



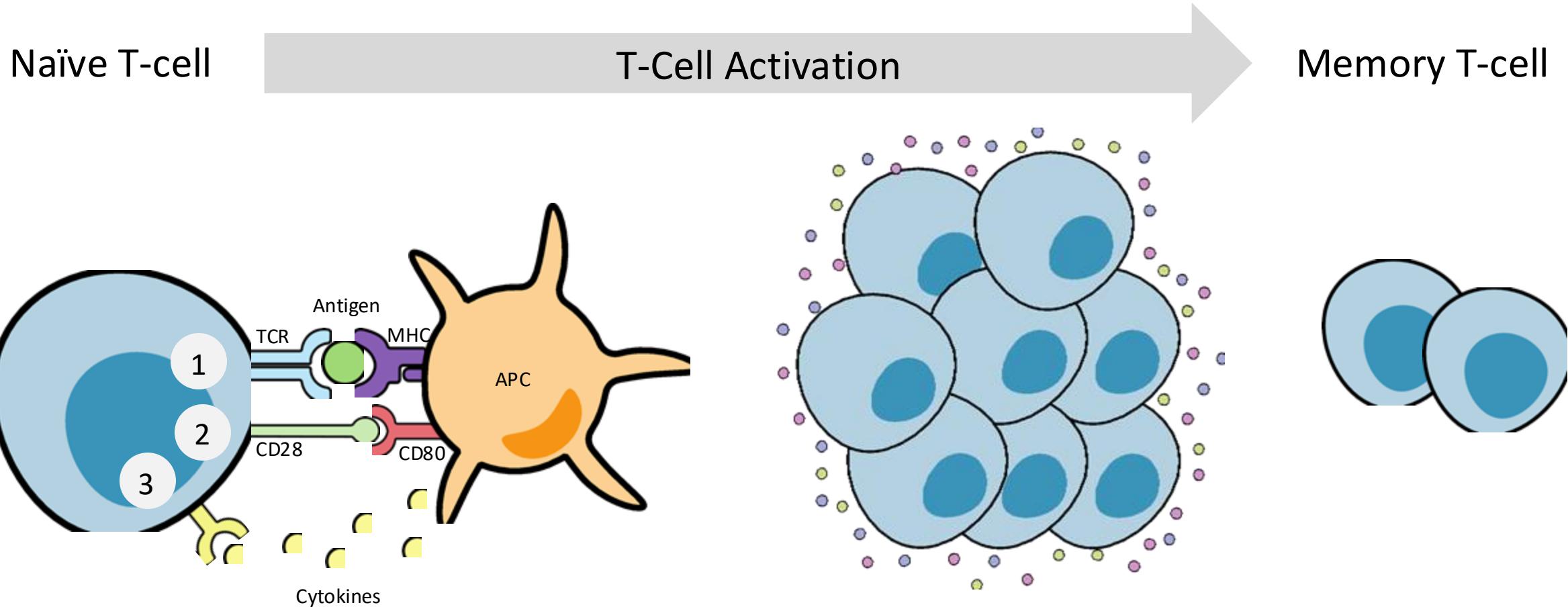
Trynka Lab



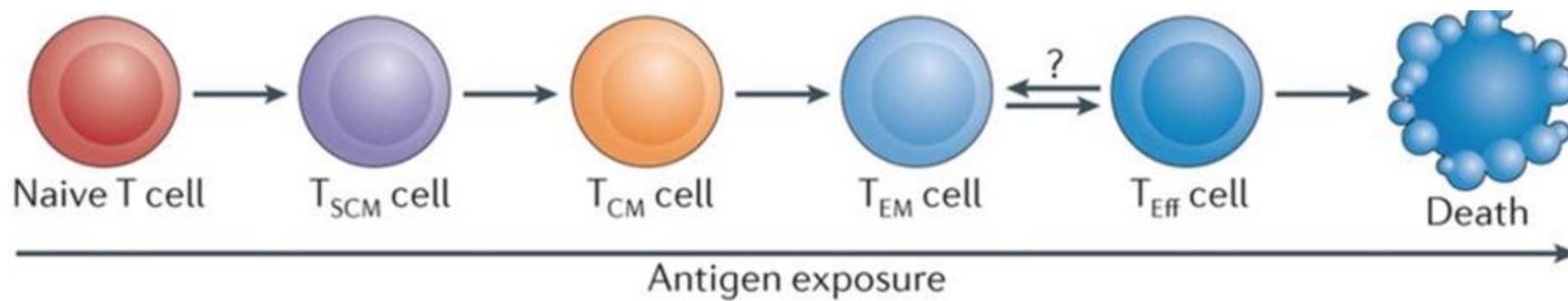
Unprecedented insights into immune system regulation with single-cell technologies

Gosia Trynka
Group Leader, Wellcome Sanger Institute
Science Director, Open Targets

Immune disease GWAS variants pinpoint the role of CD4+ T cells



Heterogeneity of T cells



T cells are critical for directing the immune system

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Milestone | 06 December 2022

T cells

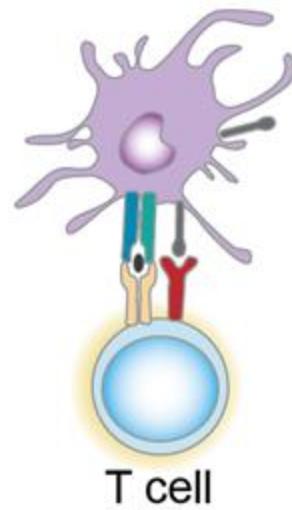
T cells are specialized lymphocytes that have vital roles in the immune system. Since their initial description in the 1960s, they have become a major focus of immunology research. In this Nature Milestone on T cells, we explore and celebrate pivotal studies that advanced our understanding of various aspects of T cell biology, including their functions in health and disease and potential for therapeutic application.



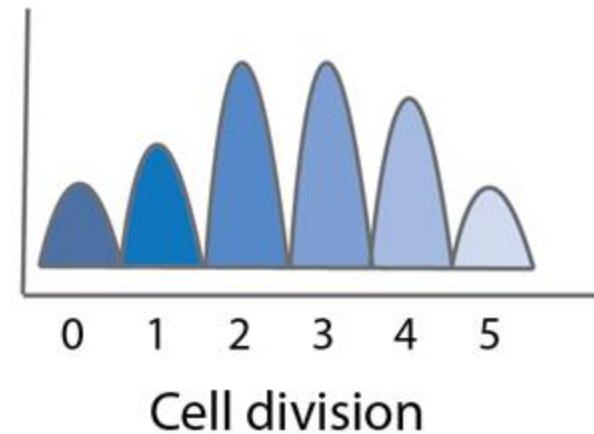
- Application of scRNAseq to study cell response to stimuli *in vitro*

T cells differentiate to perform different functions

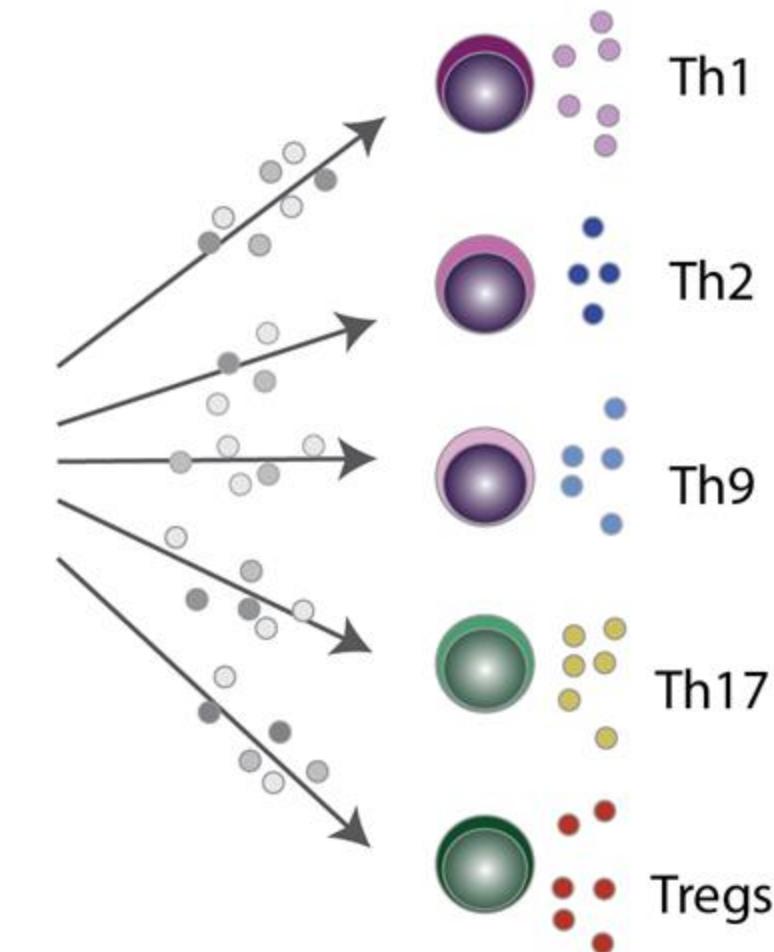
Activation



Proliferation

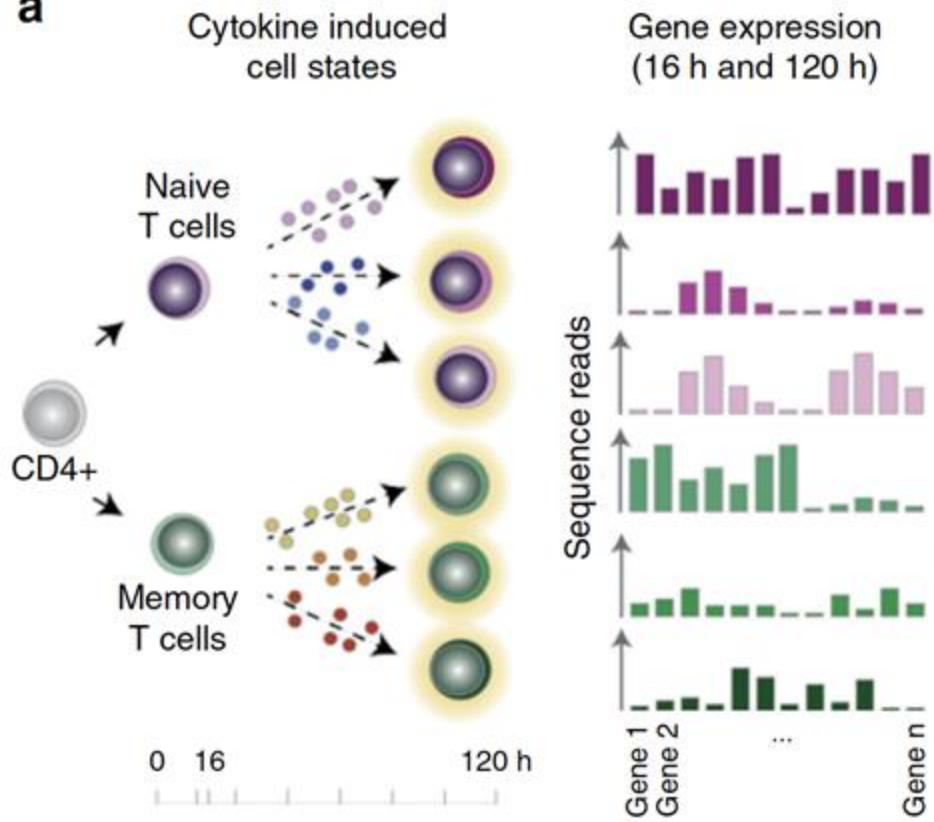


Differentiation



Response to cytokines across different CD4 T cells (scRNA-seq)

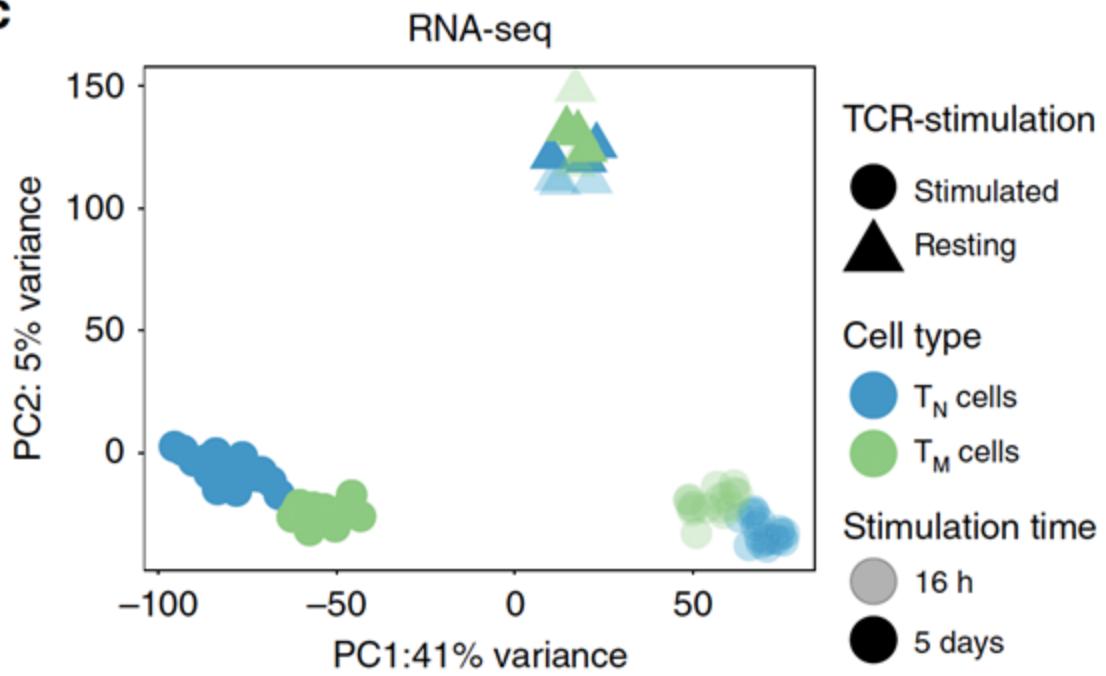
a



T cell state	TCR-stimulation	Cytokines
Th0	anti-CD3/anti-CD28	None
Th1	anti-CD3/anti-CD28	IL12, anti-IL4
Th2	anti-CD3/anti-CD28	IL4 anti-IFNγ
Th17	anti-CD3/anti-CD28	TGFβ, IL6, IL23, IL1β anti-IFNγ, anti-IL4
iTreg	anti-CD3/anti-CD28	TGFβ, IL2
IFNβ	anti-CD3/anti-CD28	IFNβ
Resting	None	None

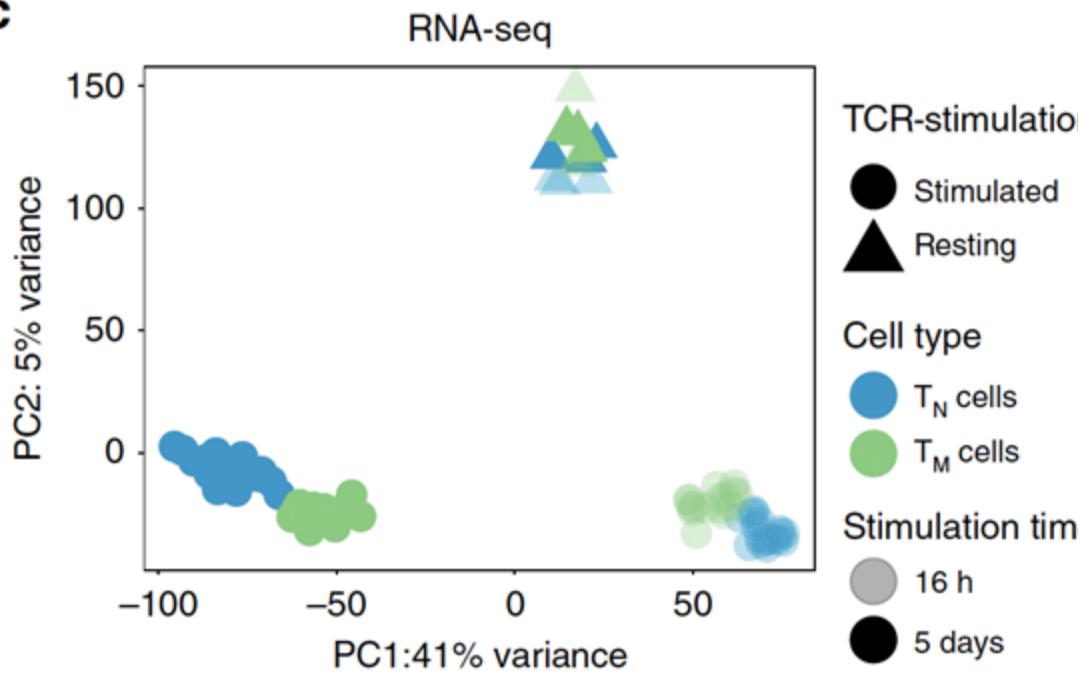
Cytokines induce cell type specific gene expression programmes

c

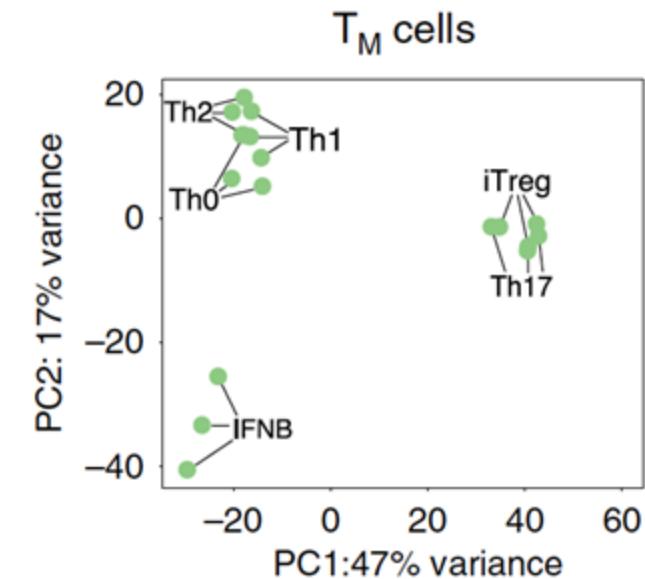
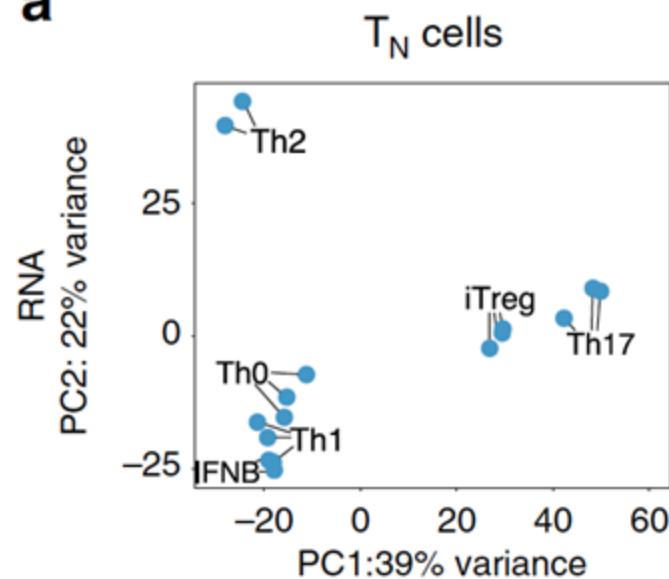


