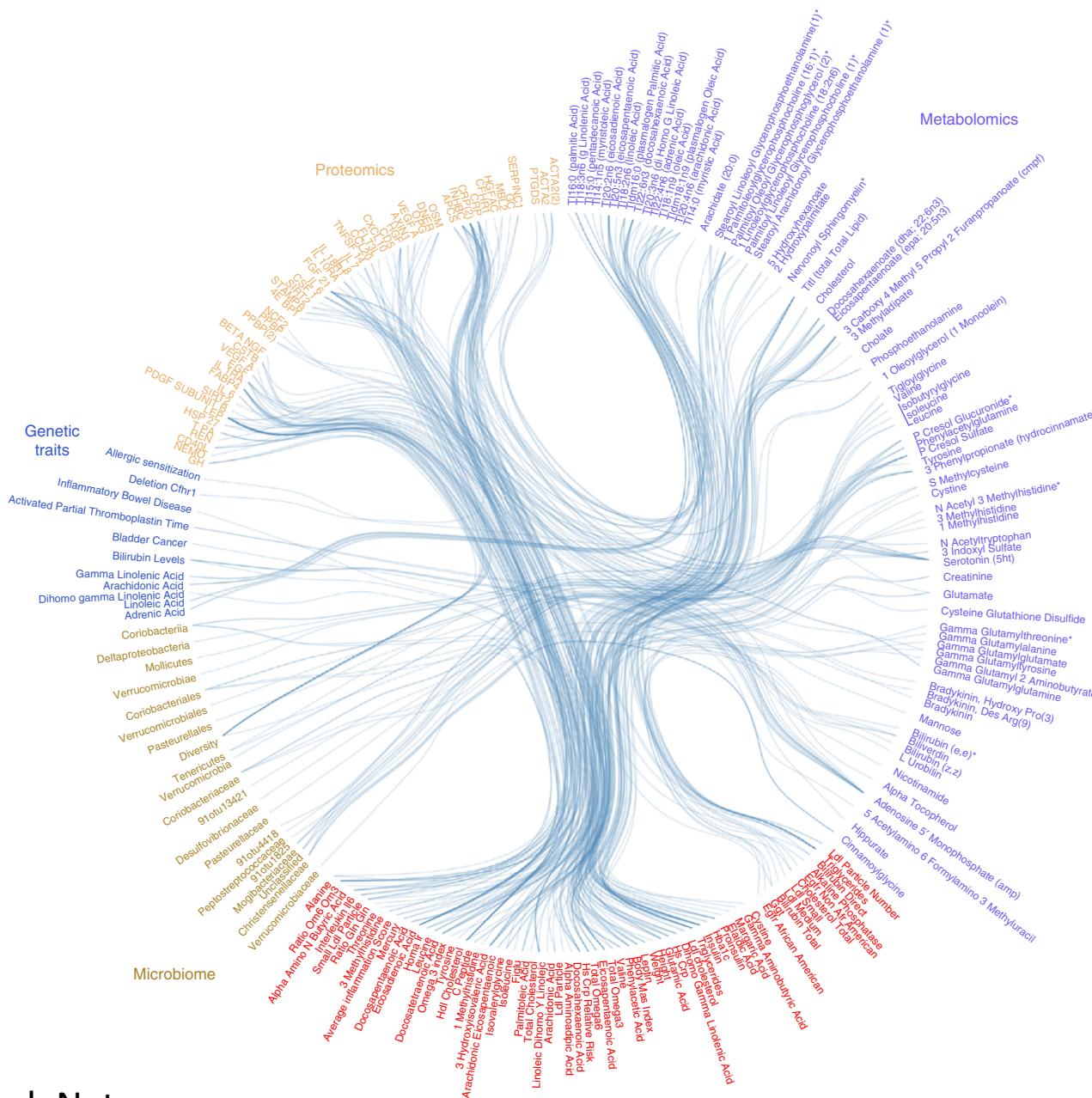
d**e****f**

a**b**

Price et al. Nature Biotechnology 35, pages 747–756 (2017)

A wellness study of 108 individuals using personal, dense, dynamic data clouds





Price et al. Nature Biotechnology 35, pages 747–756 (2017)

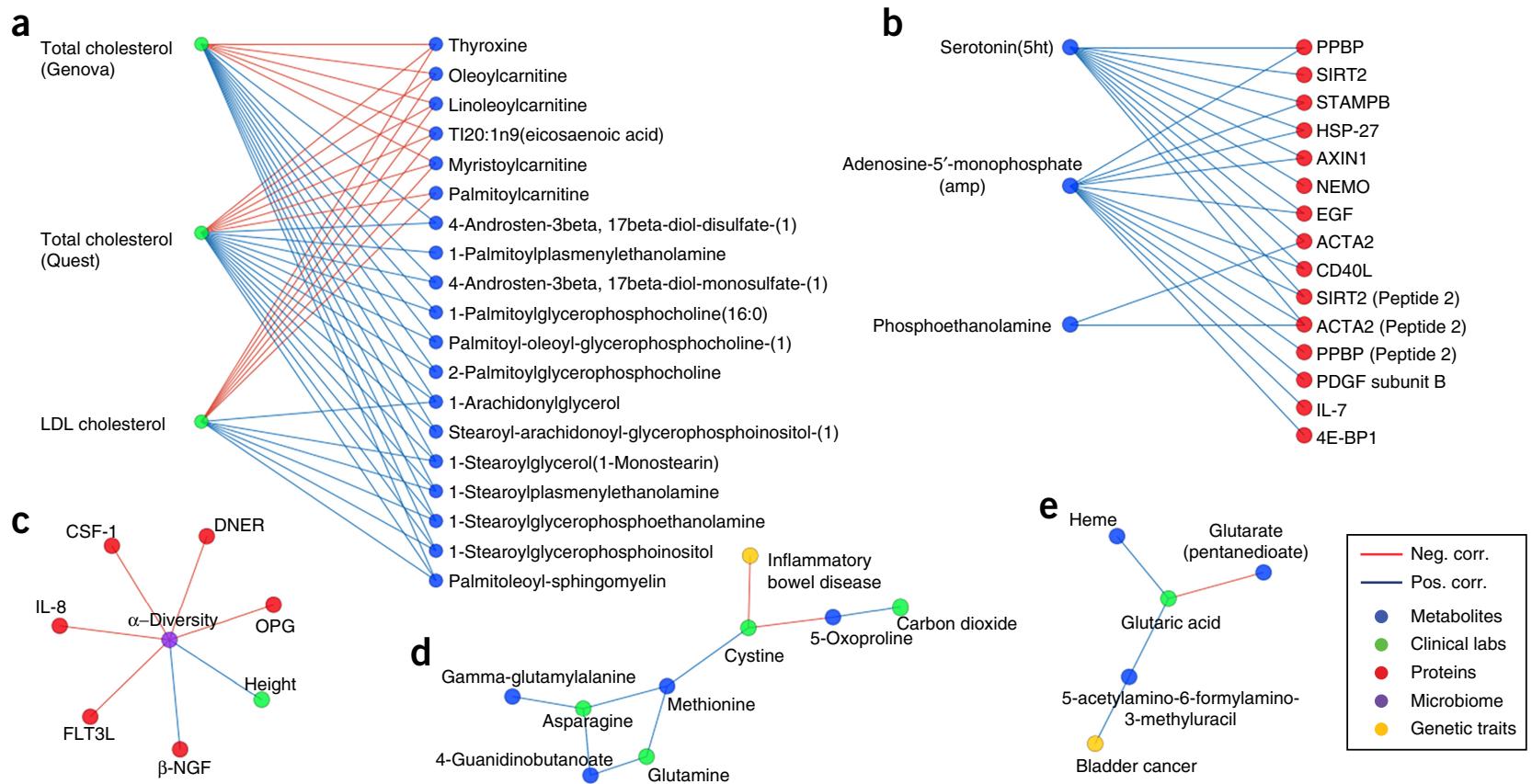
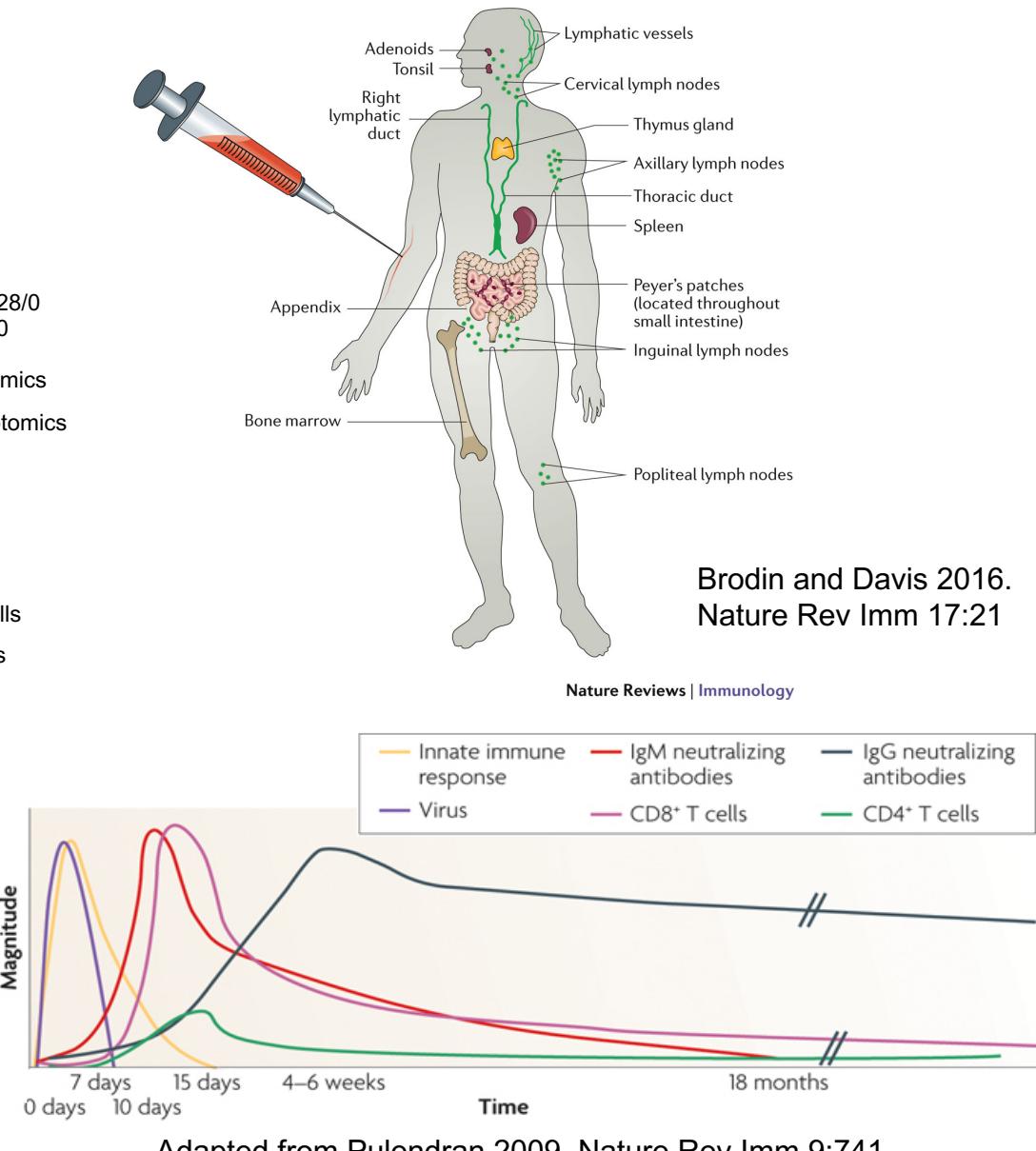
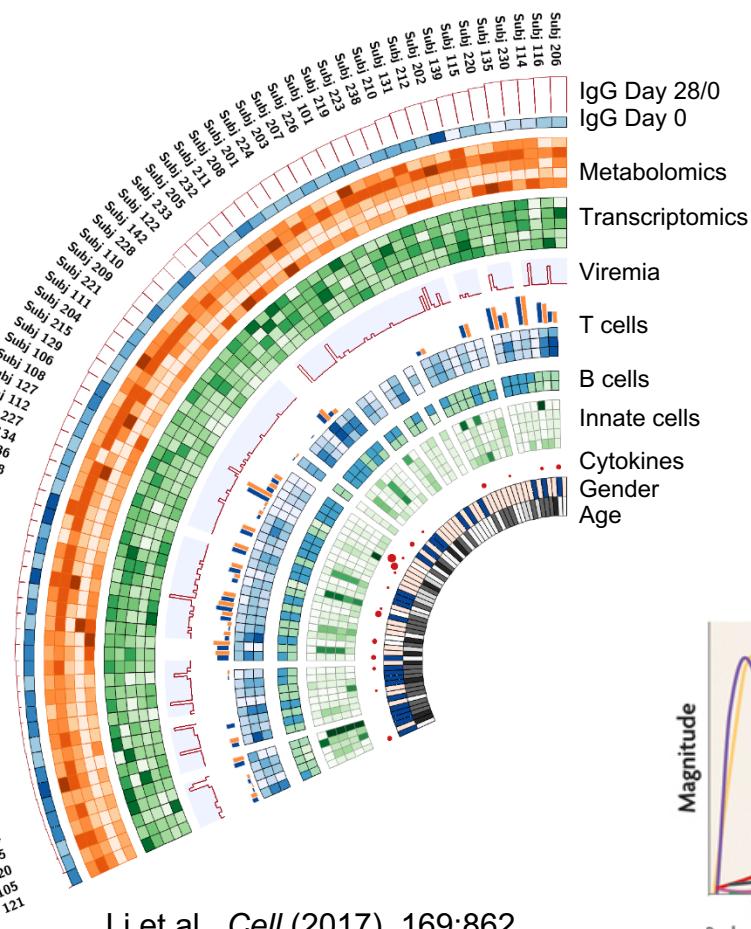


Figure 4 Cholesterol, serotonin, α -diversity, IBD, and bladder cancer communities. **(a)** Cholesterol community. **(b)** Serotonin community. **(c)** α -diversity community. **(d)** The polygenic score for inflammatory bowel disease is negatively correlated with cystine. **(e)** The polygenic score for bladder cancer is positively correlated with 5-acetylamino-6-formylamino-3-methyluracil (AFMU).

