

Computational methods for studying continuous biological processes

Zhicheng (Jason) Ji

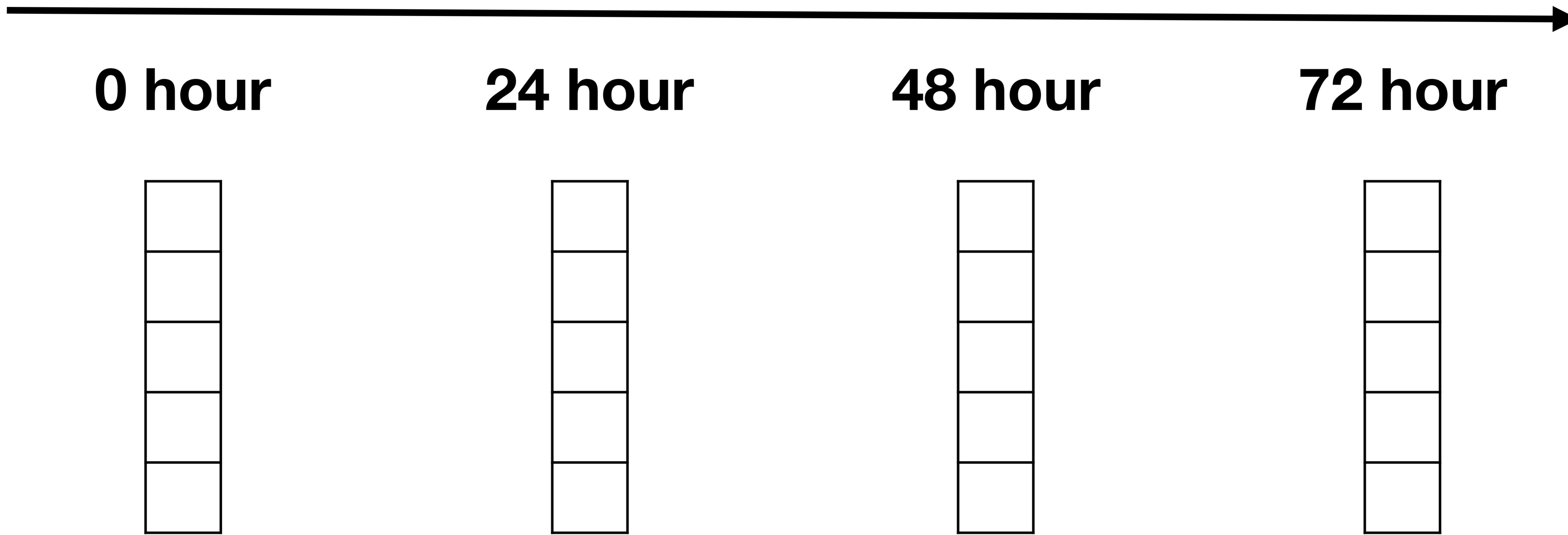
Department of Biostatistics and Bioinformatics

Duke University School of Medicine

Continuous biological processes

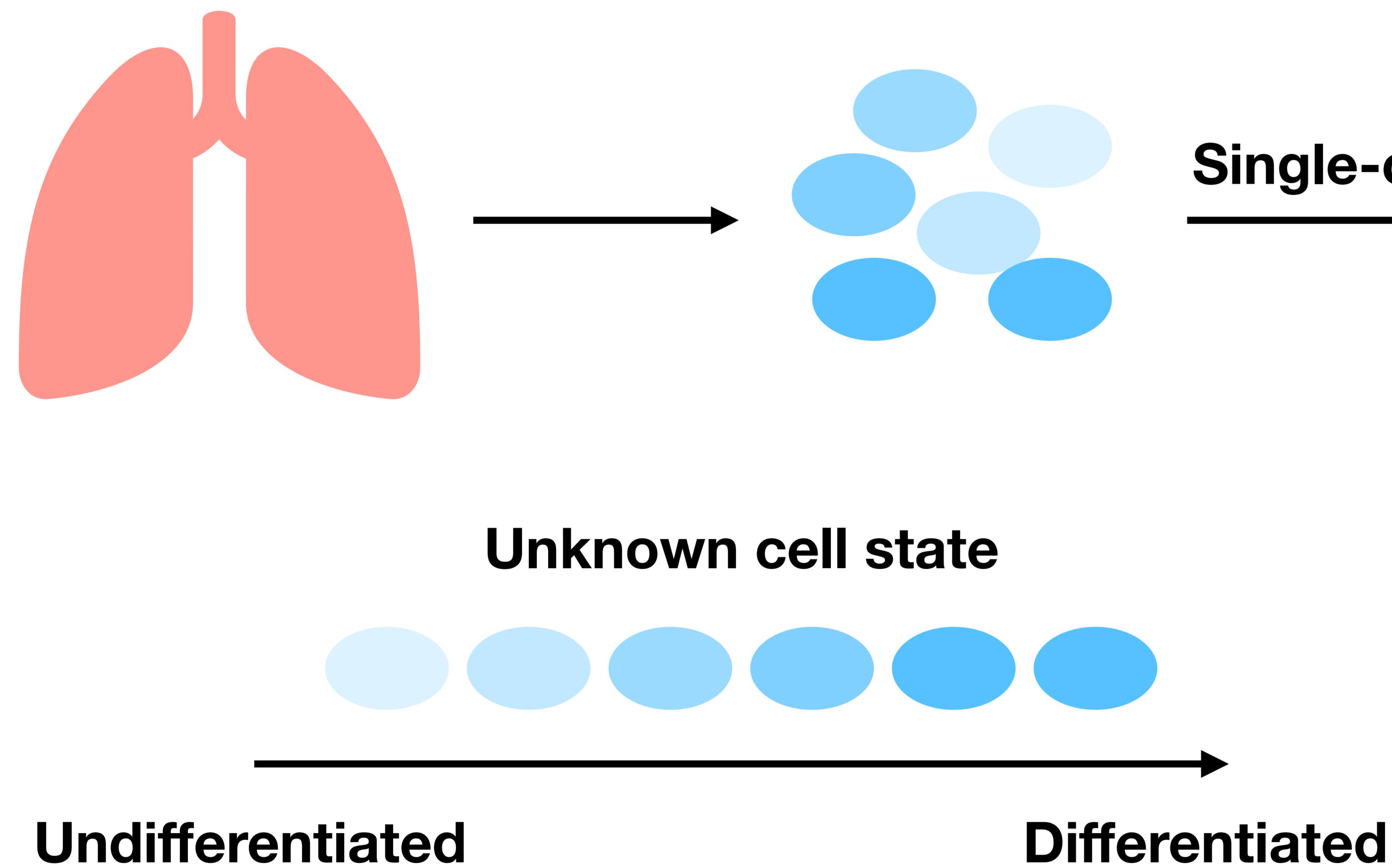
- Tissue development
- Immune response
- Tumor progression

Time-course bulk experiments

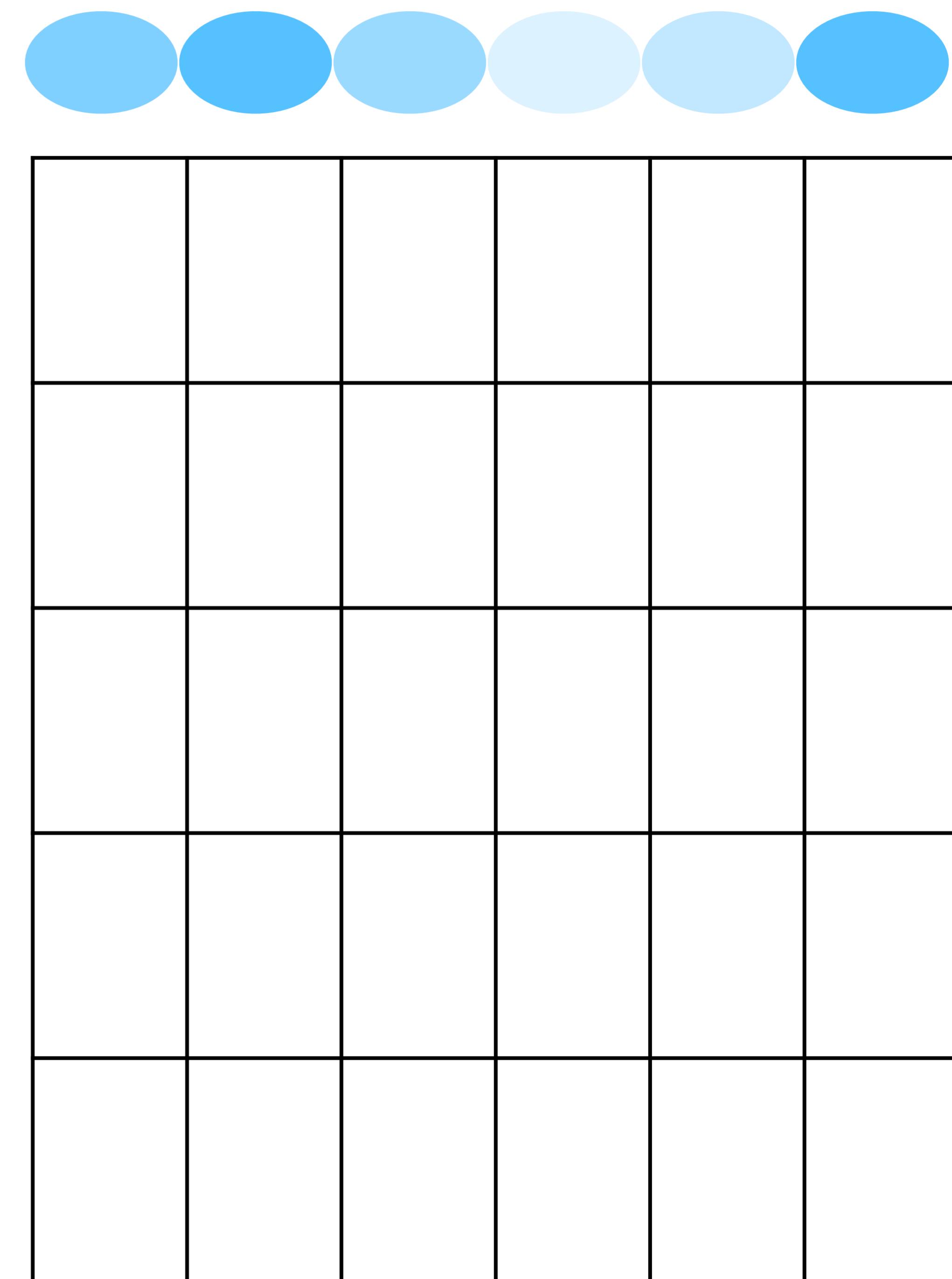


1. Longitudinal sampling may not be feasible
2. Cell type proportions confound gene expression
3. Hard to study multiple branches