Cytokines induce cell type specific gene expression programmes

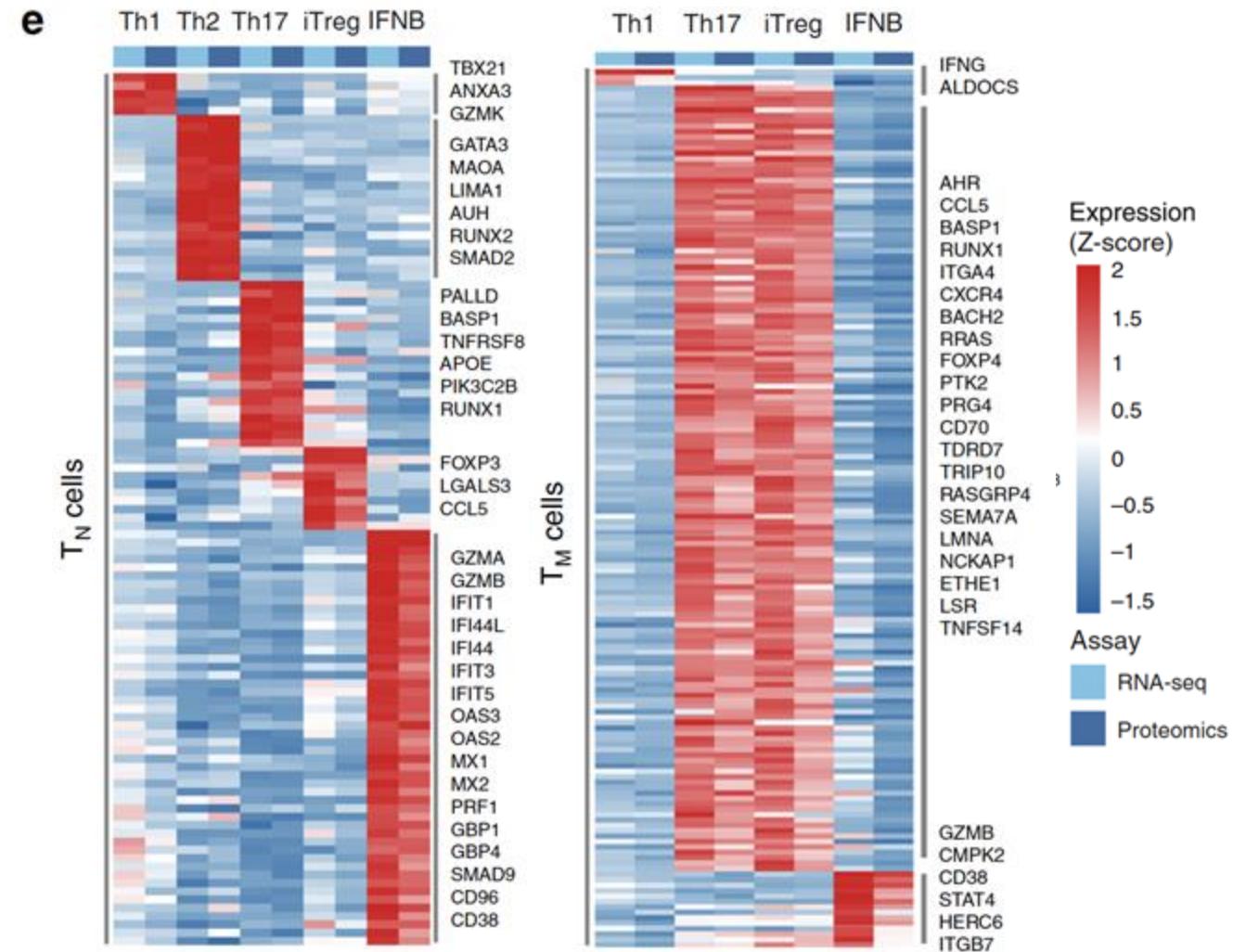
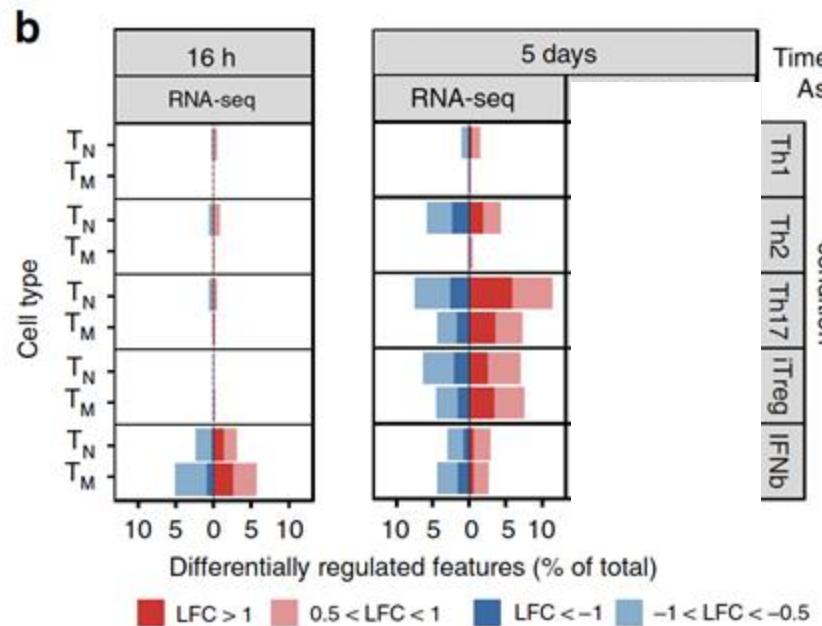
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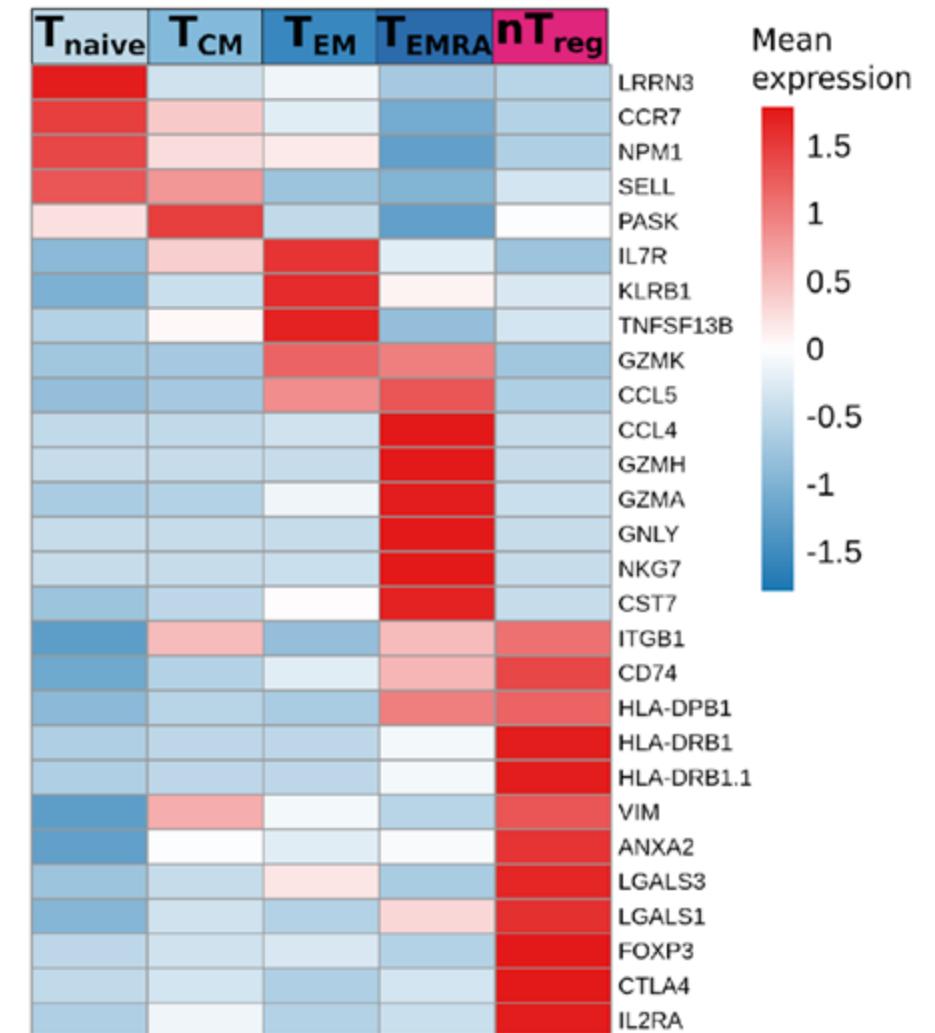
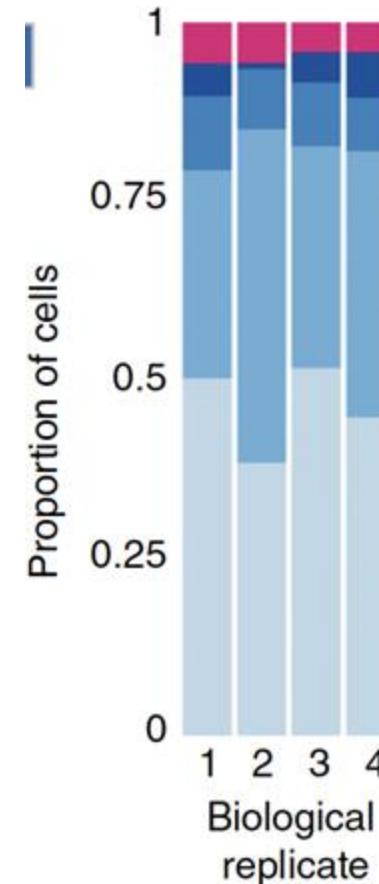
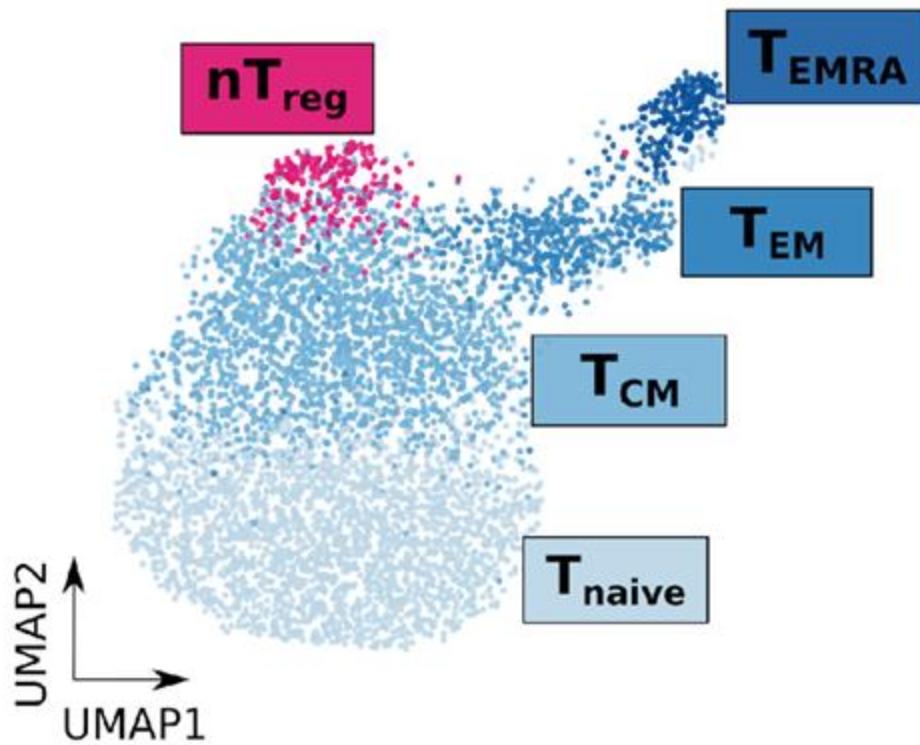
Cytokines induce cell type specific gene expression programmes



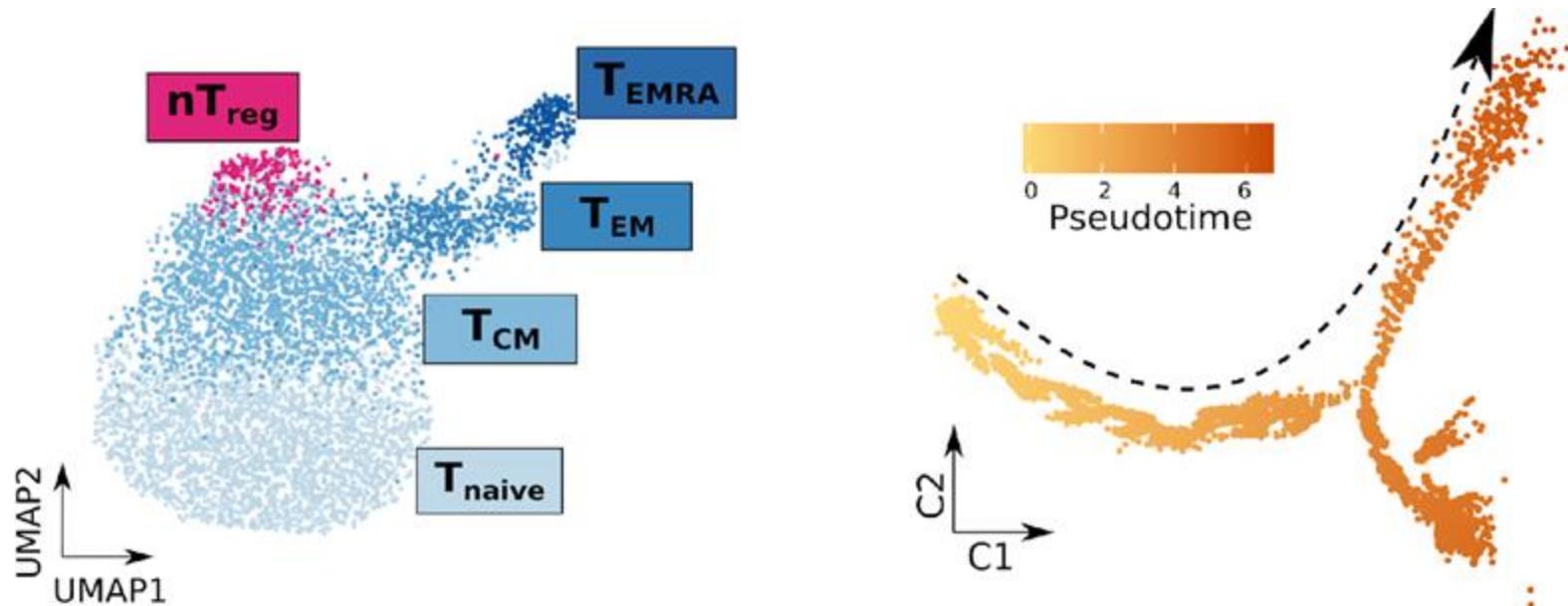
What drives the cell type differences:

- T_M as a whole do not respond
- A subset of T_M responds but is masked in bulk RNAseq

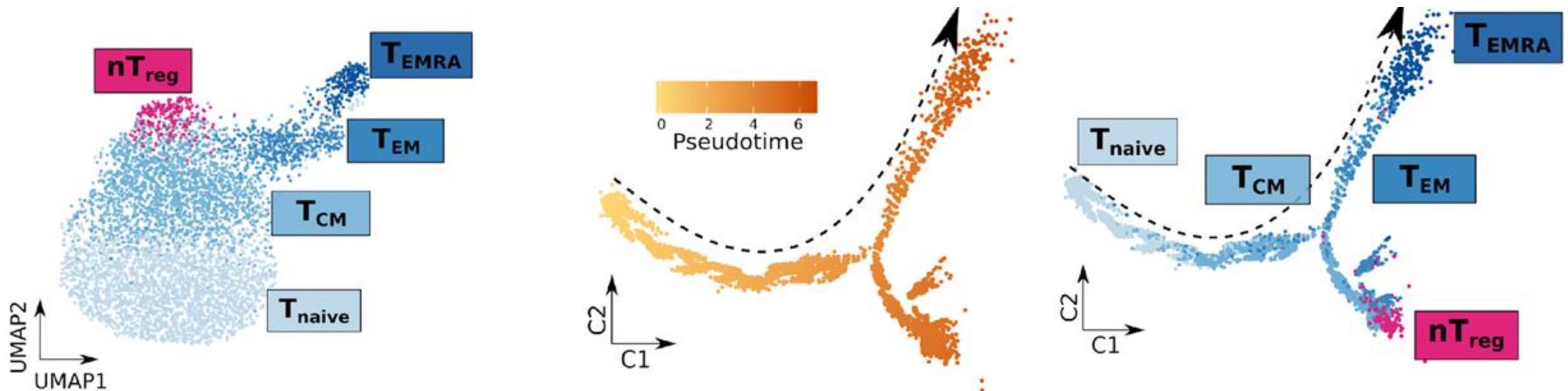
scRNAseq recapitulates major subsets of CD4+ T cells



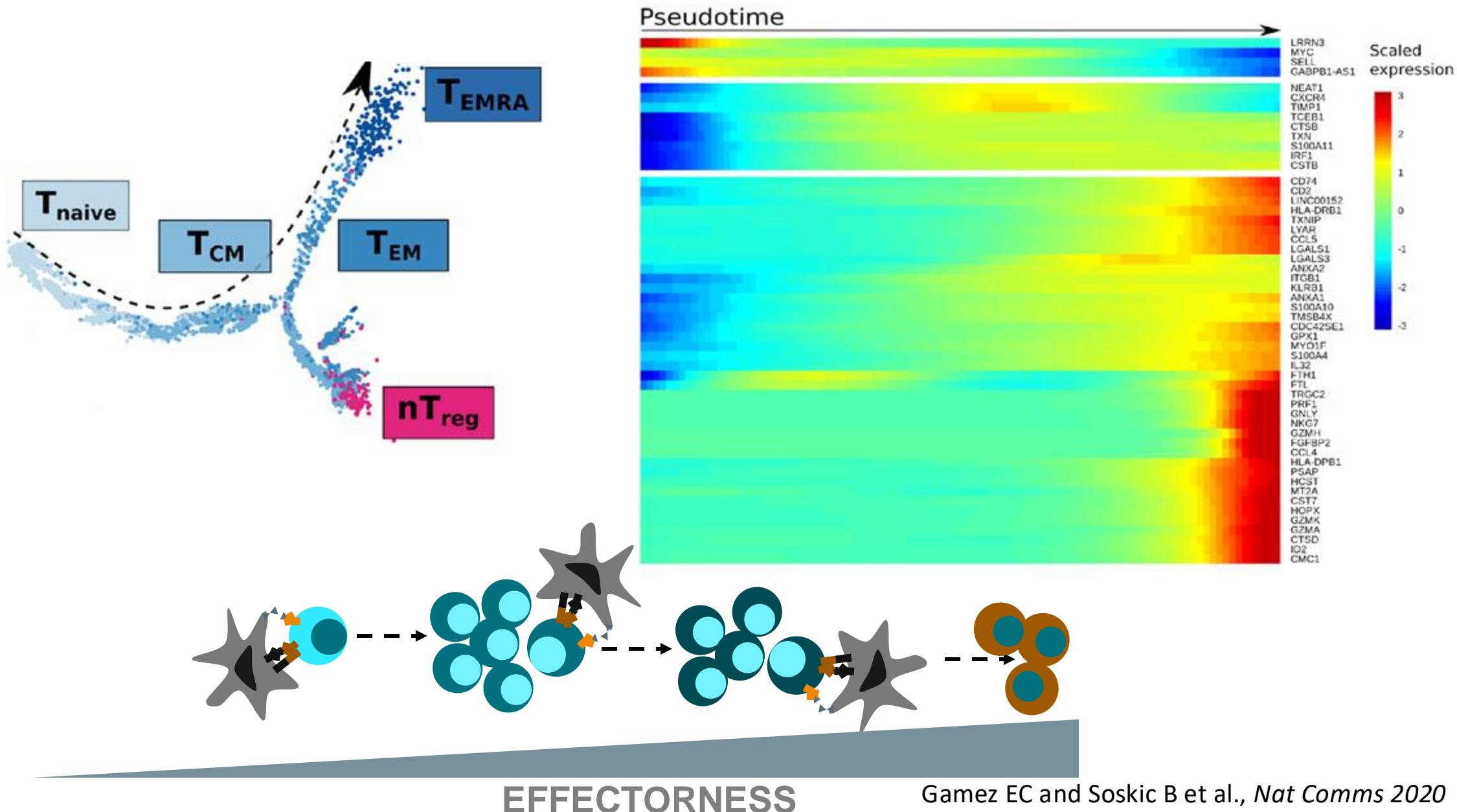
CD4+ T cells for a transcriptional continuum



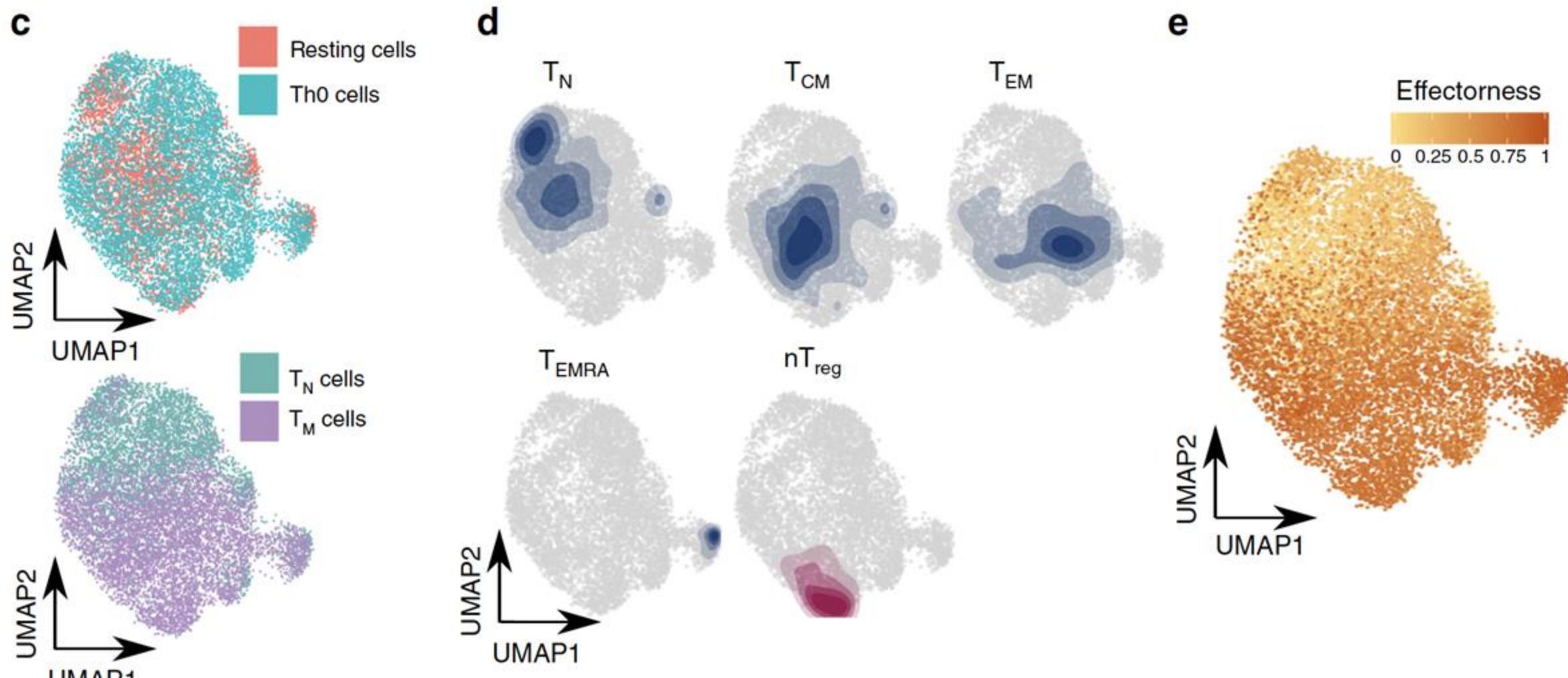
CD4+ T cells for a transcriptional continuum



CD4+ T cell continuum reflects activation history

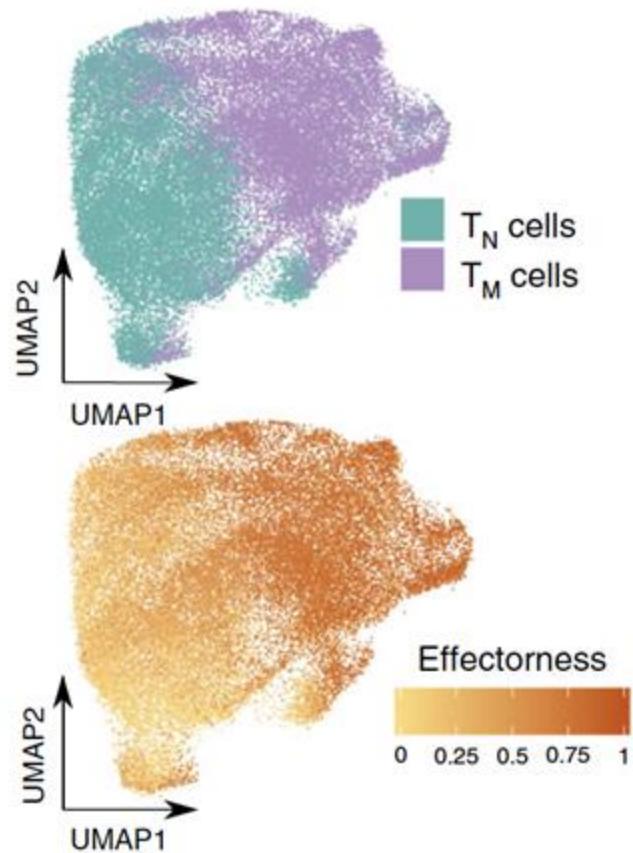


Effectiveness is reflected in stimulated cells



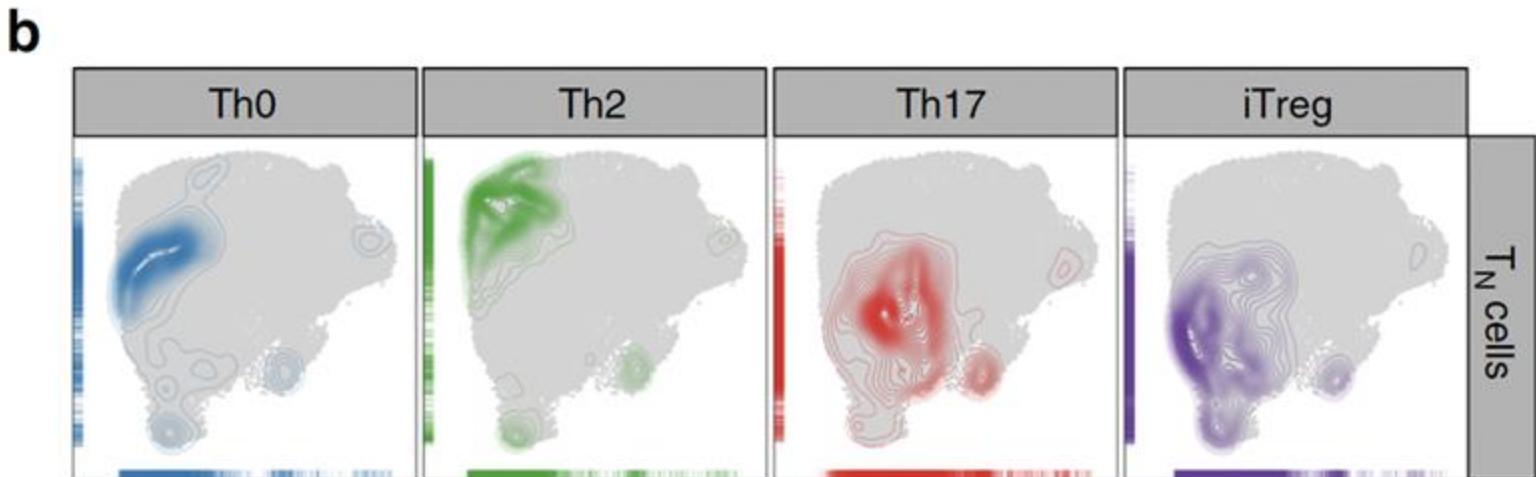
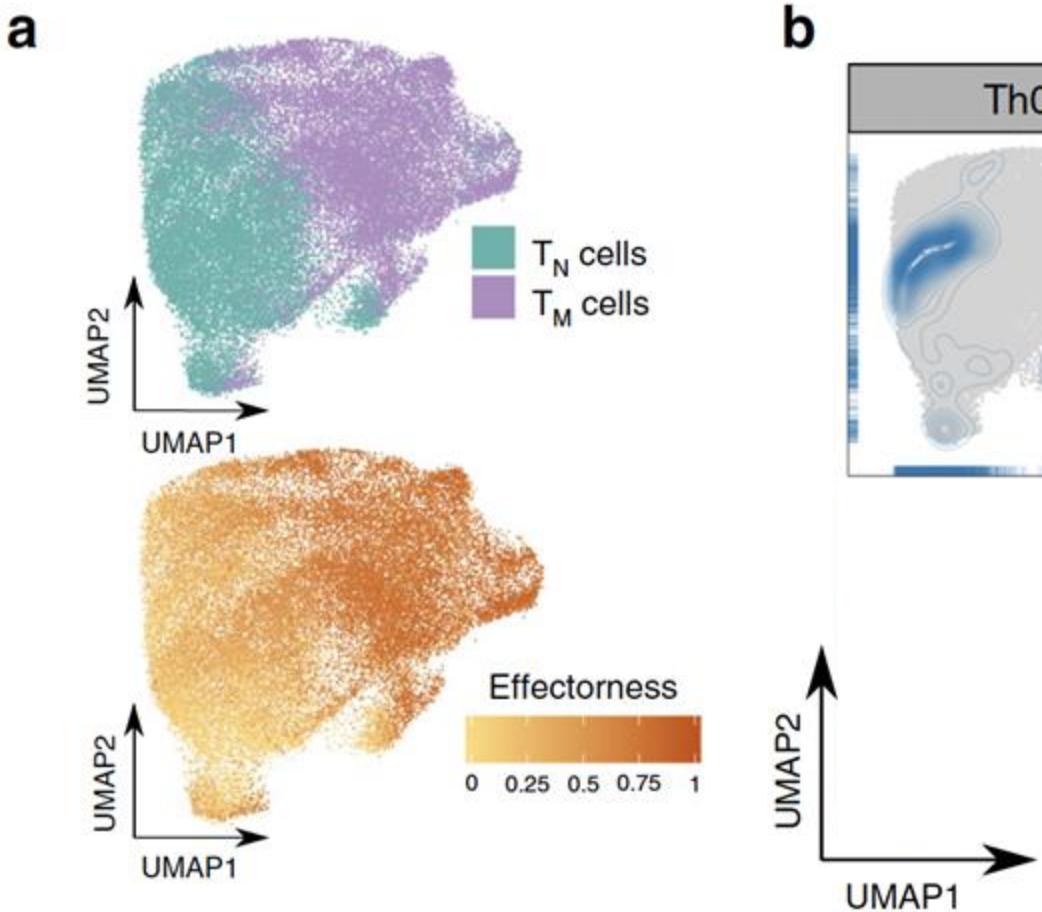
Effectiveness shapes the response to cytokines