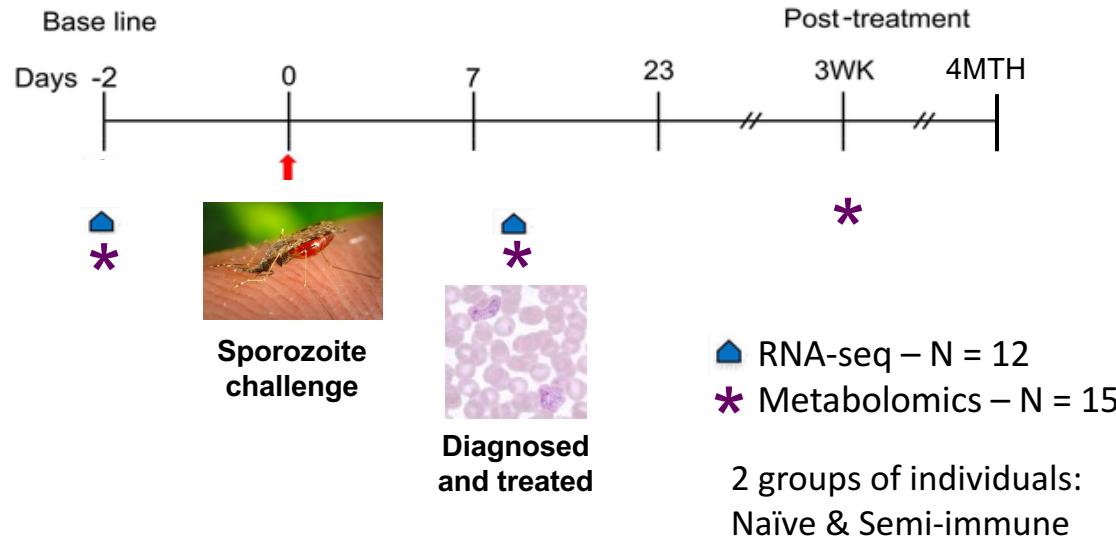
❑ Examples in human immunology

Studying human immunology





Controlled infection with *Plasmodium vivax* in human volunteers

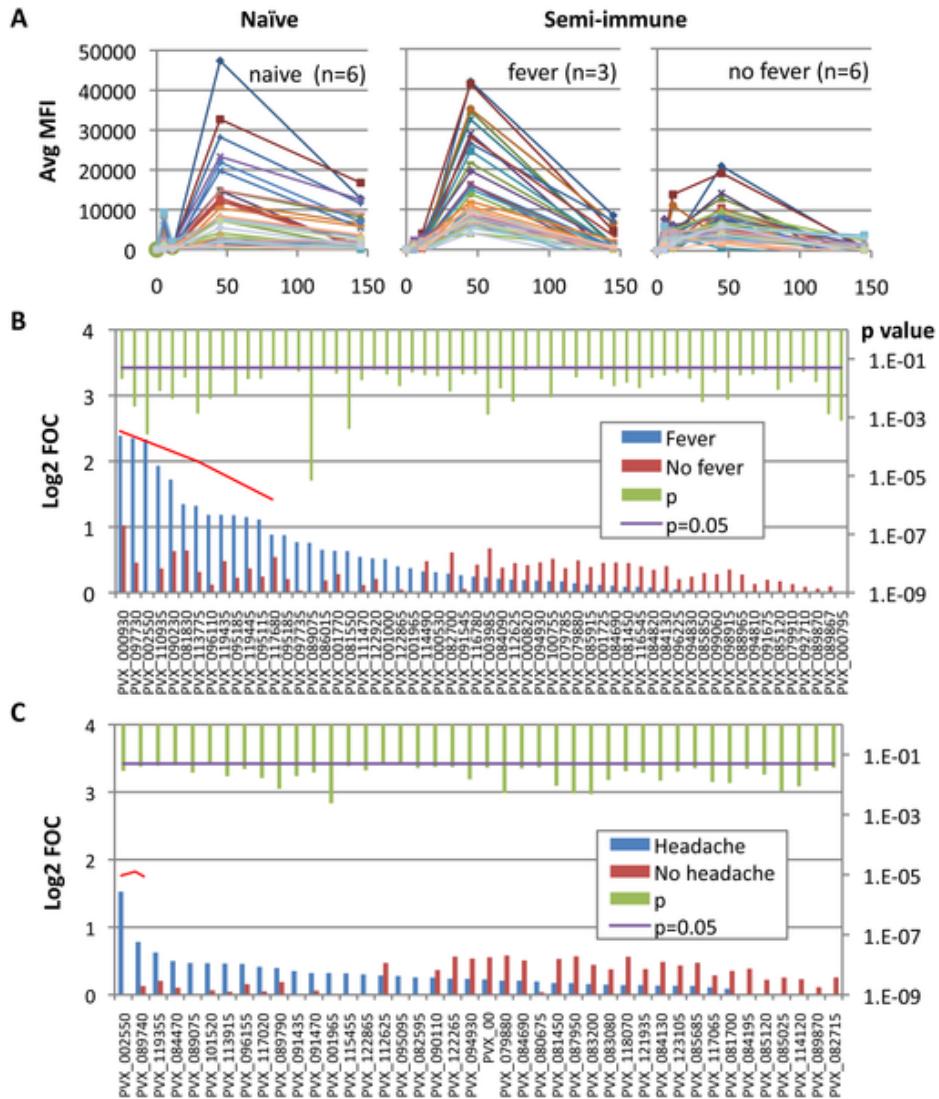


Luiz Gustavo
Gardinassi

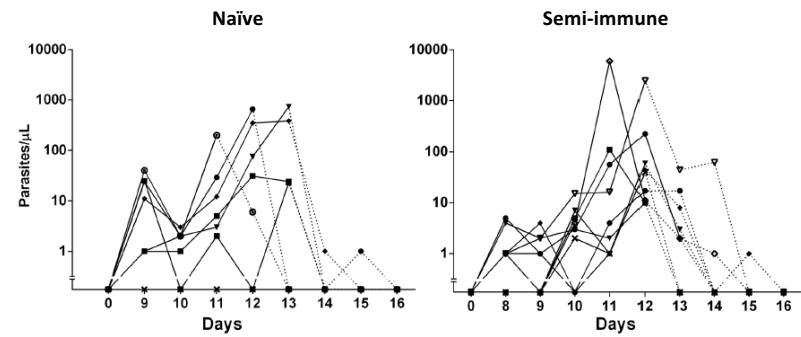
Modified from: Rojas-Pena et al. 2015 – Plos Neglect. Trop. Dis.
Collaboration with Myriam Arévalo-Herrera, Sócrates Herrera and Mary Galinski

Clinical difference by prior history

- Antibody profile associated with clinical protection.



Course of parasitemia

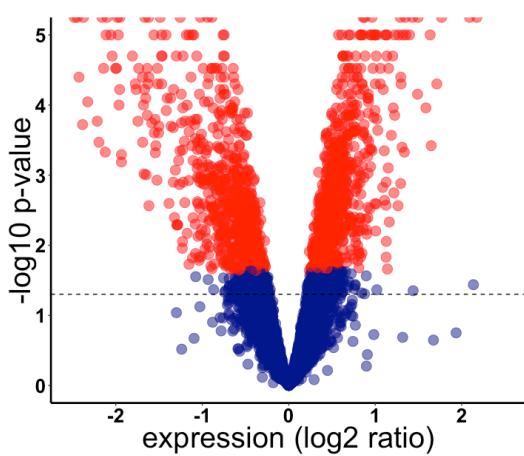


Arévalo-Herrera M, et al. (2014).
PLOS ONE 9(6): e99754

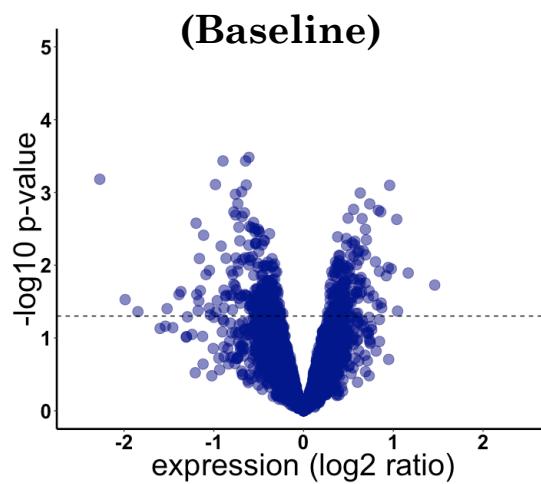
Arévalo-Herrera M, et al. (2016)
PLOS Neglected Tropical Diseases 10(3): e0004563.

Transcriptomics: Differentially Expressed Genes

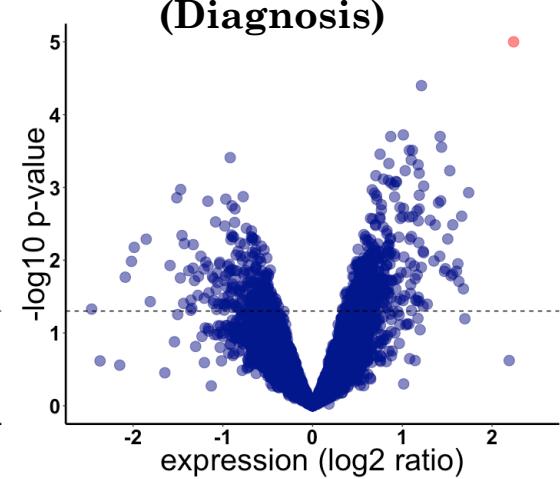
**Diagnosis
vs
Baseline**



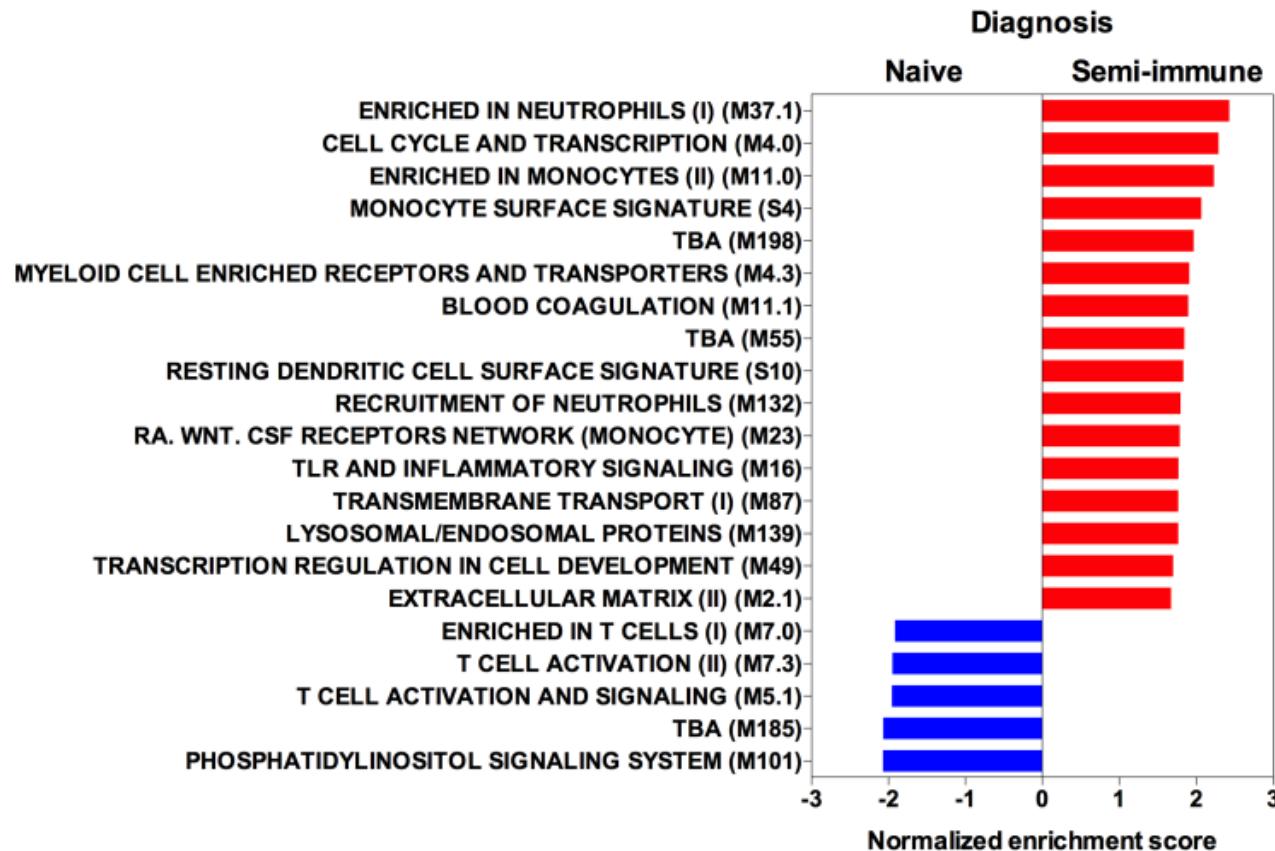
Naive vs Semi-immune



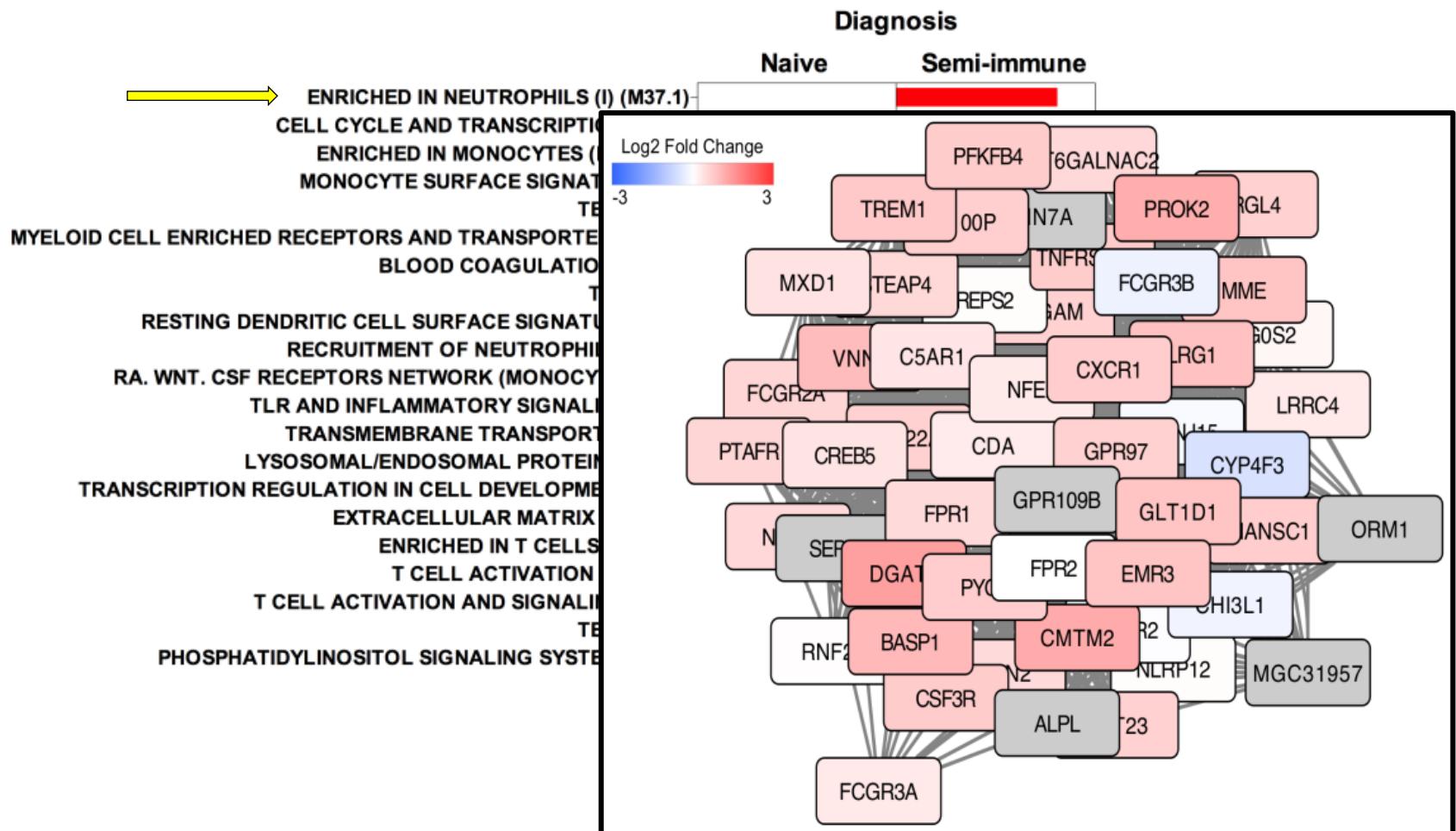
(Diagnosis)