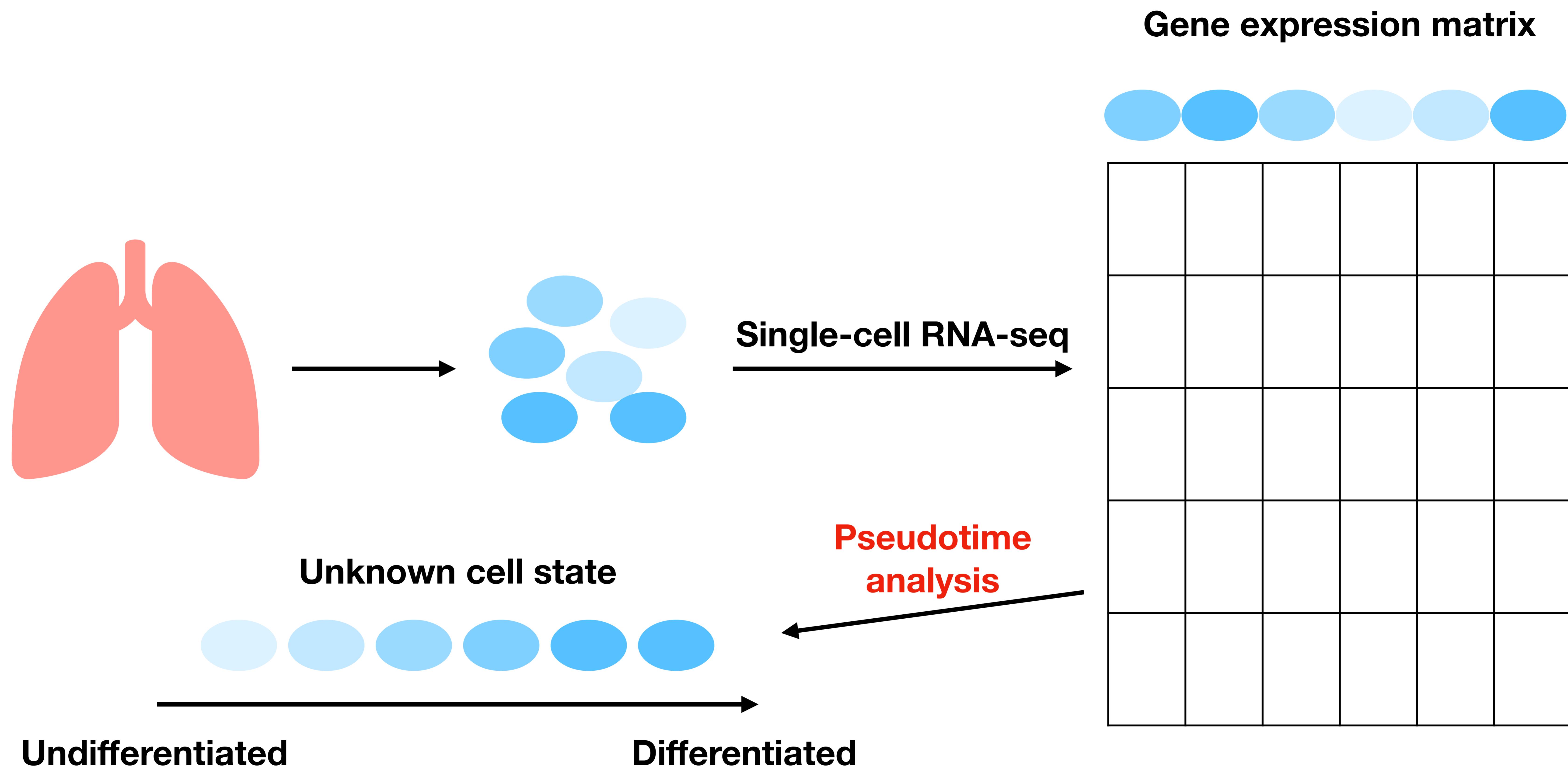
Single-cell RNA-seq



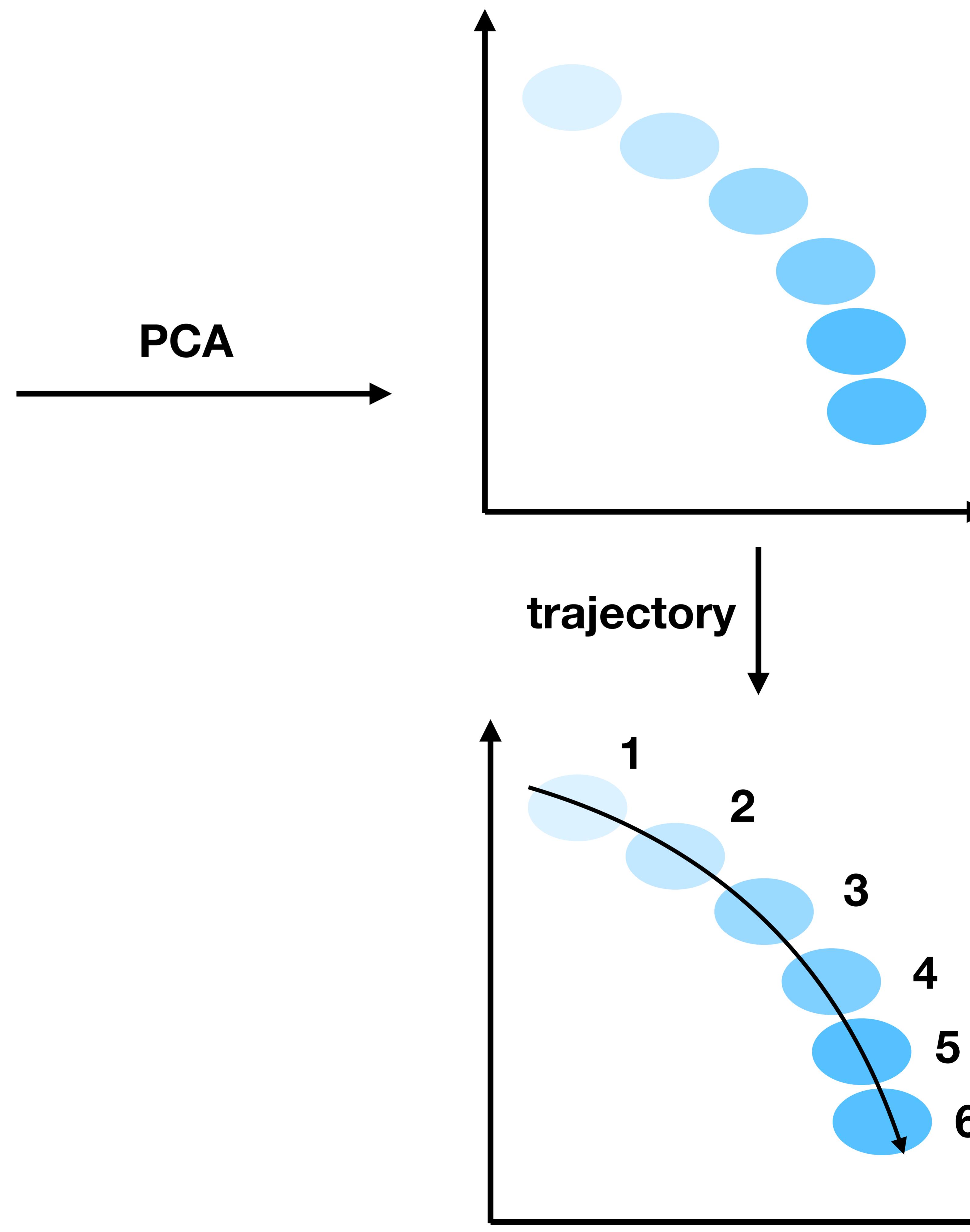
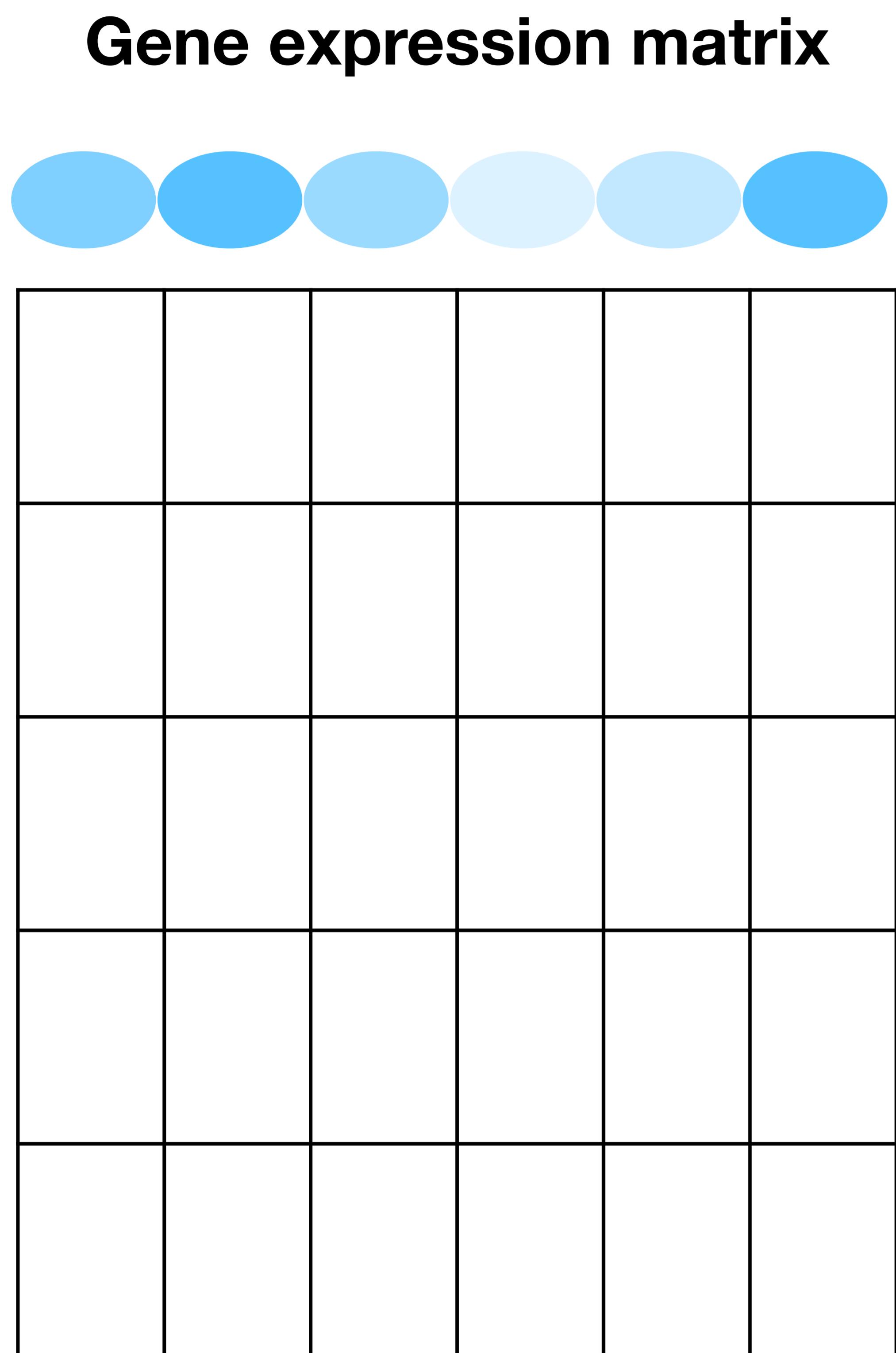
Gene expression matrix



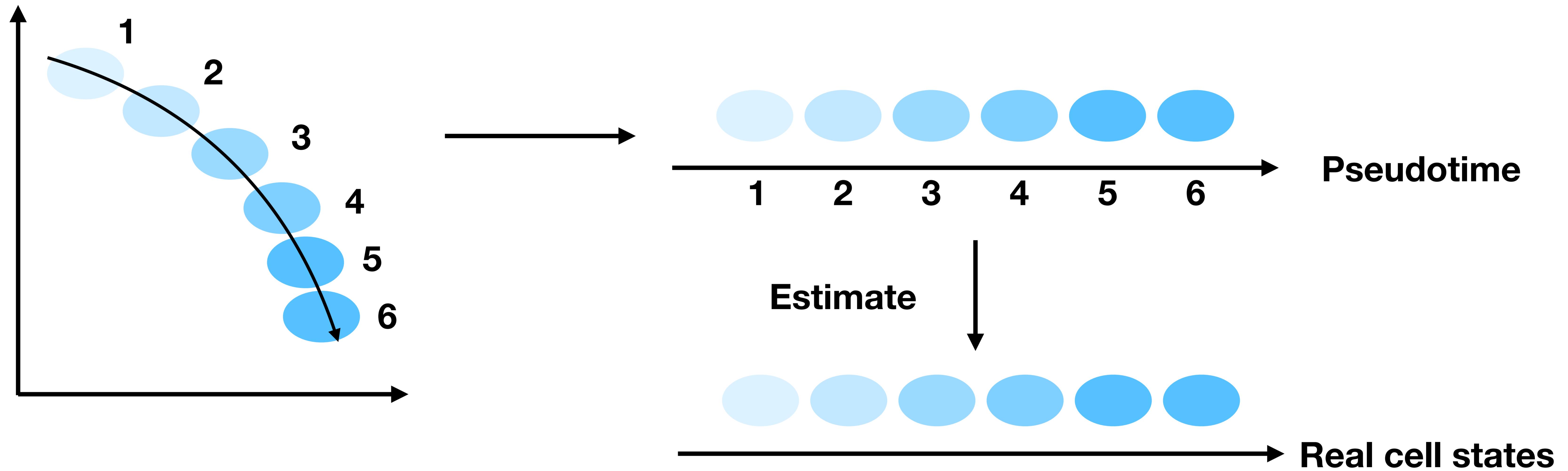
Single-cell RNA-seq



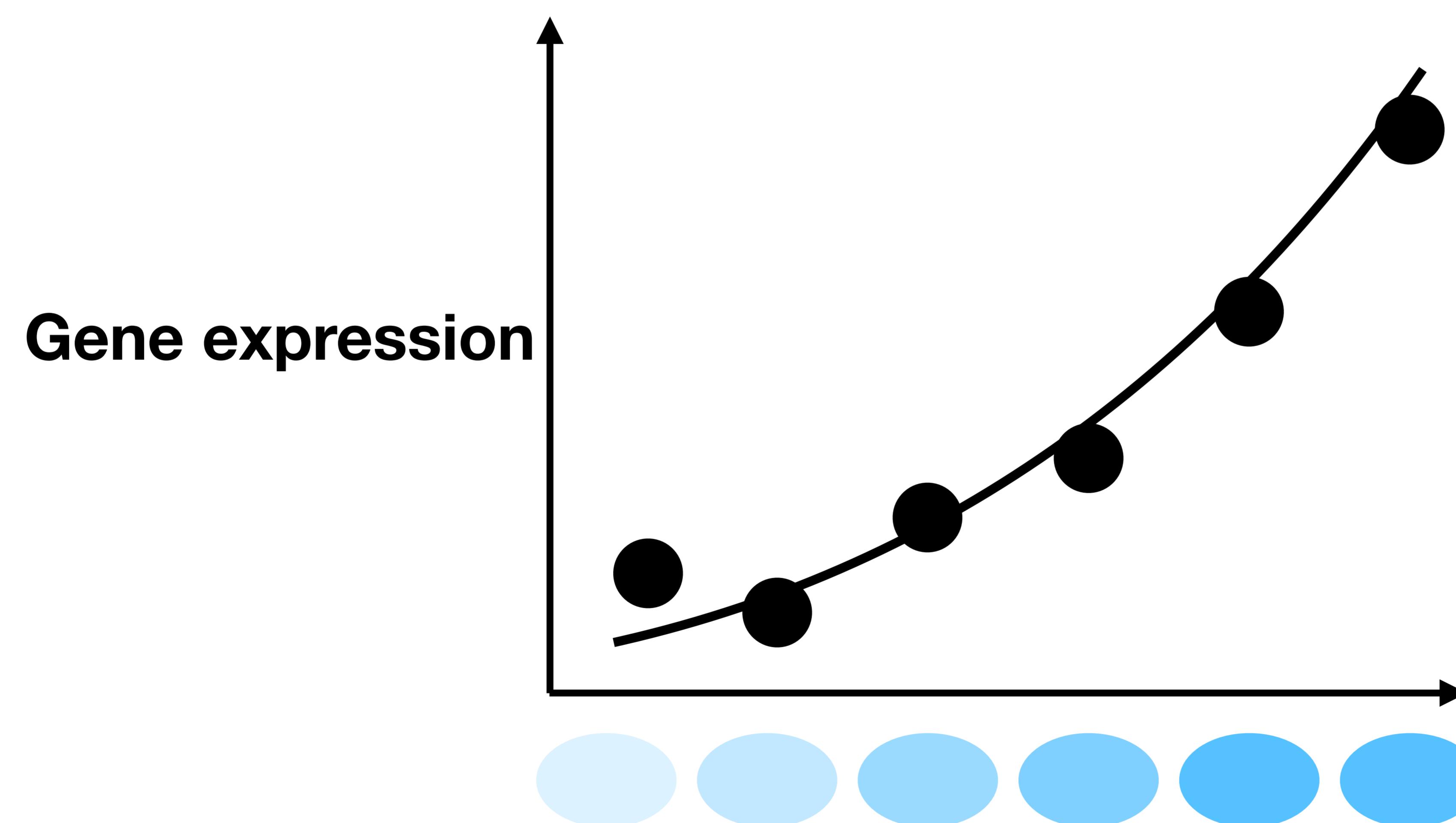
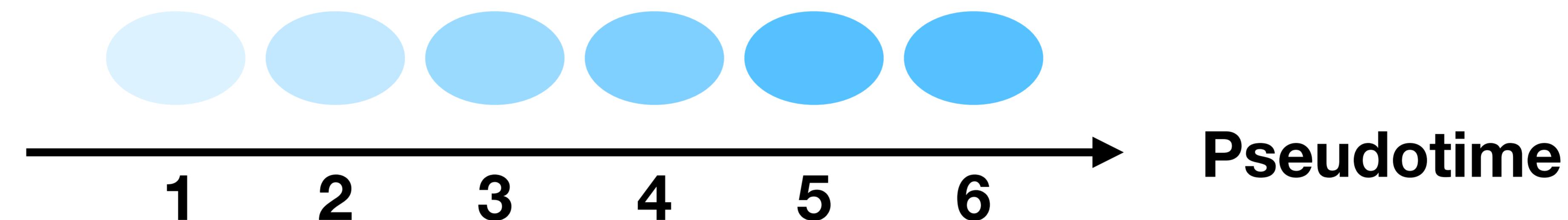
Pseudotime analysis