a

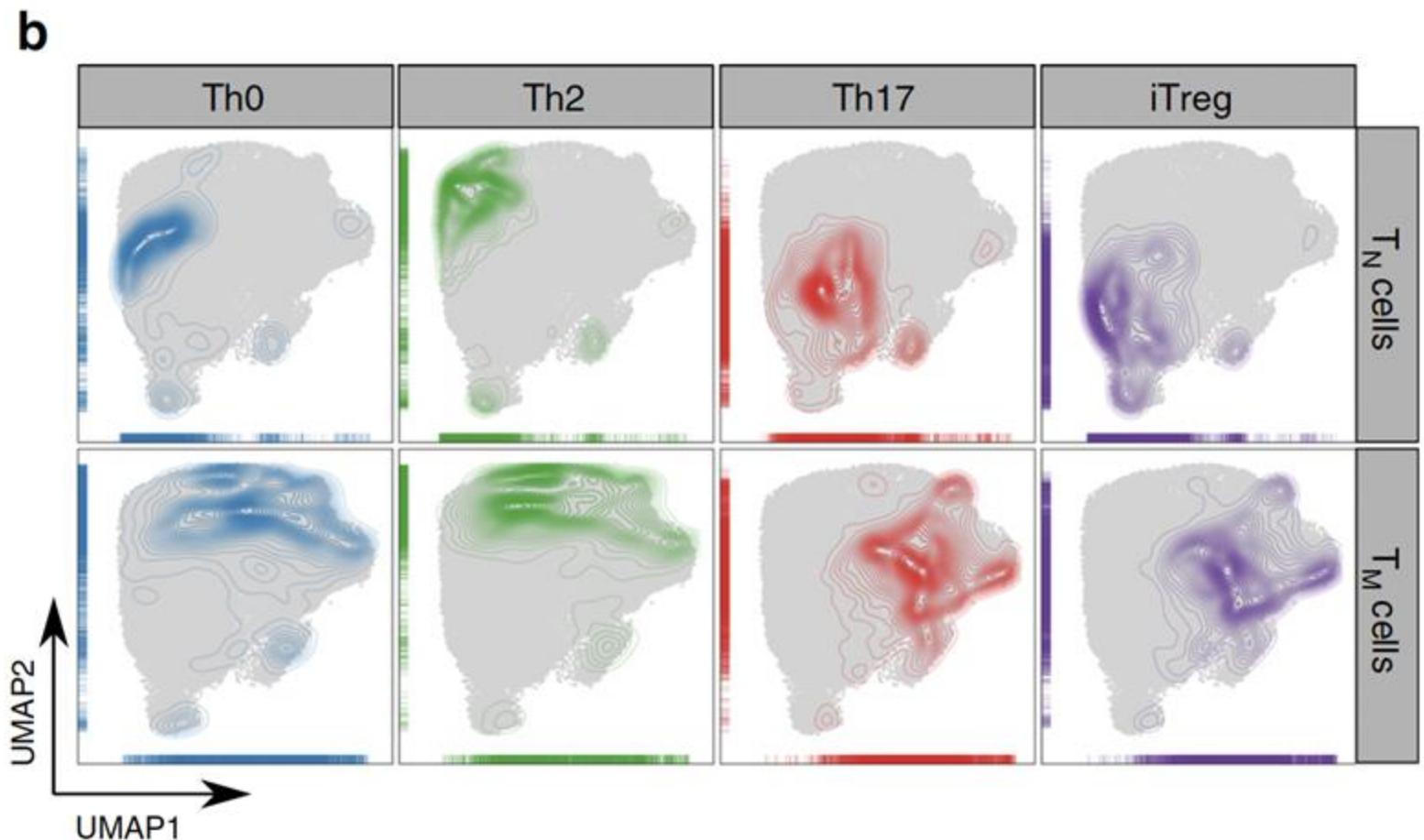
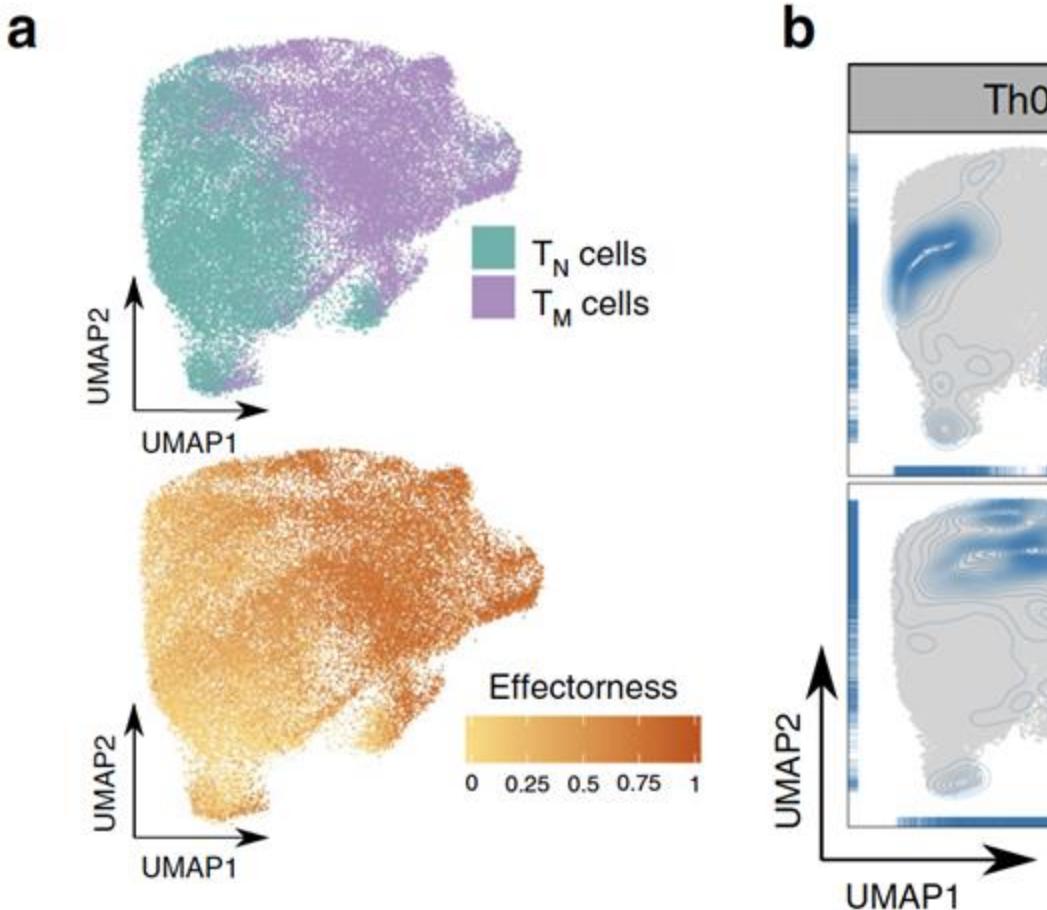


Cells exposed to cytokine polarization preserve their effectiveness properties

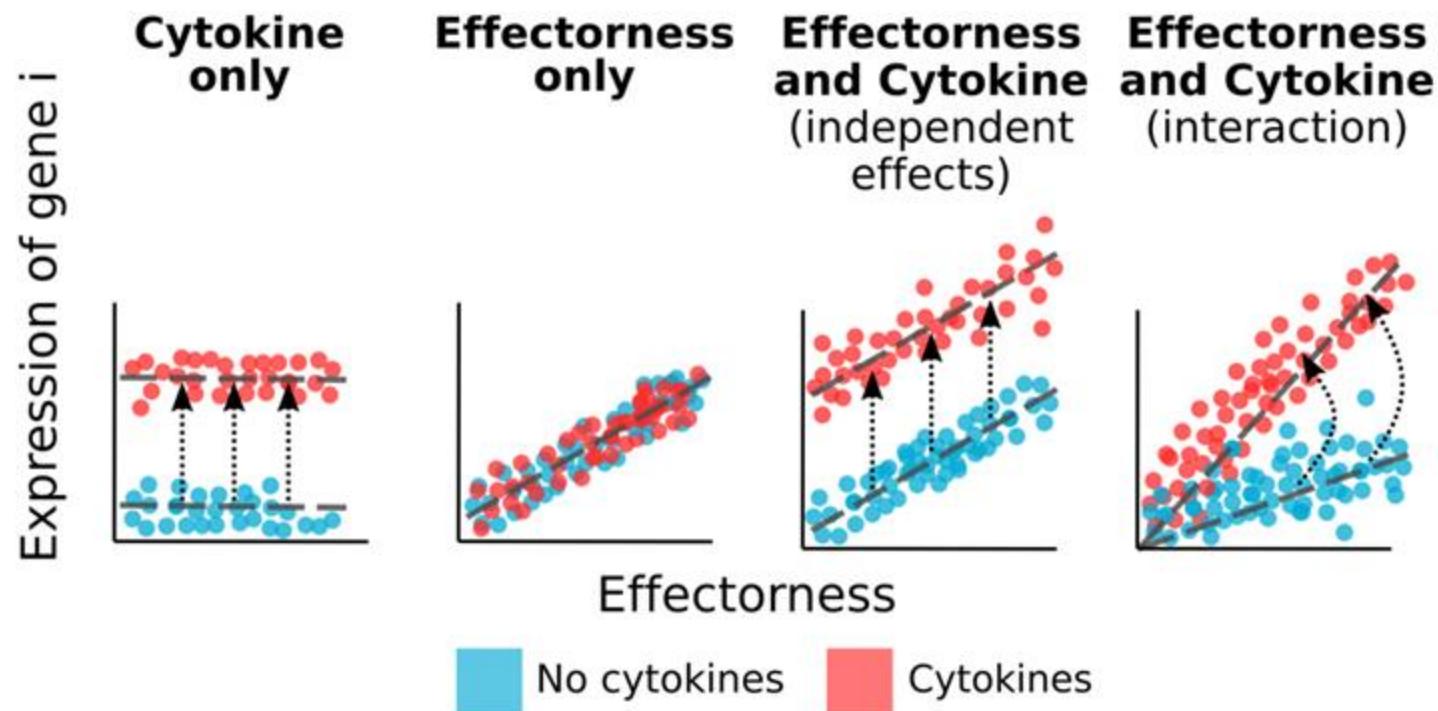
Effectiveness shapes the response to cytokines



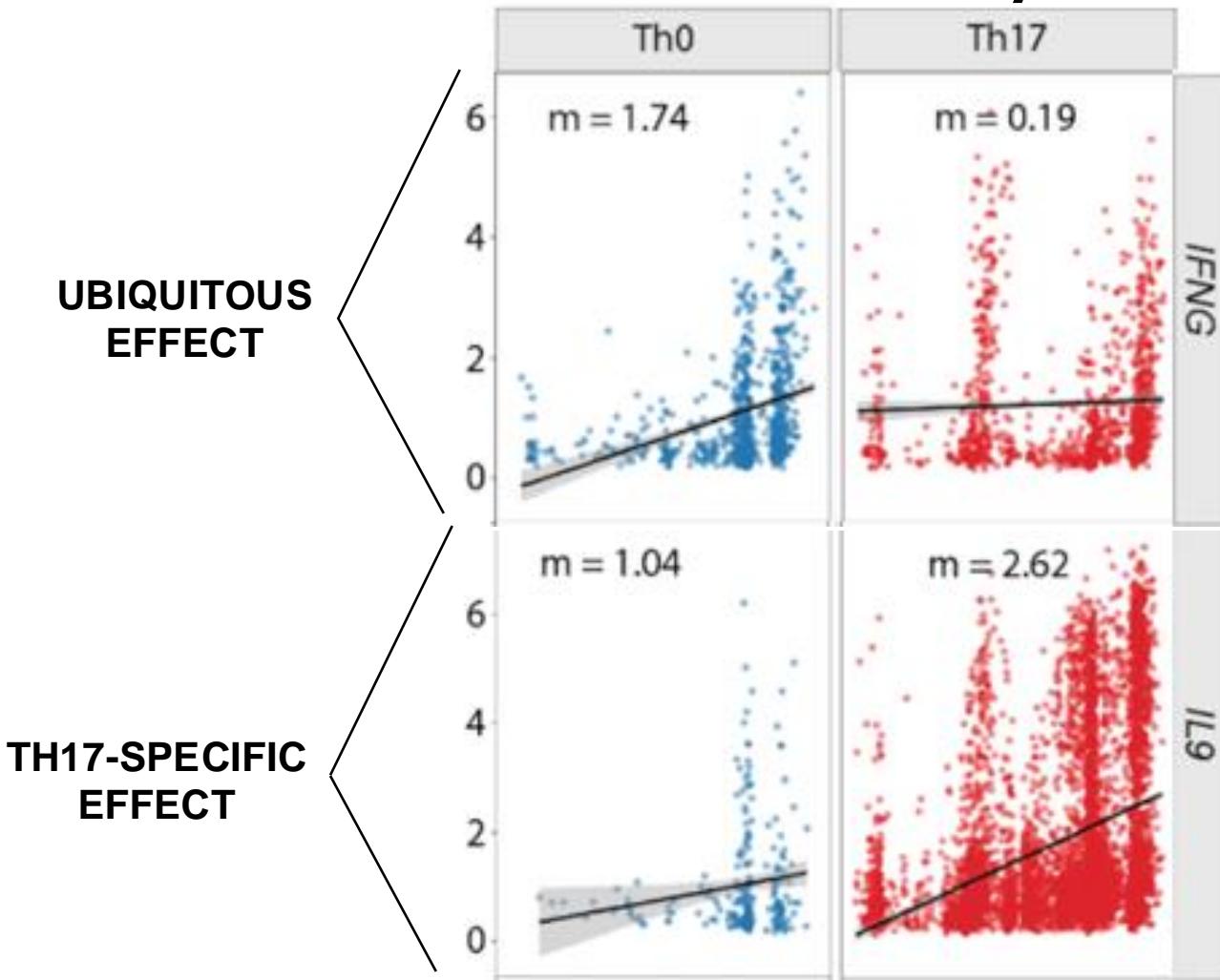
Effectiveness shapes the response to cytokines



Modelling gene expression interactions between effectorness and cytokine ctimulation



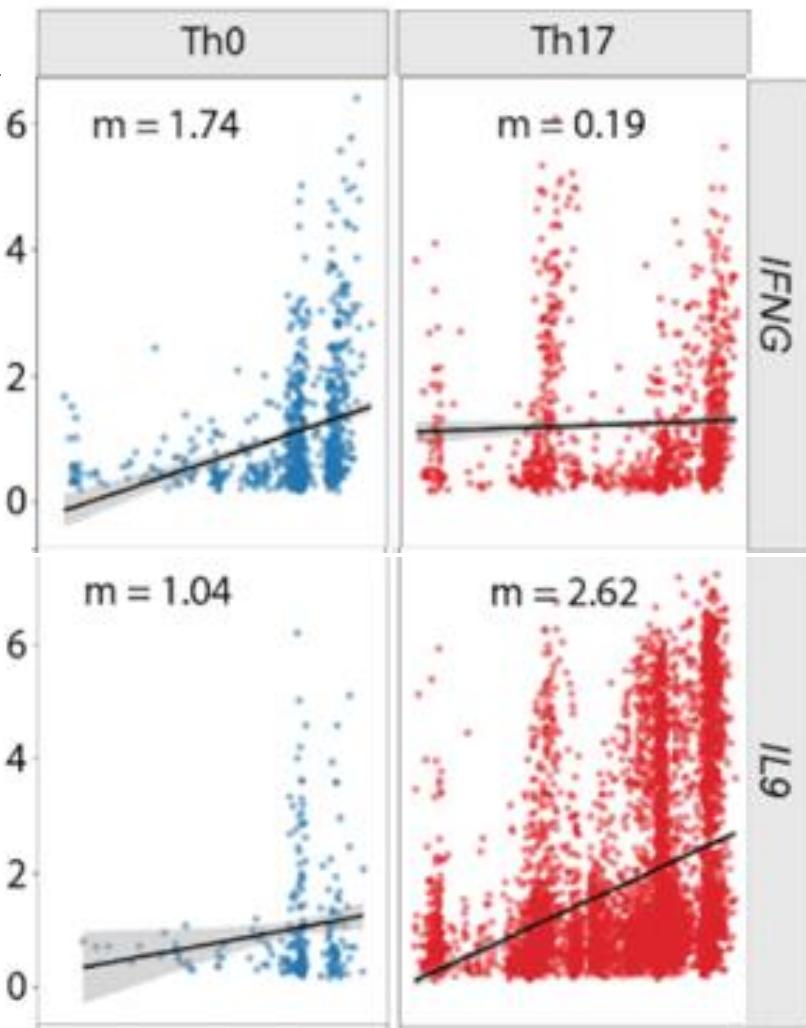
Gene expression is regulated by effectorness and cytokines



- 210 genes are significantly associated with effectornes
- 203 also regulated by cytokines,
- 191 with interaction effect
- 12 genes with cytokine specific effect

UBIQUITOUS EFFECT

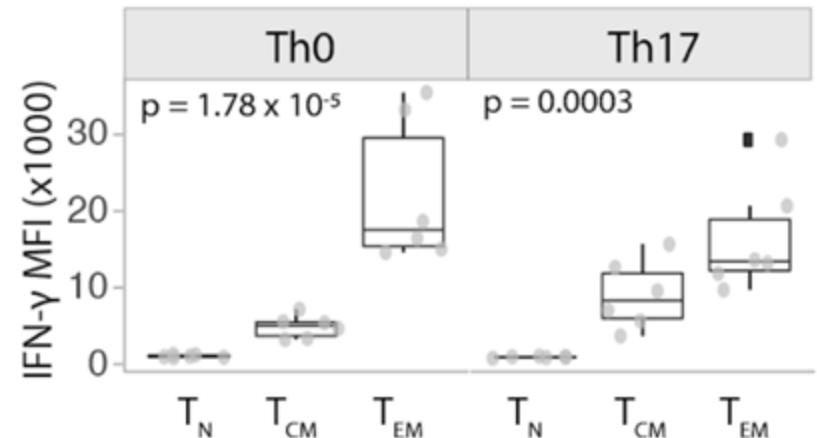
TH17-SPECIFIC EFFECT



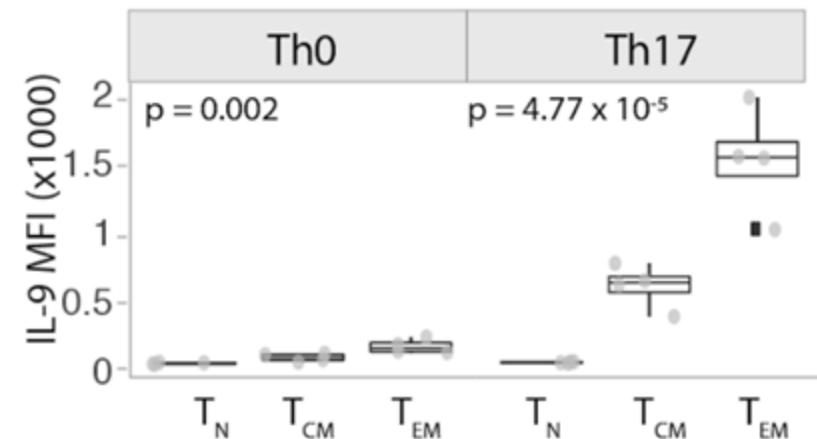
IFNG

IL9

IFN γ

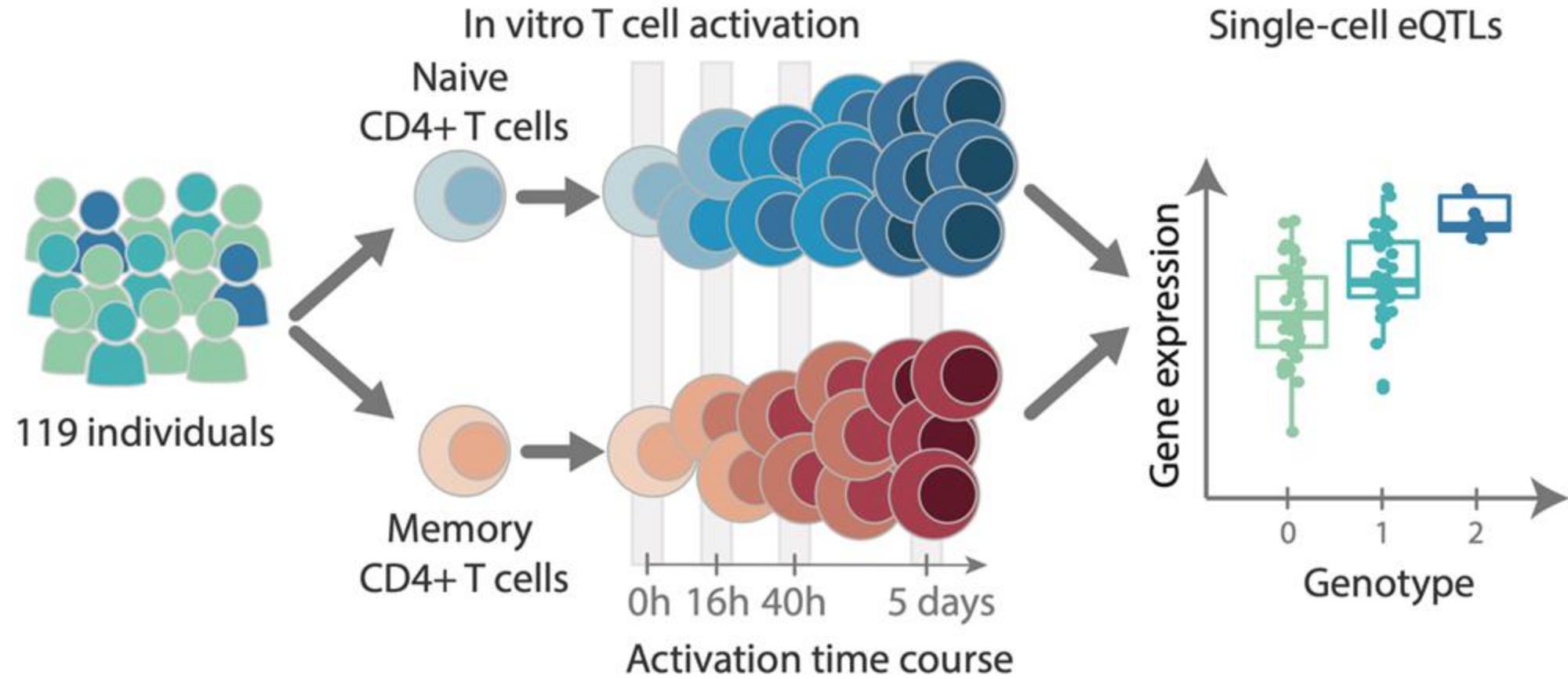


IL-9

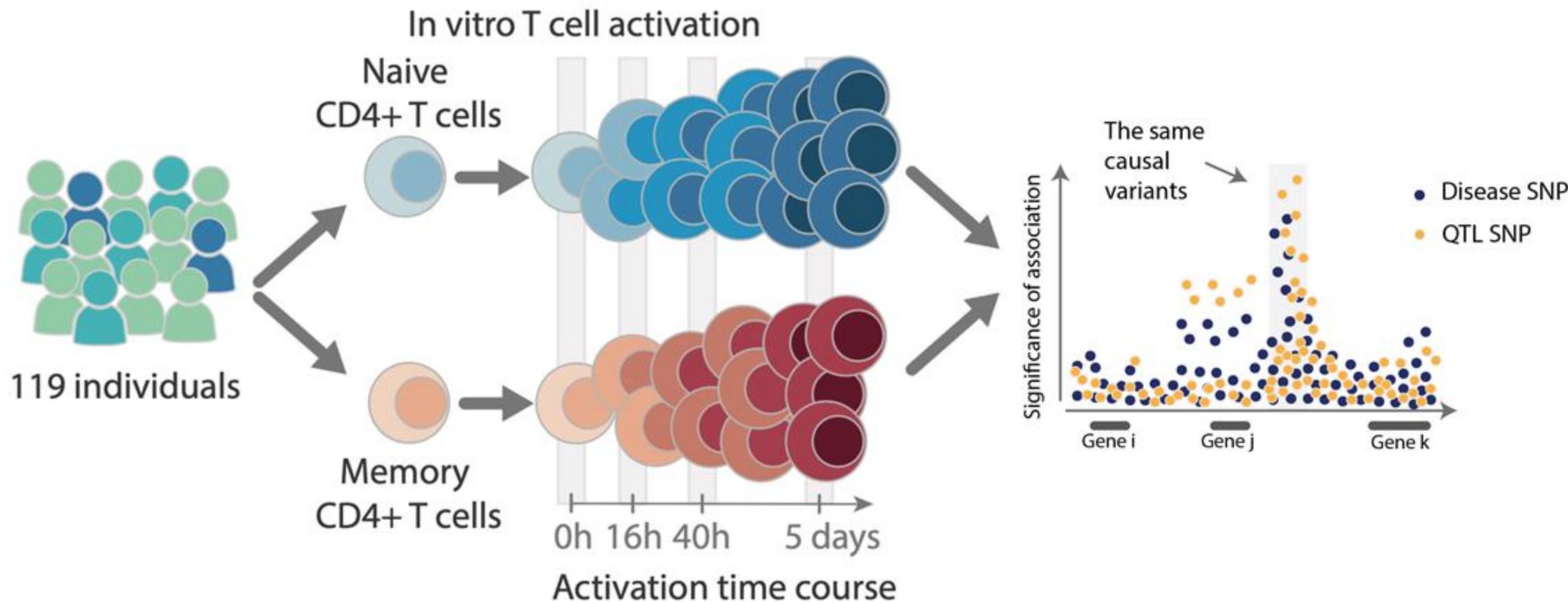


- Application of scRNAseq to study cell response to stimuli in vitro
- Application of scRNAseq to study how genetic variants regulated gene expression