BTM difference btw Naïve vs Semi-immune

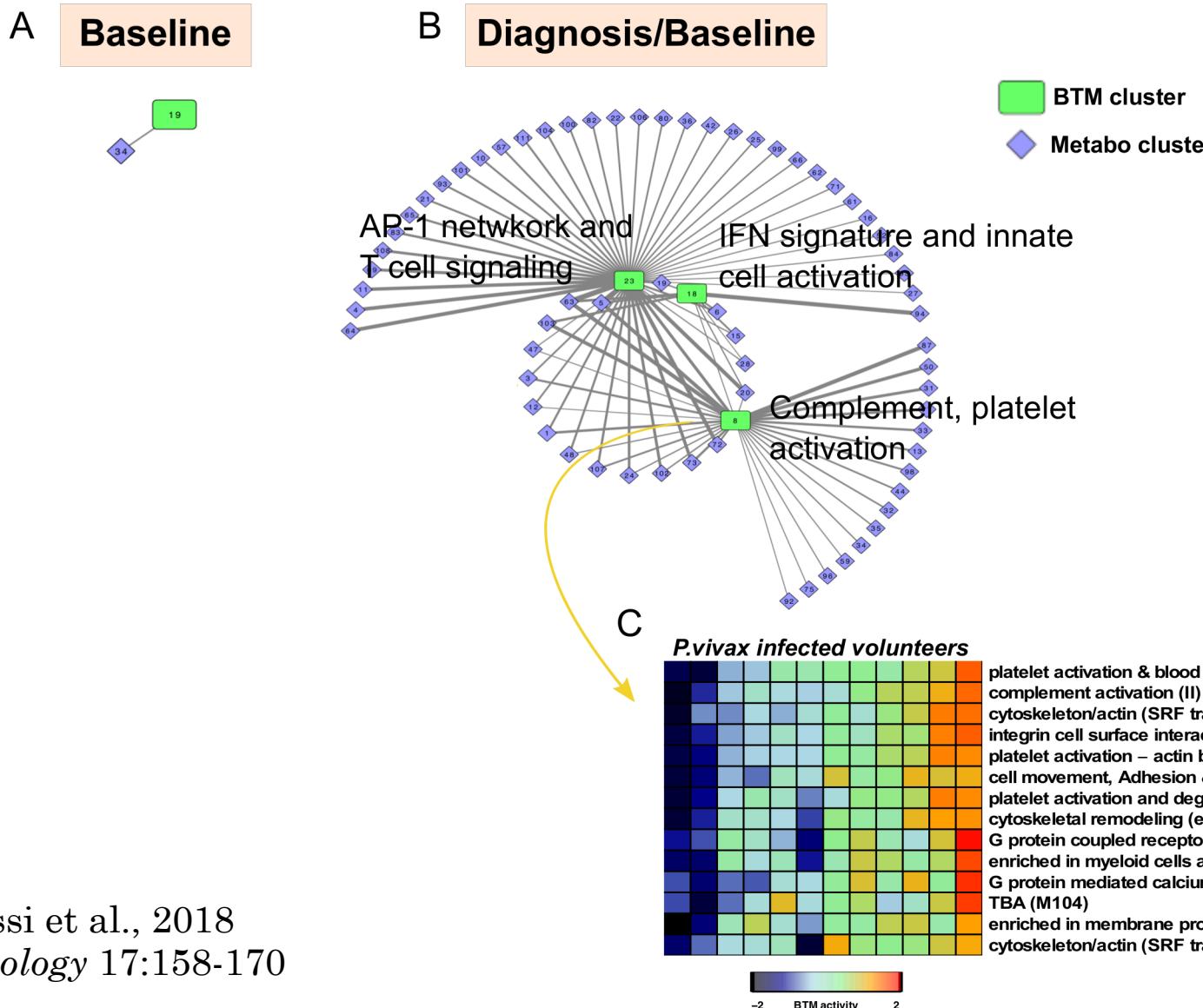


BTM difference btw Naïve vs Semi-immune

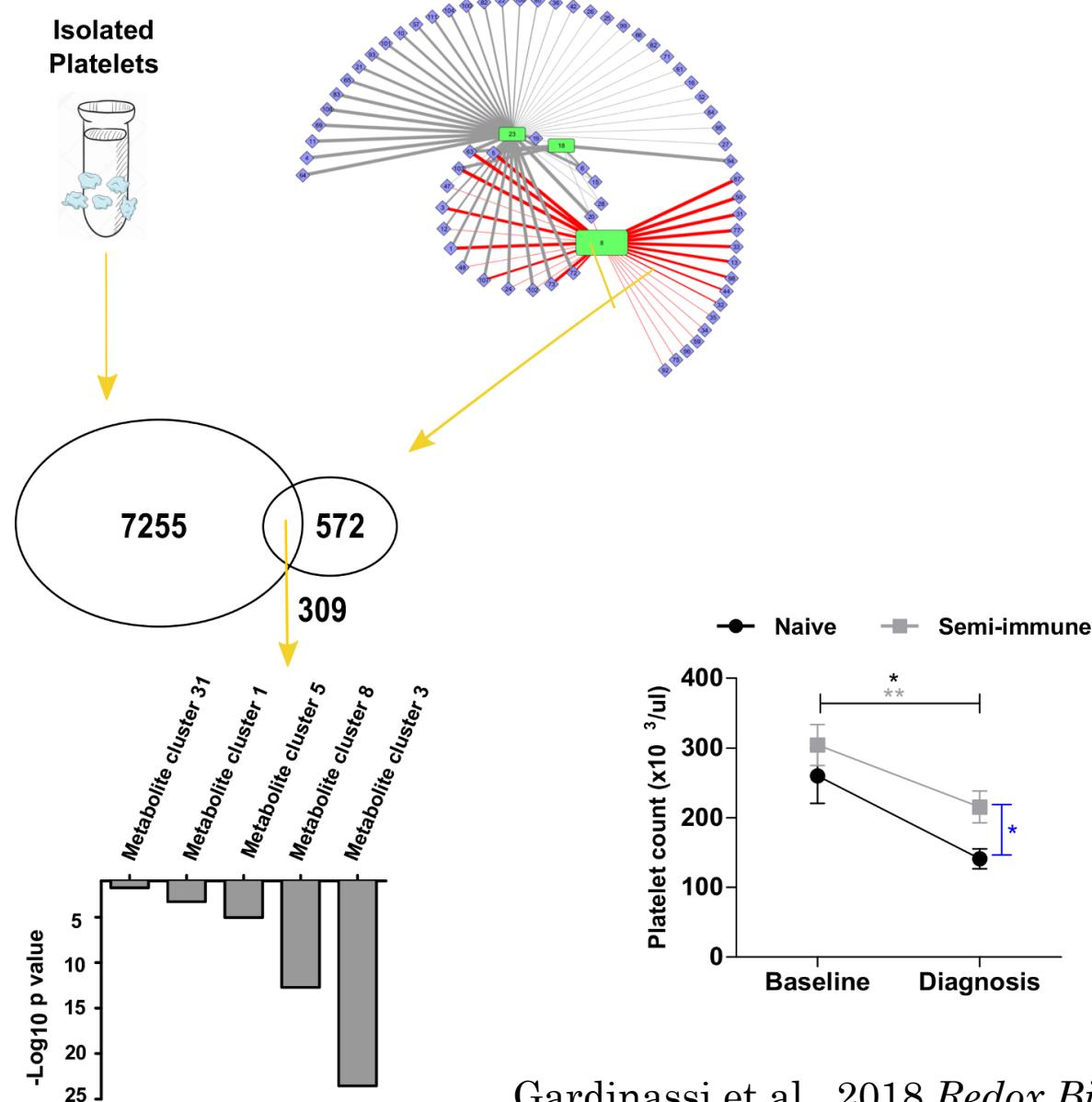


Malaria infection

Transcriptomics x Metabolomics



Platelet metabolome for confirmation



Acknowledgement

Method Development

Dean P. Jones Emory University SOM
Bali Pulendran Emory Vaccine Center
Rafi Ahmed Emory Vaccine Center
Mark Mulligan Emory Vaccine Center, Hope Clinic

Colombia Study

Luiz Gustavo Gardinassi, ViLinh Tran, Ken Liu,
Dean P. Jones
Emory University SOM, Dept. Medicine
Mary Galinski, Regina Joice Cordy
Emory University, Yerkes National Primate Center
Socrates Herrera Valencia, Myriam Arevalo-Herrera
Caucaseco Scientific Research Center, Cali, Colombia
Greb Gibson, Monica L. Rojas-Peña
Georgia Institute of Technology

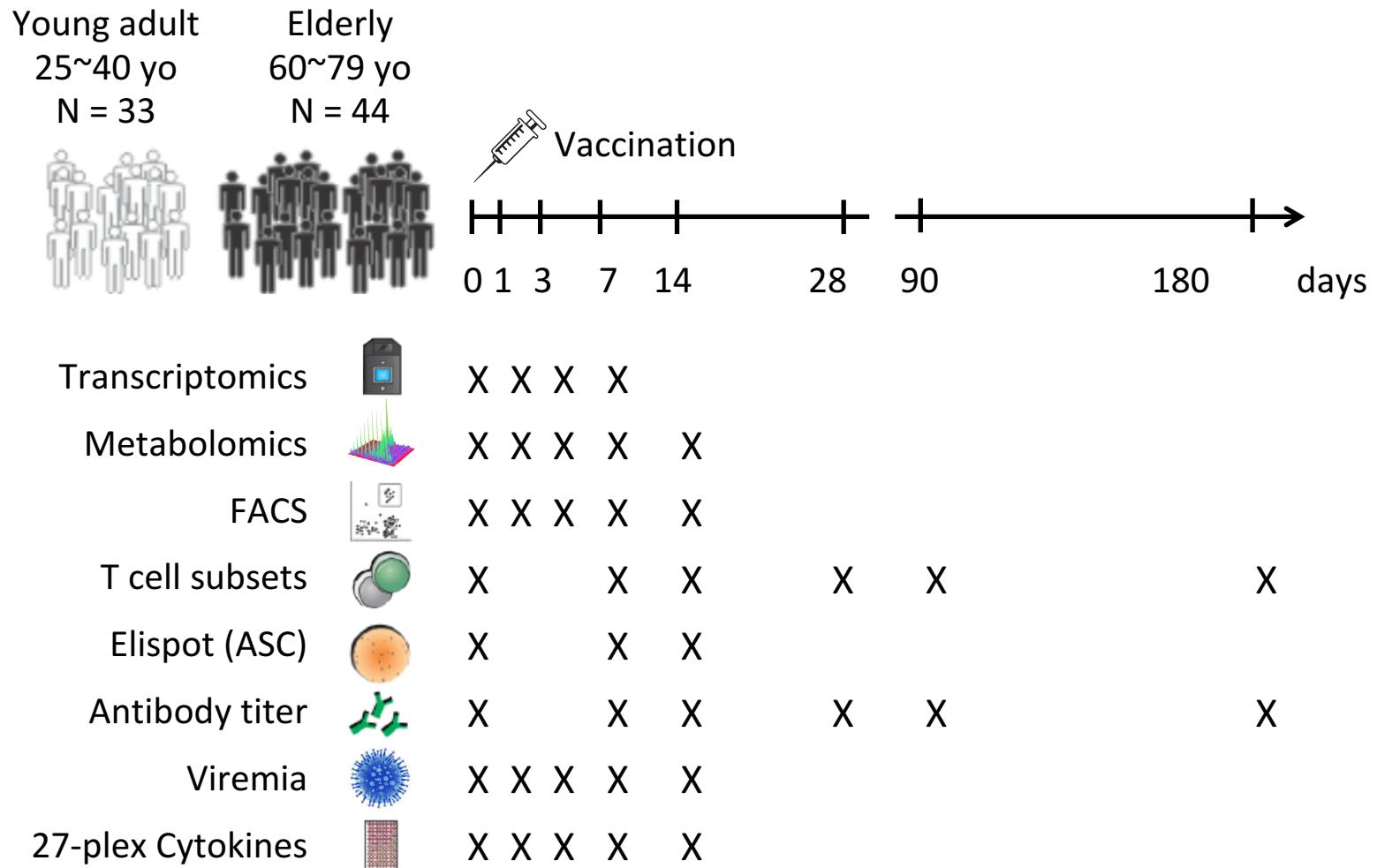


Acknowledgement of research supports from US National Institutes of Health (NIAID HHSN272201200031C, U19AI090023, HHSN272201300018I, NIEHS P30 ES019116, U2CES026560, P50ES026071, NIDDK R01DK107900, NIAID R01AI121252), DoD DARPA (W911NF-16-C-0008), EPA (83615301) and California Breast Cancer Research Program (21UB-8002).

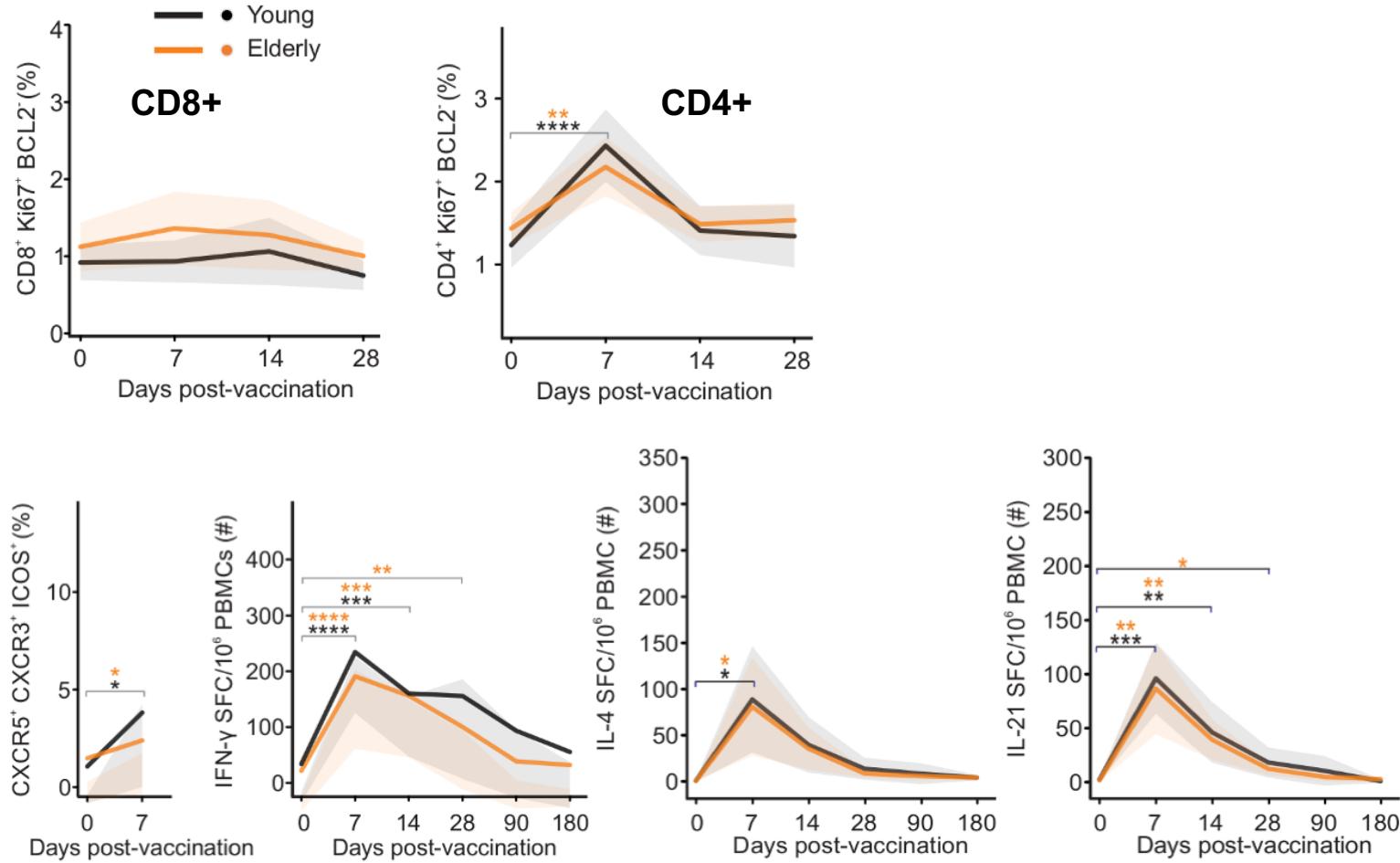
The herpes zoster vaccine Zostavax®

- Licensed for prevention of Herpes zoster (shingles) by reactivation of varicella zoster virus (VZV)
- 14X Varivax (Live attenuated Oka strain)
- 51.3% reduction in HZ incidence (44.2-57.6)
- 66.5% reduction in postherpetic neuralgia pain (47.5-79.2) (Oxman MN et al. NEJM 2005)
- HIPC clinical study 2011-2012 (VAX005)