Pseudotime analysis

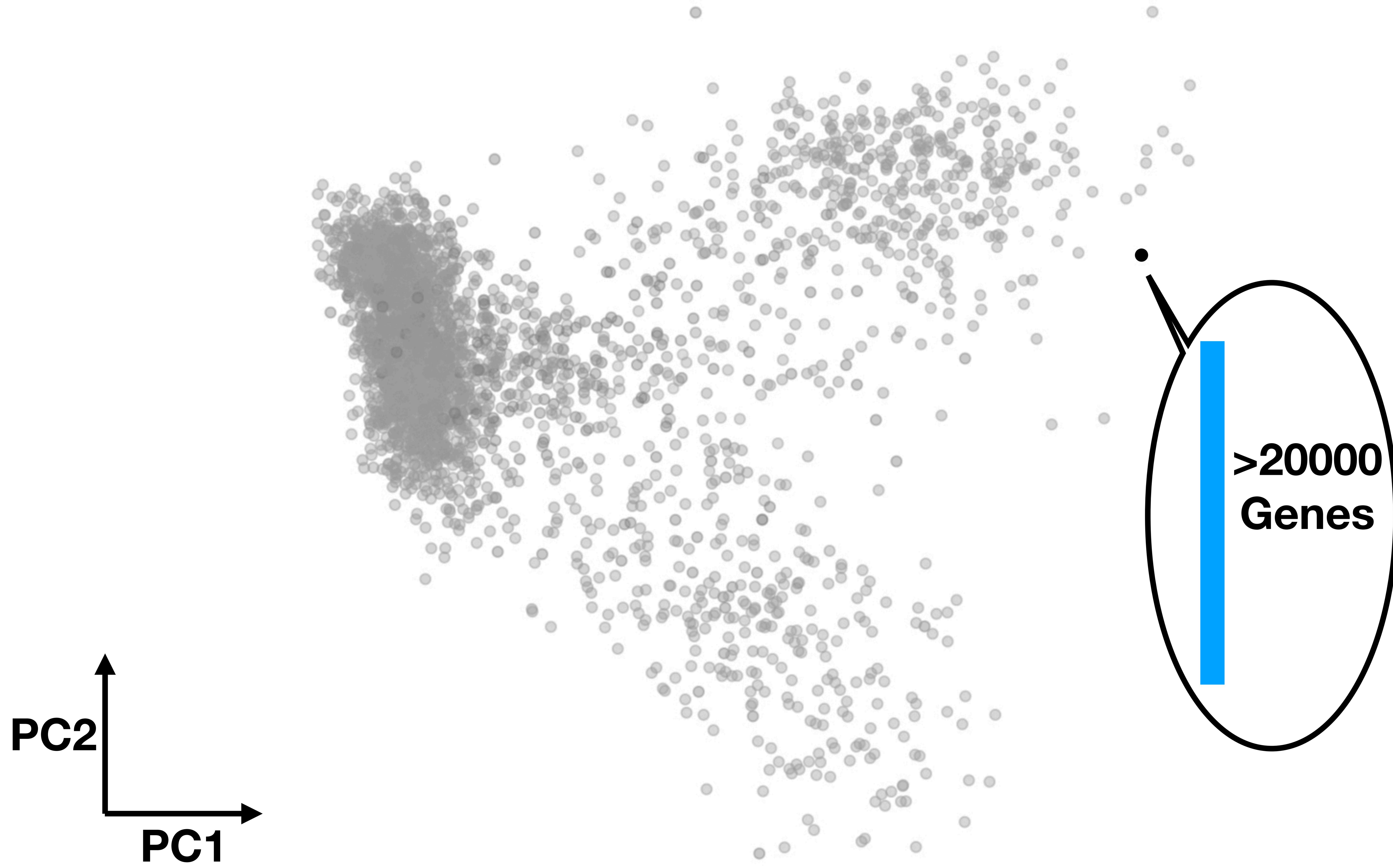


Pseudotime analysis

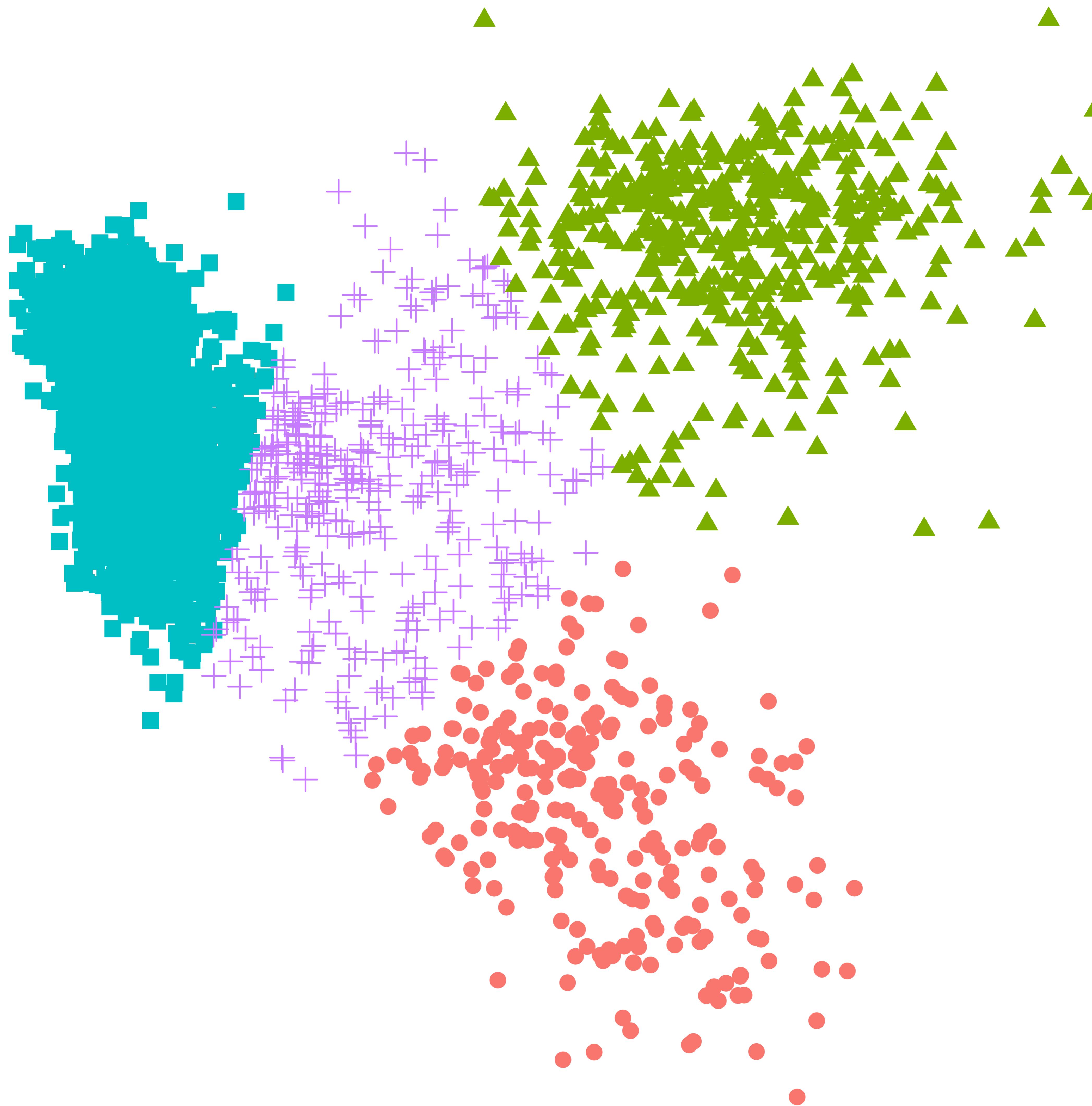


Example single-cell RNA-seq data

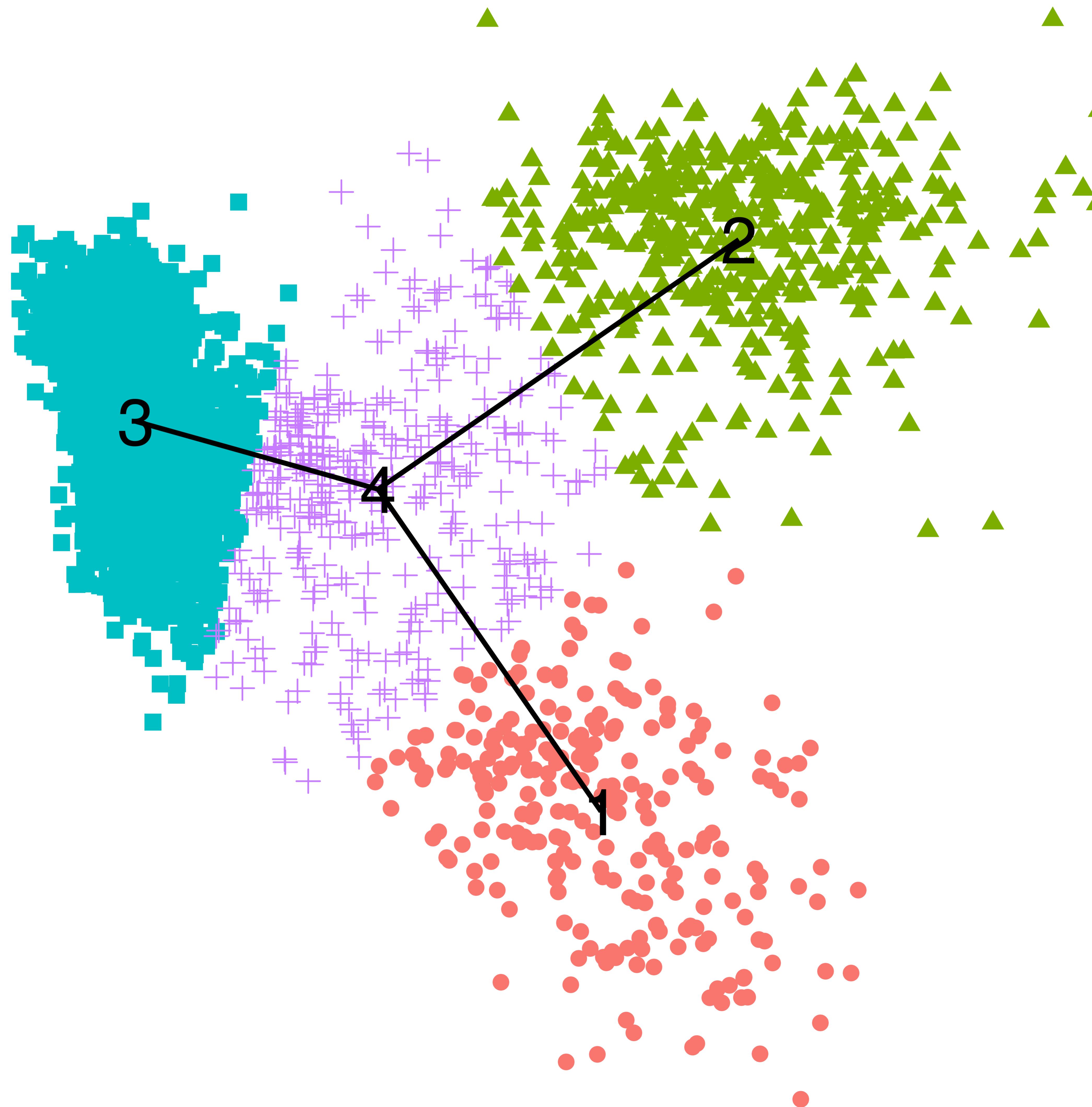
Human Bone Marrow from HCA



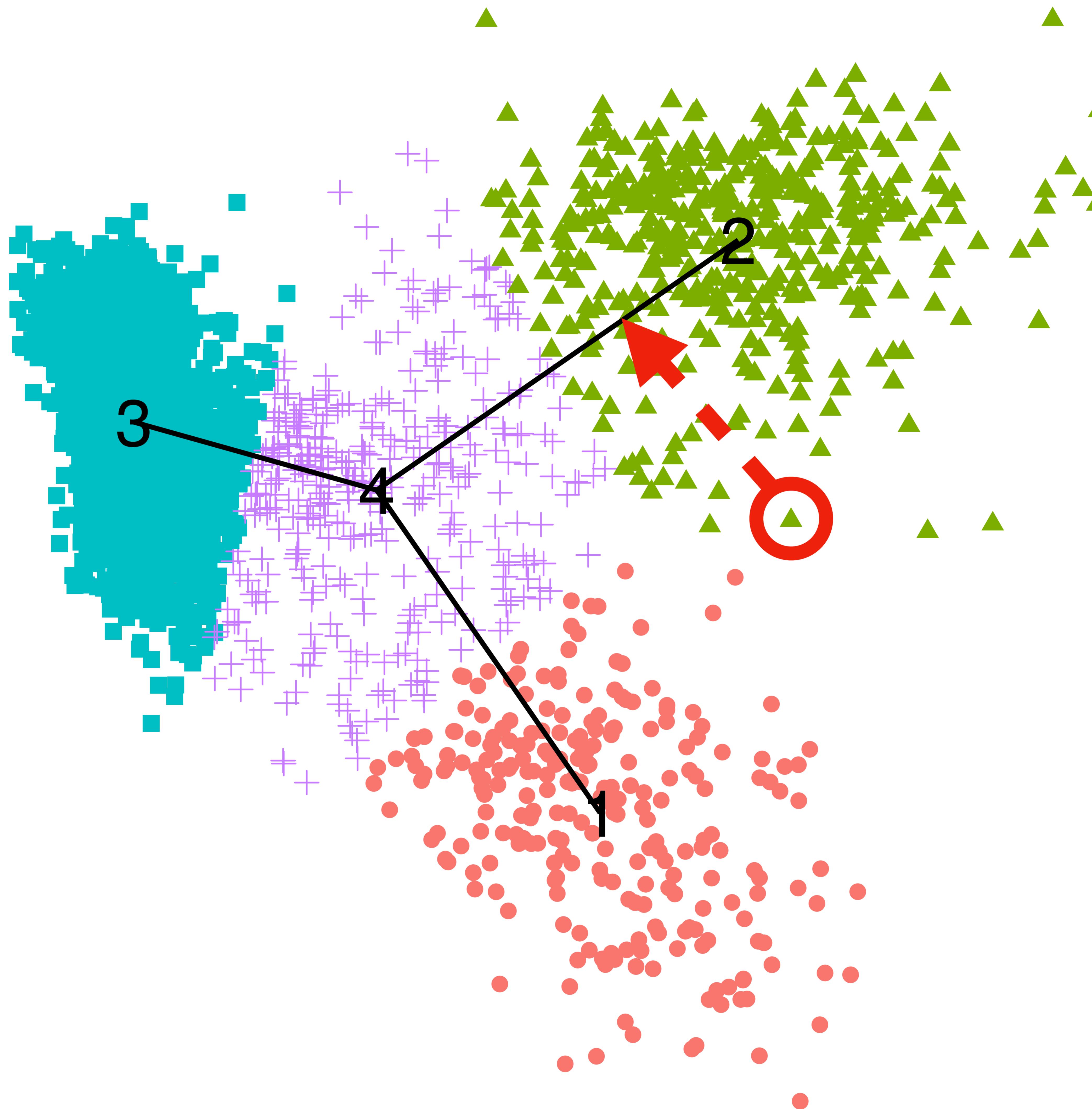
TSCAN: cluster-based minimum spanning tree