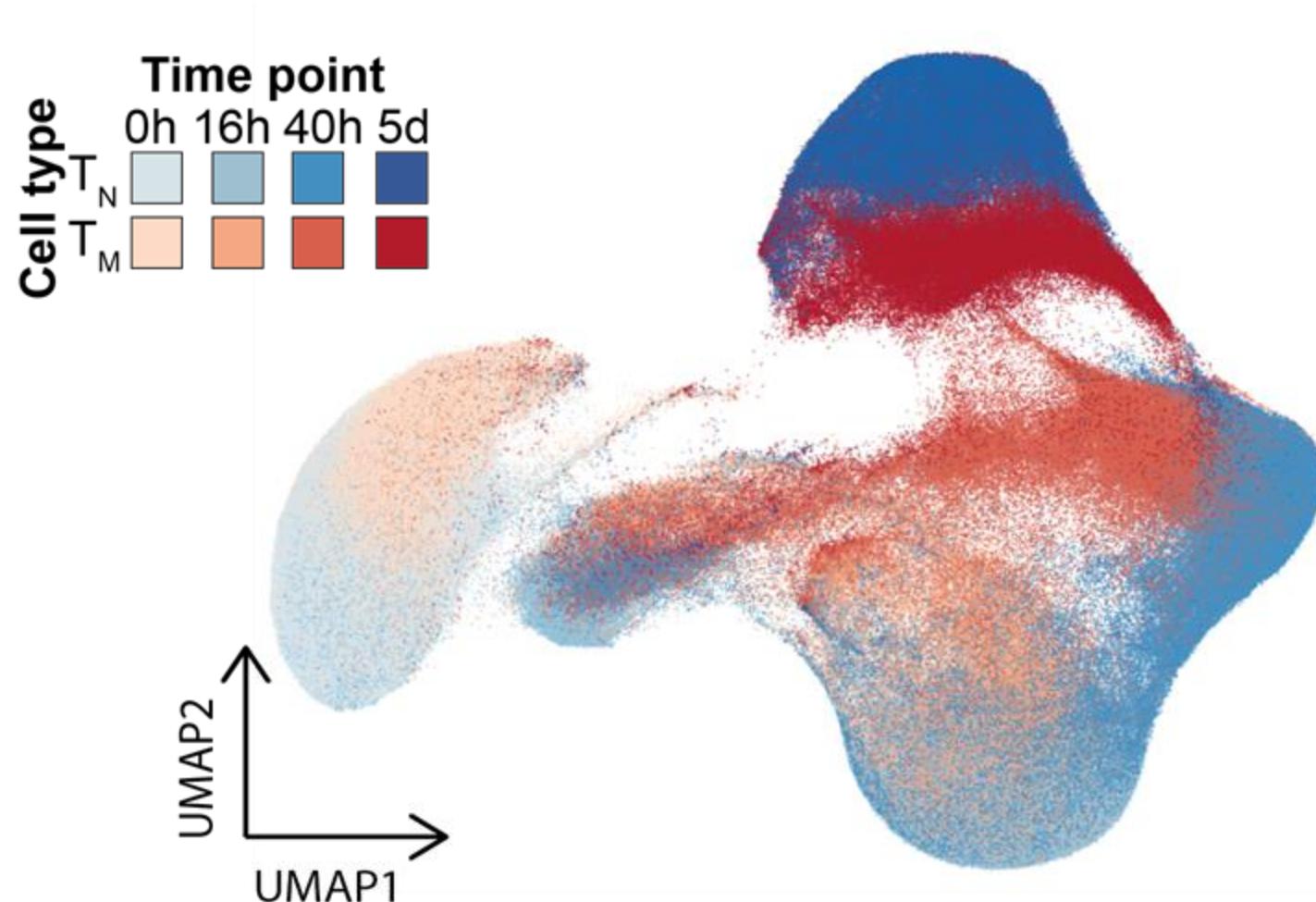
Mapping gene expression regulation during T cell activation



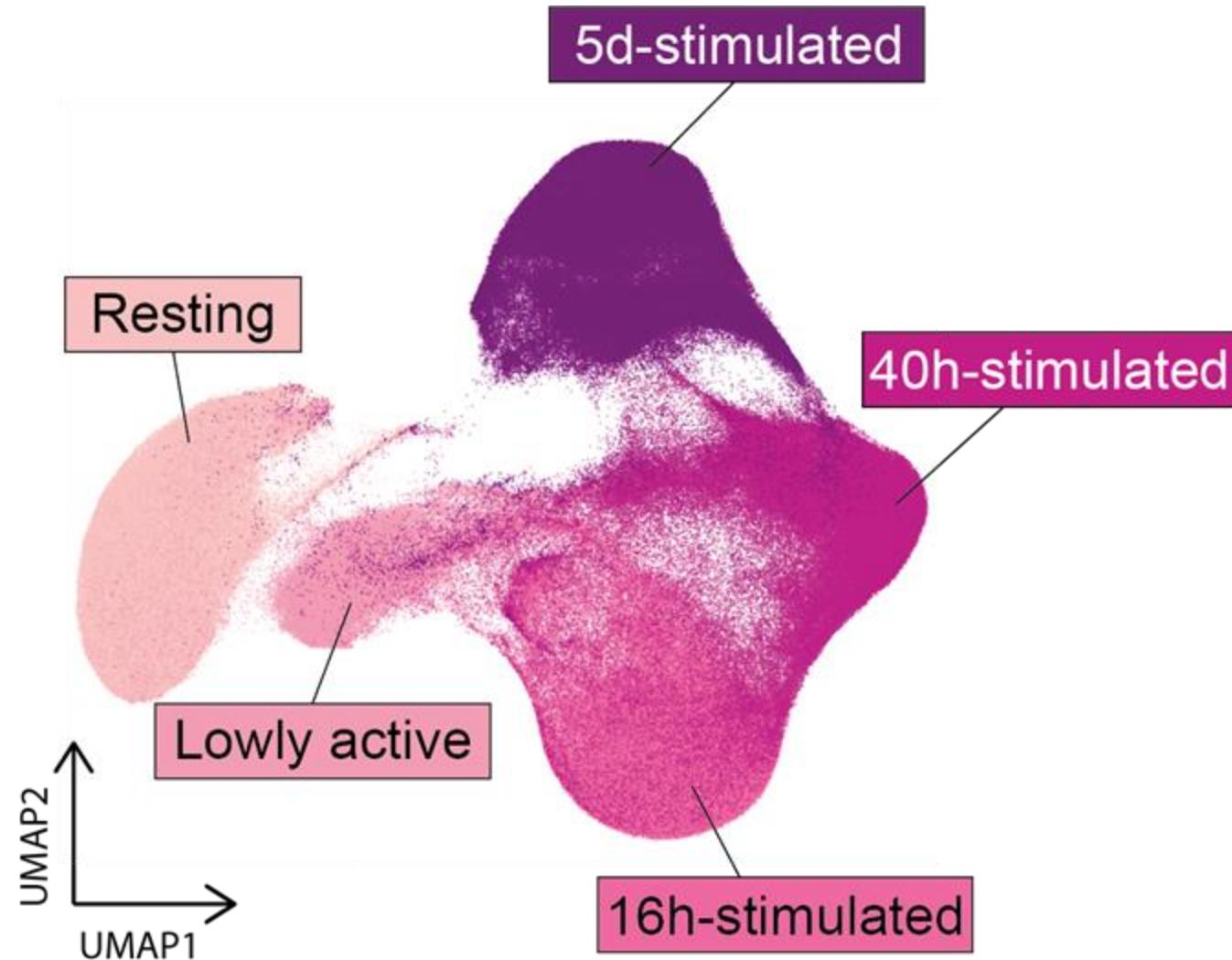
Identifying disease causal genes through colocalisation



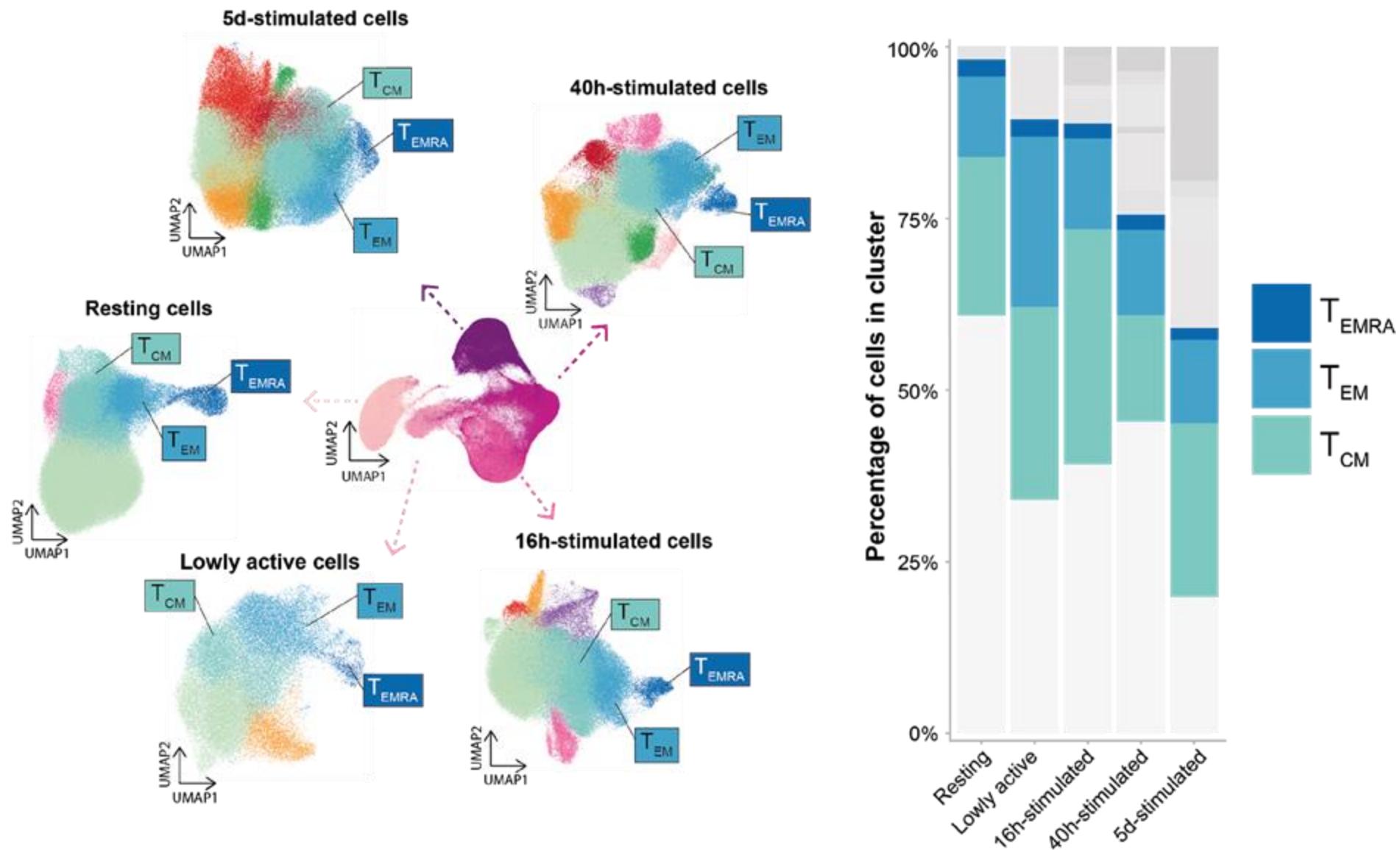
A T cell activation map constructed from 655,349 single cells



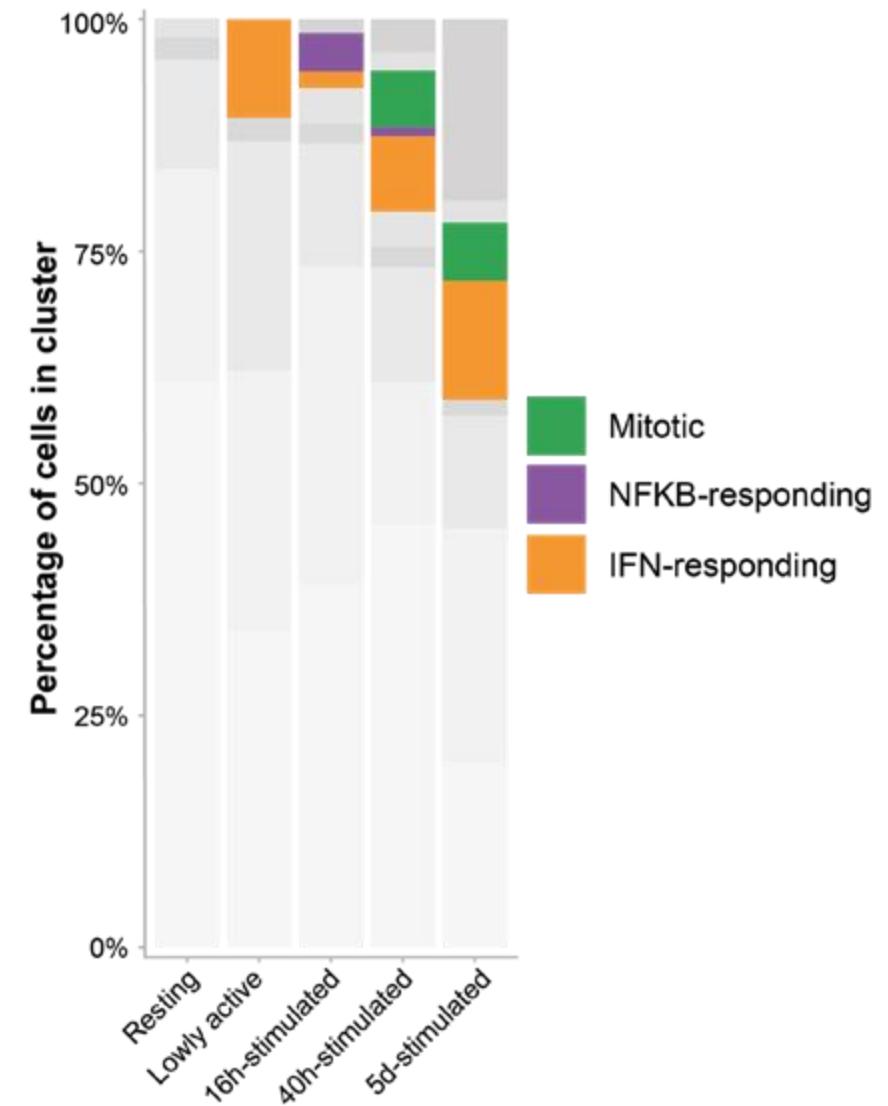
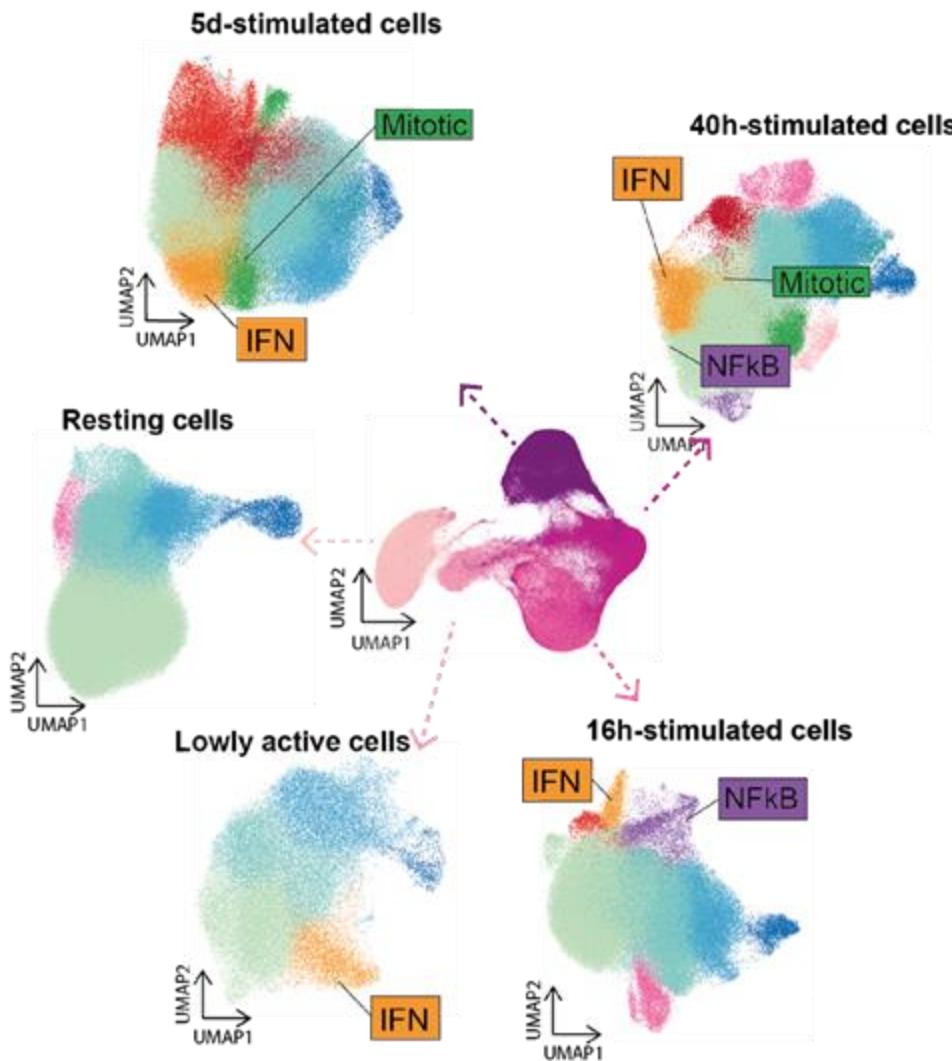
Distinct cell states during CD4+ T cell activation



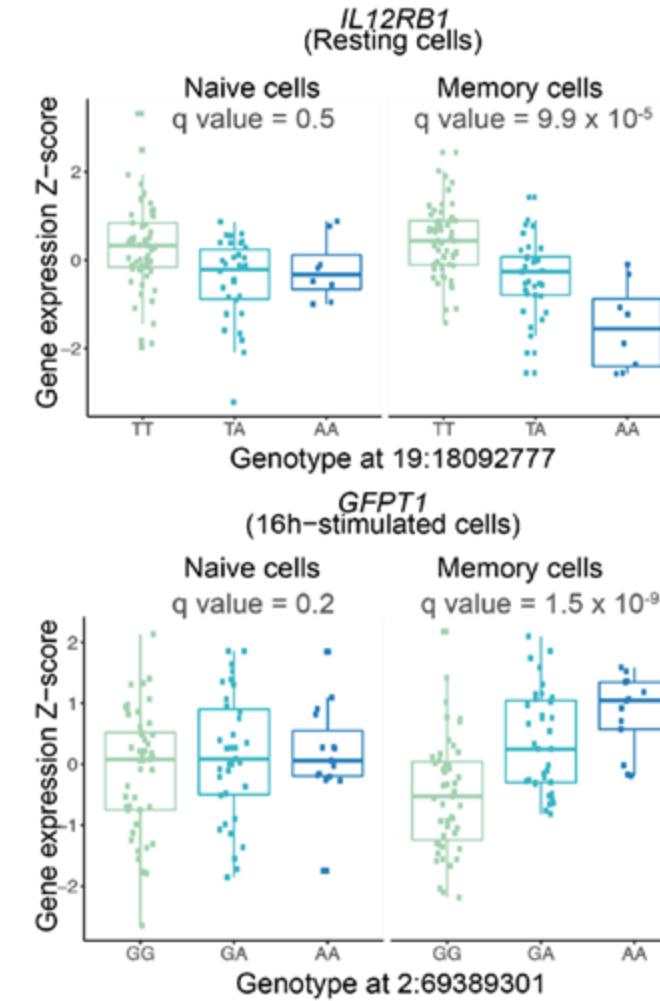
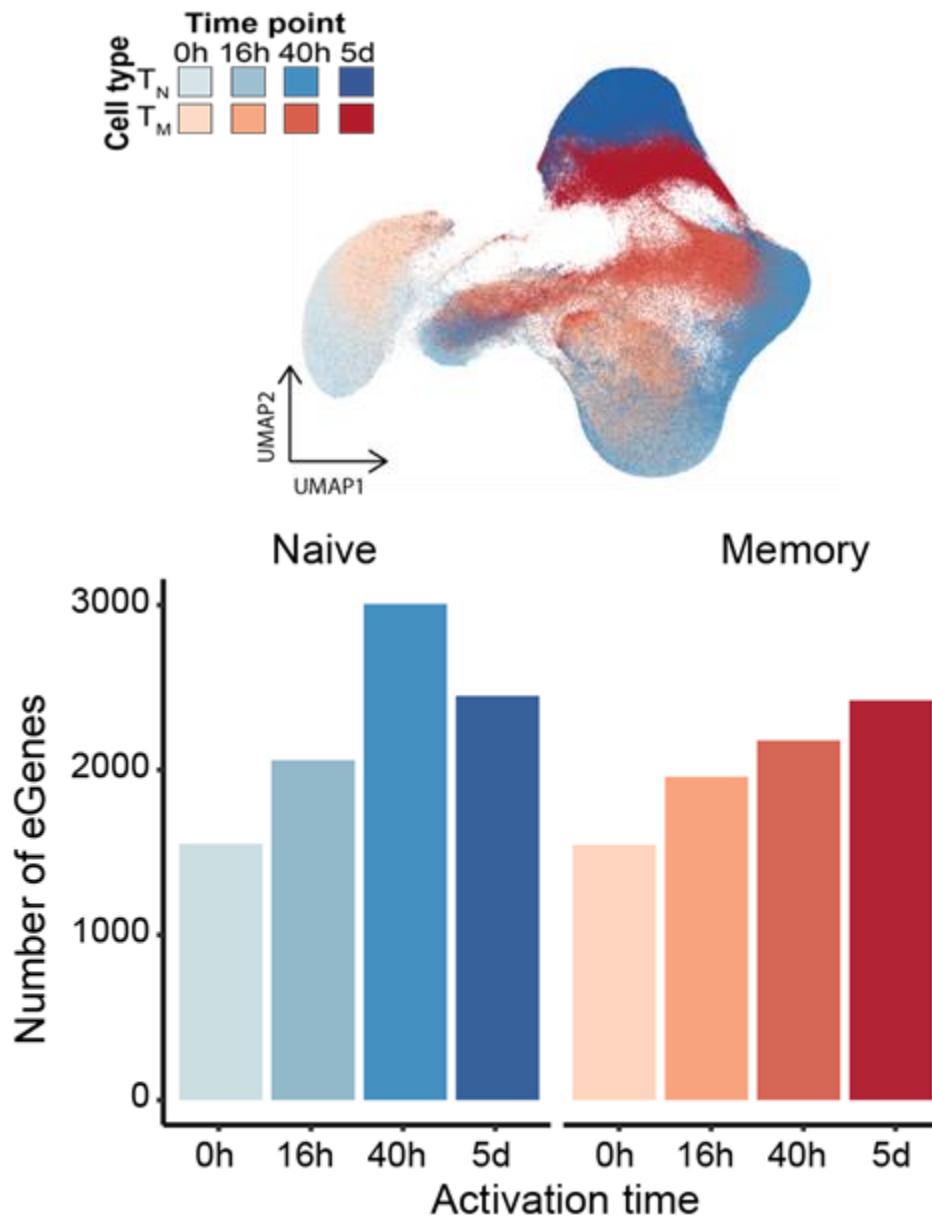
CD4+ T cells form 38 distinct clusters