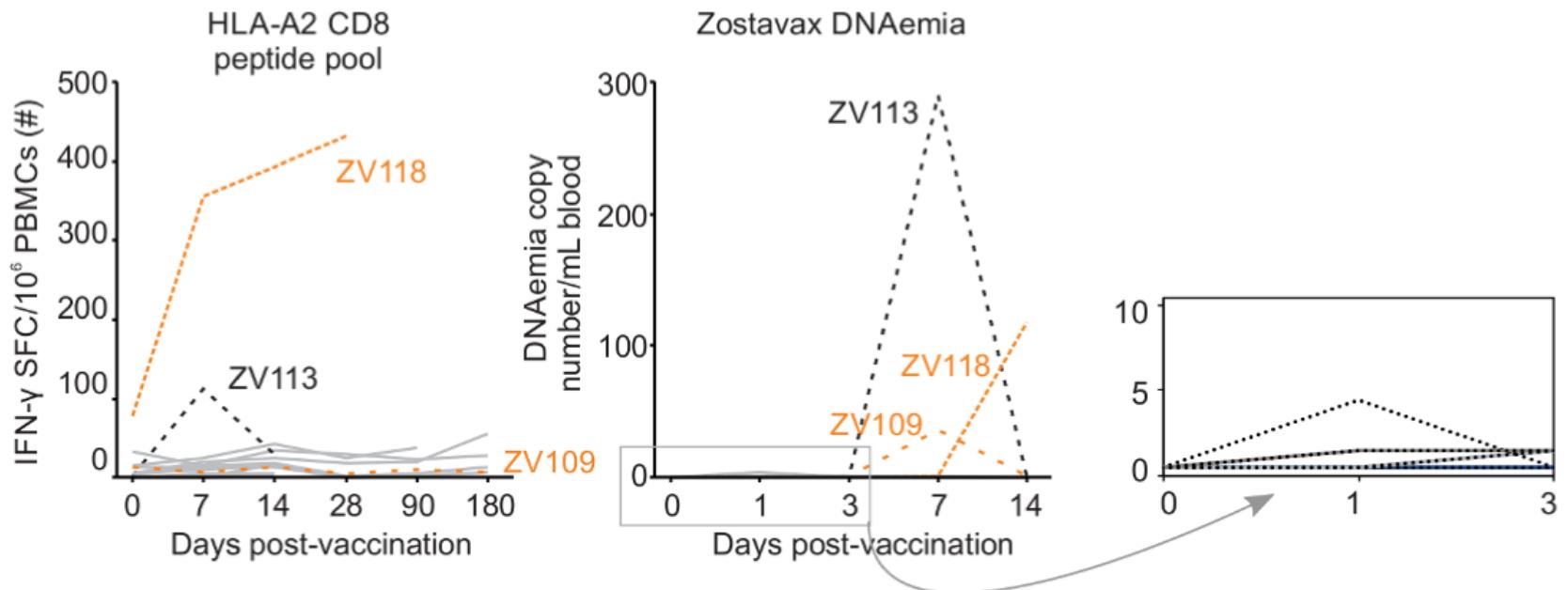
VZV study design



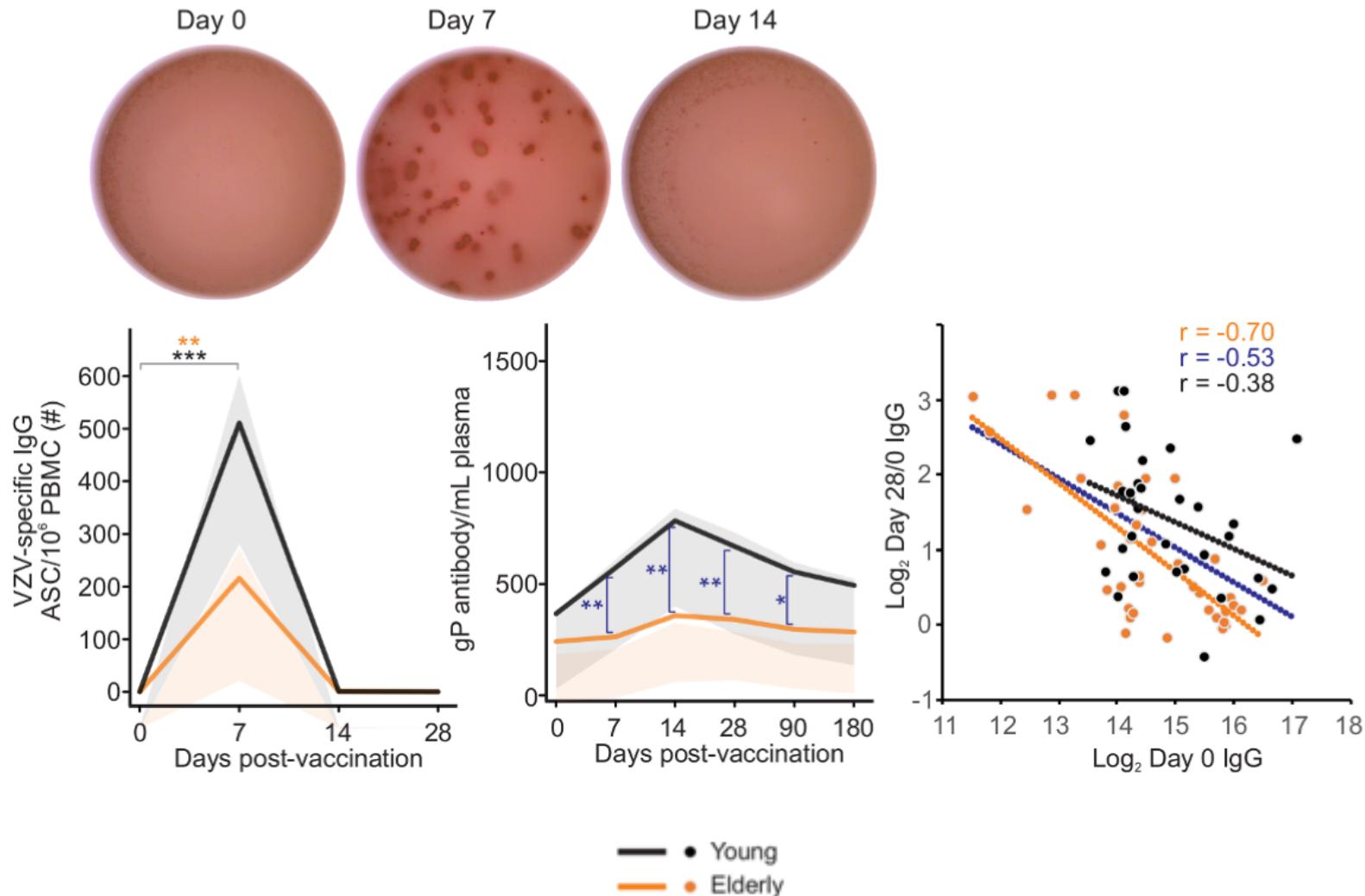
VZV induced T cell responses



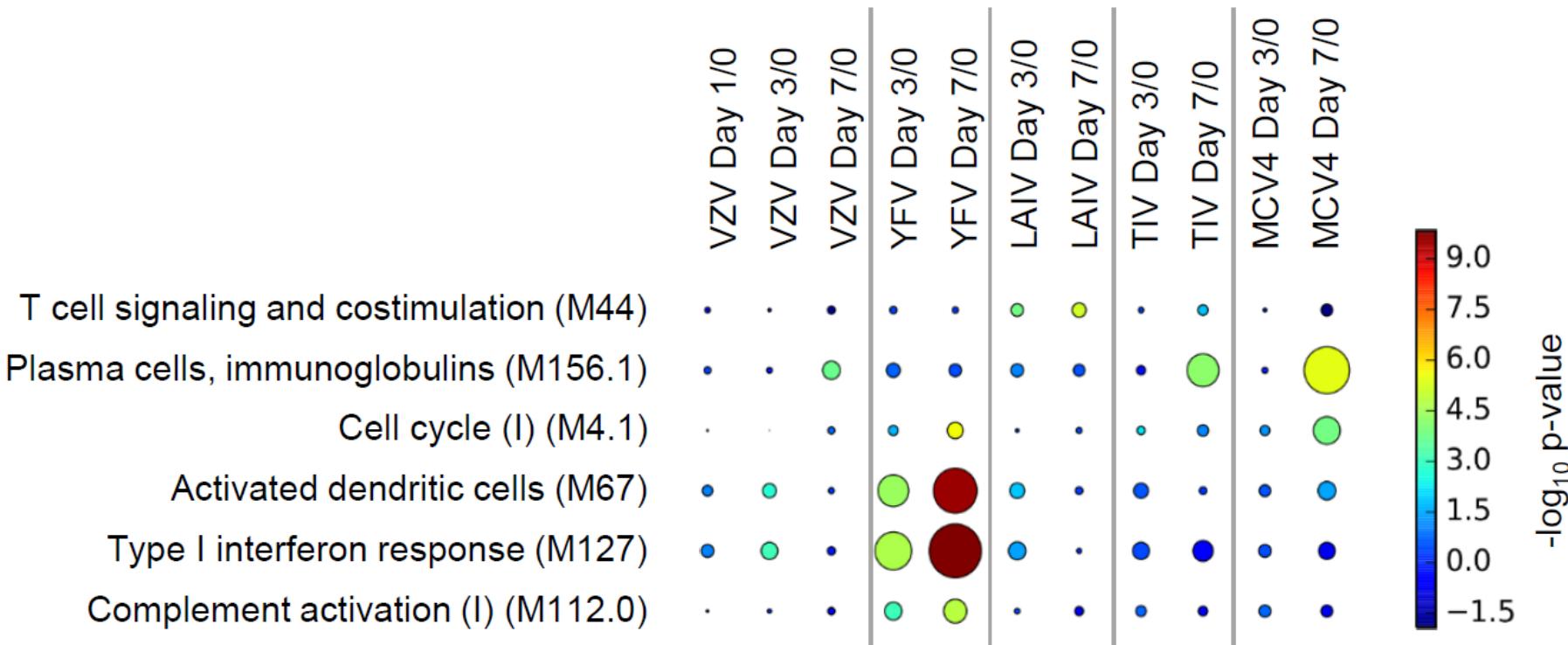
Sporadic CD8⁺ T cell response coincided with viral DNAemia



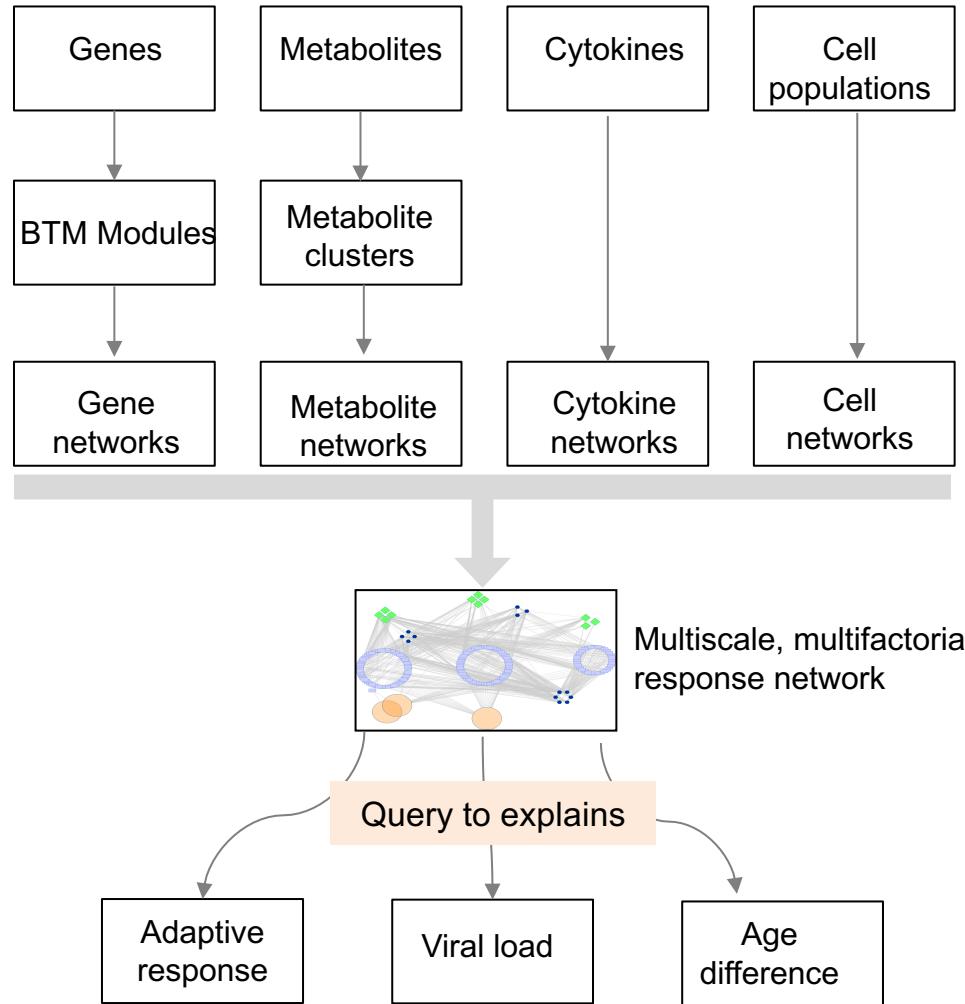
VZV-specific IgG response



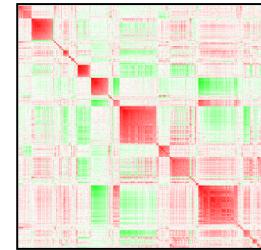
BTM analysis transcriptomics: Limited IFN response to VZV