TSCAN: cluster-based minimum spanning tree

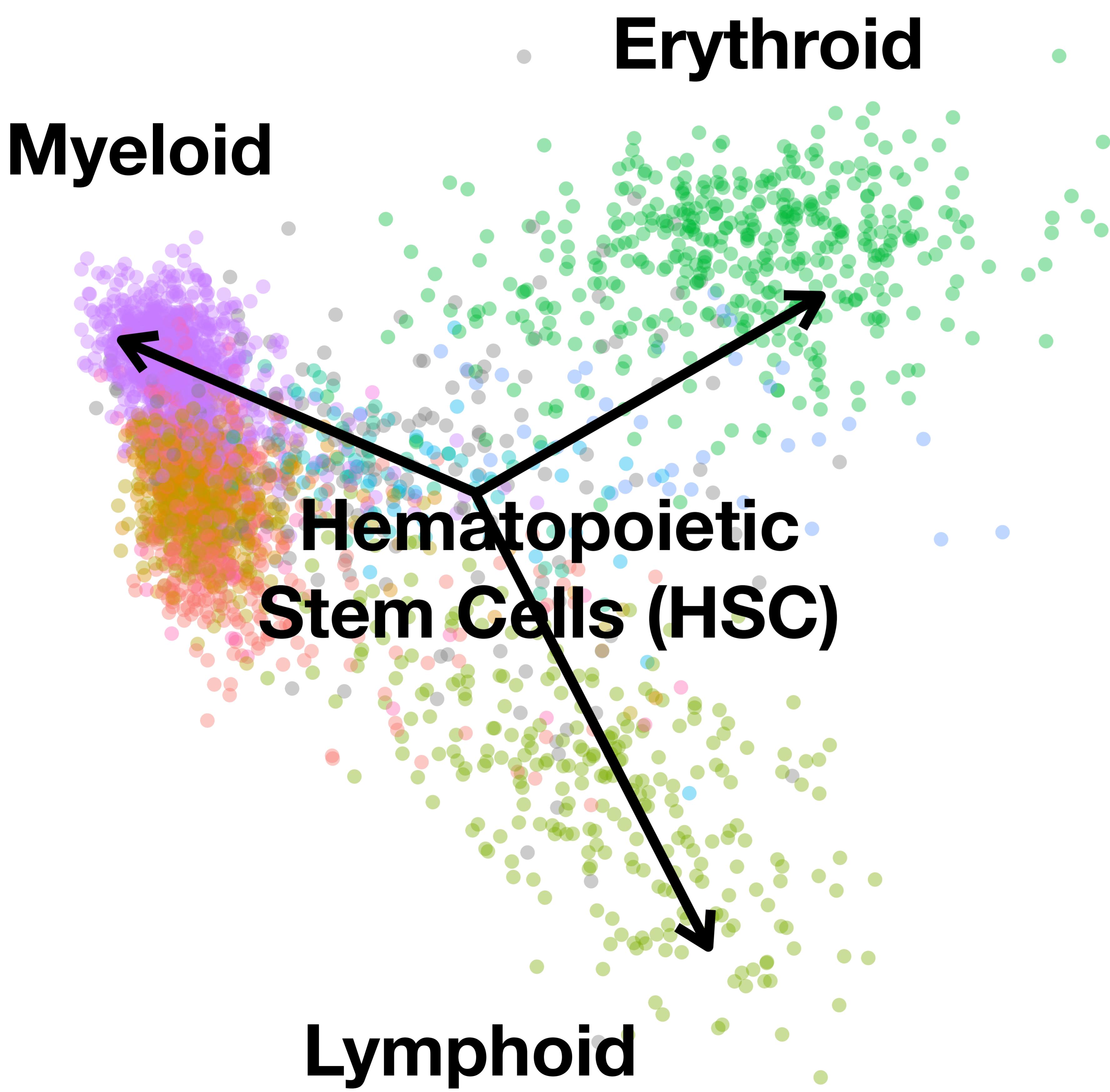


TSCAN: cluster-based minimum spanning tree

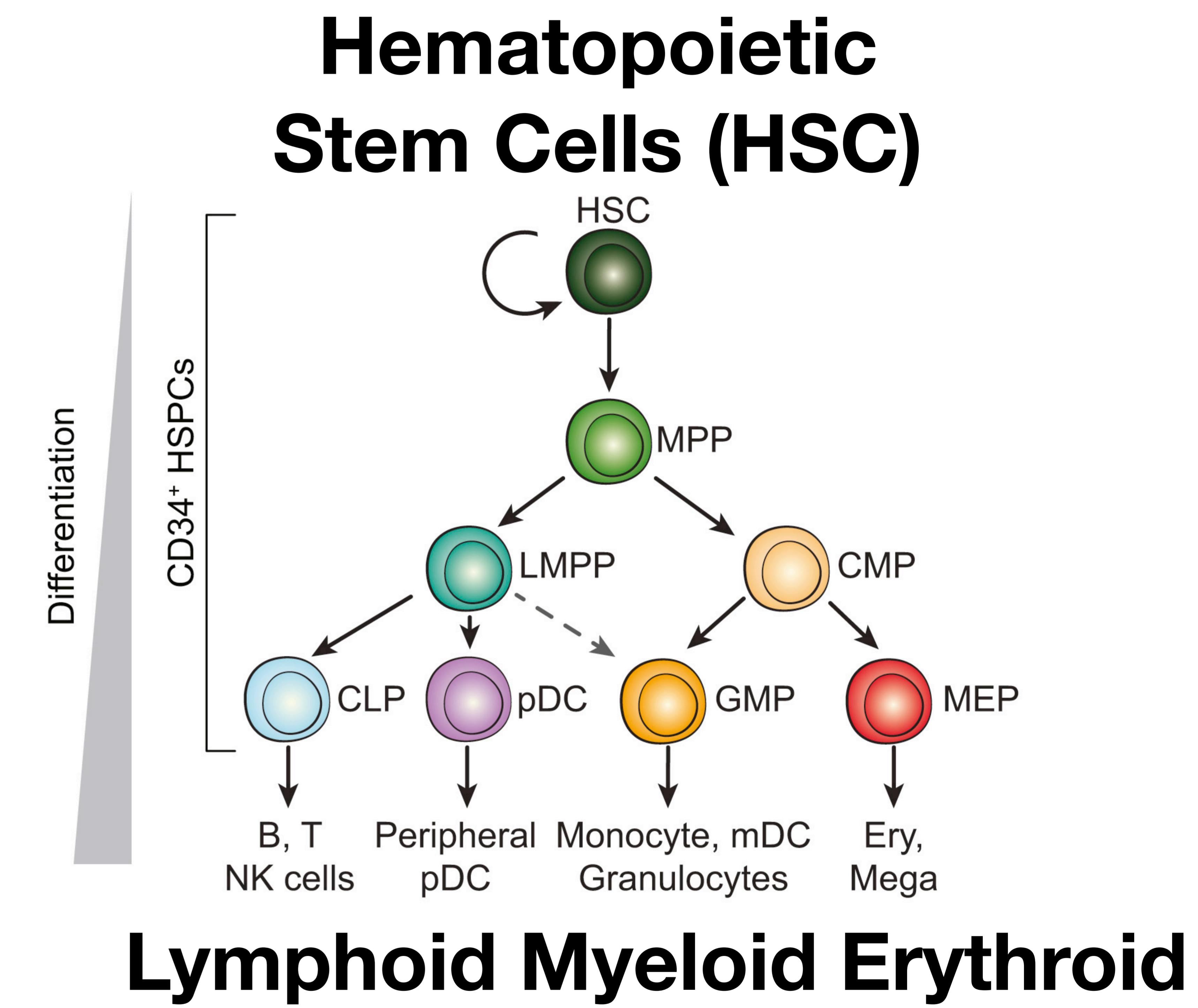


Pattern in scRNA-seq data matches with known biology

Single-cell Data



Known Biological Process



Lymphoid Myeloid Erythroid

Buenrostro et al. Cell (2018)

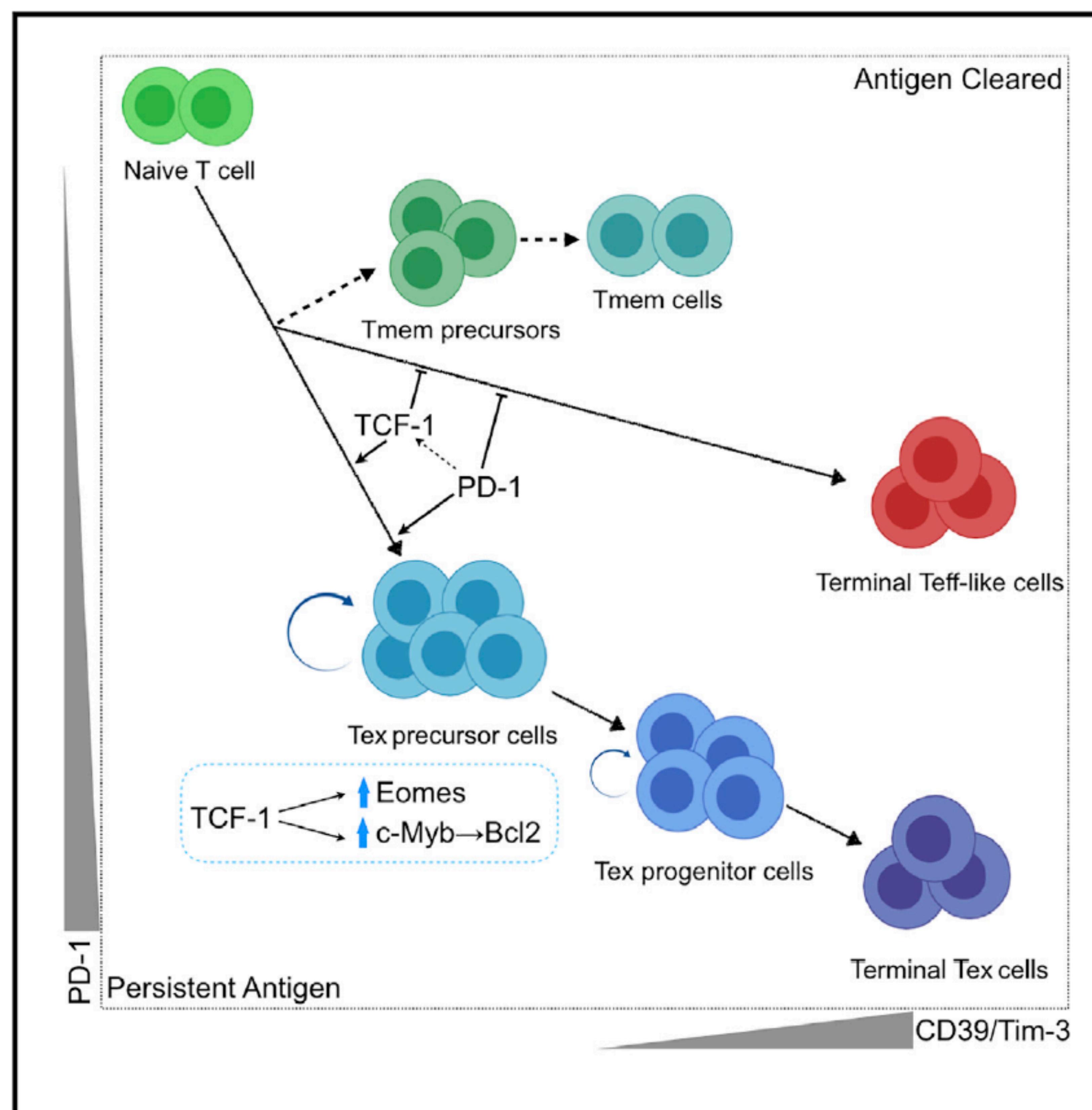
Real application: T cell exhaustion

Article

Immunity

TCF-1-Centered Transcriptional Network Drives an Effector versus Exhausted CD8 T Cell-Fate Decision

Graphical Abstract



Authors

Zeyu Chen, Zhicheng Ji,
Shin Foong Ngiow, ..., Golnaz Vahedi,
Hongkai Ji, E. John Wherry