CD4+ T cells form 38 distinct clusters



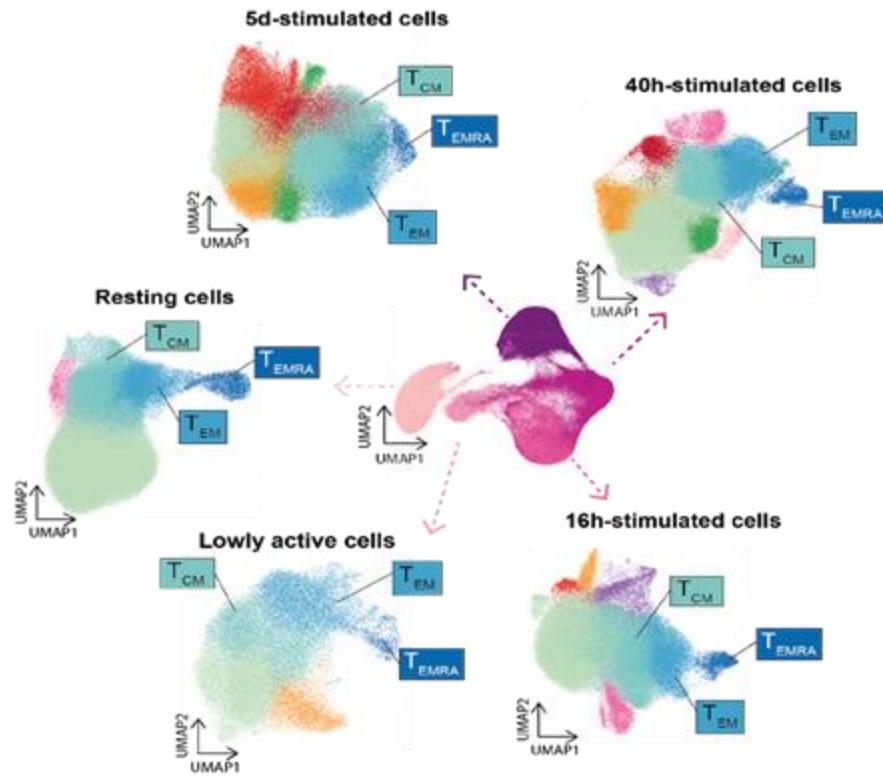
6,407 eQTLs during CD4+ T cell activation



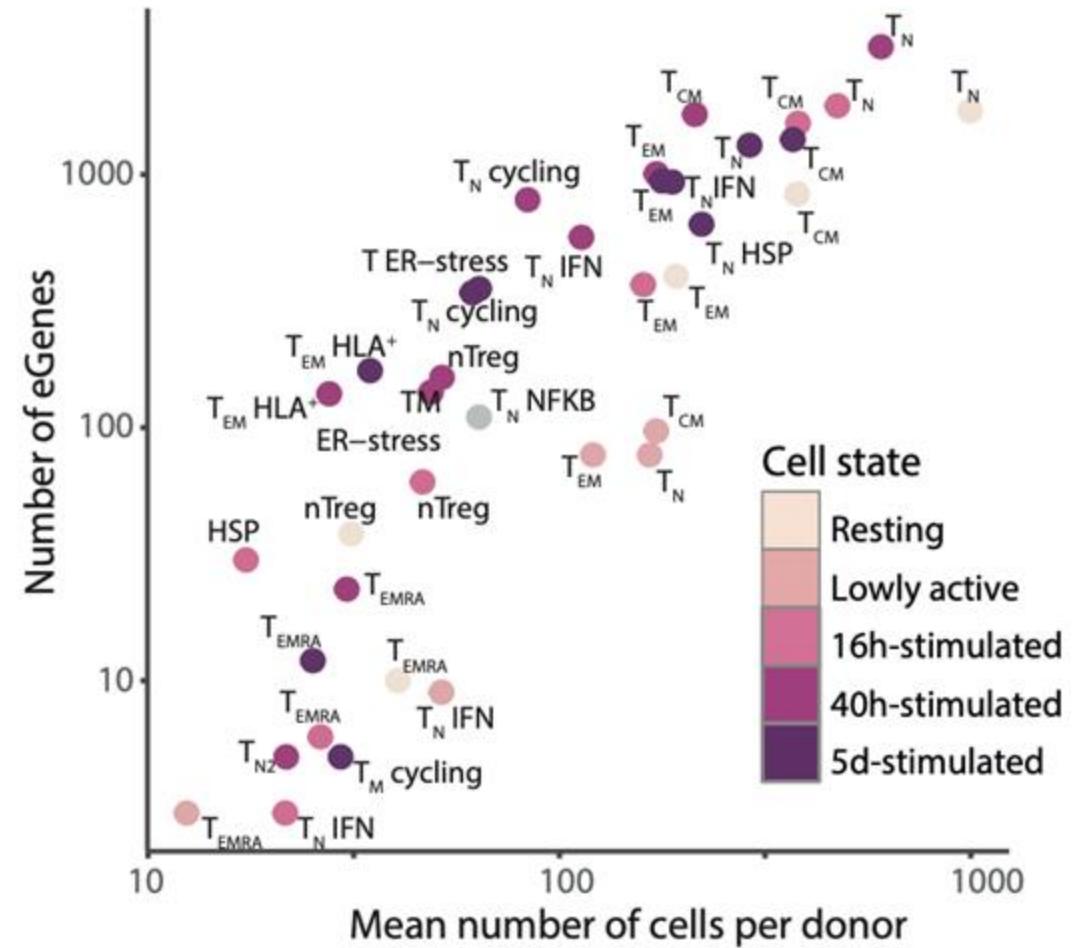
Cell type specific effects

Cell type and state specific effects

Subpopulation-specific eQTLs

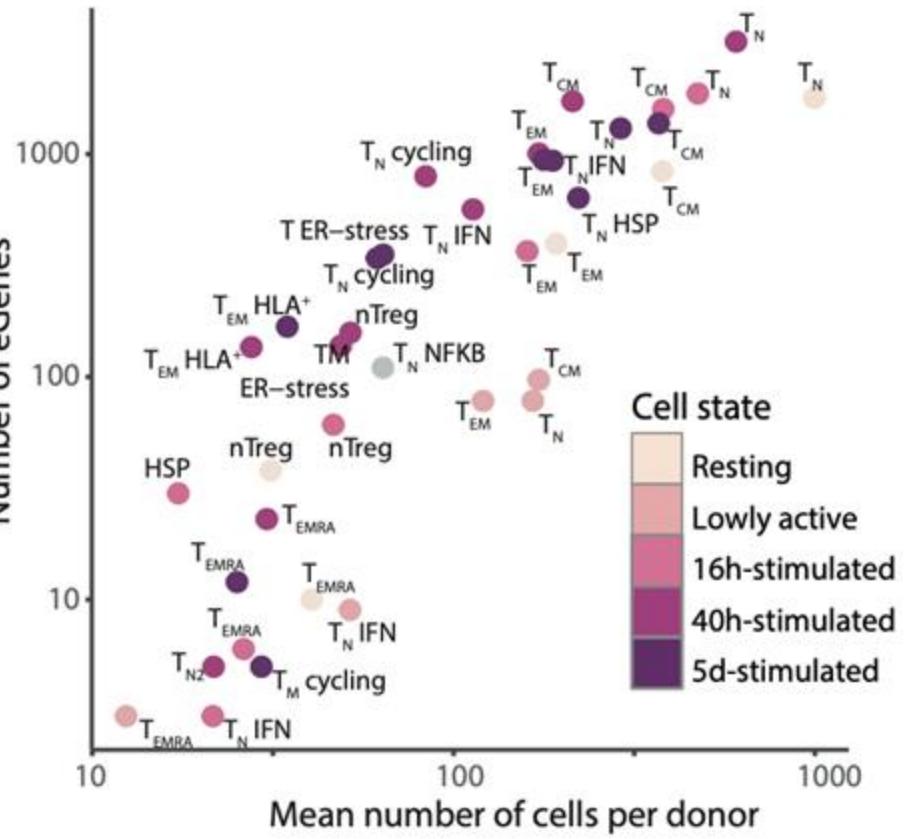


G.

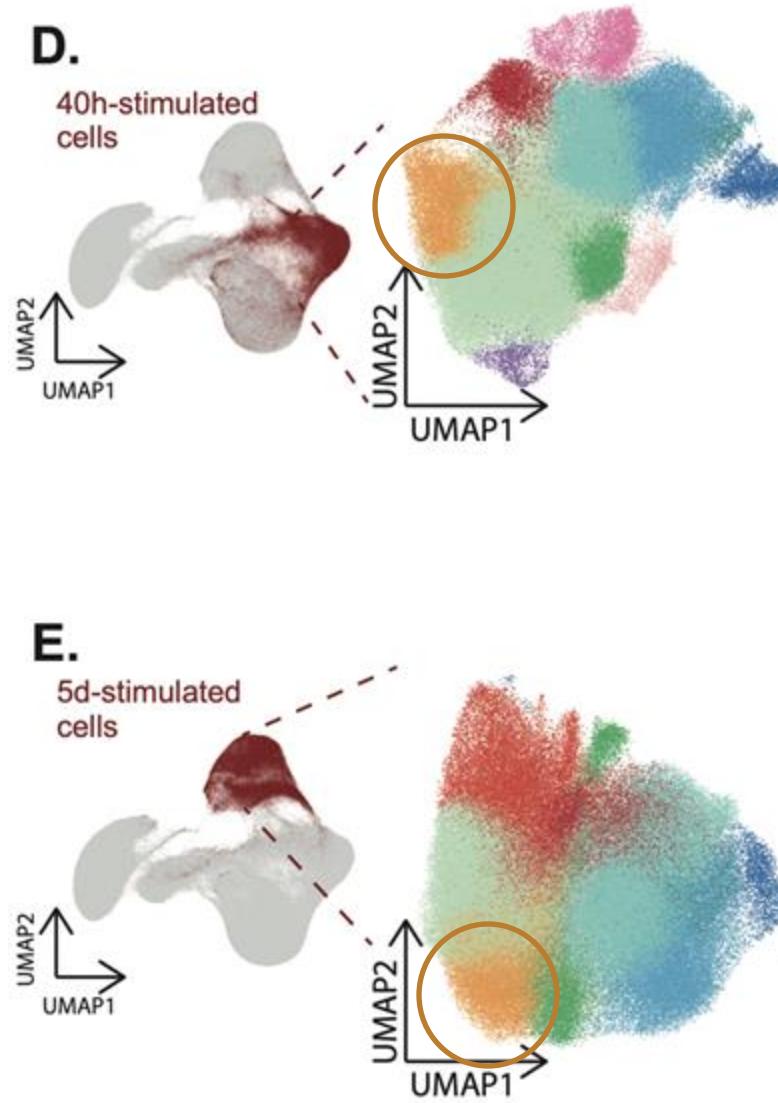


Subpopulation-specific eQTLs

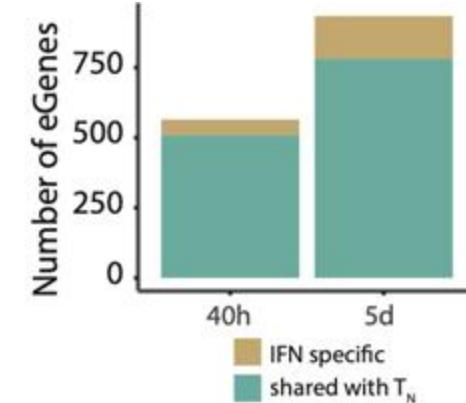
G.



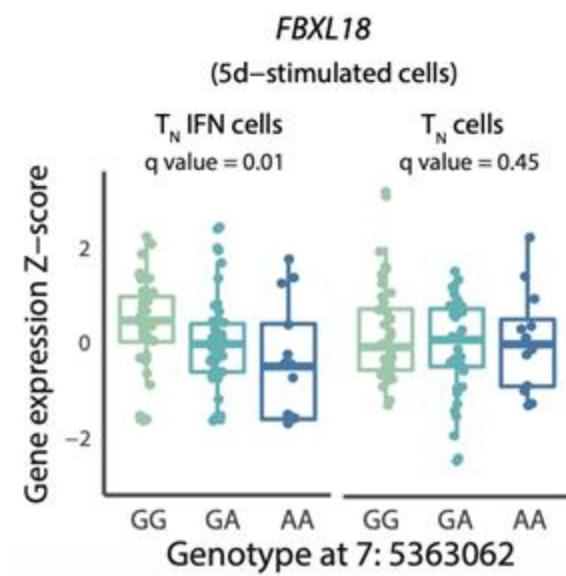
D.



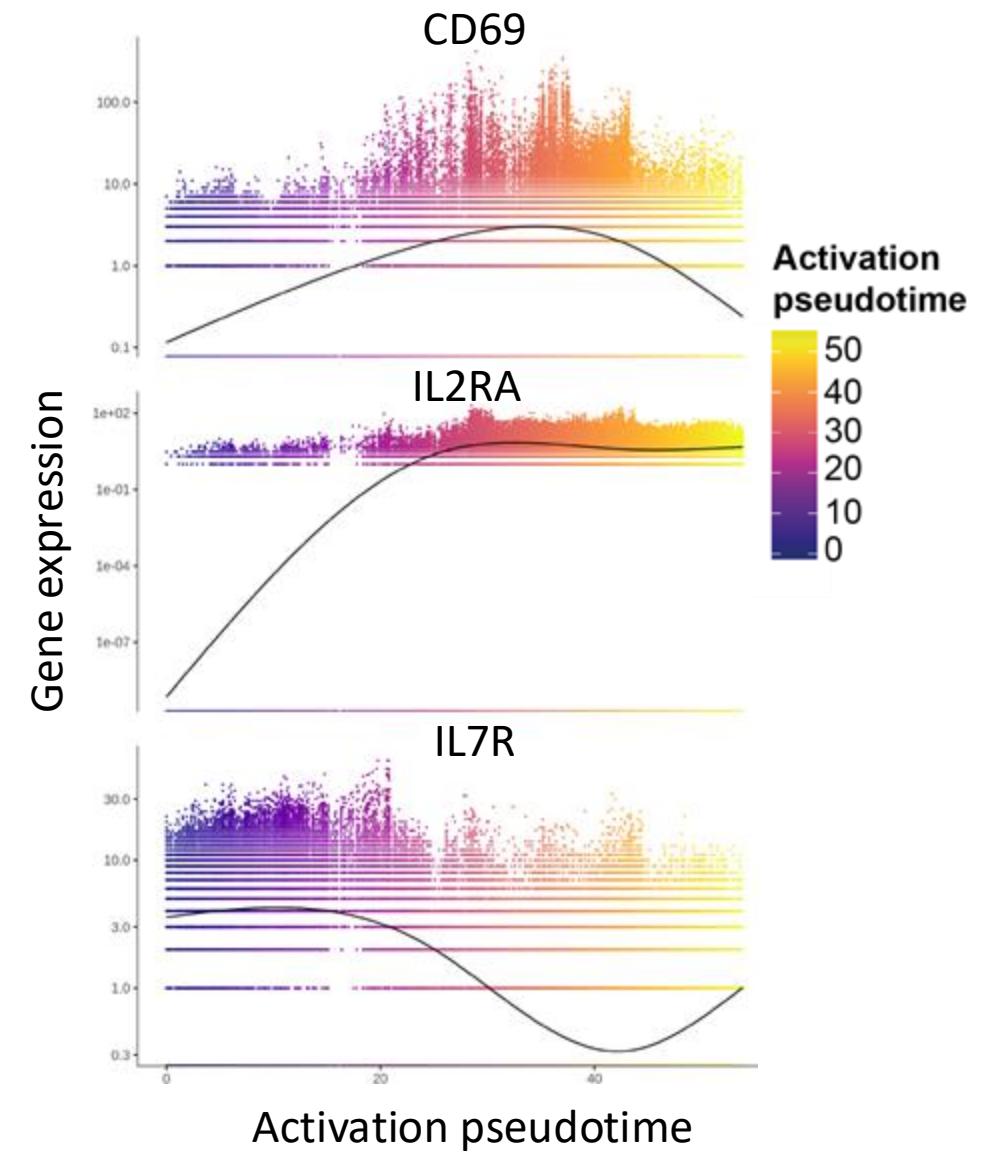
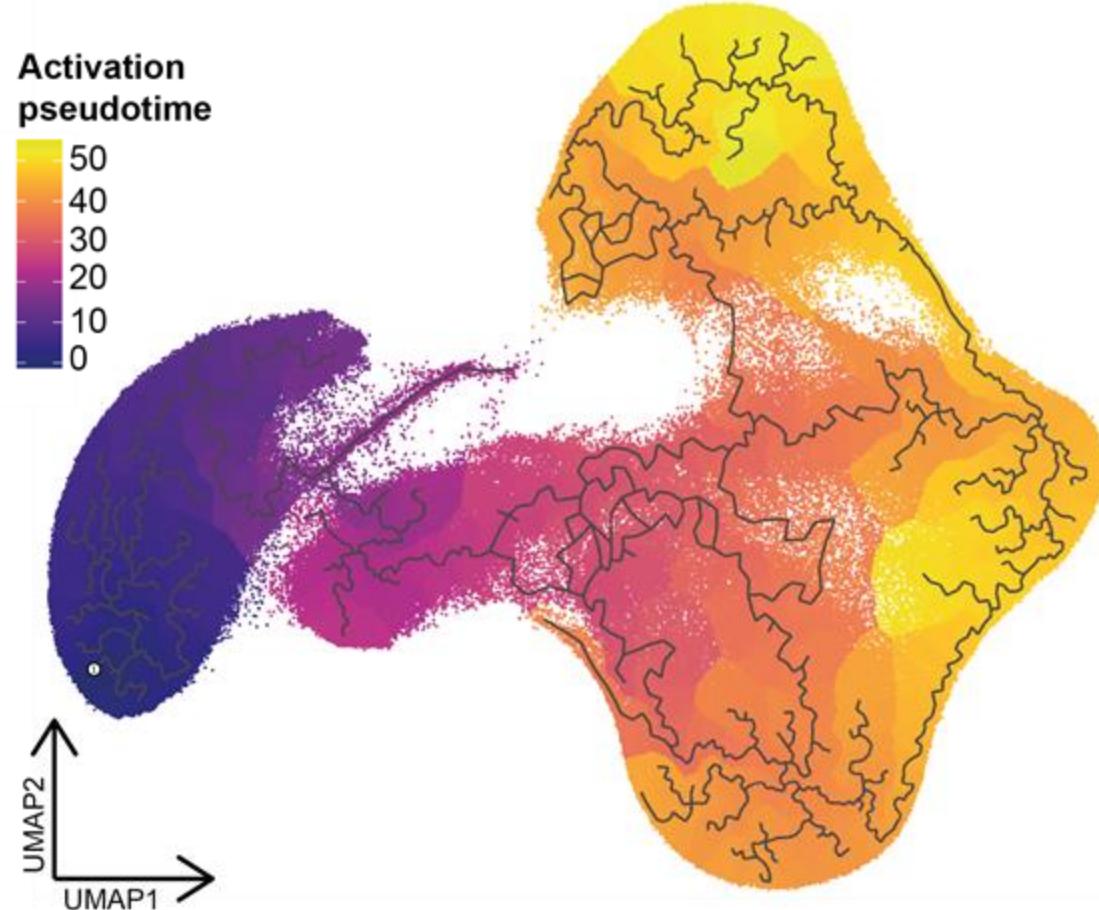
Number of eGenes



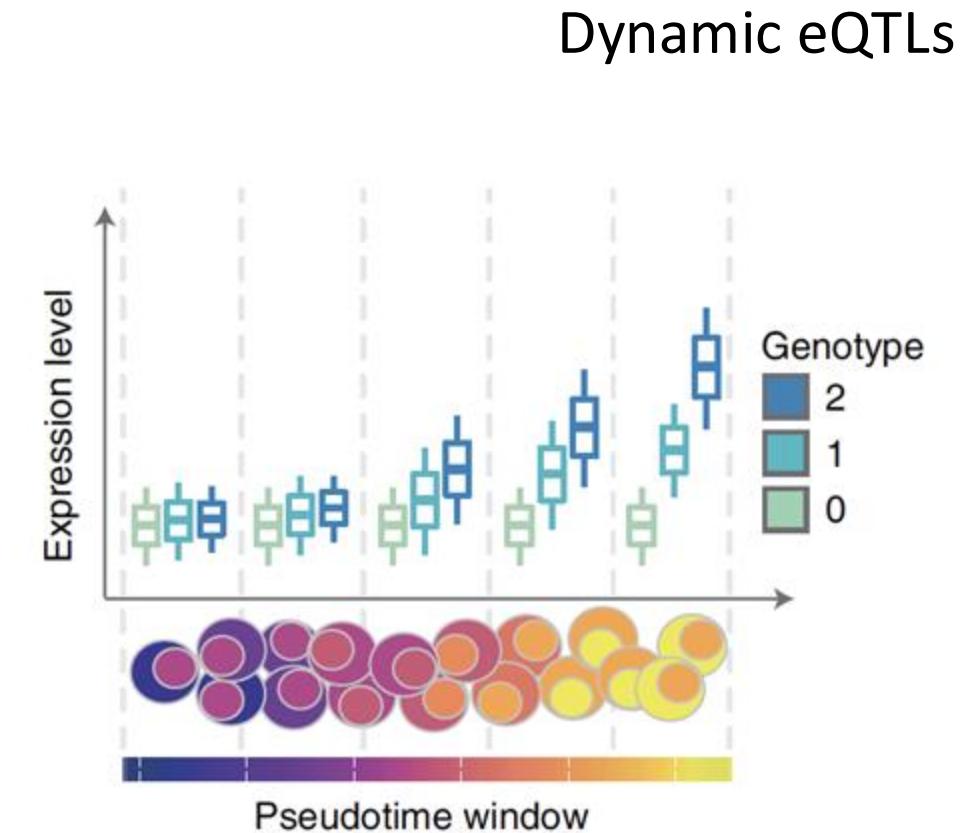
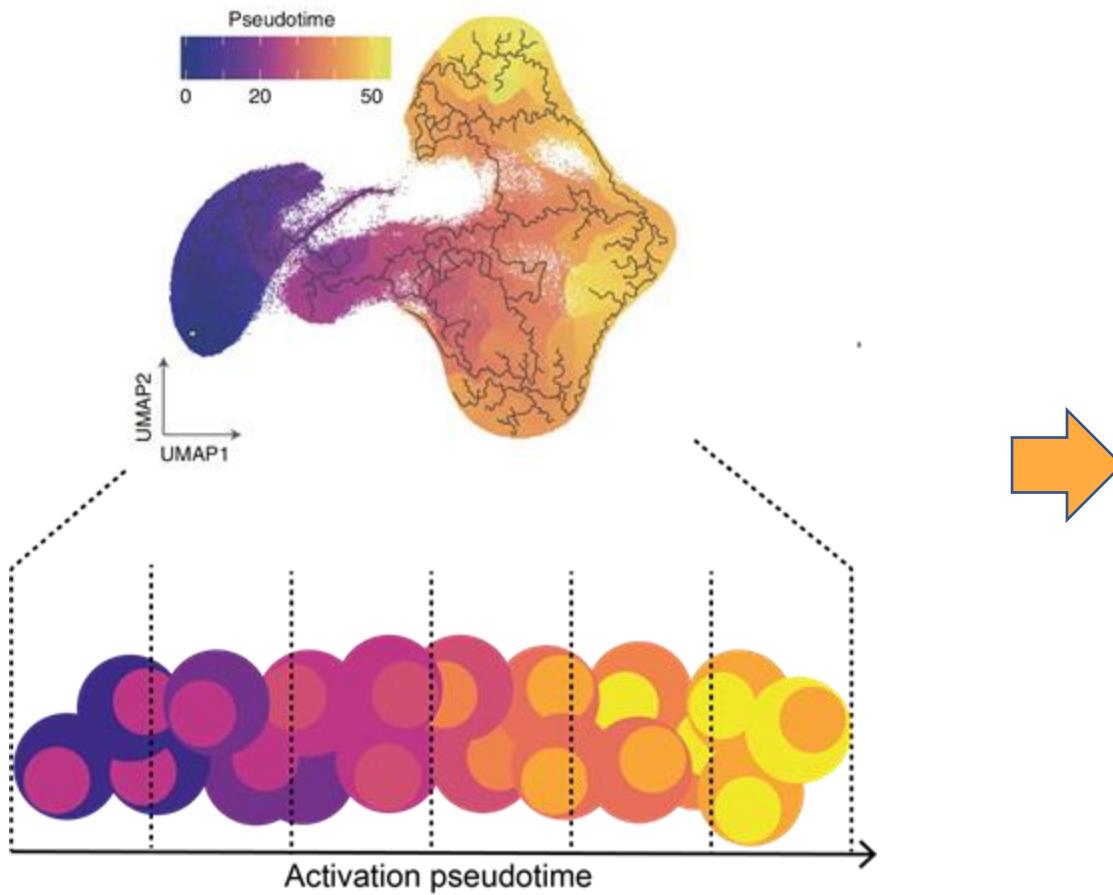
E.