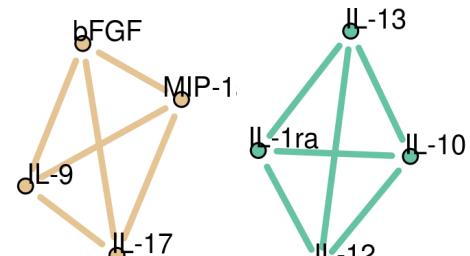
Integrating multiple data types



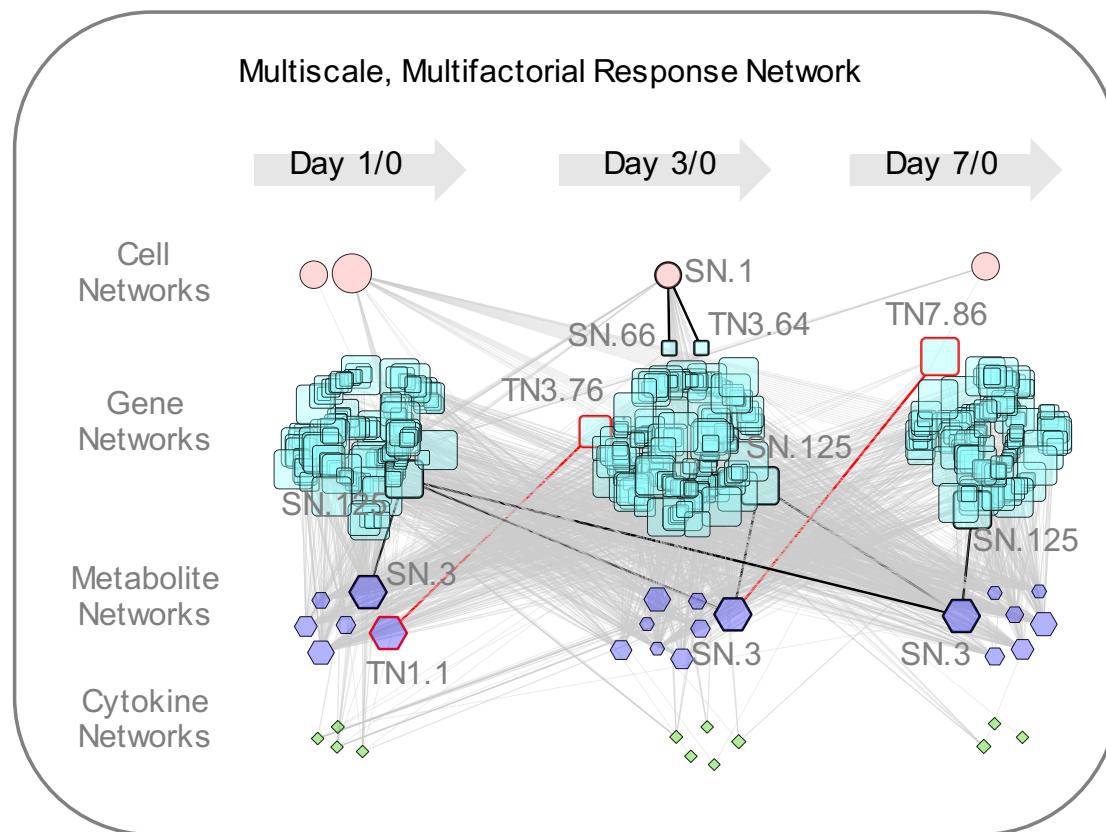
Metabolite clusters



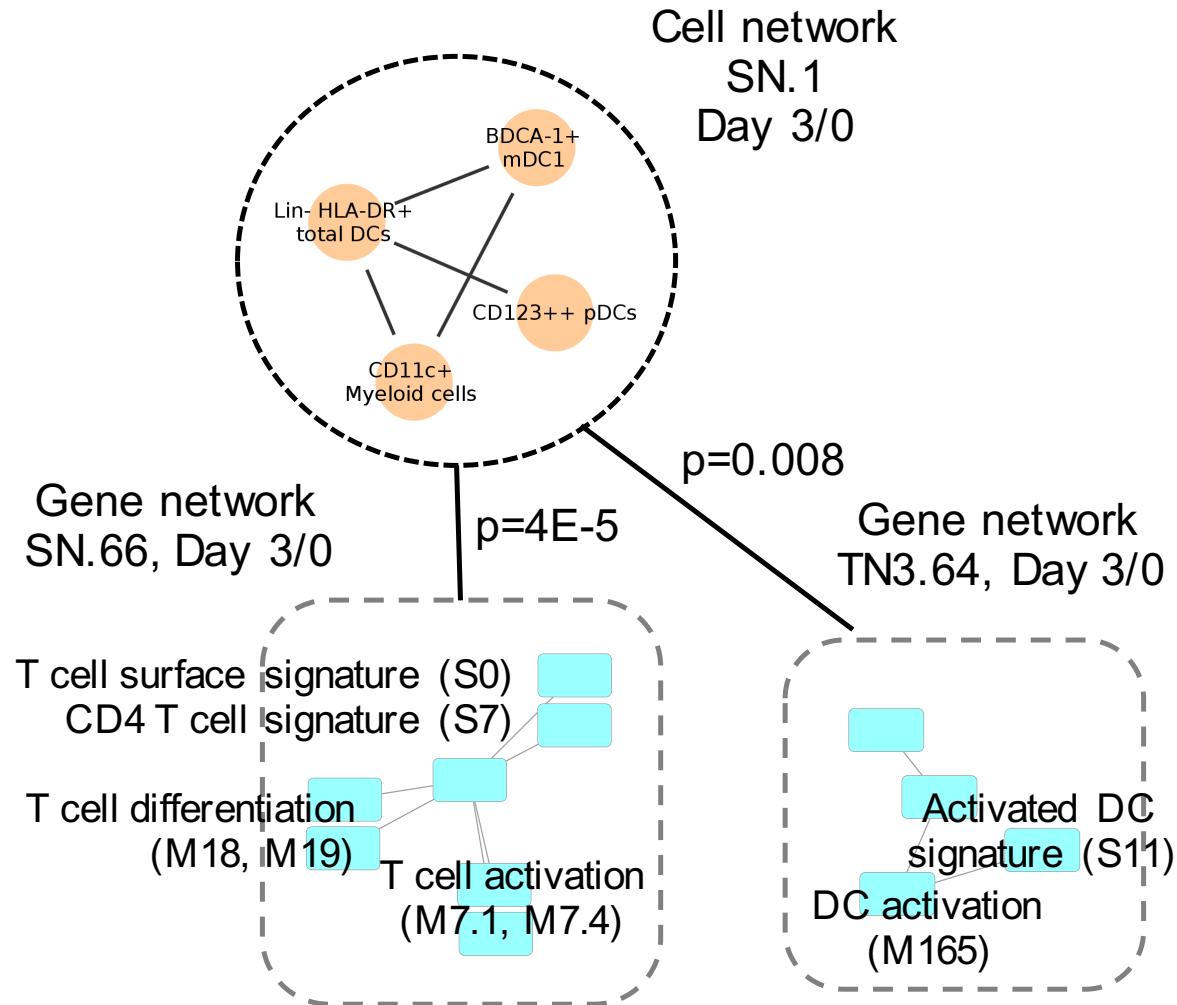
Cytokine networks



Multiscale, Multifactorial Response Network (MMRN) to vaccination

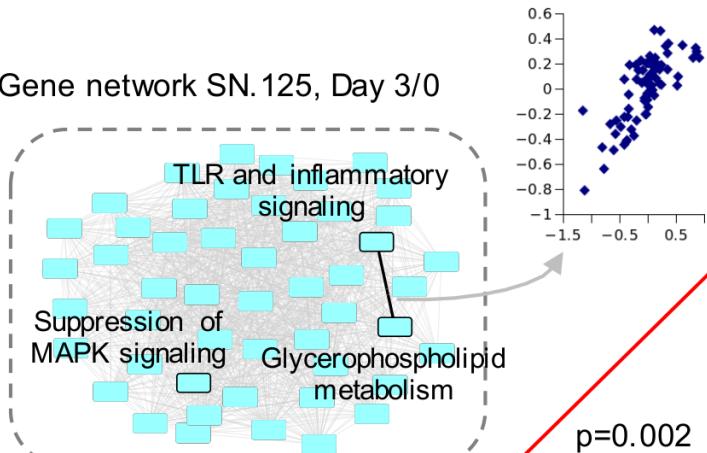


MMRN example

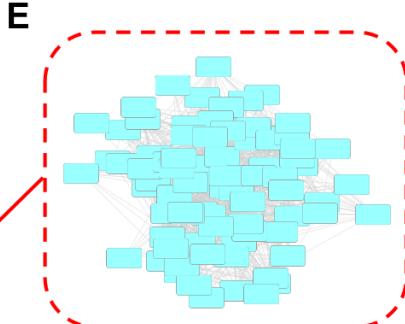


MMRN example

C Gene network SN.125, Day 3/0



E

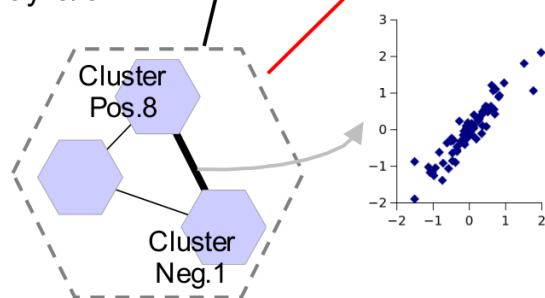


Gene network TN7.86, Day 7/0



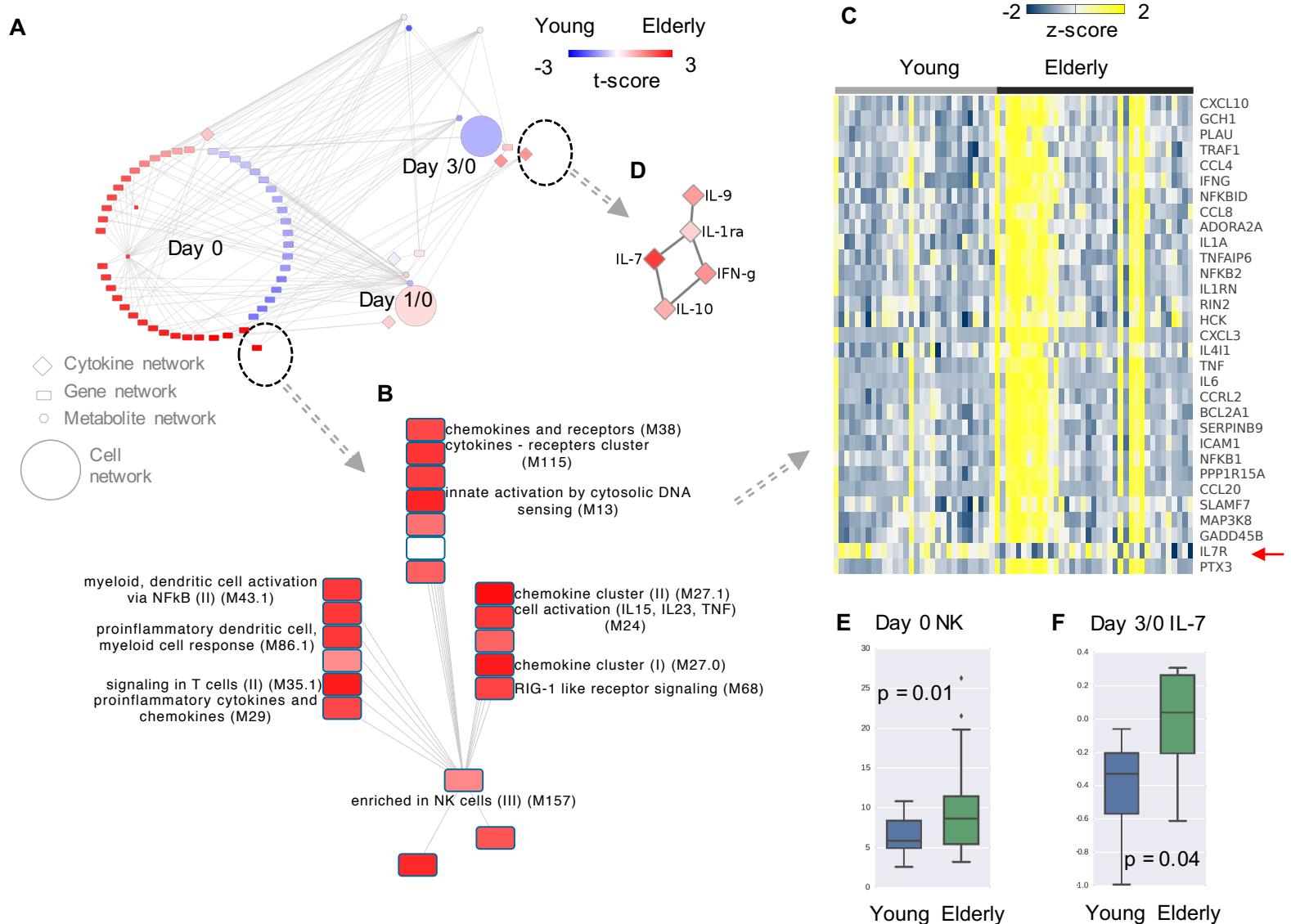
D

Metabolite network SN.3, Day 3/0

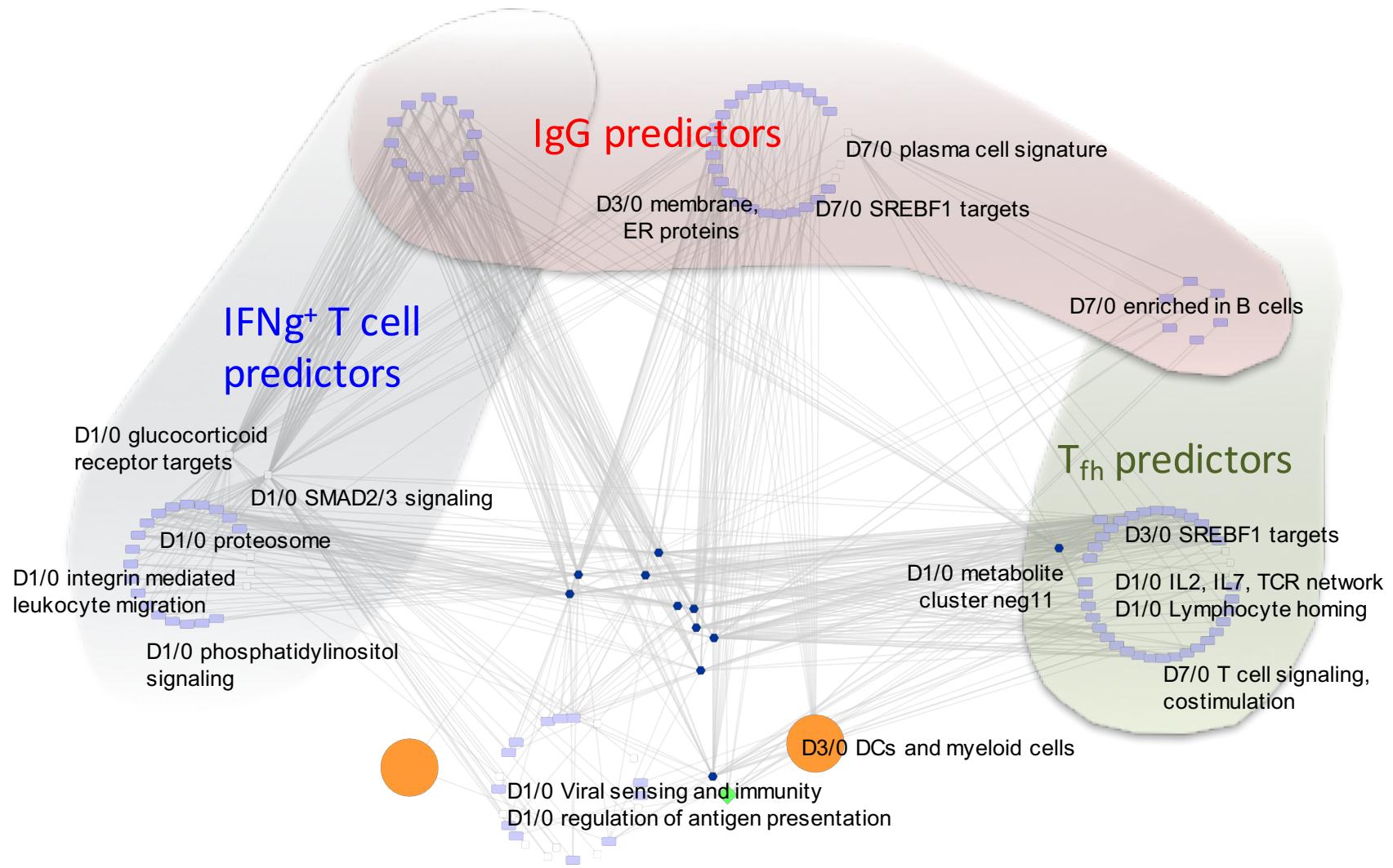


- respiratory electron transport
- CD4 T cell signature
- transcription elongation
- nucleotide metabolism
- T cell surface, activation enriched in B cells (IV)
- BCR signaling
- inositol phosphate metabolism
- phosphatidylinositol signaling
- purine nucleotide biosynthesis

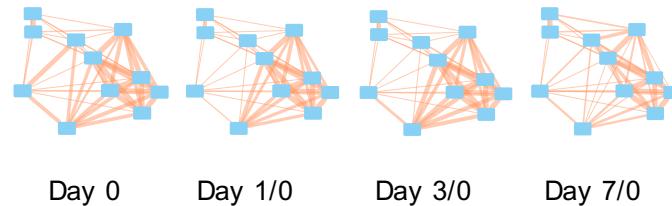
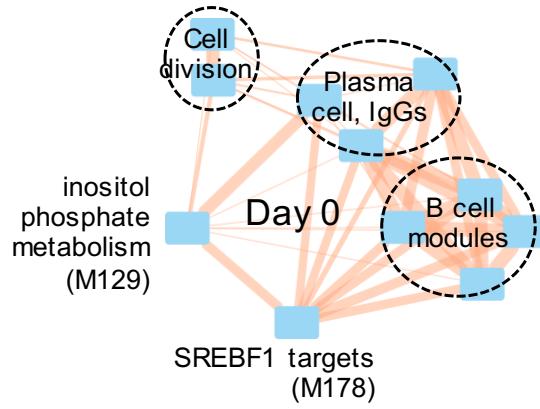
MMRN associated with age



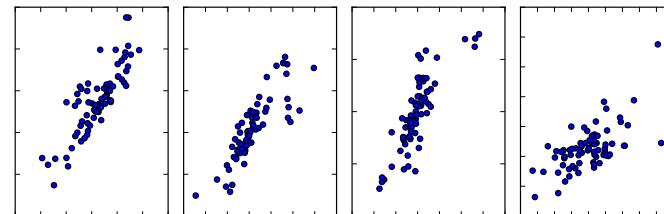
Predictors of T cell and antibody responses are connected in a redundant network



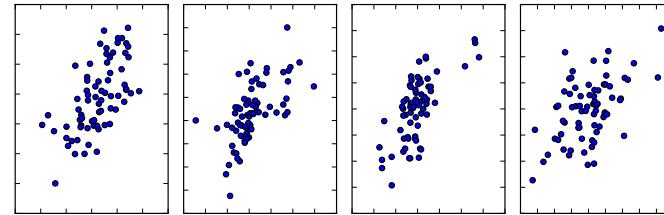
Example of network redundancy and kinetics



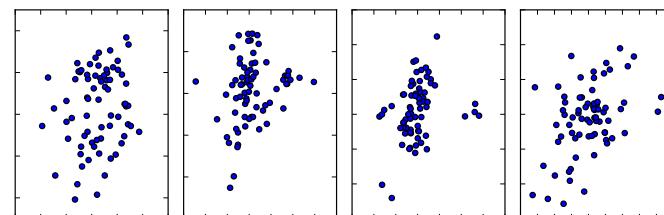
plasma cells & B cells, IgGs (M156.0)



SREBF1 targets (M178)