Correspondence

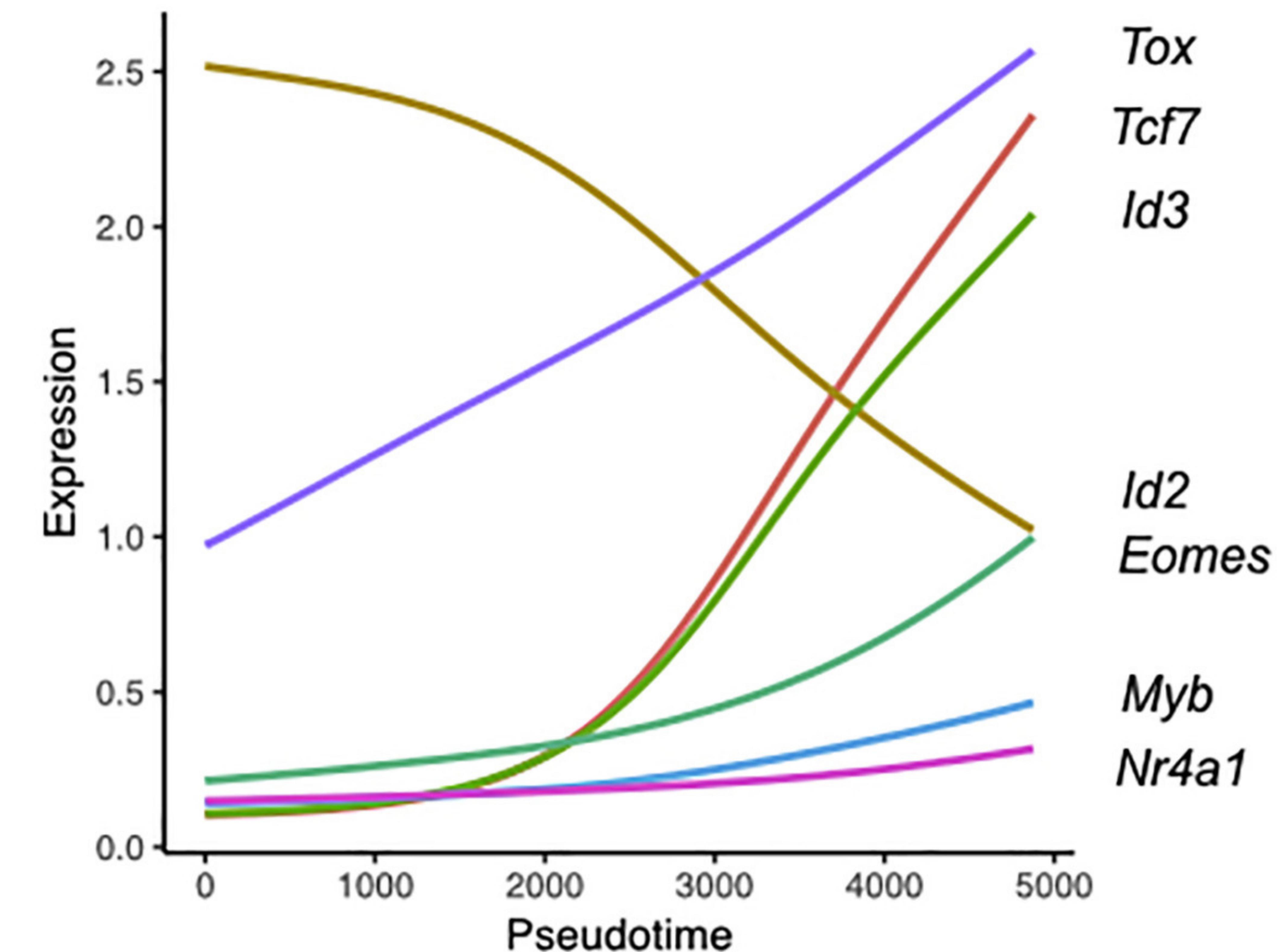
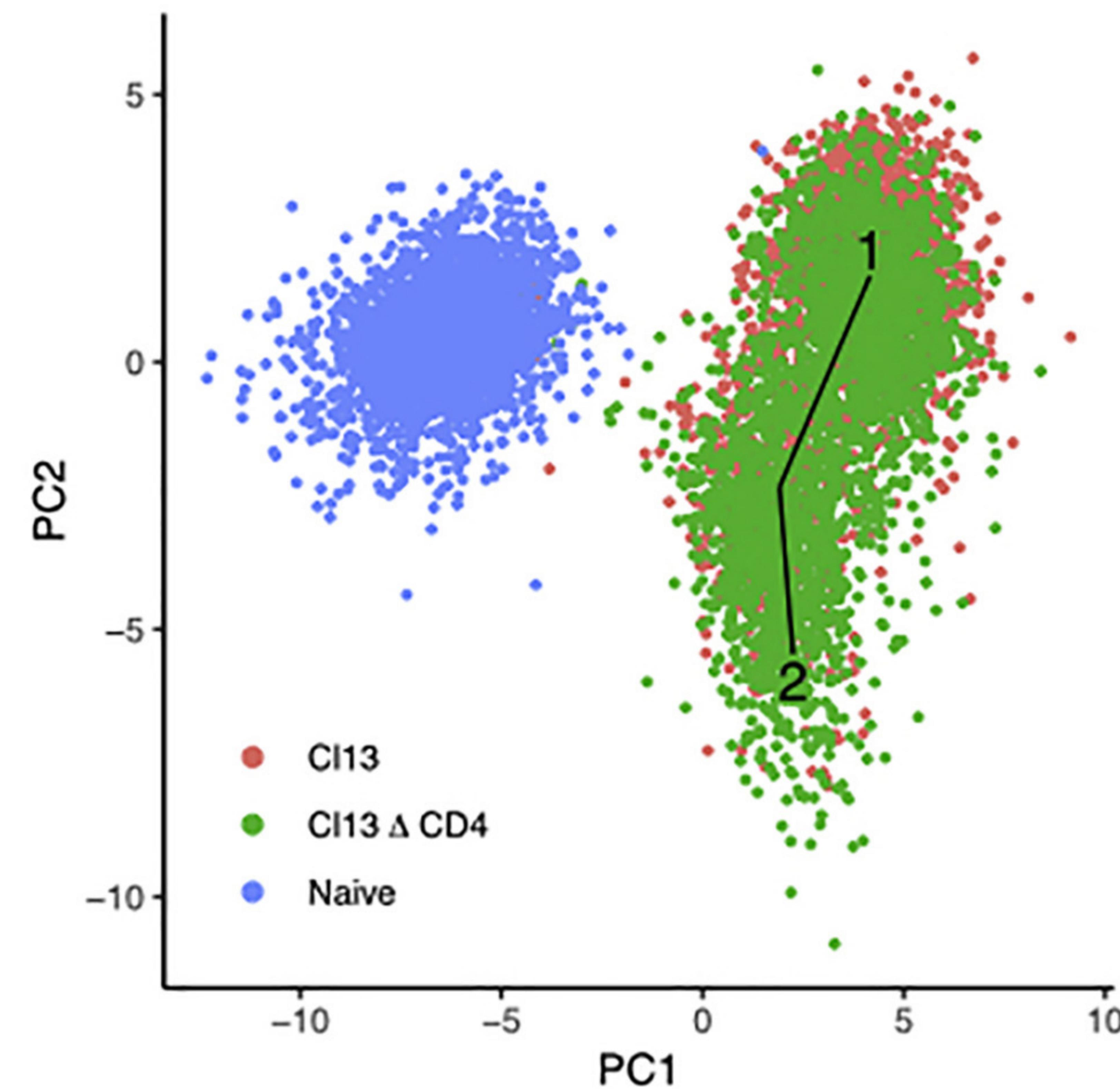
wherry@pennmedicine.upenn.edu

In Brief

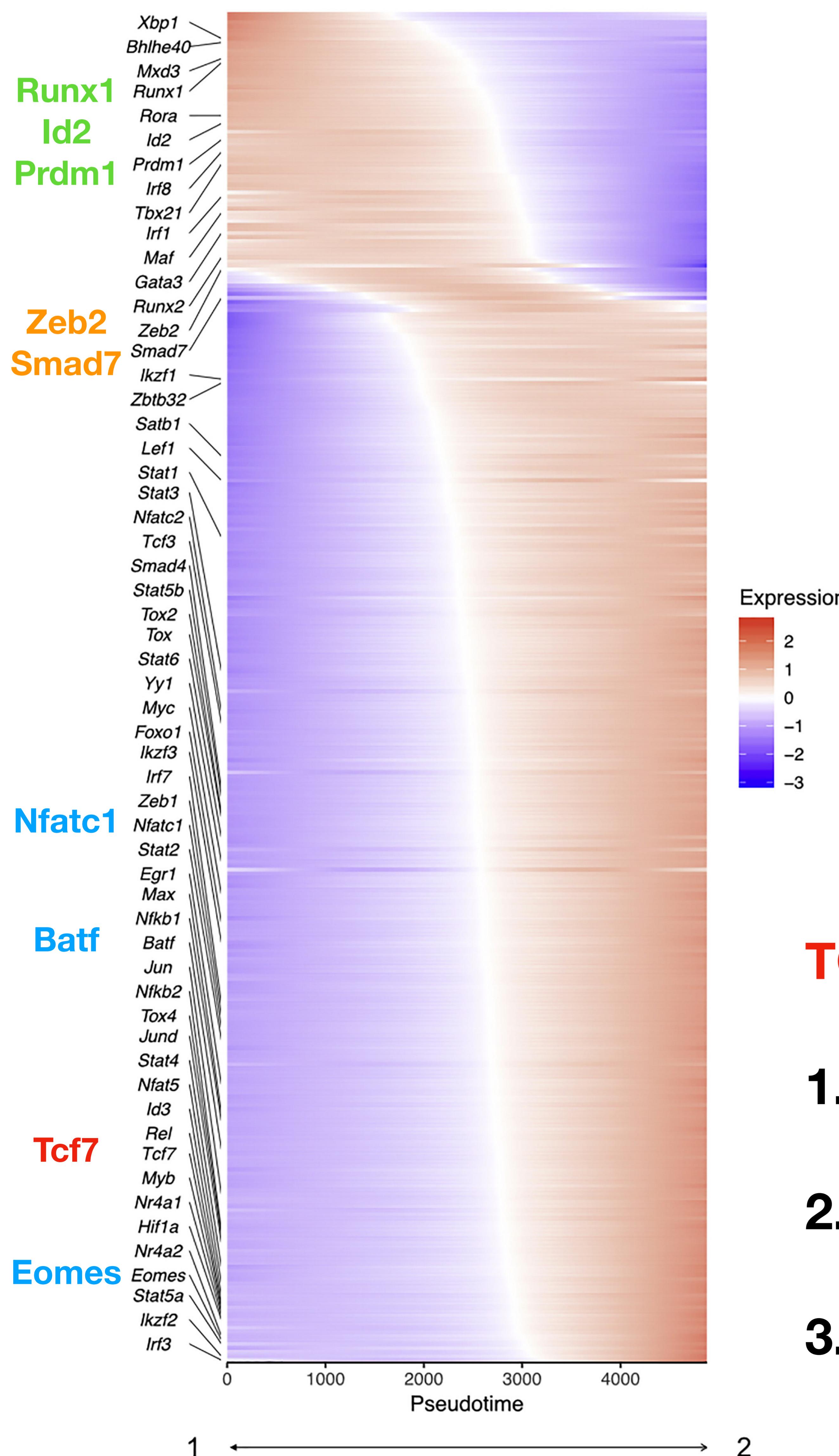
The initiation of the T cell exhaustion program remains poorly understood. In this study, Chen et al. define an effector (Teff) versus exhausted (Tex) CD8 T cell binary-fate decision during chronic infection and find that TCF-1 supports the Tex precursor development by antagonizing Teff-like cell differentiation through multiple transcription factors.

Real application: T cell exhaustion

Tcf7 encodes TCF-1

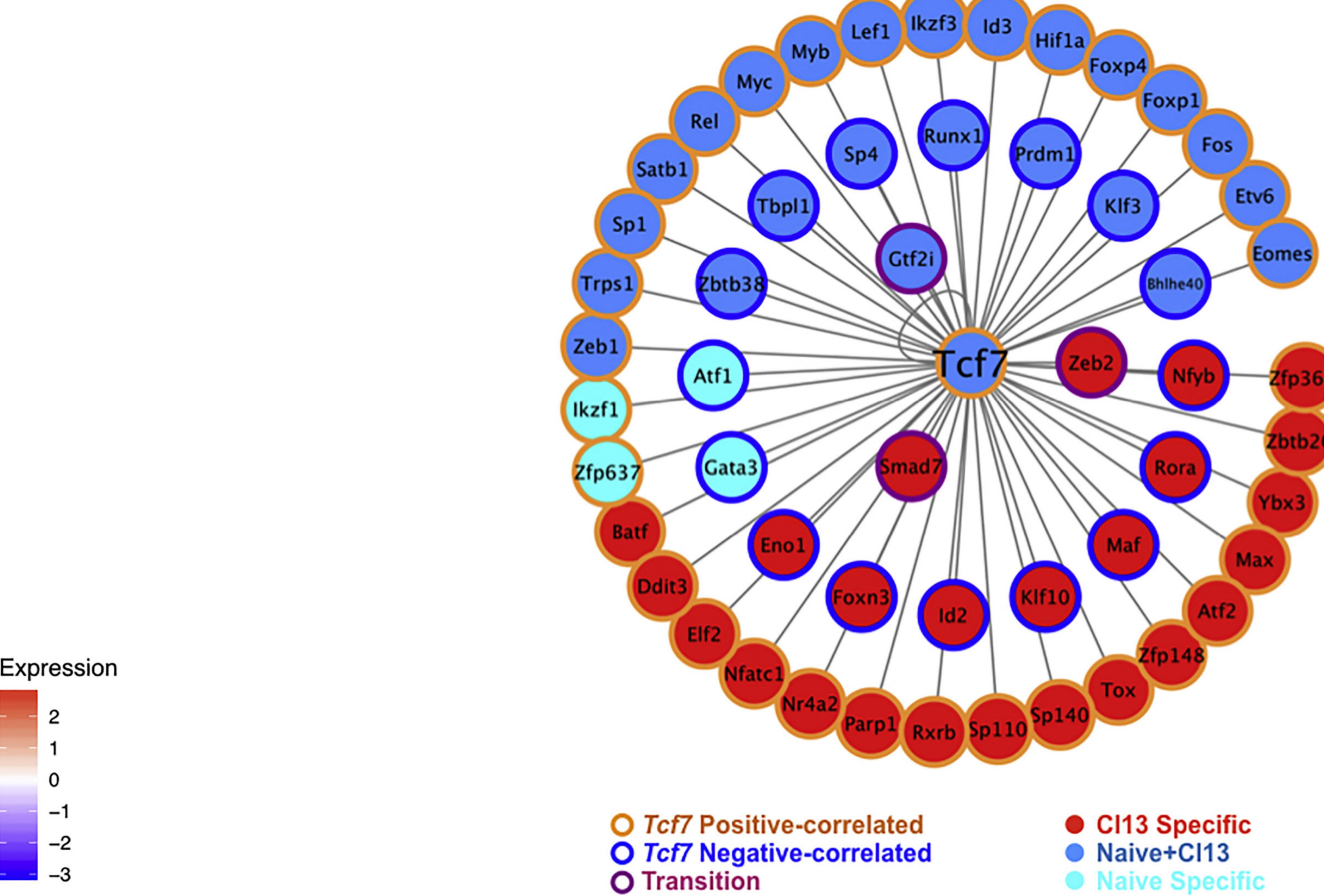


Real application: T cell exhaustion

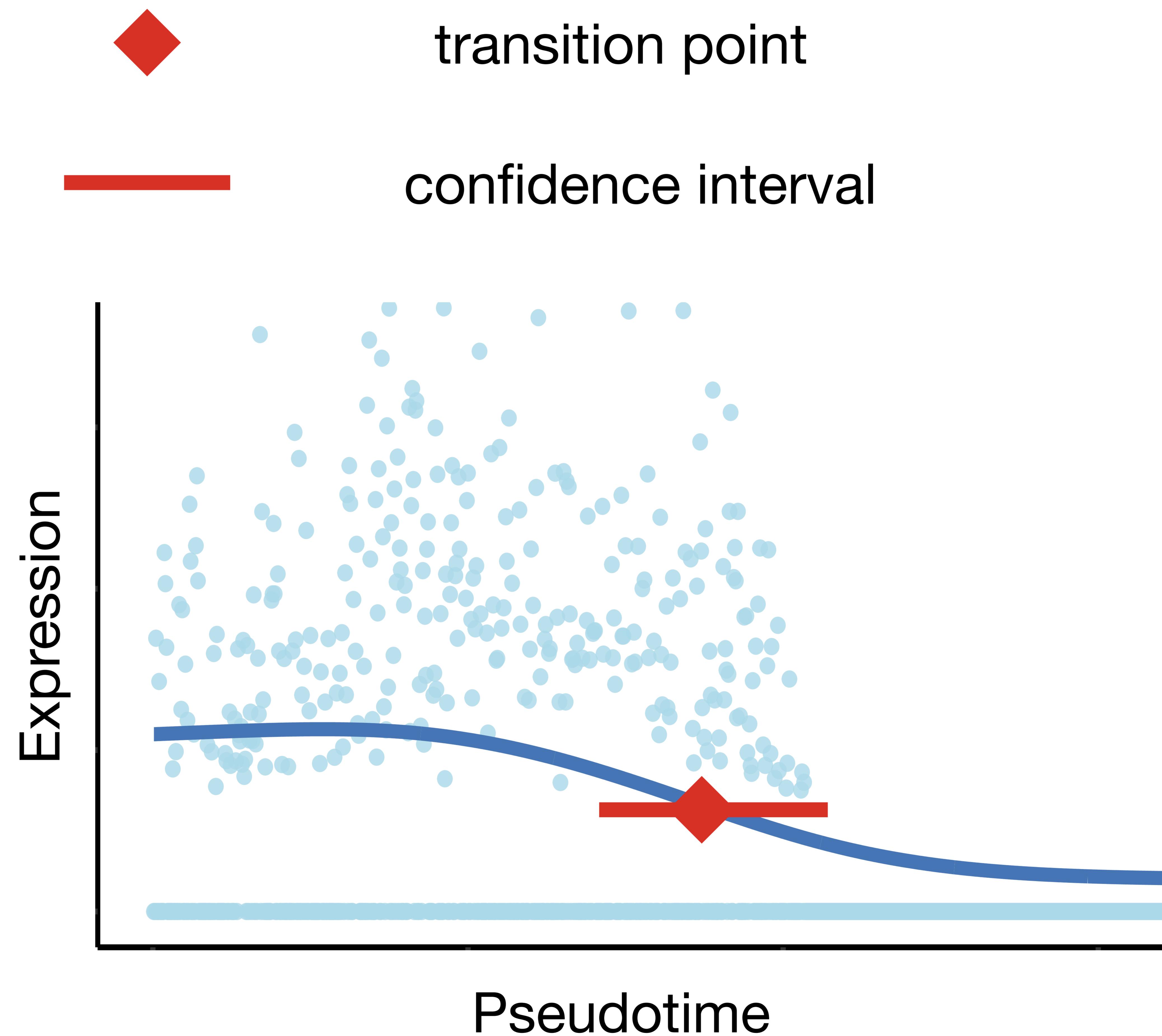


TCF-1 was predicted to:

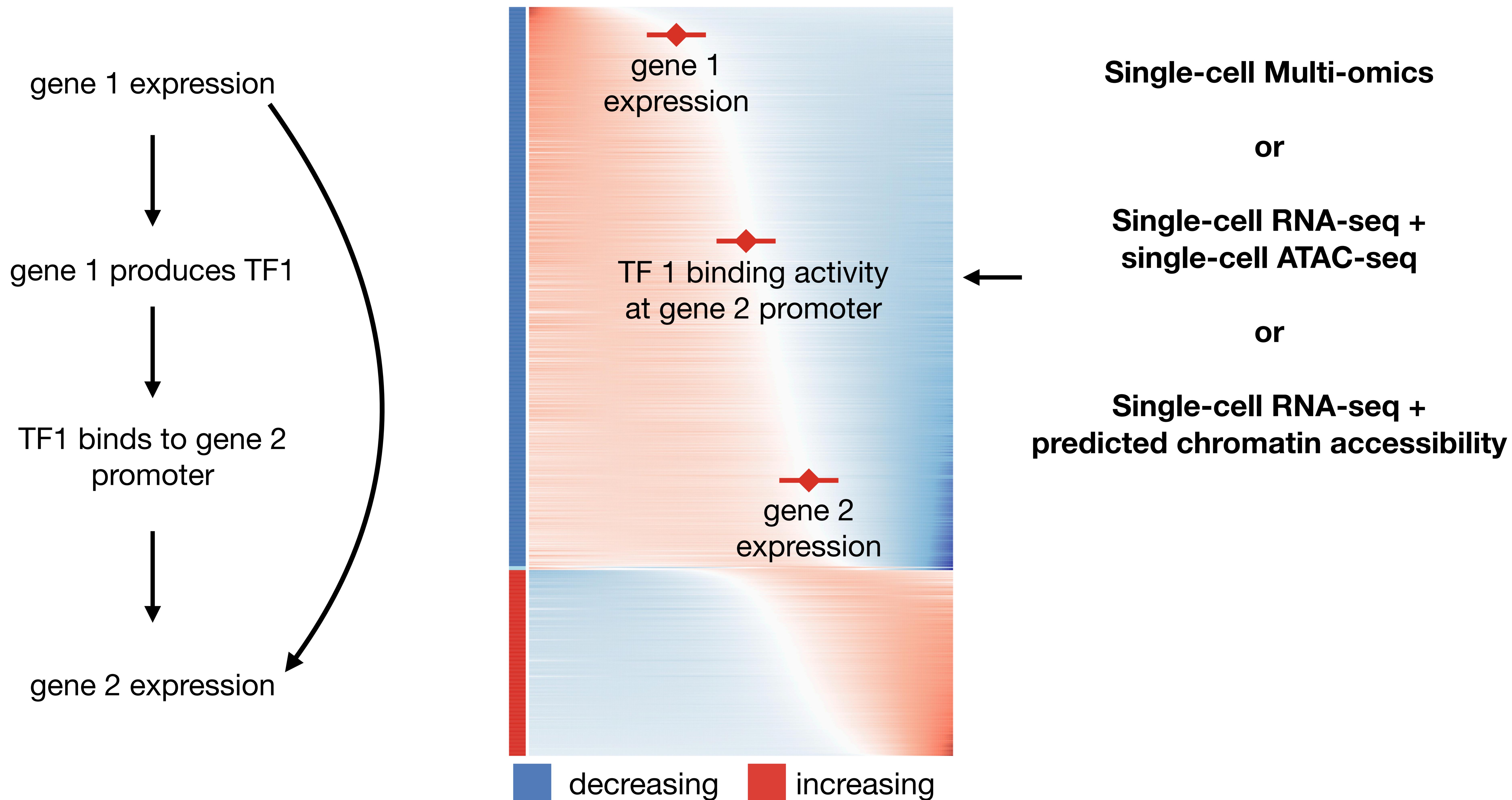
1. repress genes in Teff cell differentiation (**Id2, Prdm1, Runx1**)
2. promote expression in fostering exhaustion (**Eomes, Batf, Nfatc1**)
3. have a more complex regulatory connection to **Smad7, Zeb2**



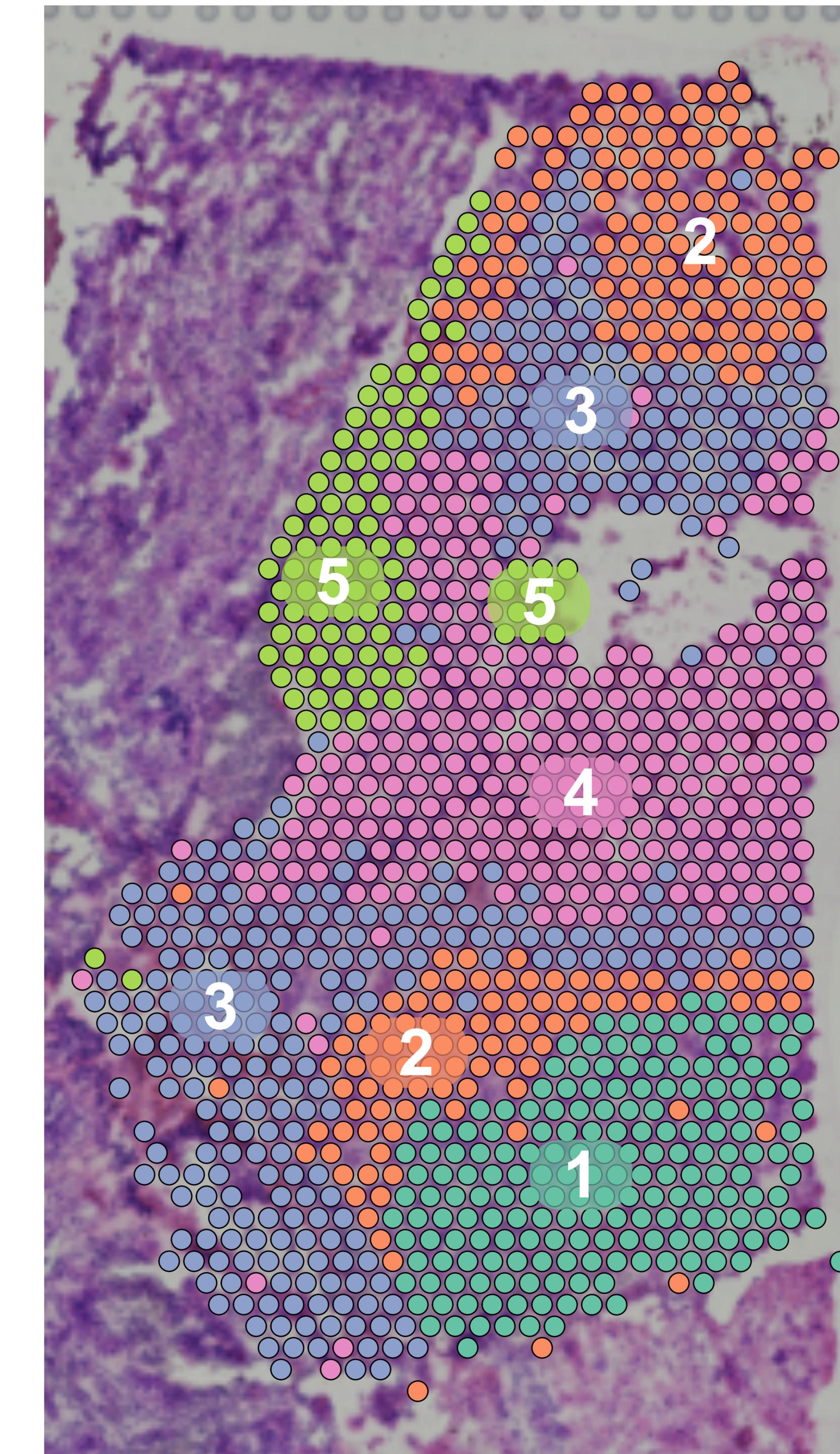
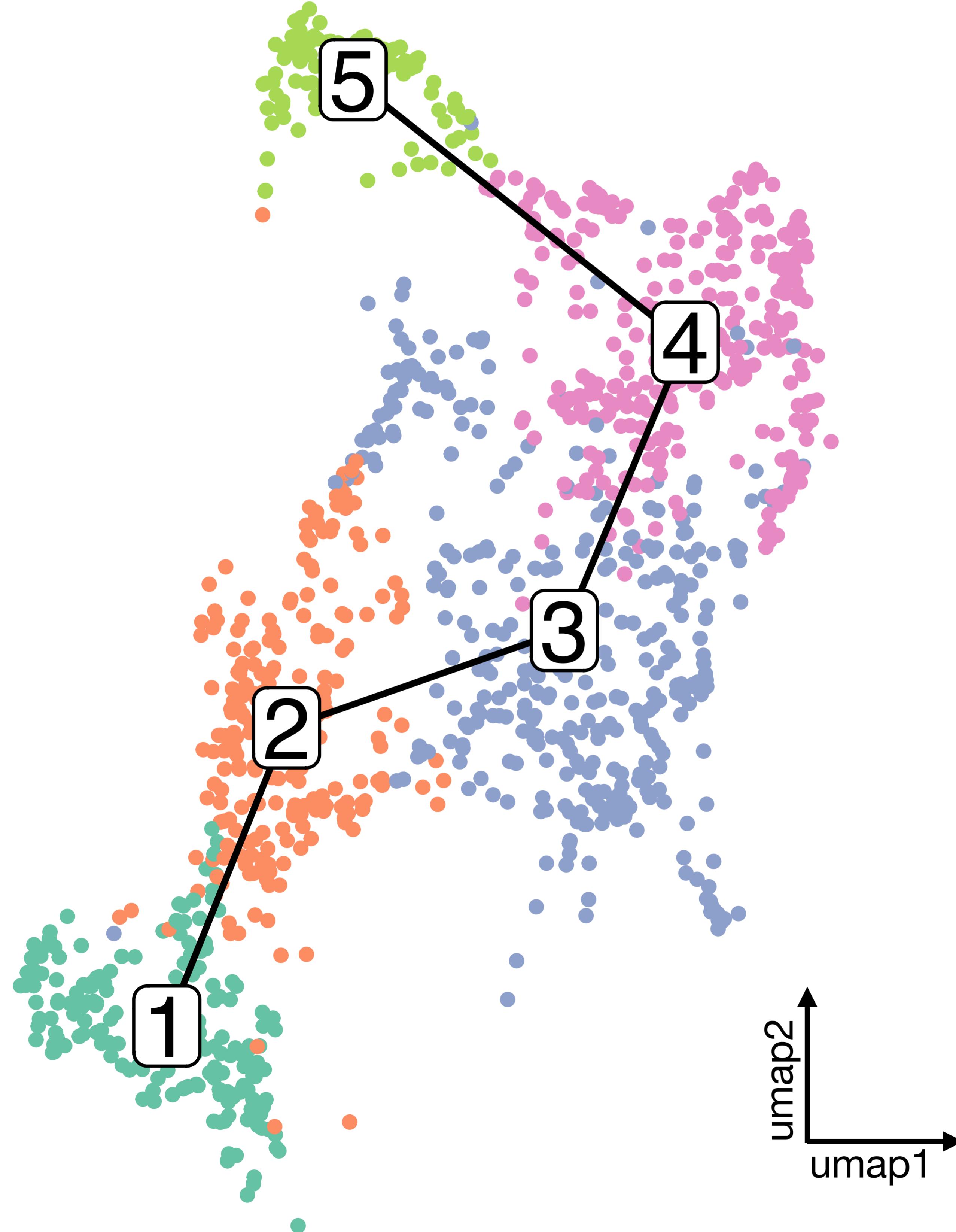
Work in progress 1: gene regulatory dynamics