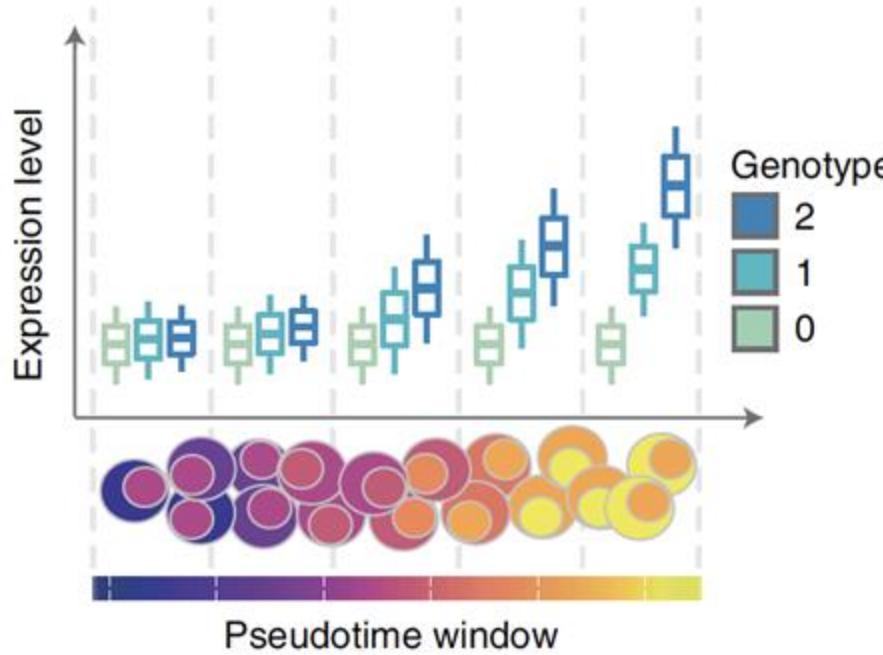
Trajectory of CD4+ T cell activation



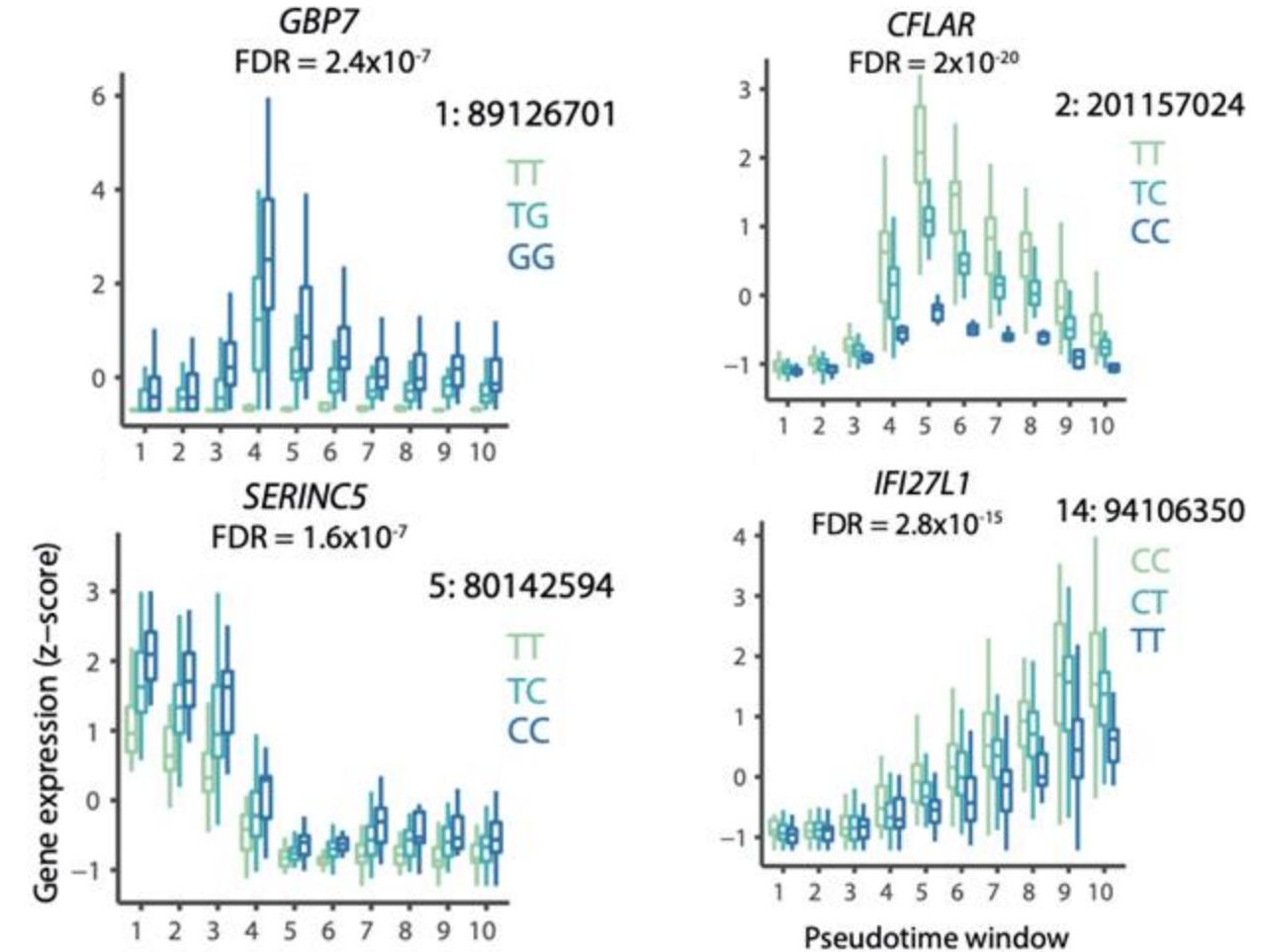
Identifying eQTLs with time-dependent effect sizes



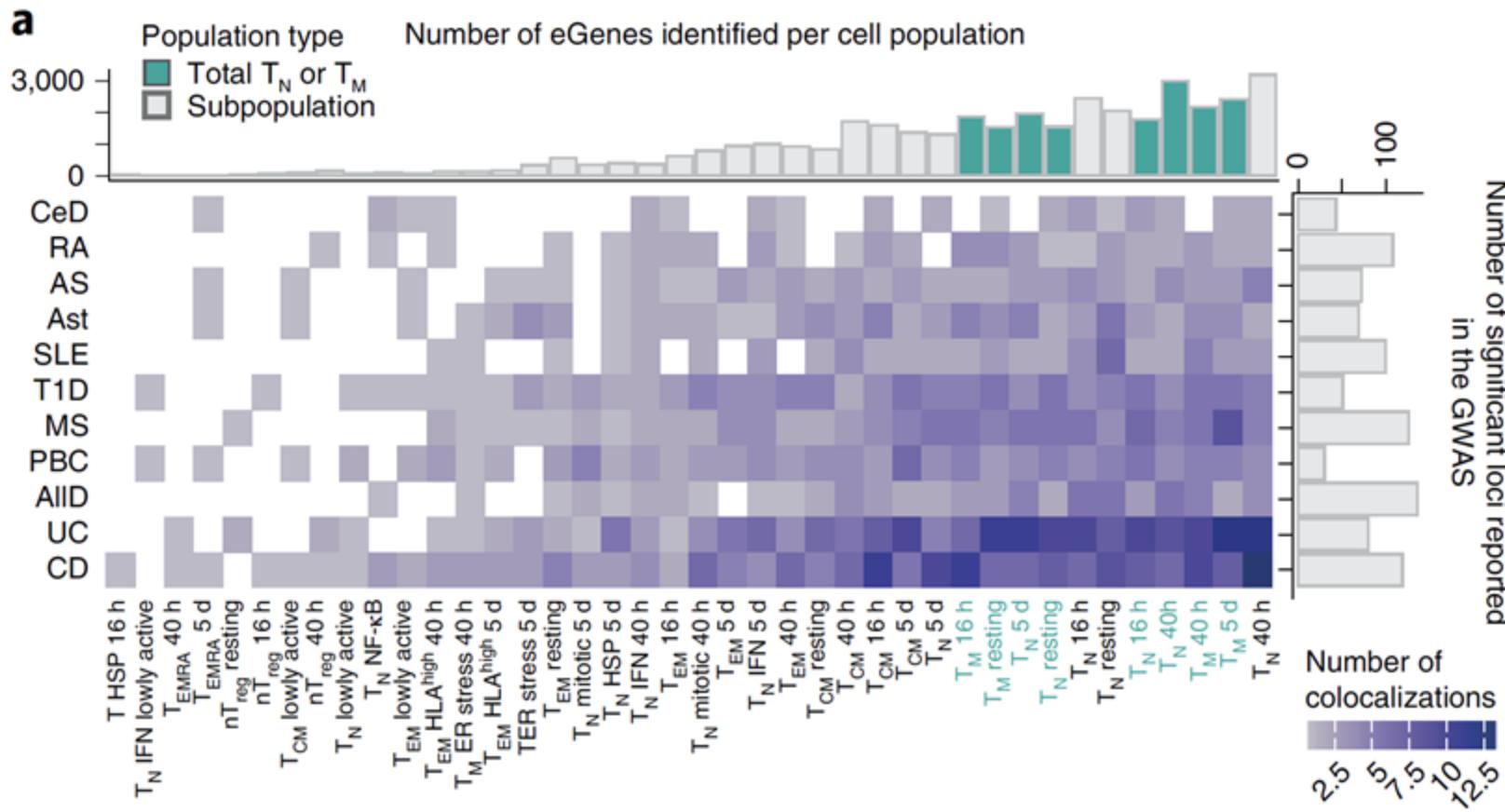
eQTLs with time-dependent effect sizes



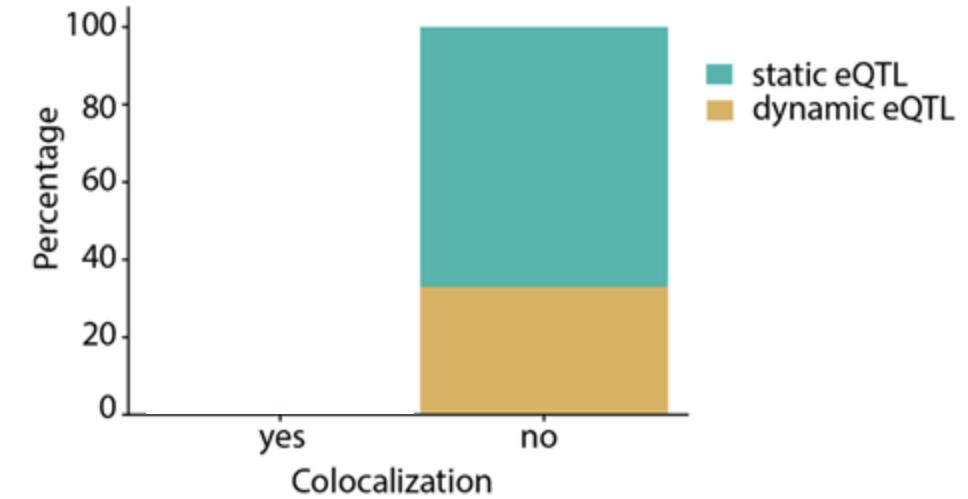
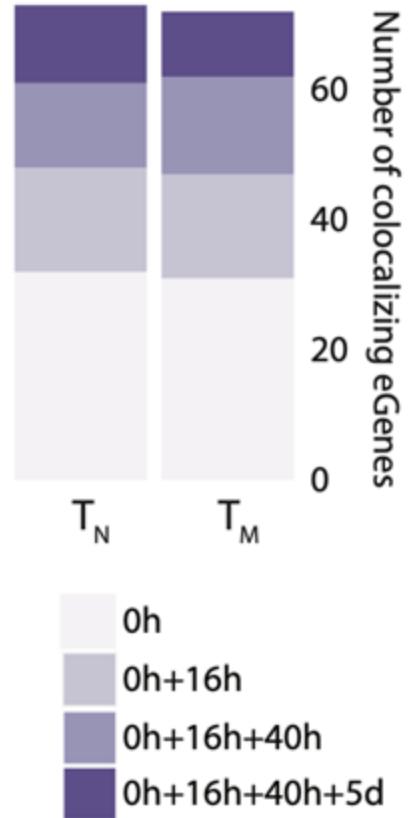
2,265 eGenes (30%) are dynamically regulated during T cell activation



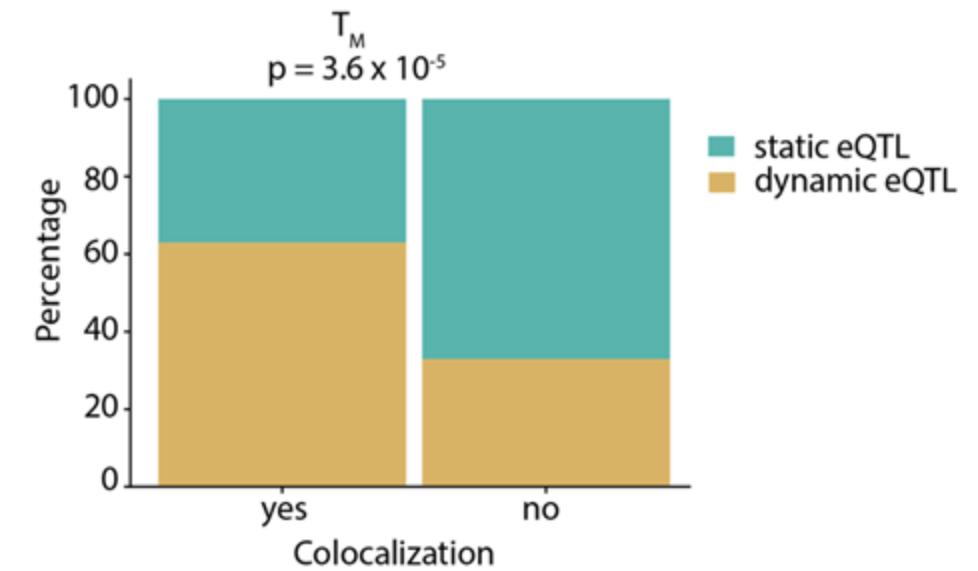
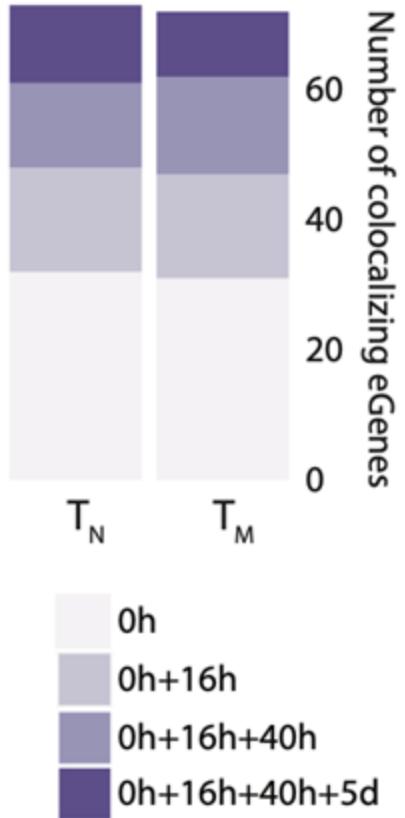
127 genes prioritised via colocalisation with 11 immune disease GWAS