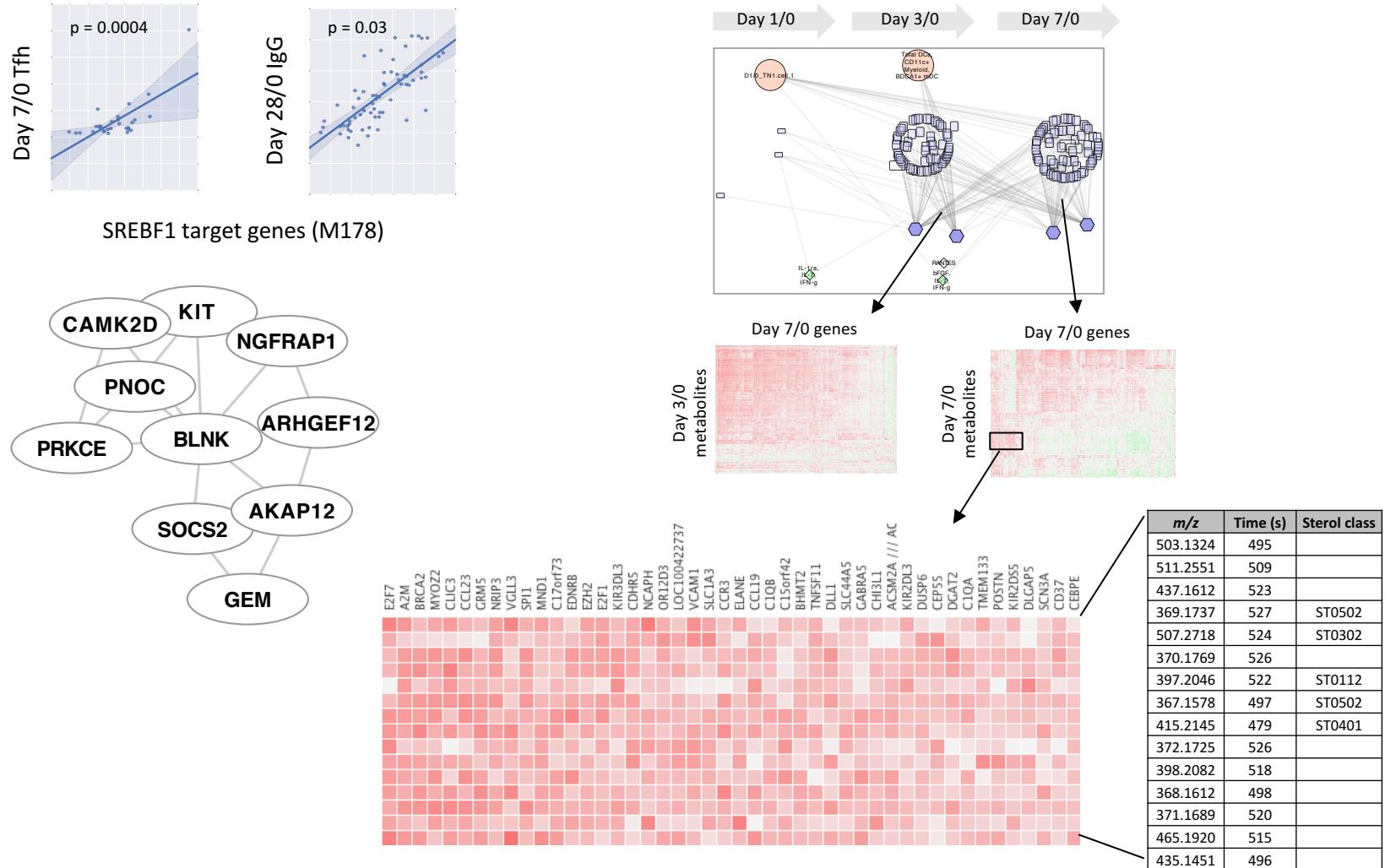


inositol phosphate metabolism (M129)

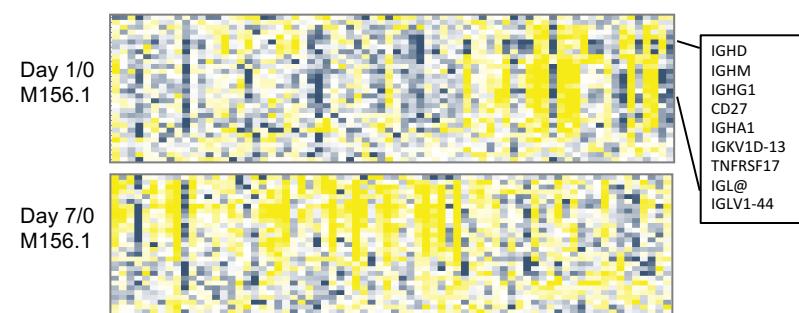
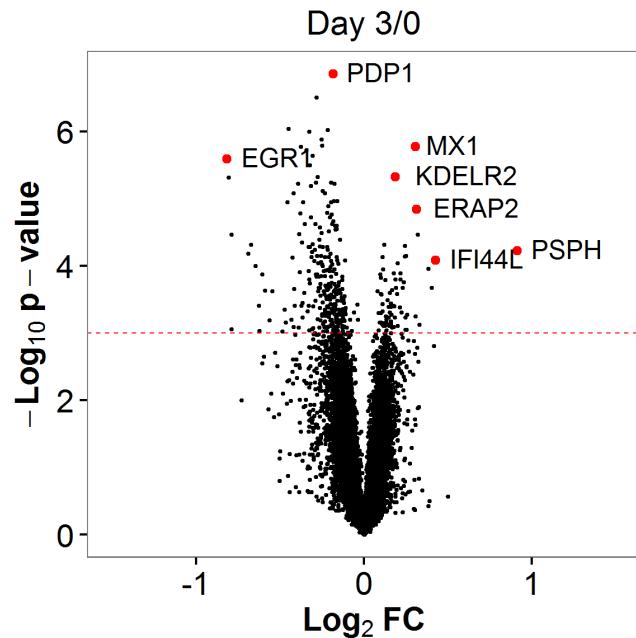


enriched in B cells (II) (M47.1)

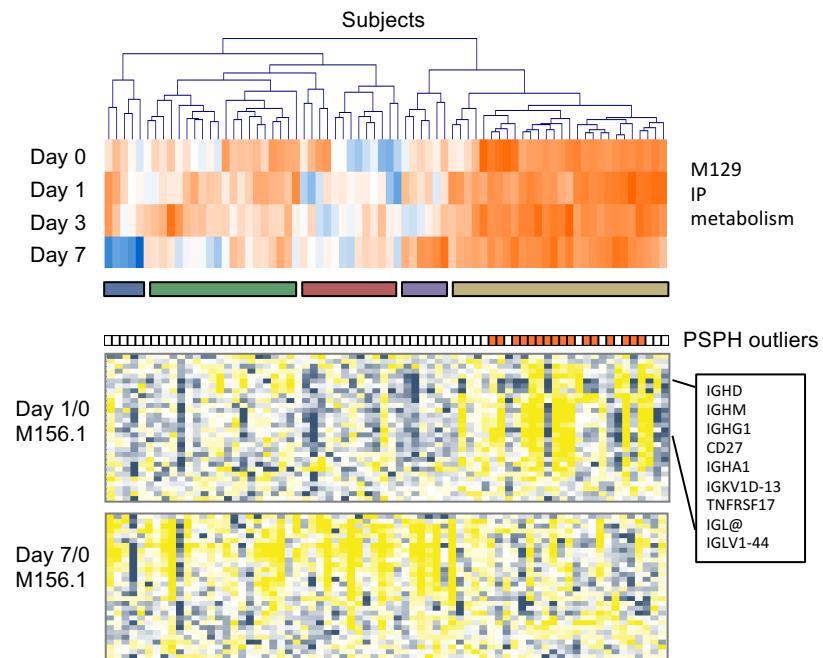
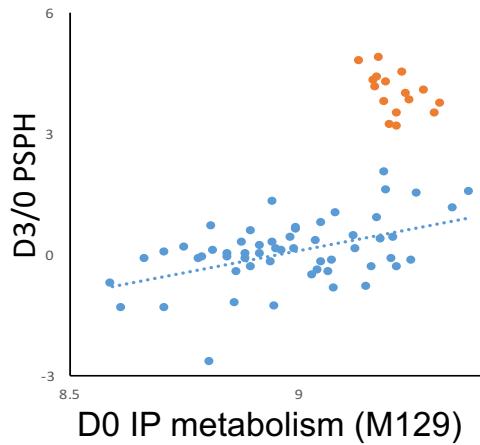
SREBF1 targets predict T cell and antibody responses



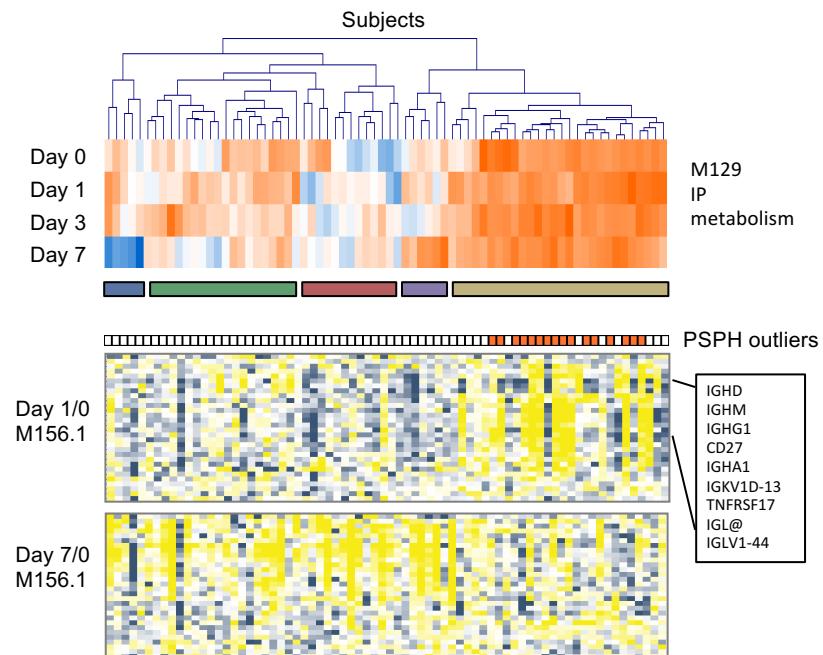
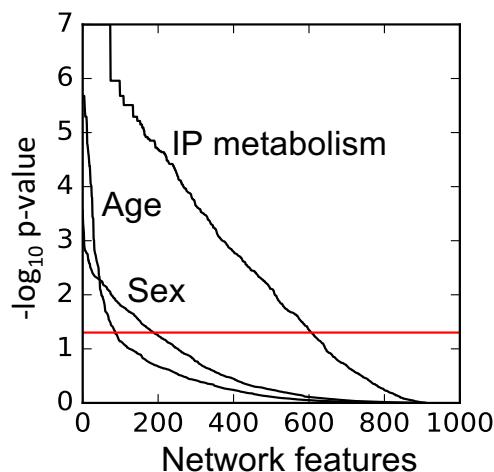
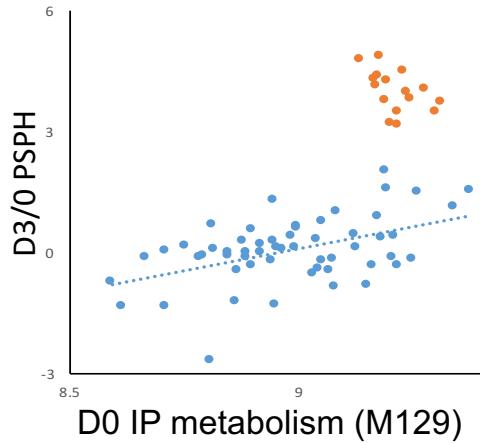
The puzzle of PSPH and an outlier group



The puzzle of PSPH and an outlier group explained by Inositol phosphate metabolism



The puzzle of PSPH and an outlier group explained by Inositol phosphate metabolism



Study summary

- MMRN (HiCoNet) as an effective approach of integrating multiple data types
- Extensive connections found between metabolomics, transcriptomics and others; Different data types can cross-validate each other
- Plasma metabolite activities appear to precede cell transcriptomics
- Sterol metabolism integrates cellular and humoral responses
- Metabolic phenotype, such as inositol phosphate metabolism, influences immune outcome

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Megan McCausland
Chris Chiu

Mark Mulligan
Nadine Rouphael
Aneesh Mehta
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University of Colorado

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Myron Levin
Jennifer Canniff

La Jolla Institute for Allergy and Immunology

Alex Sette
Bjoern Peters
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Kalpit Vora
Sheri Dubey
Janet Sei
Joseph Antonello
Eberhard Durr
Kelly Collins

University of California San Diego

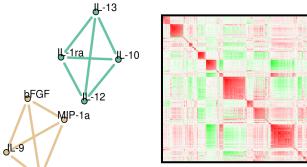
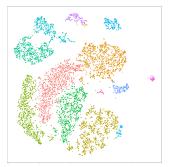
Shankar Subramaniam
Thomas Hagen