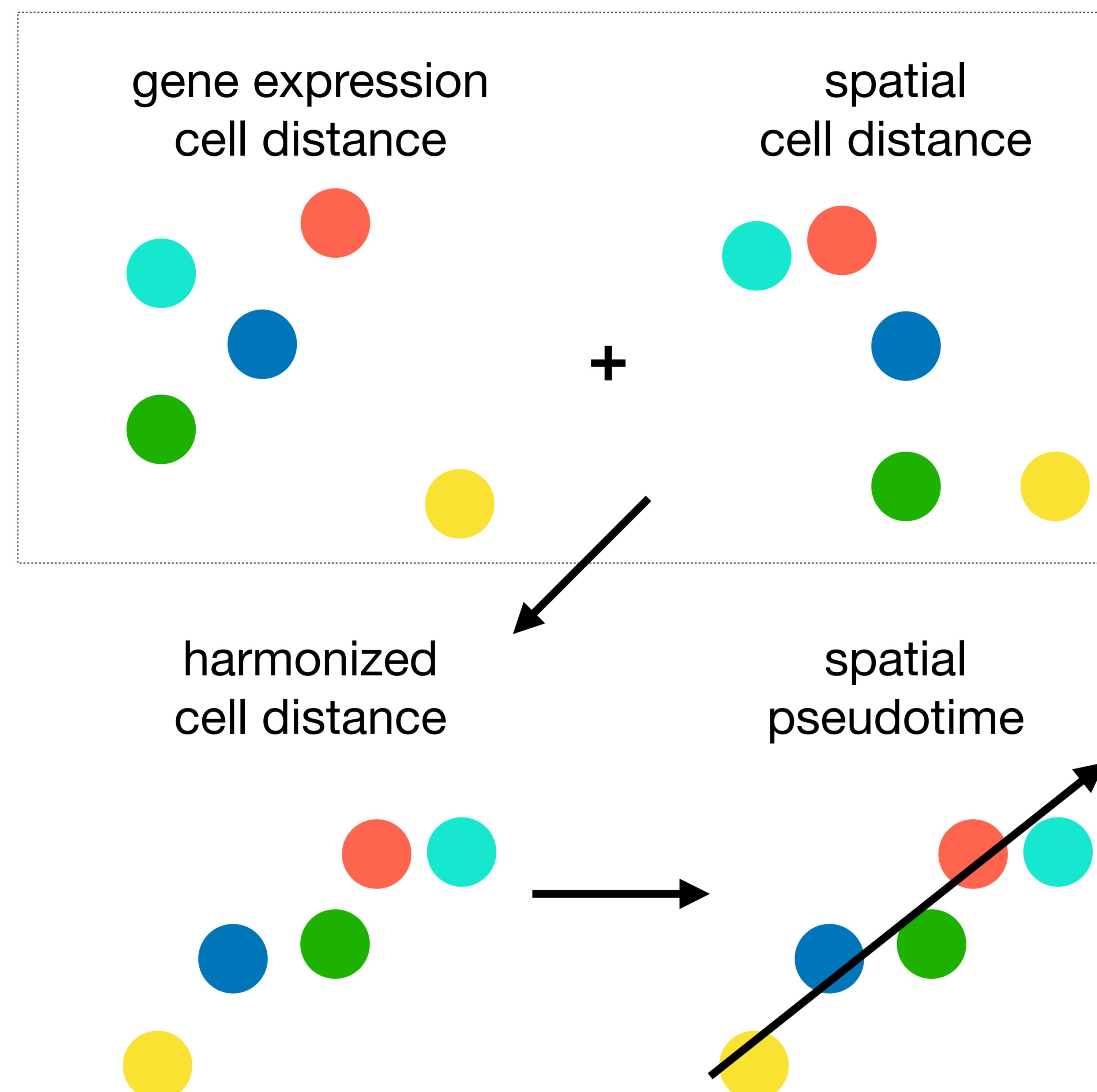
Work in progress 1: gene regulatory dynamics



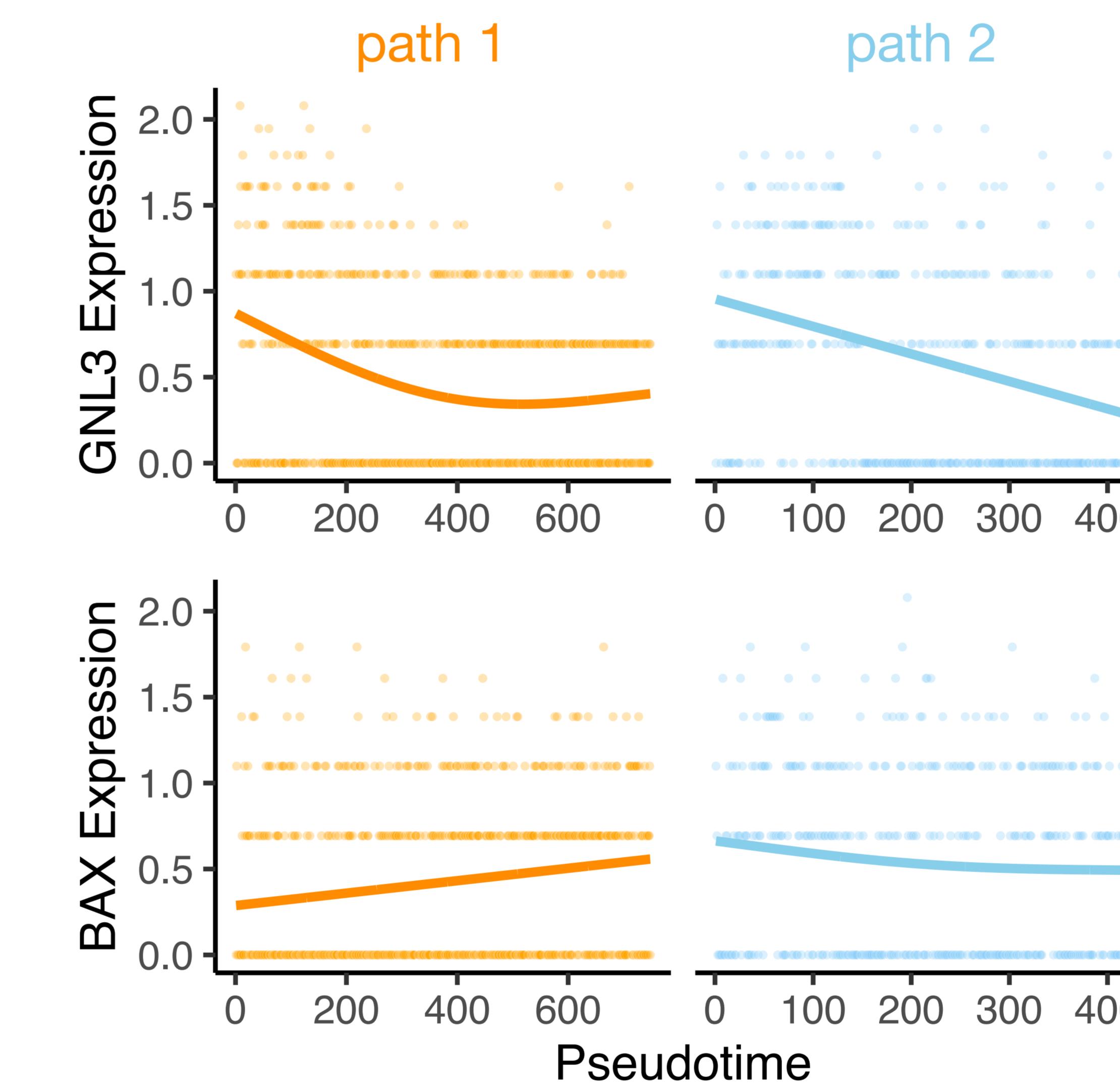
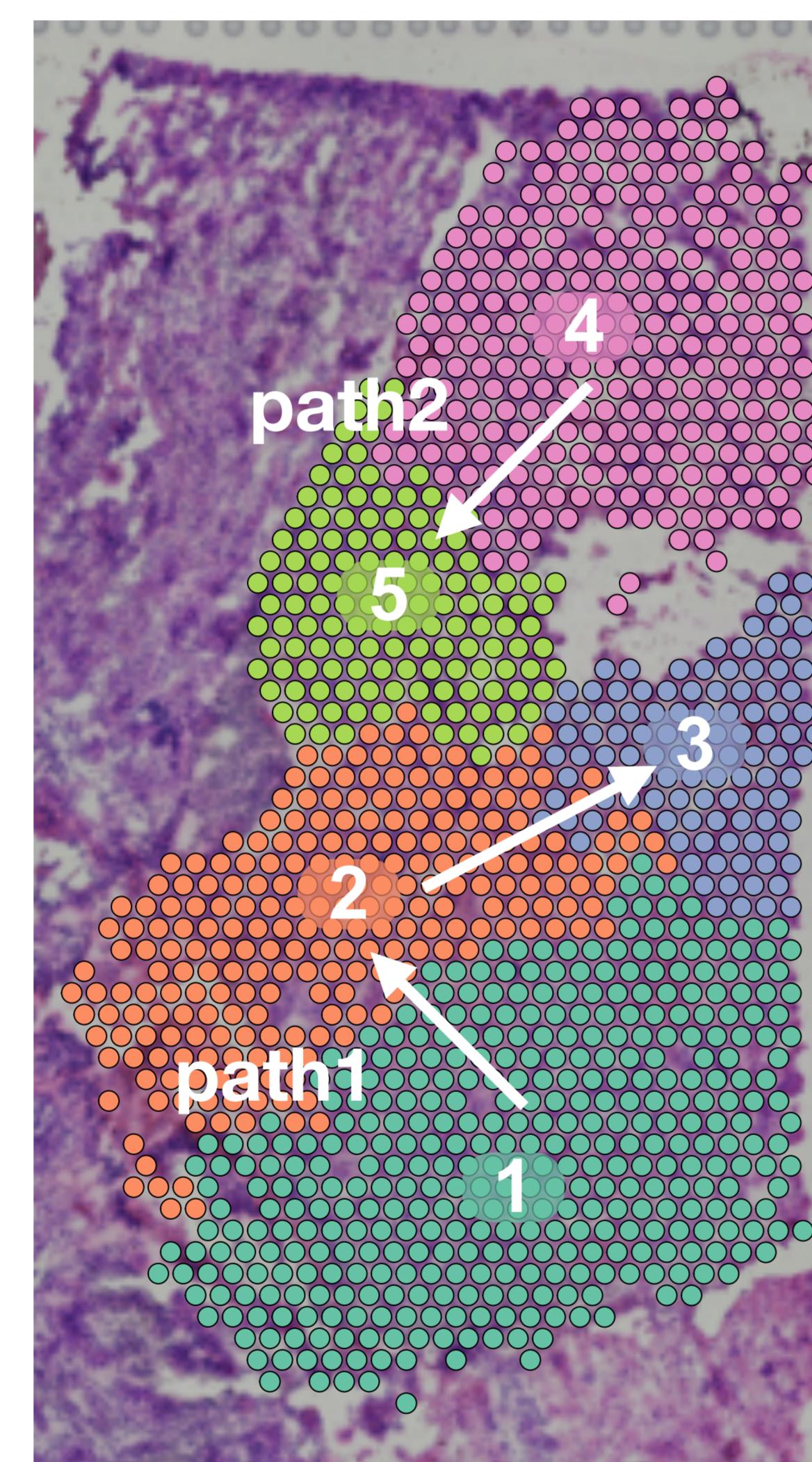
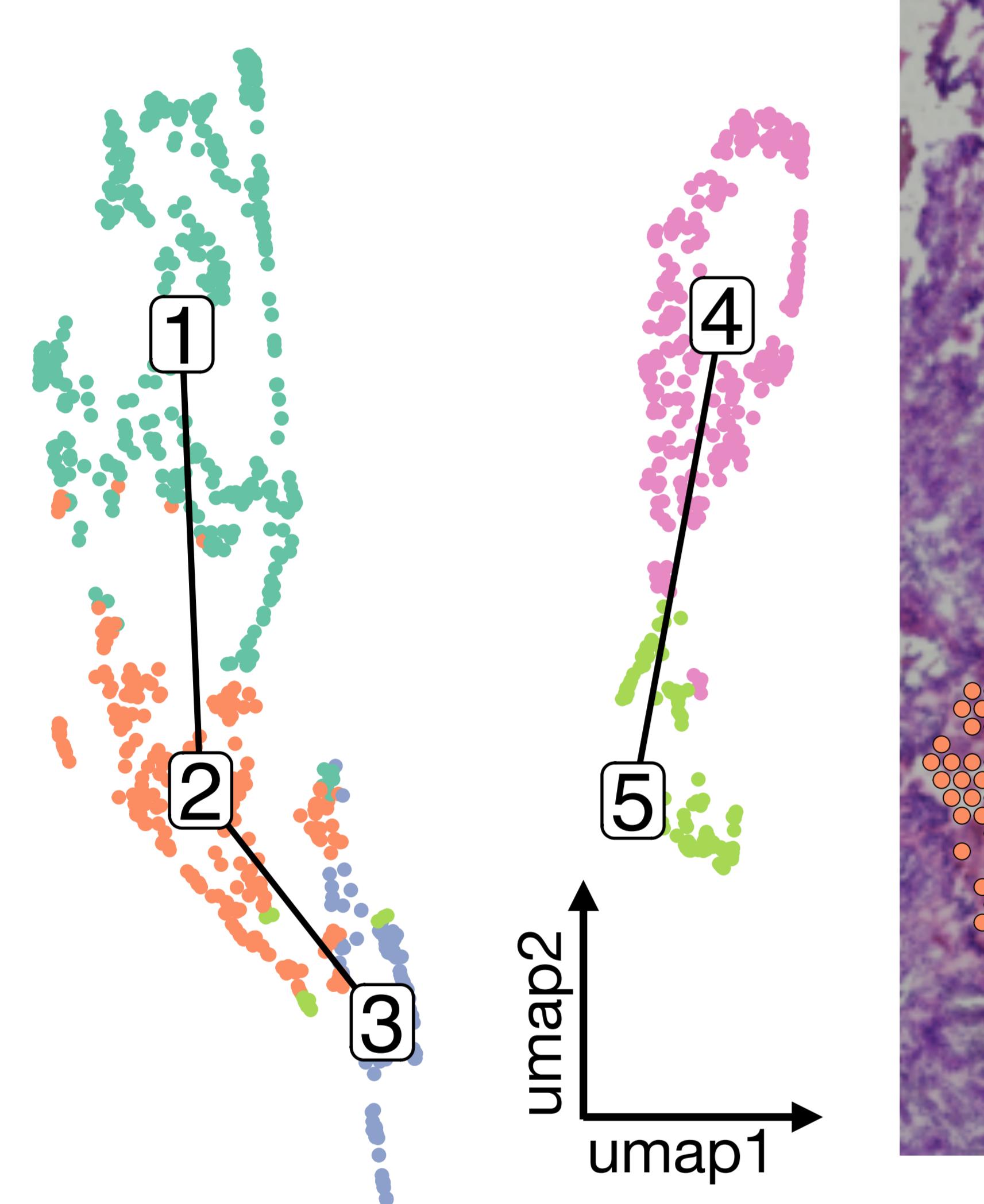
Work in progress 2: spatial-temporal trajectories