127 genes prioritised via colocalisation with 11 immune disease GWAS

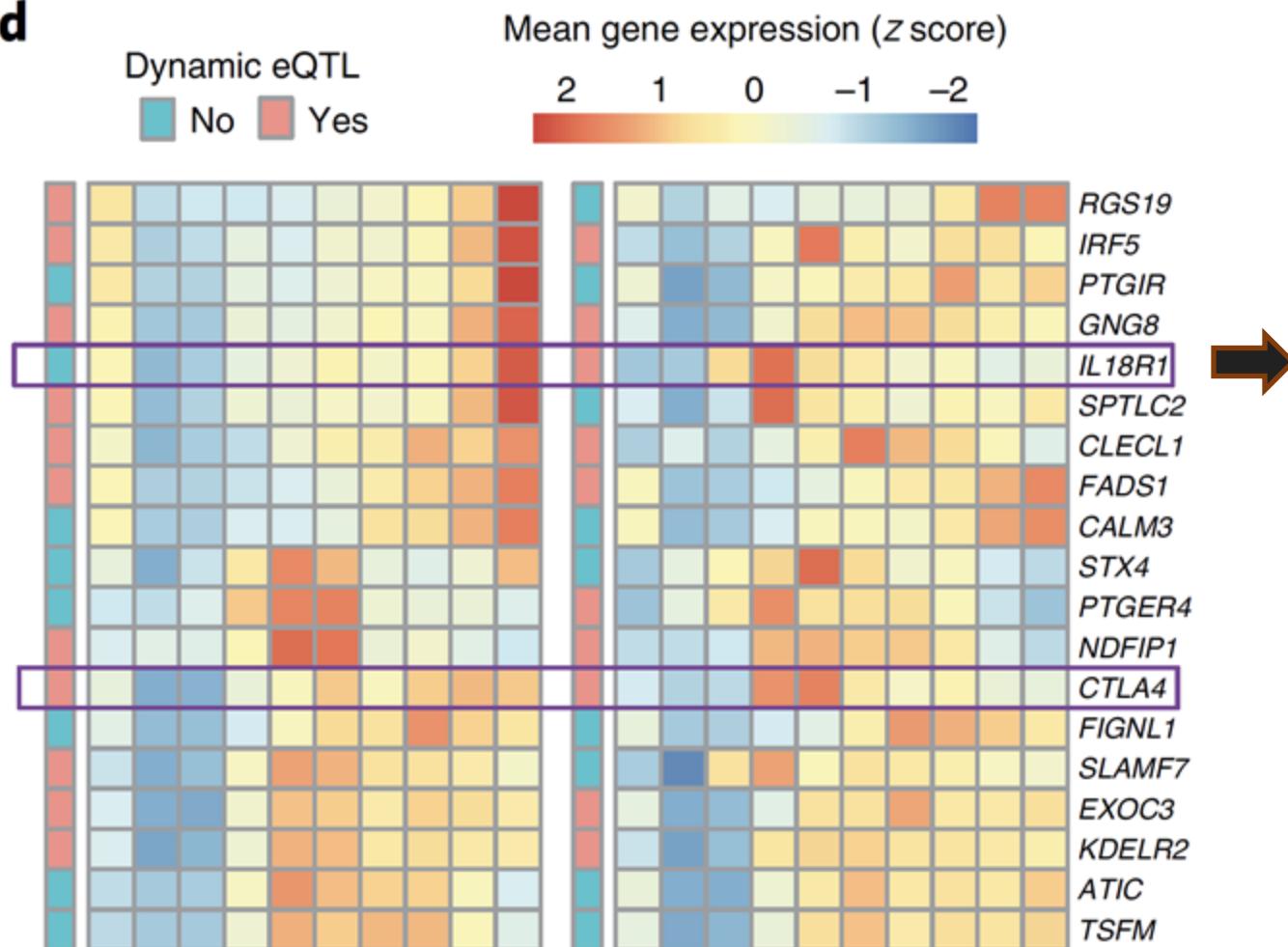


Immune disease colocalizations are enriched for dynamic eQTLs

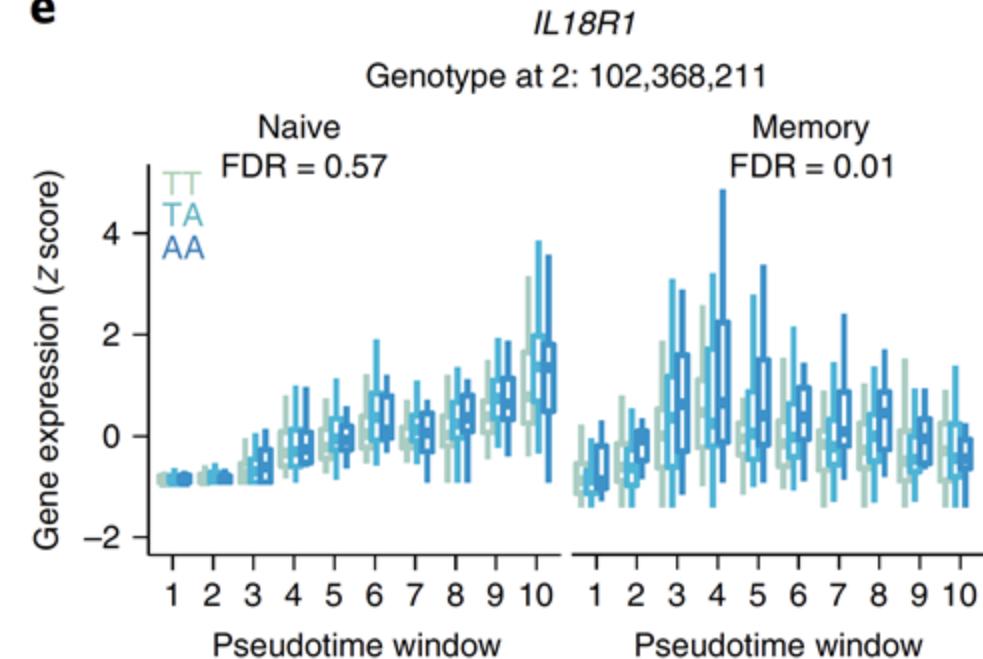


Dynamics of gene expression regulation

d

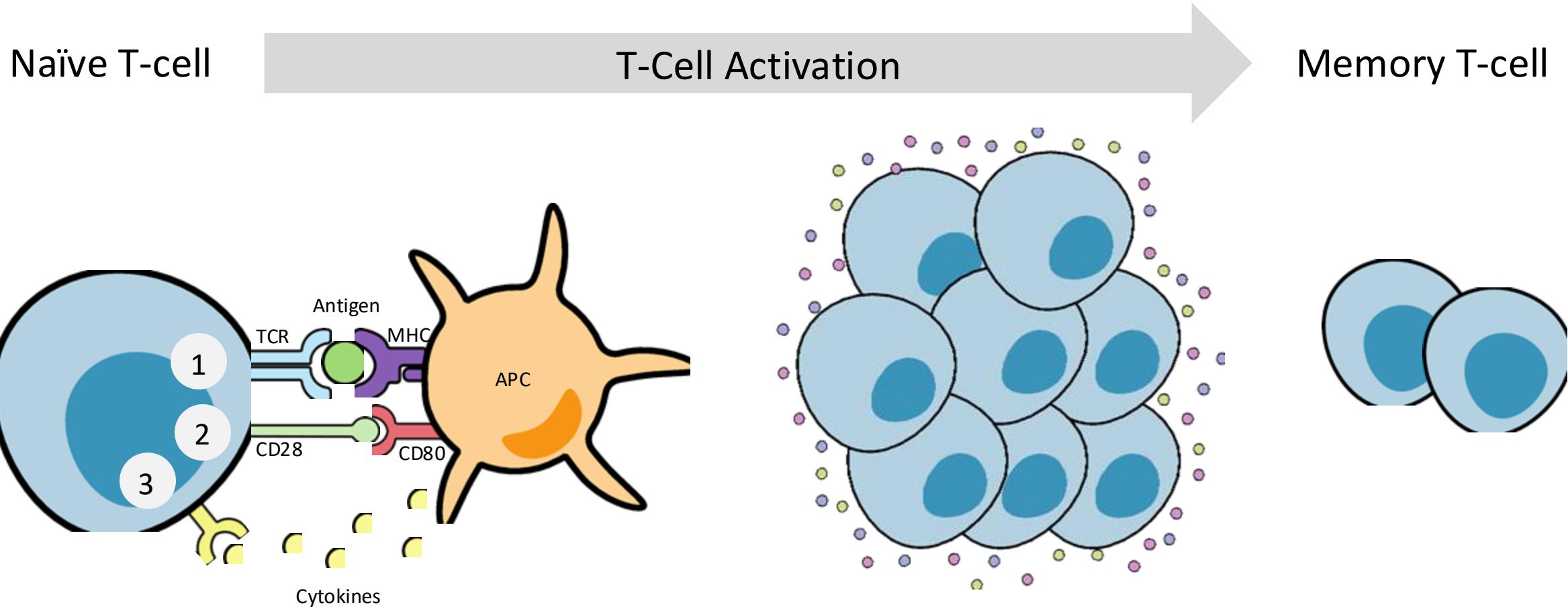


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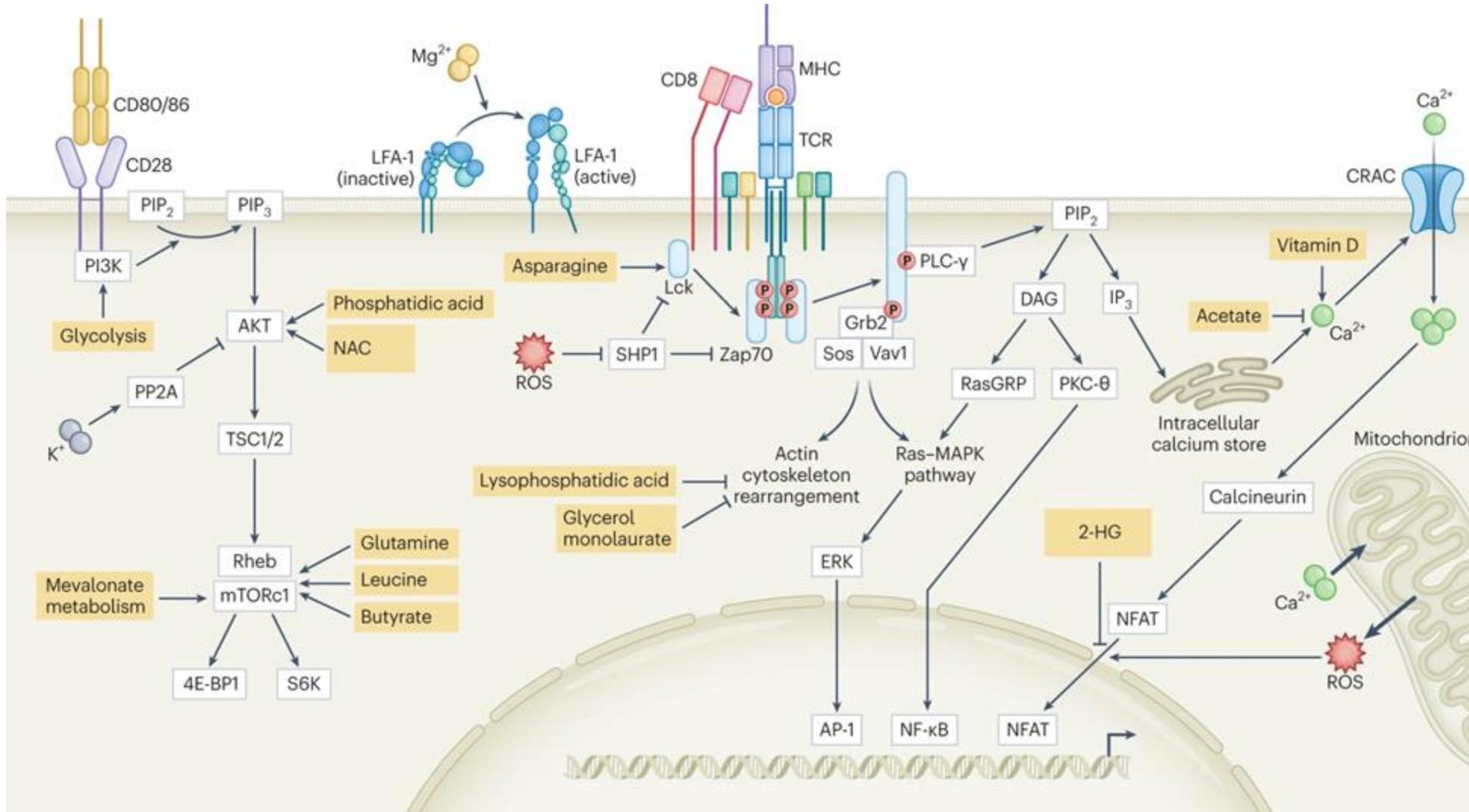


- Application of scRNAseq to study cell response to stimuli *in vitro*
- Application of scRNAseq to study how genetic variants regulated gene expression
- Application of scRNAseq to study whole transcriptional programmes

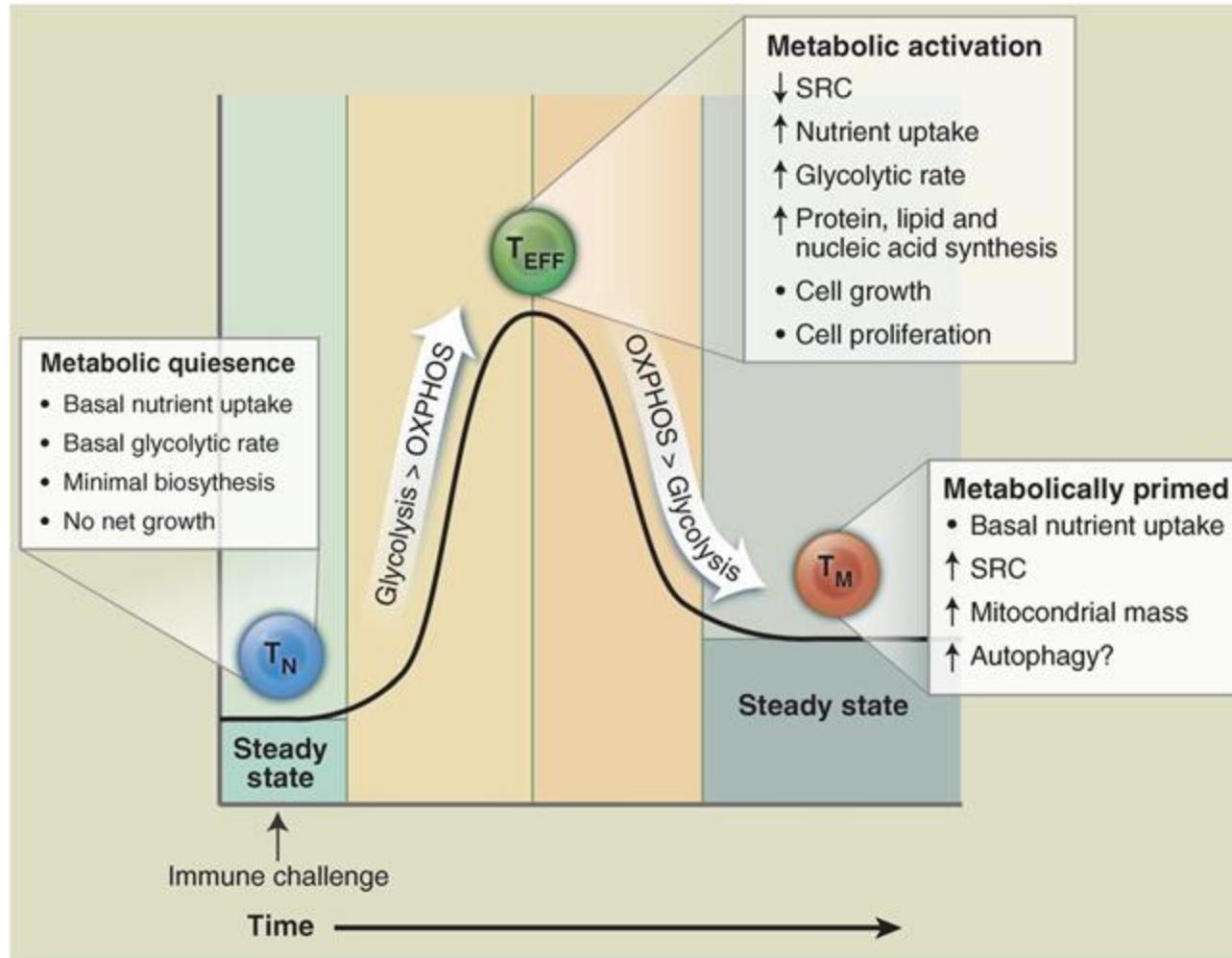
Immune disease GWAS variants pinpoint the role of CD4+ T cells



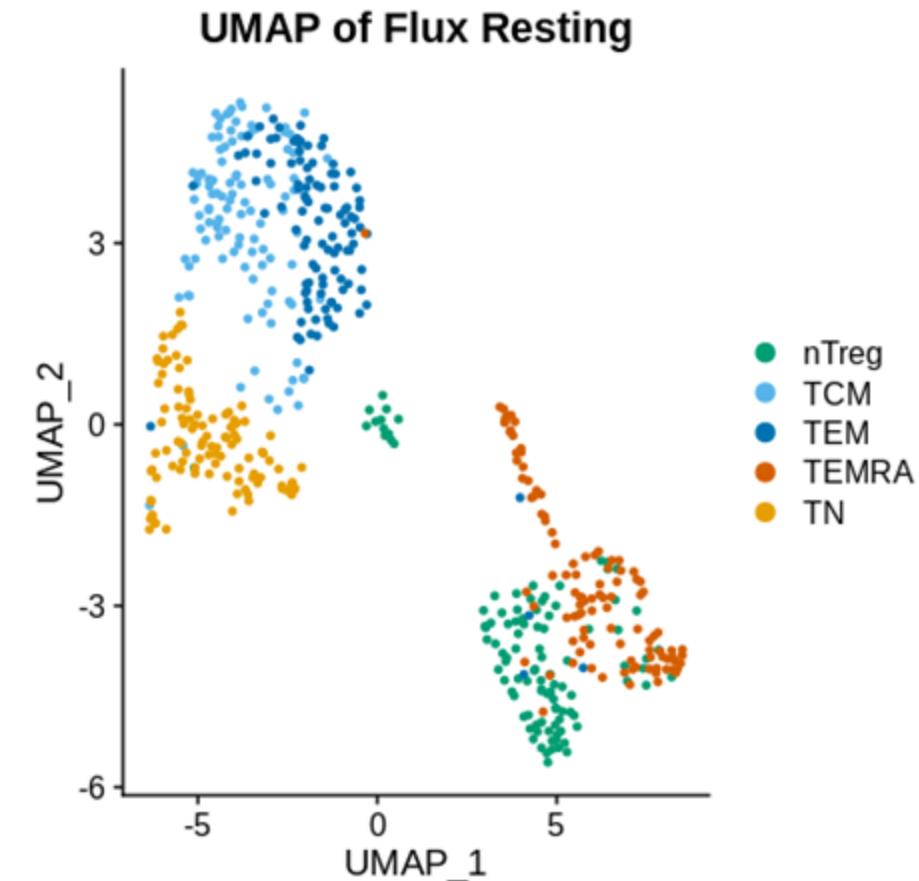
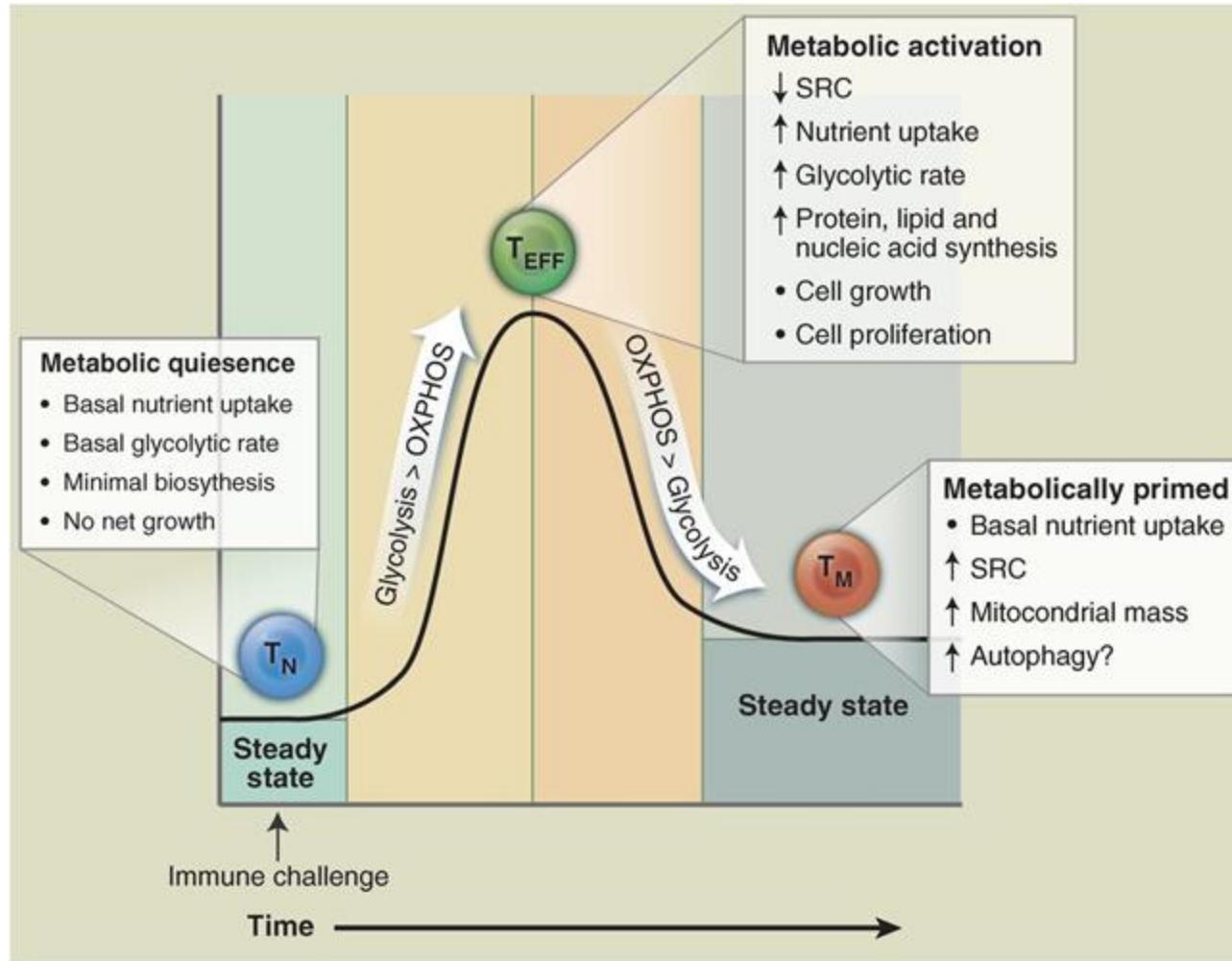
Immune disease GWAS variants pinpoint the role of CD4+ T cells



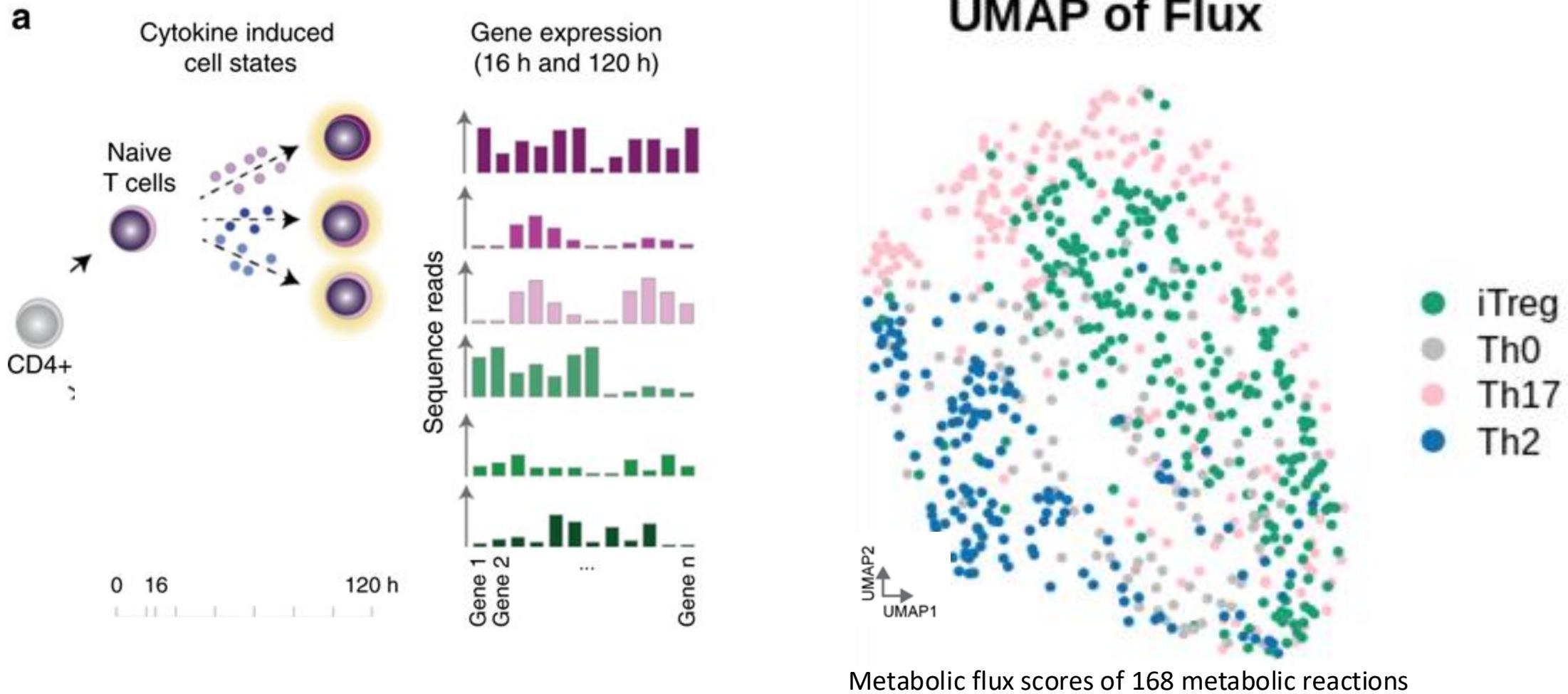
T cells undergo profound metabolic changes upon activation



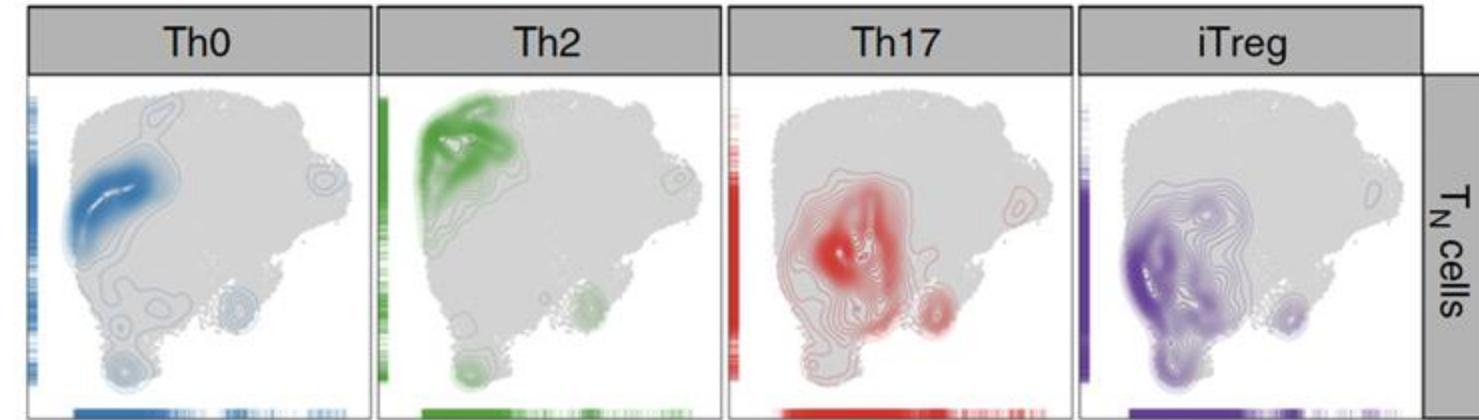
T cells undergo profound metabolic changes upon activation



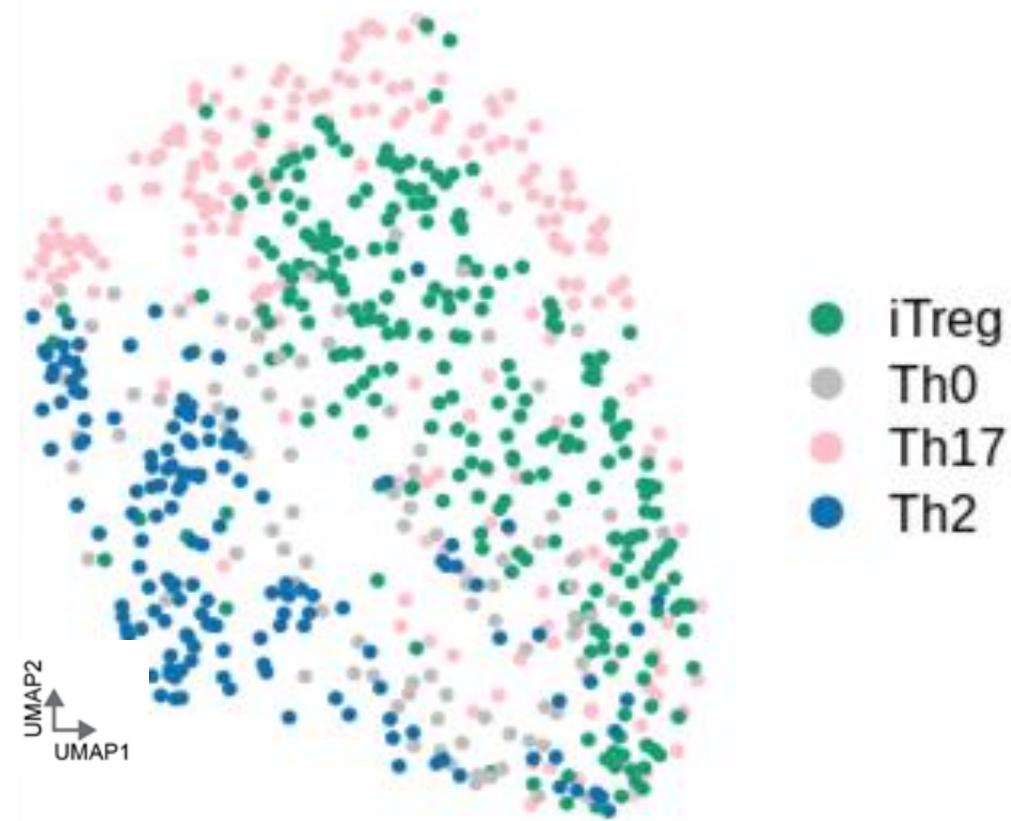
T cell metabolic states changed upon cytokine induction



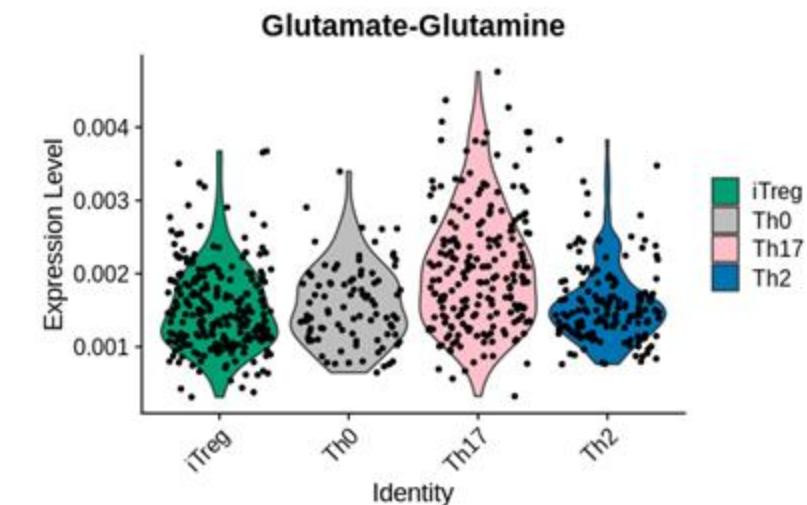
T cell metabolic states changed upon cytokine induction