Dana Farber Cancer Institute

Nick Haining

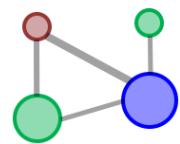


HiCoNet, a data integration tool



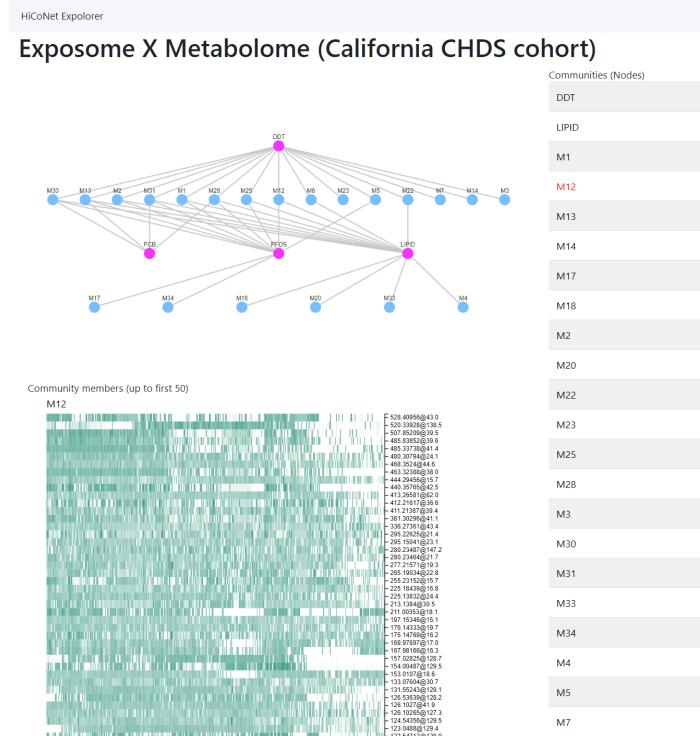
Community detection

PLS regression



Hierarchical Community Network

Web interactive data

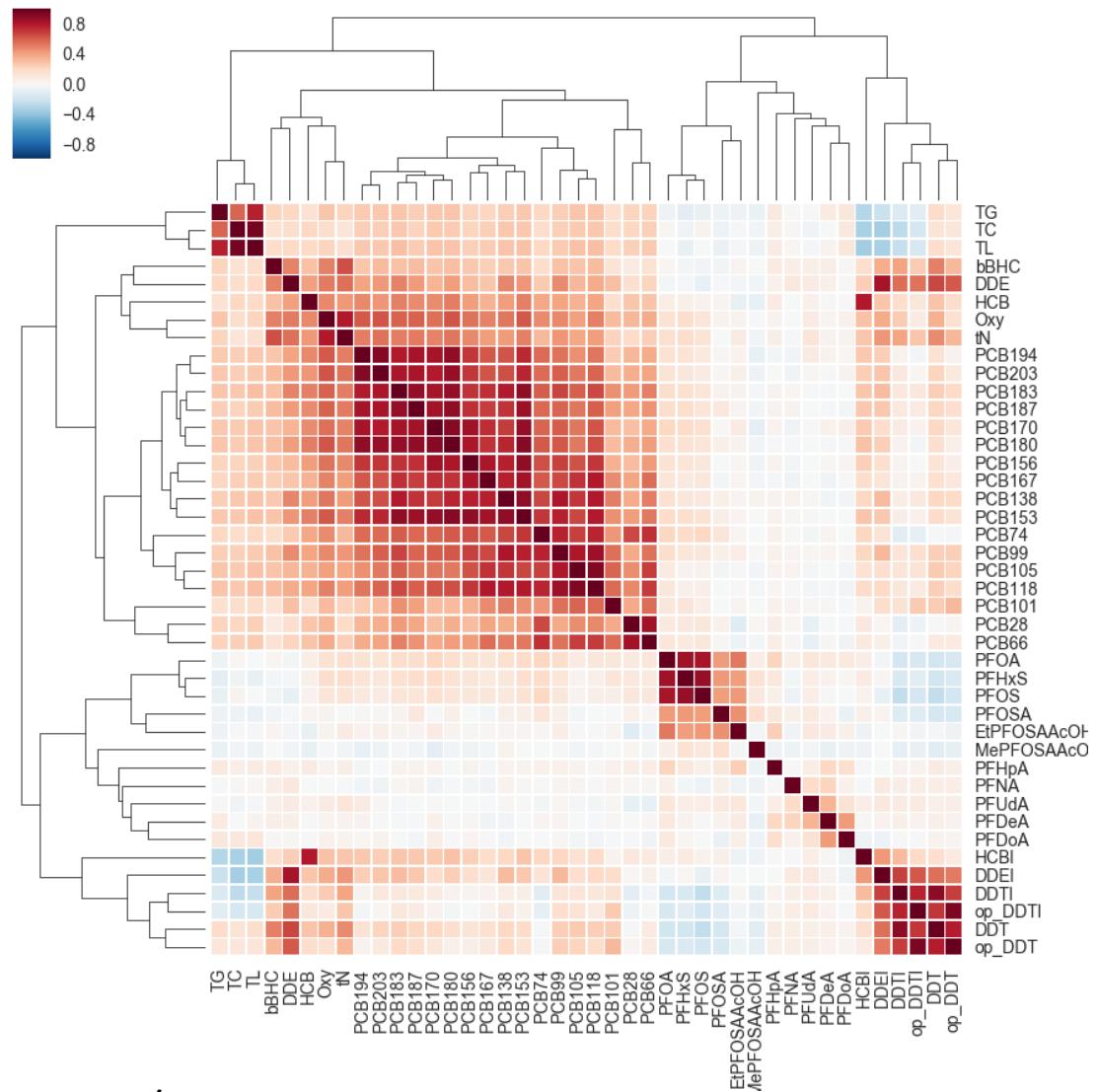


❑ Integrating Exposome and Metabolome

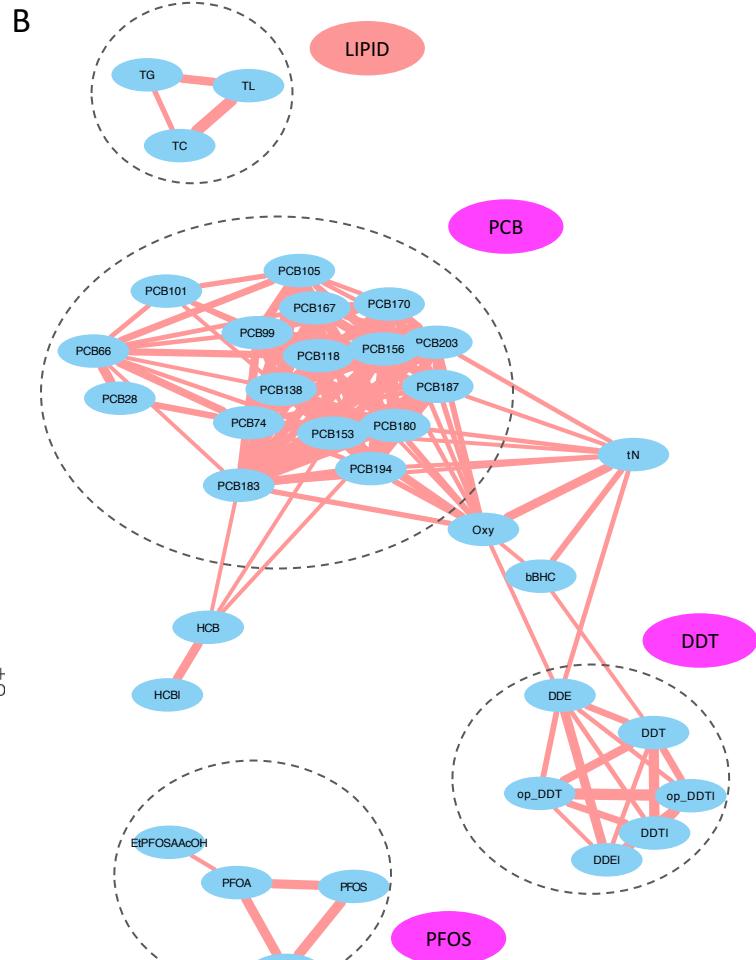
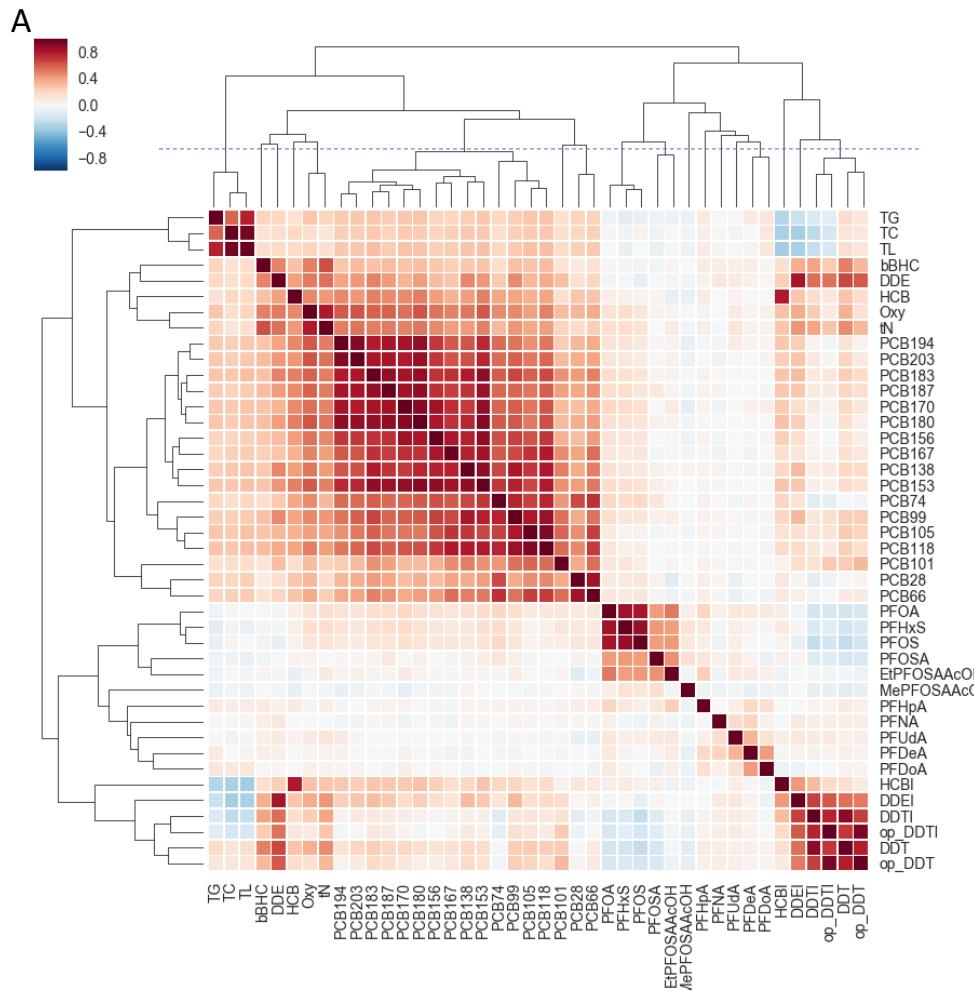
Mixed exposures (exposome)



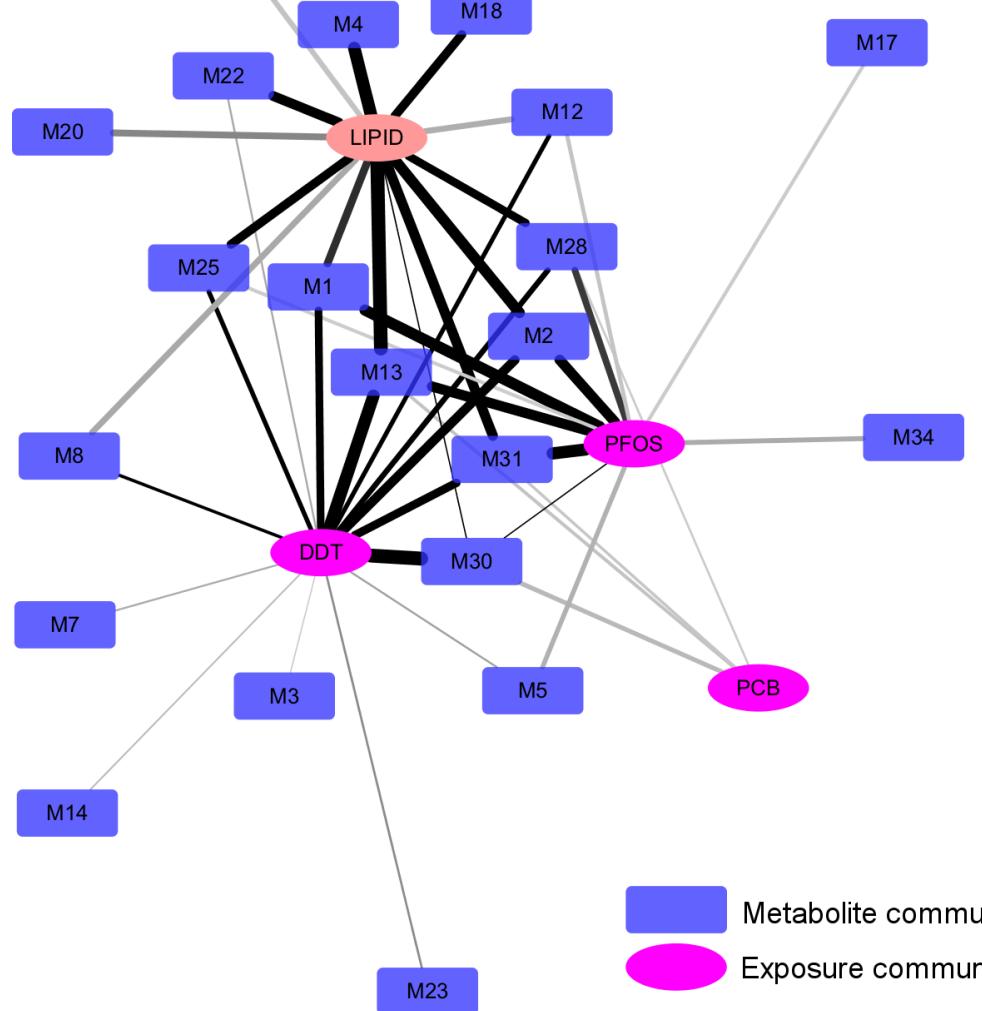
During 1959-1967
over 15,000 pregnant
women in the
Kaiser Permanente
Health Plan
joined the CHDS.



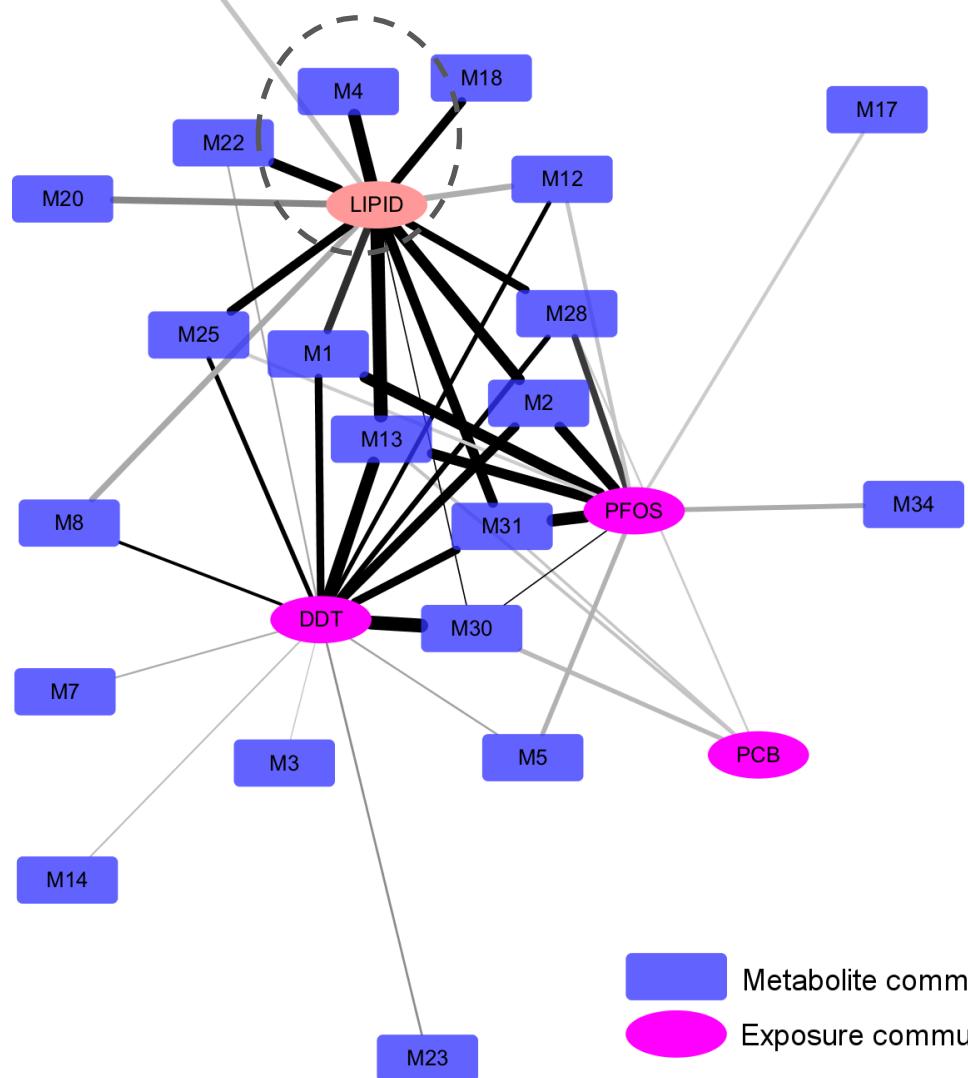
Exposure communities in CHDS data



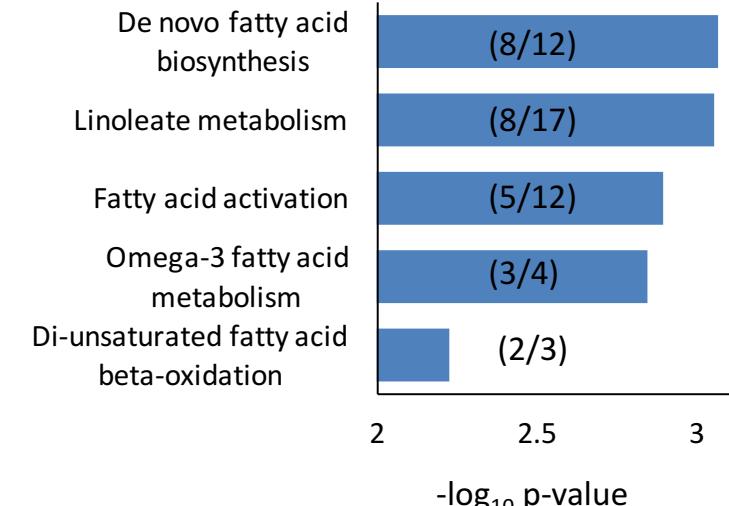
Metabolomics × Exposures



Metabolomics × Exposures

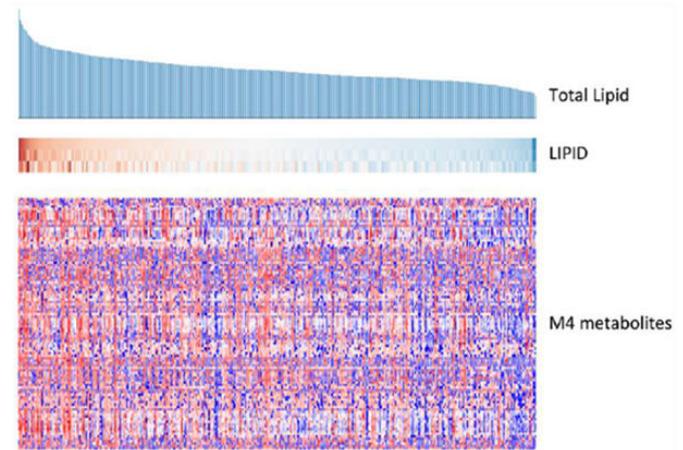
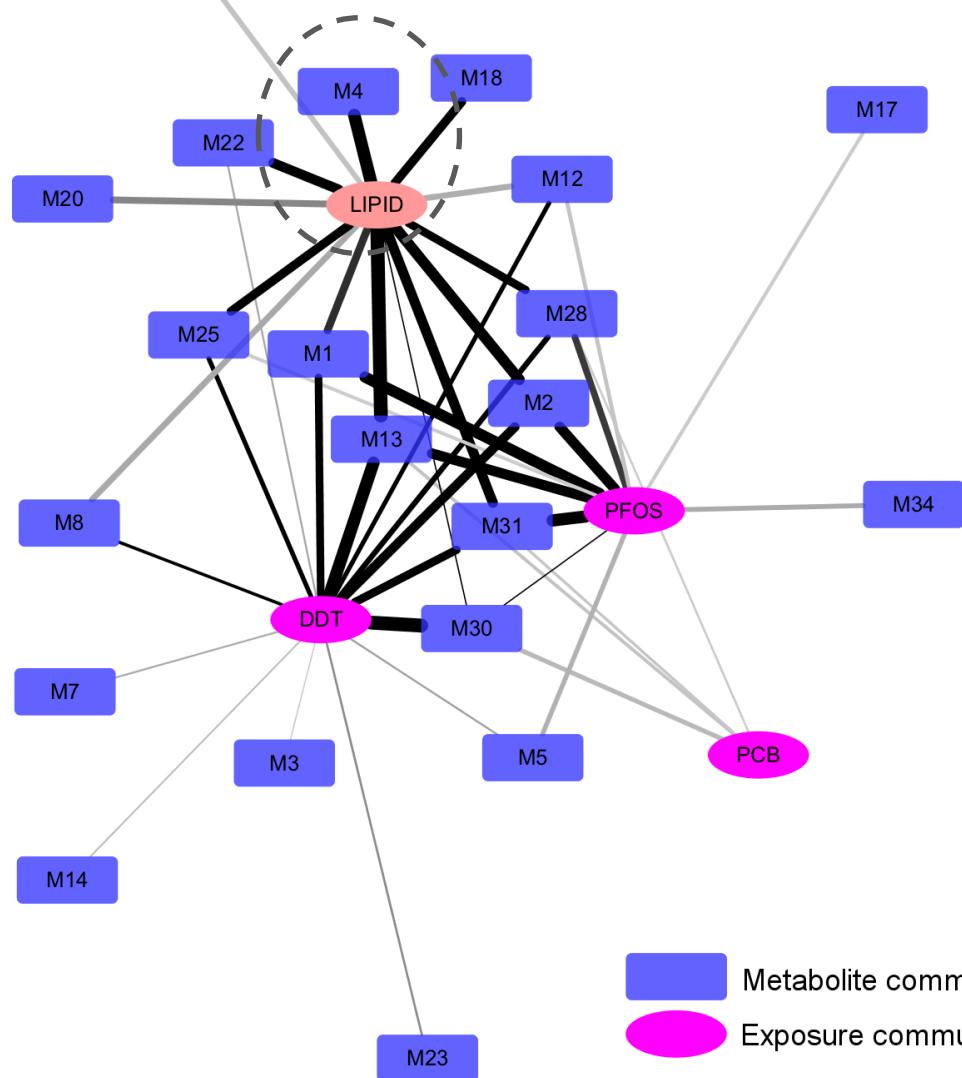


B M4 enriched pathways

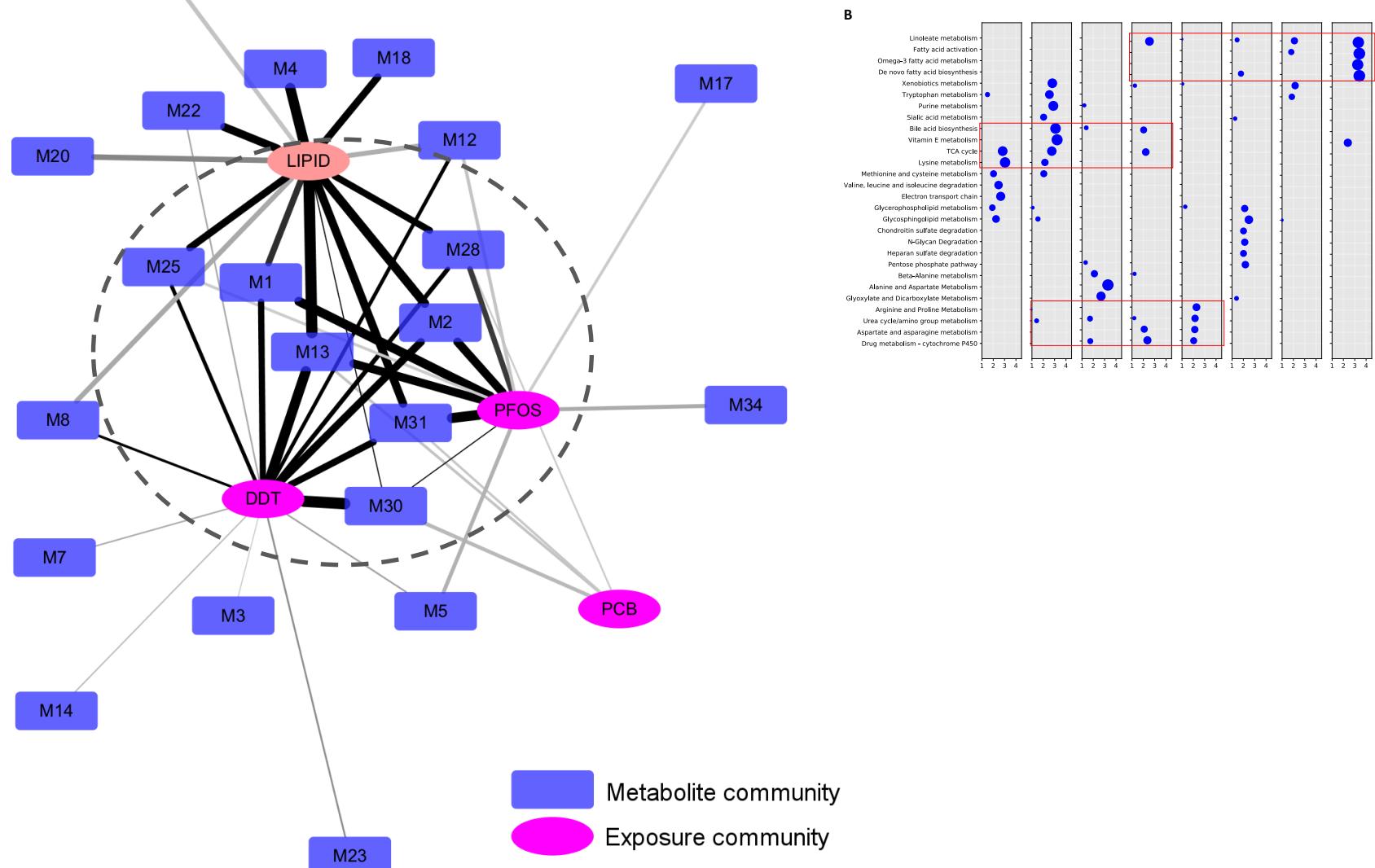


(*mummichog* result)

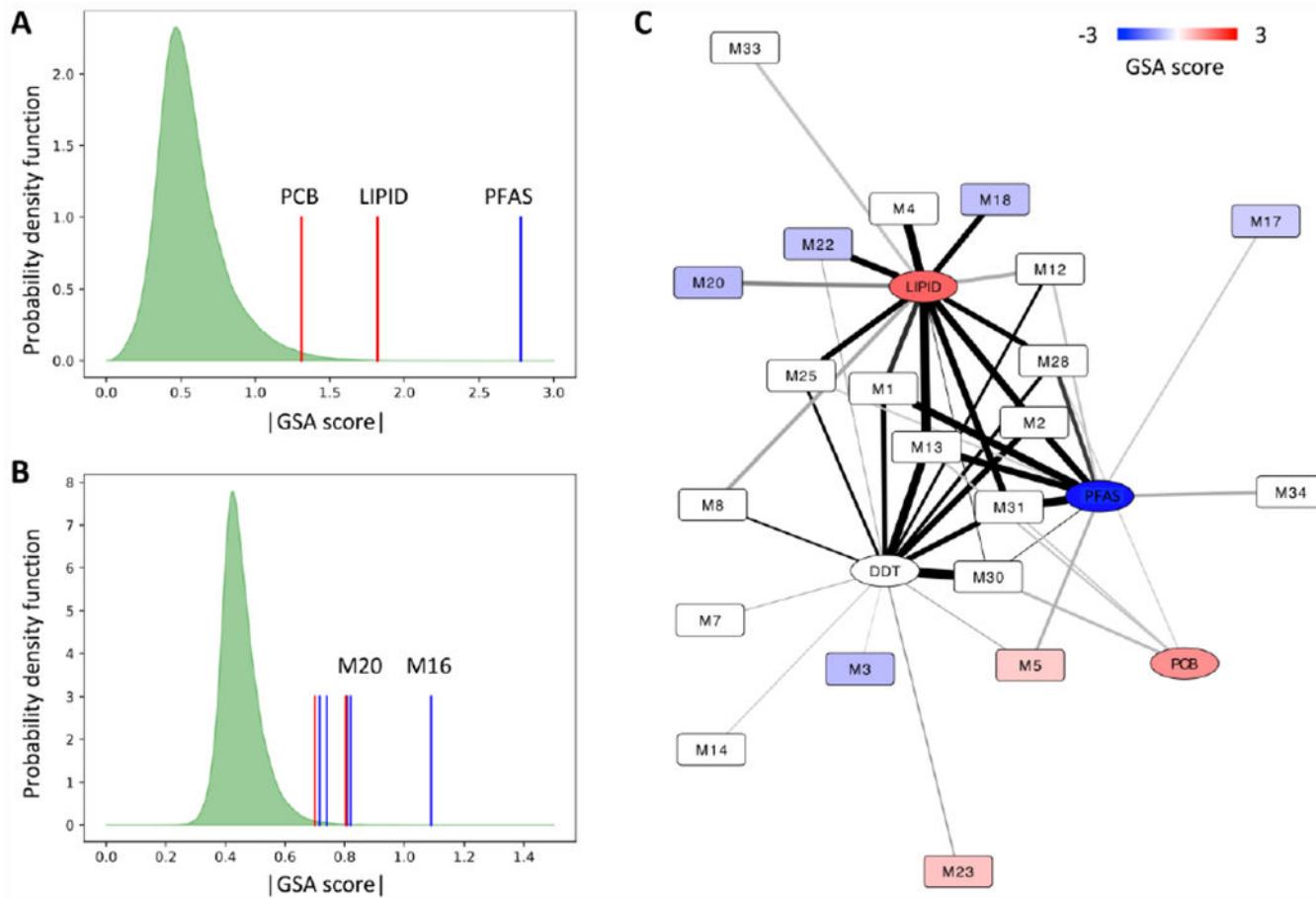
Metabolomics × Exposures



Metabolomics × Exposures



Communities associated with offspring breast cancer risk



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Nickilou Krigbaum



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HERCULES - P30ES019776

Center for Children's Health - P50ES026071, EPA 83615301

NIAID - UH2AI132345, U19AI090023

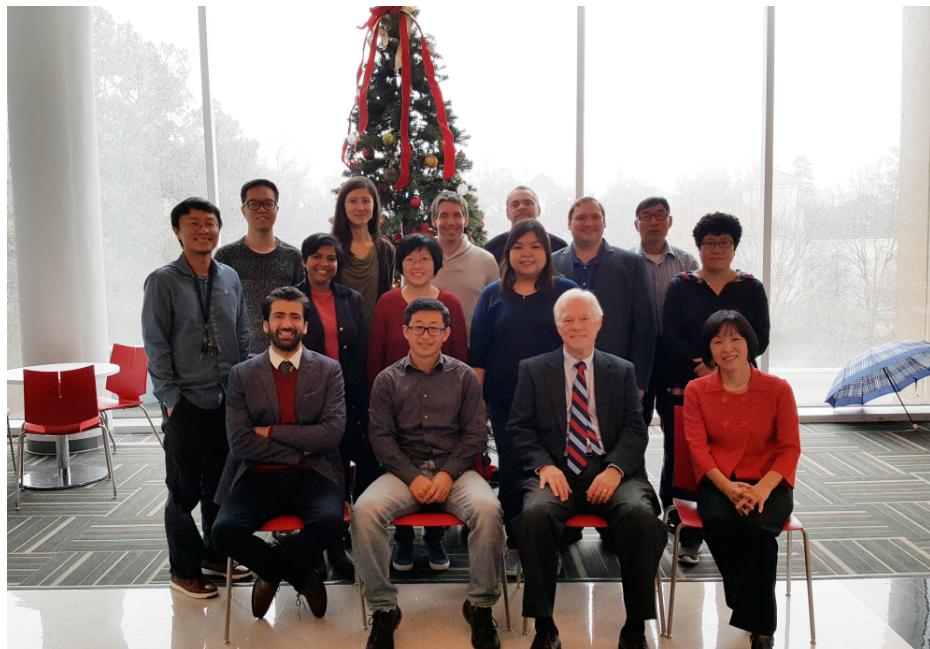
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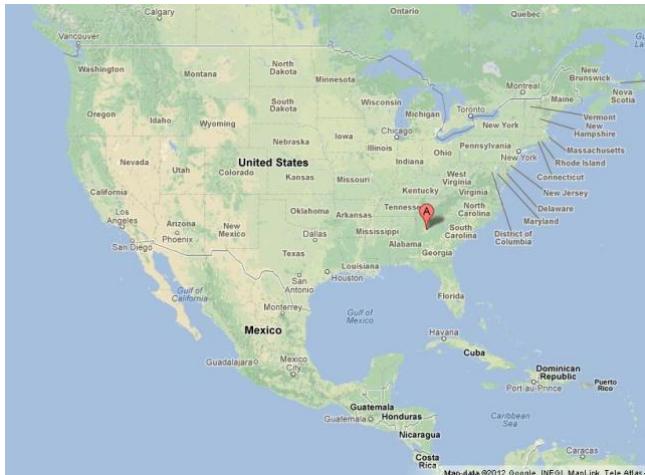
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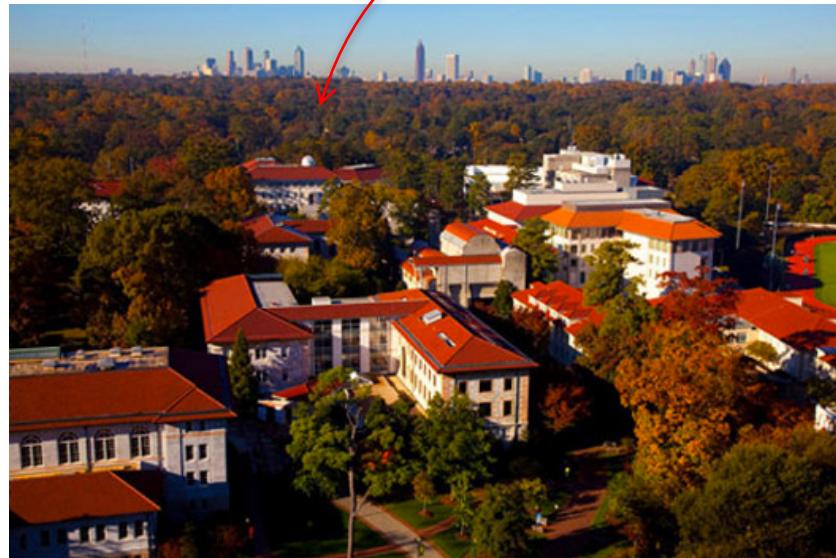
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Atlanta



? The secret Coke recipe



Emory University