UMAP of Flux

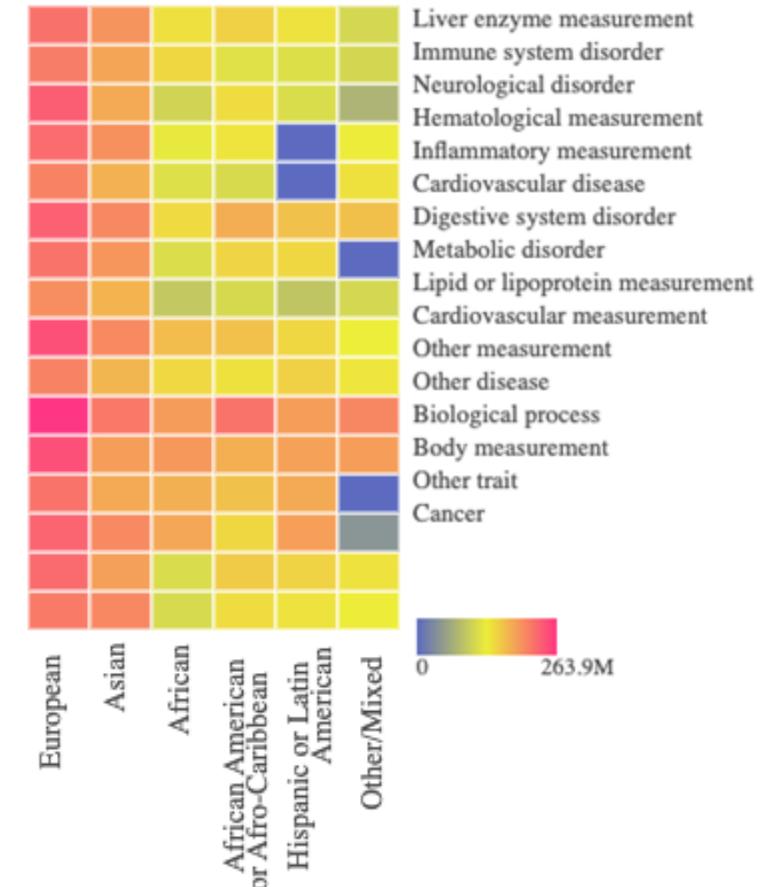
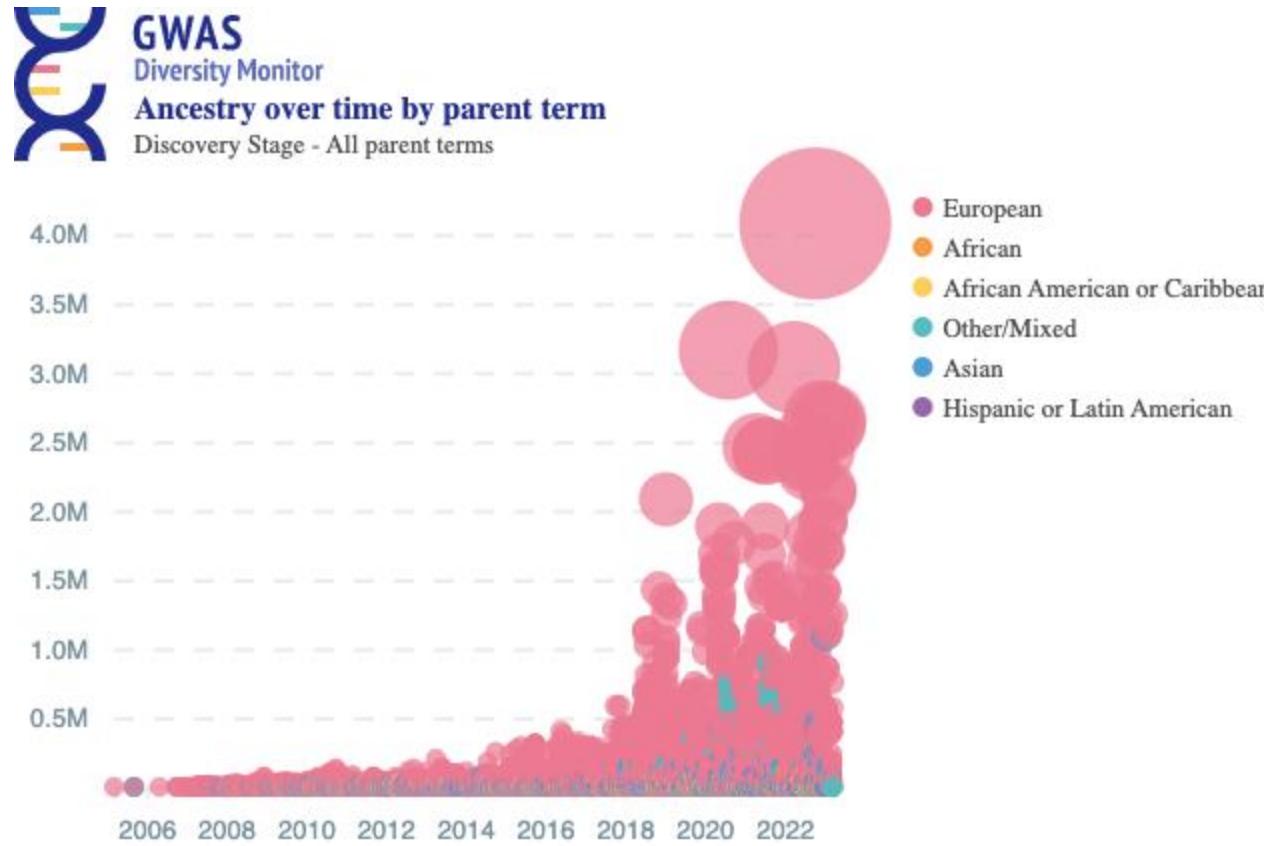


Metabolic activity differentiates cytokine induced cell types



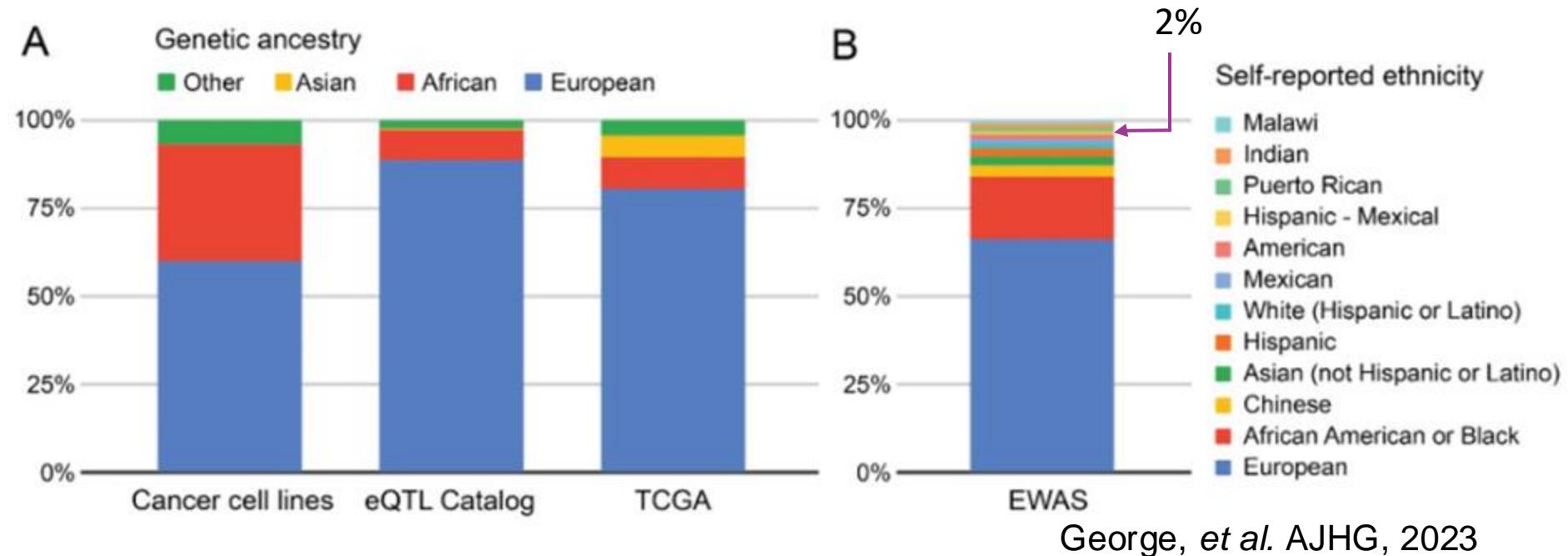


PROJECT
JAGUAR



Please cite this as: Mills, M.C and Rahal, C., (2020). 'The GWAS Diversity Monitor Tracks diversity by disease in real time'. Nature Genetics, 52, 242-243. doi: 10.1038/s41588-020-0580-y

Diversity in Genetic and Genomic studies



- LATAM shows great diversity due to constant migration and differences in ecosystems that led to adaptation leaving marks in Native American genomes.
- These factors have shaped populations with diverse genetic backgrounds in which genetic variation manifests in unique effects on complex traits, including the immune system.



AIM: address how **genetic diversity** shapes **immunity** resulting in differences in responses to infections and susceptibility to diseases

STRENGTH: **genetic richness** of Latin American populations and **environmental diversity**

HOW: use of single-cell technologies (scRNA-Seq , scATAC-Seq and scCITE-Seq) to identify how **diverse ancestries impact gene expression and the composition of immune cells**



Progress on sample collection



Total collected: 469 samples

Aim: 1080 samples

Sep 2nd, 2024



Colombia

In progress



Peru

58 samples



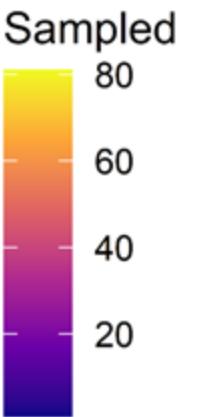
Chile

83 samples



Mexico

120 samples



Uruguay

In progress



Argentina

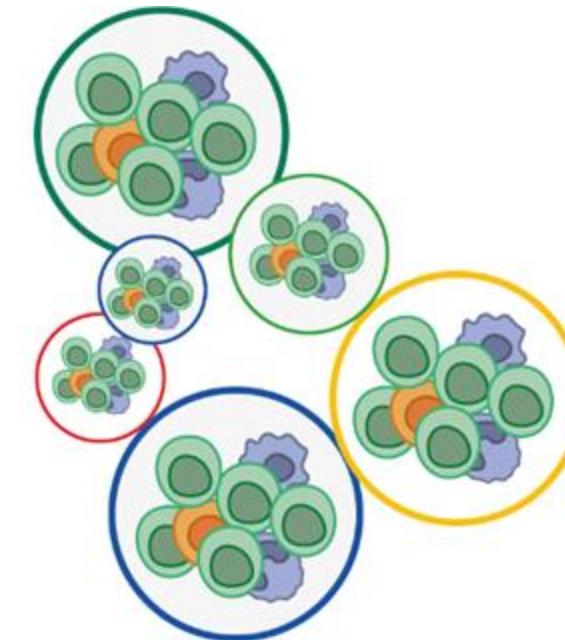
103 samples



Mapping immune cell diversity across Latin America



1080 Latin American participants



PBMC collection & genetic profiling

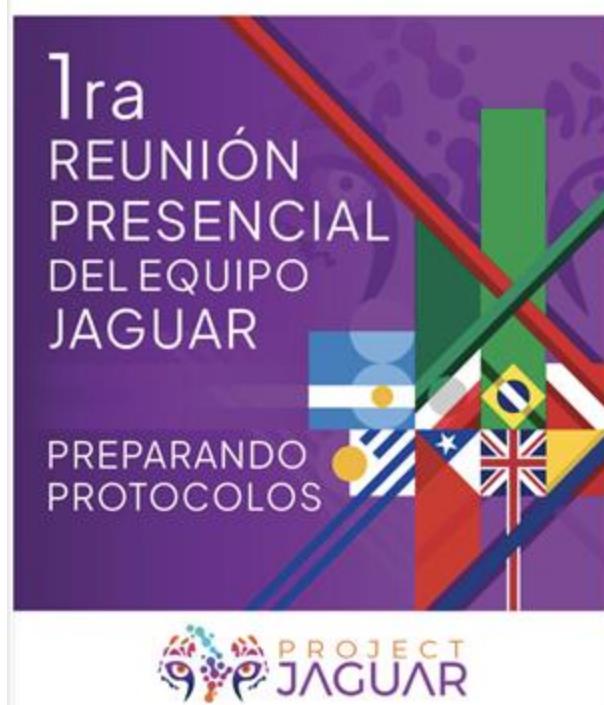


single cell omics



Training and standardisation

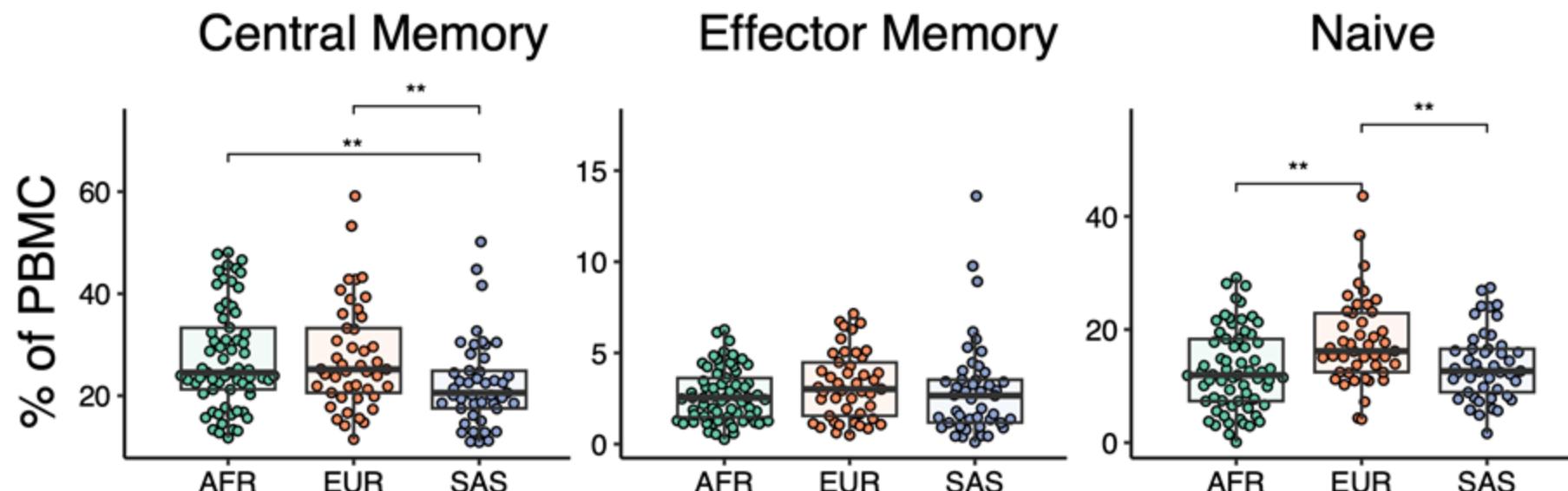
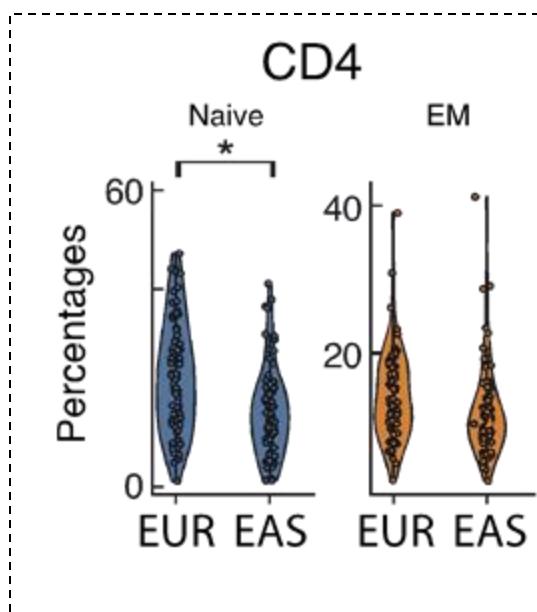
Standardized sampling protocol across countries with high cell viability before and after shipment



Can we expect ancestry driven differences in
immune system composition?

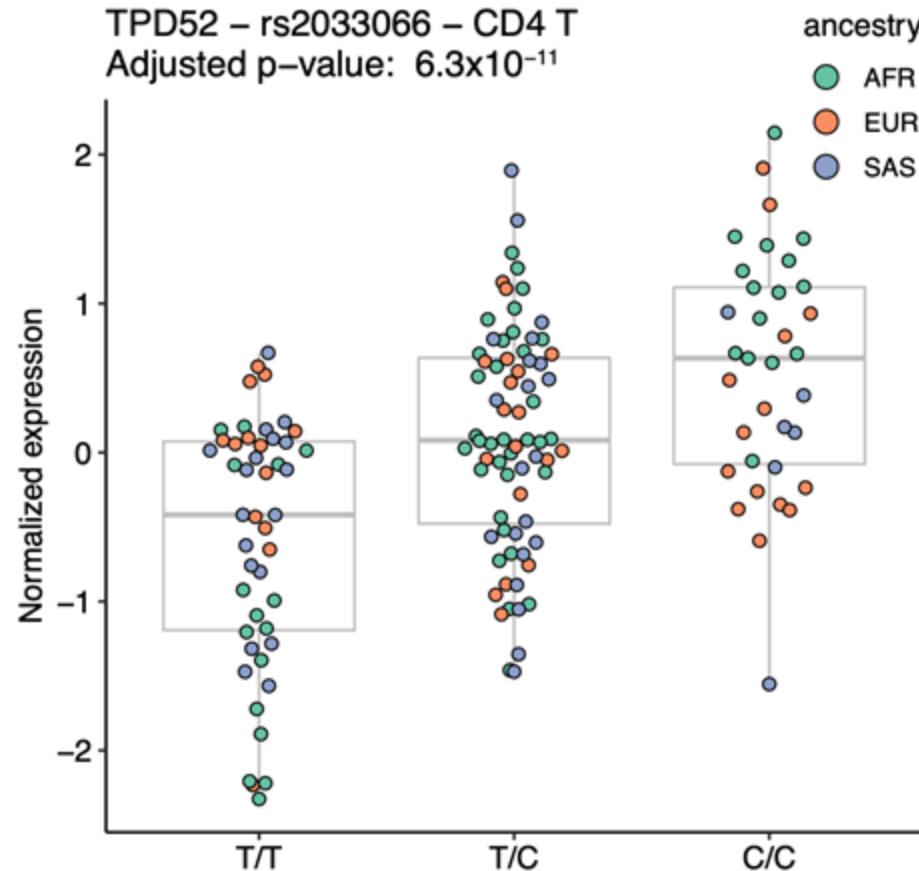
CD4+ naïve T cell proportions are highest in Europeans

CD4+ T cells

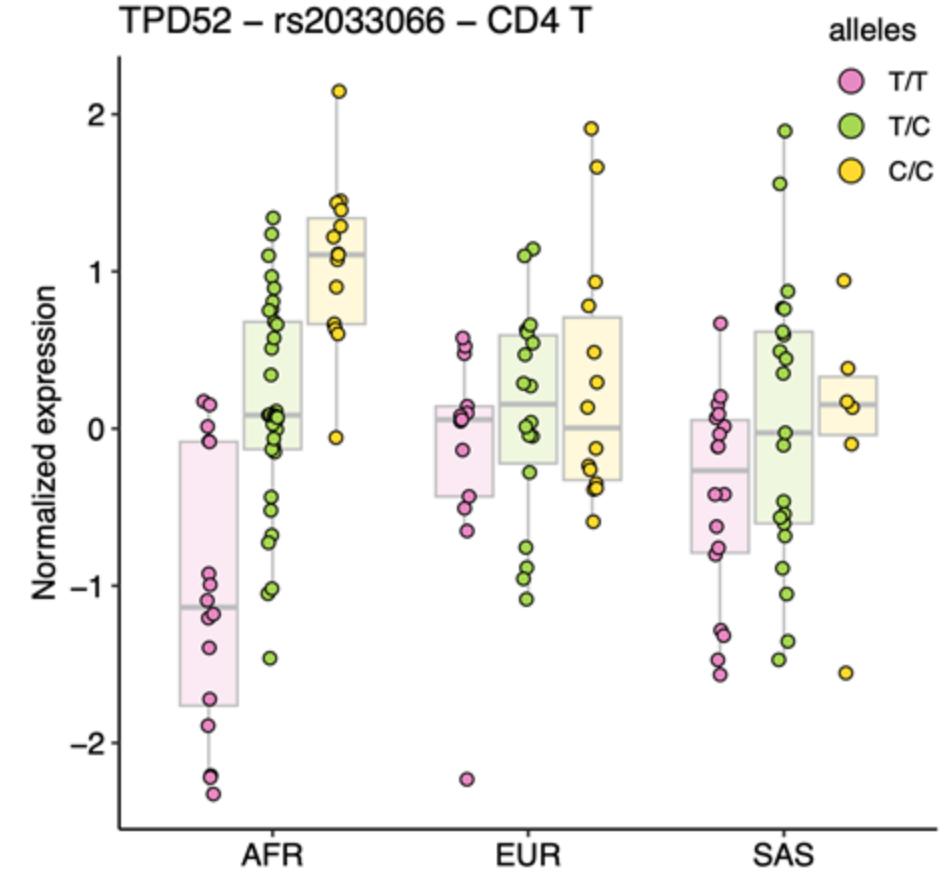
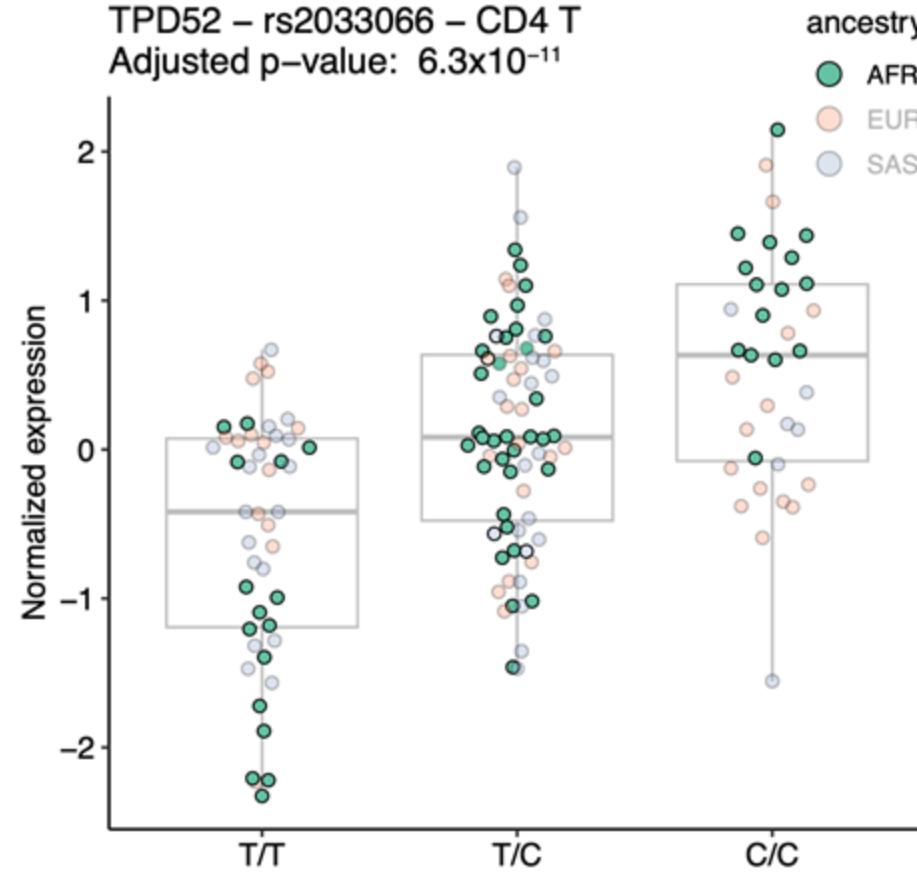


Adapted from Perez, Richard K., et al. "Single-cell RNA-seq reveals cell type-specific molecular and genetic associations to lupus." *Science* (2022)

CD4 naïve *TPD52* - an example of ancestry specific eQTL



CD4 naïve *TPD52* eQTL strongest in African ancestry



MPhil in Genomic Science

<https://www.sanger.ac.uk/about/study/masters-programmes>



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PROJECT JAGUAR



Marcela Katherine
Sjöberg Herrera
Chile



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And all the team members and volunteers!!!

**Chan
Zuckerberg
Initiative**



Open Targets



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Sarah Cooper Sanger



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Blagoje Soskic,
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