Work in progress 2: spatial-temporal trajectories



Work in progress 2: spatial-temporal trajectories

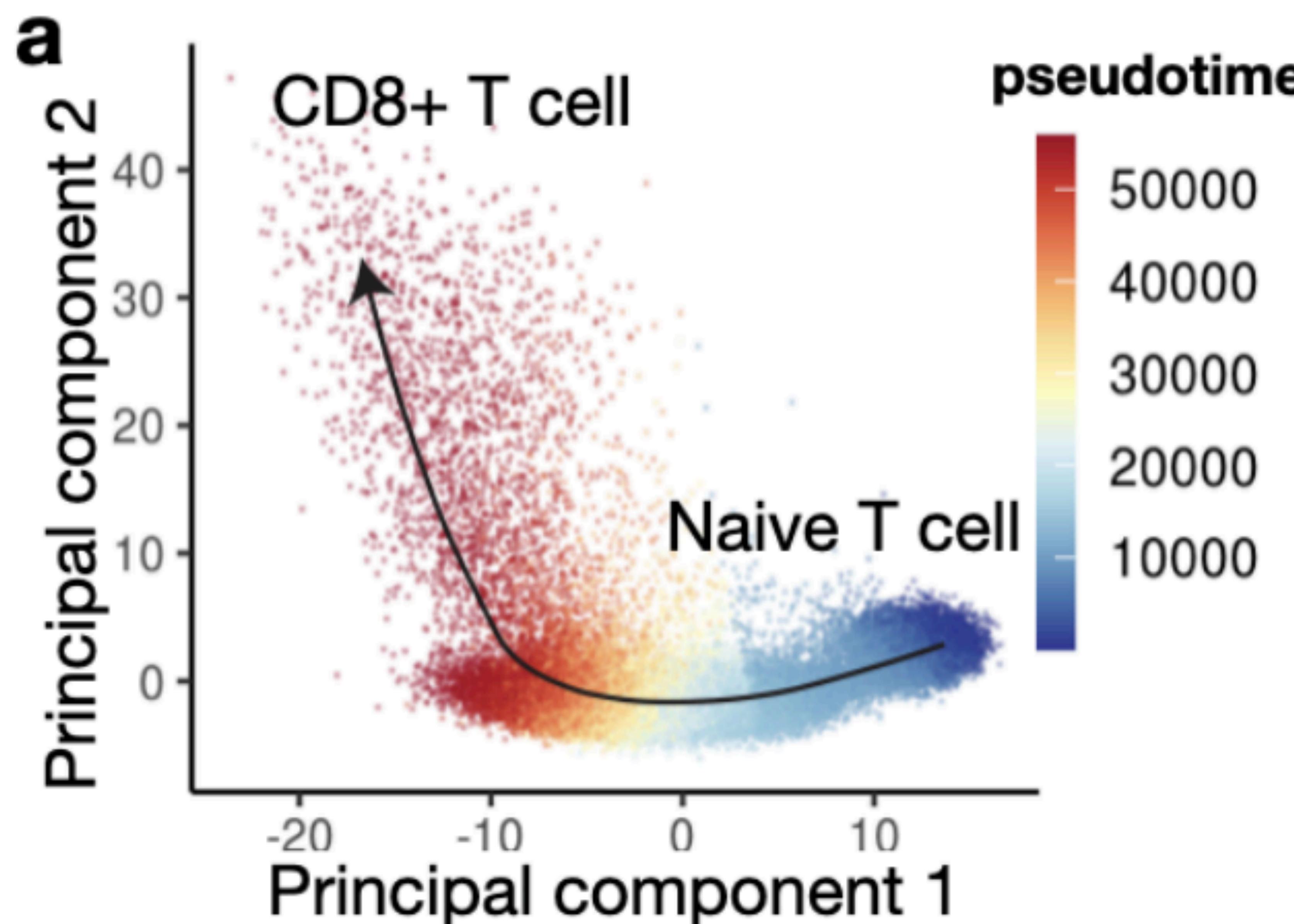
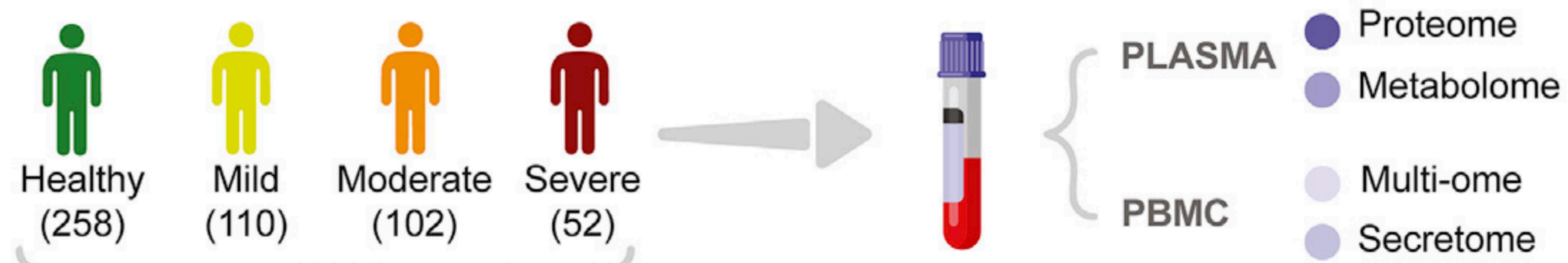


GNL3 (nucleostemin)
expressed in cancer stem cells

BAX
induces apoptosis in glioblastoma

Work in progress 3: multi-sample analysis

Integrated cross-omic analysis of COVID-19 patients and healthy participants



Genes with differential pattern between mild and severe patients along pseudotime?

Work in progress 3: multi-sample analysis



bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

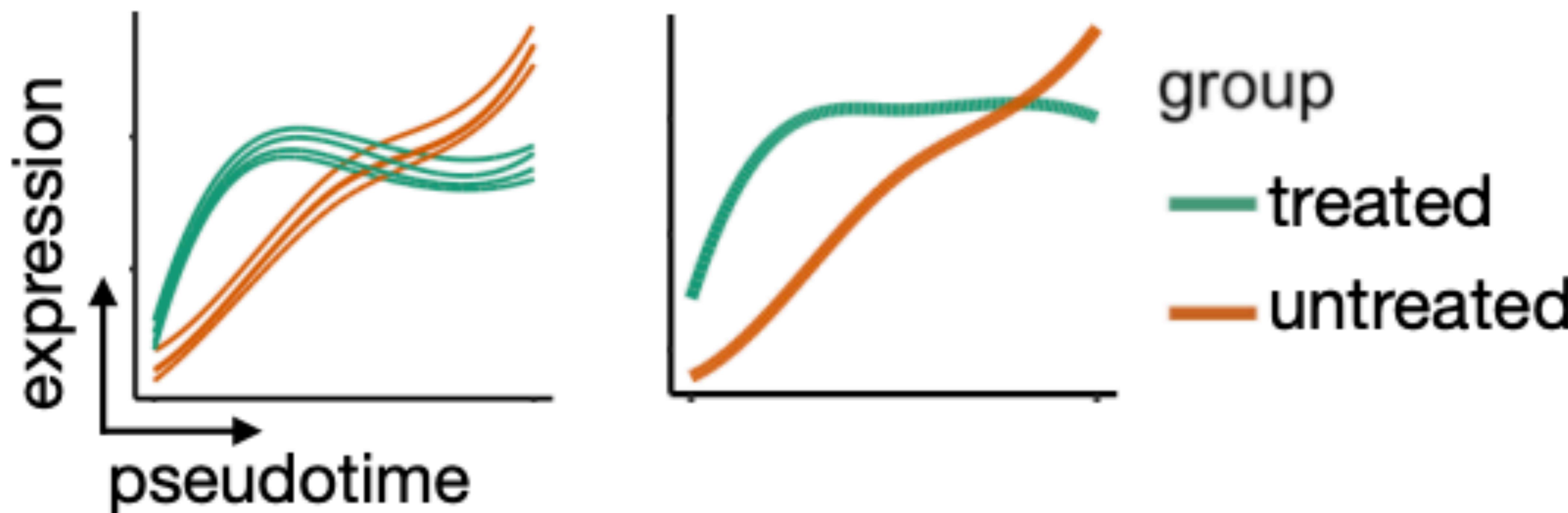
New Results

Follow this preprint

A statistical framework for differential pseudotime analysis with multiple single-cell RNA-seq samples

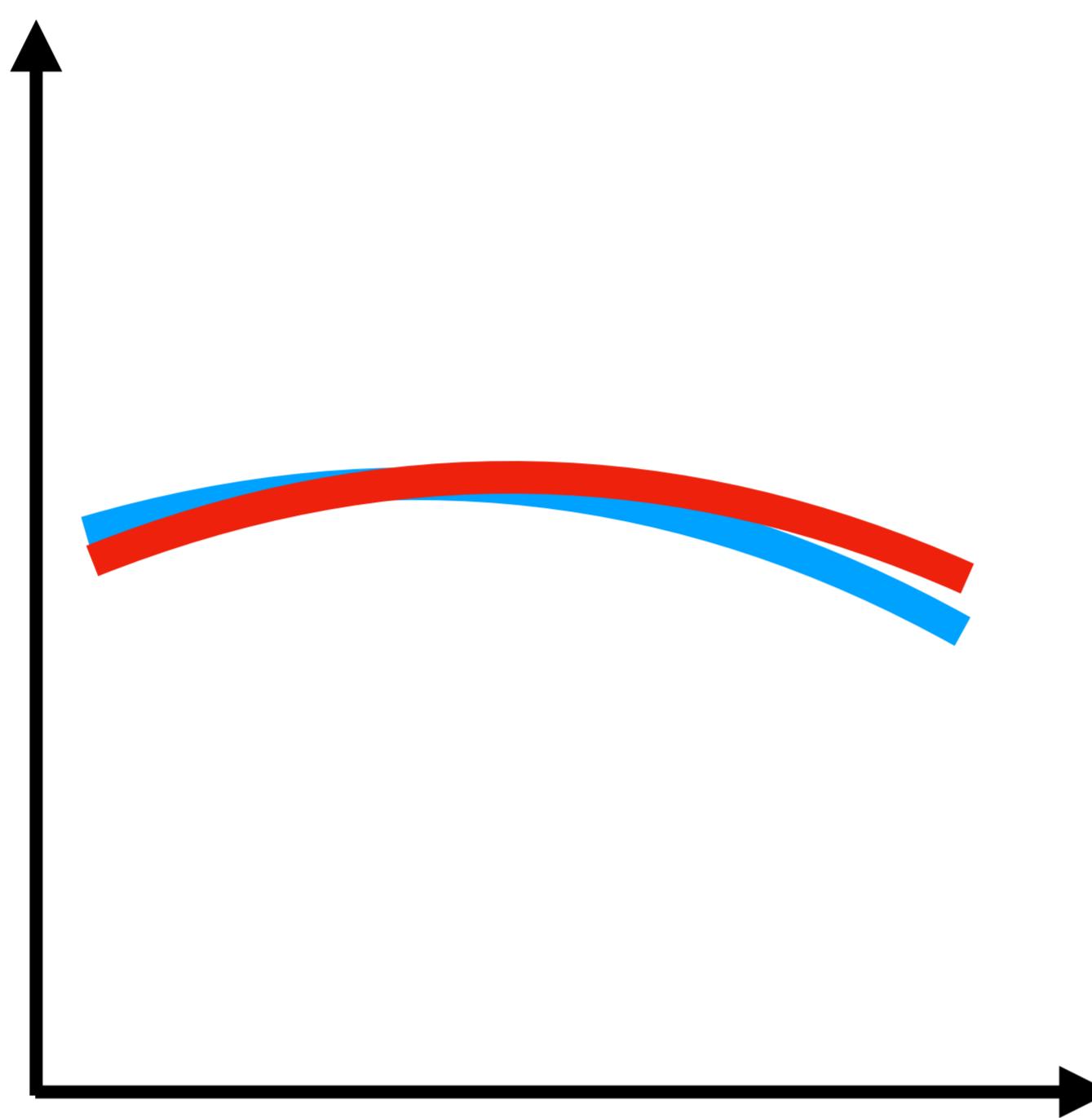
$$\Phi_S(\mathbf{X}_S\beta + \mathbf{u}_S)$$

$$\Phi_S \mathbf{X}_S \beta$$

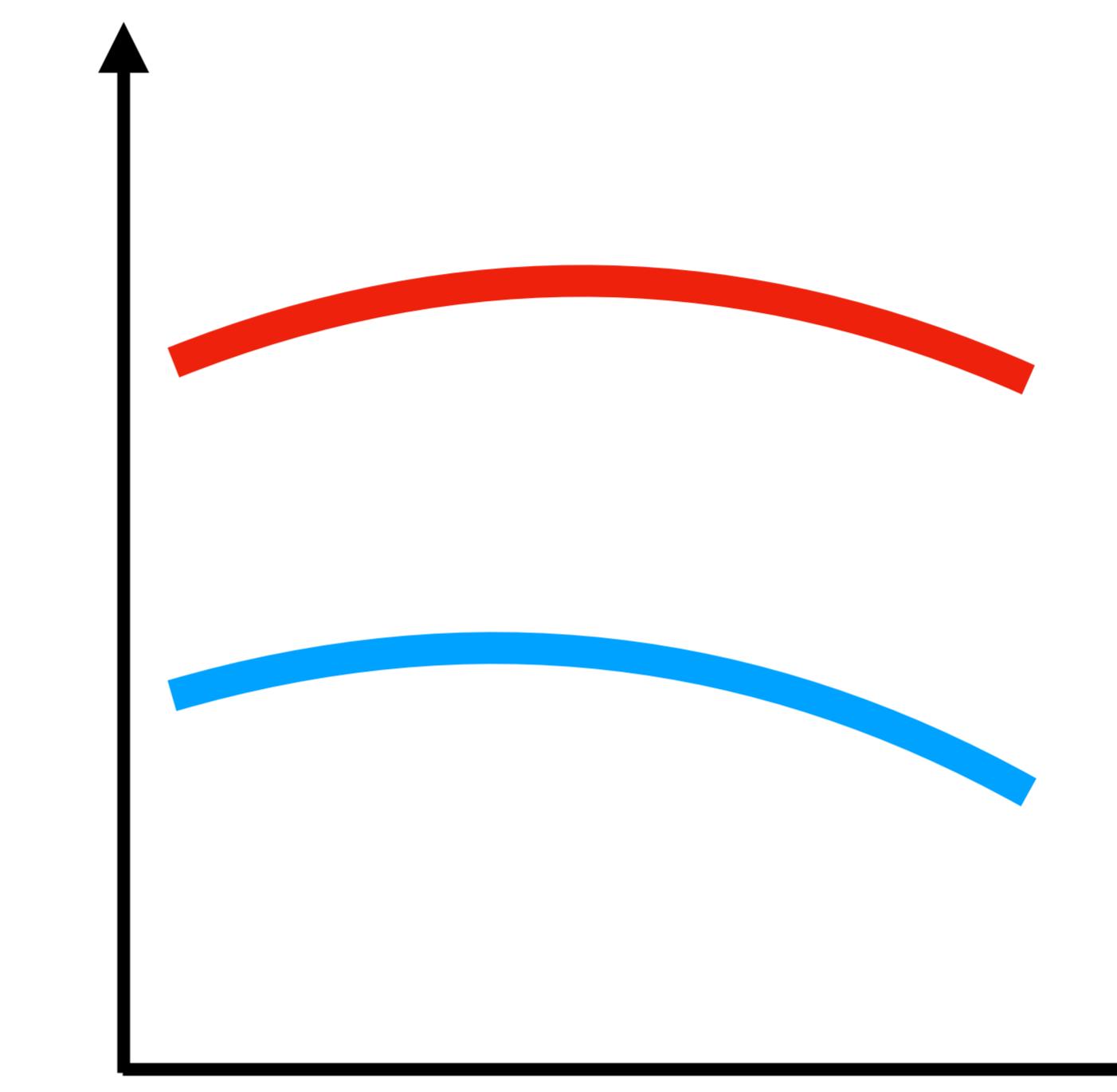


Work in progress 3: multi-sample analysis

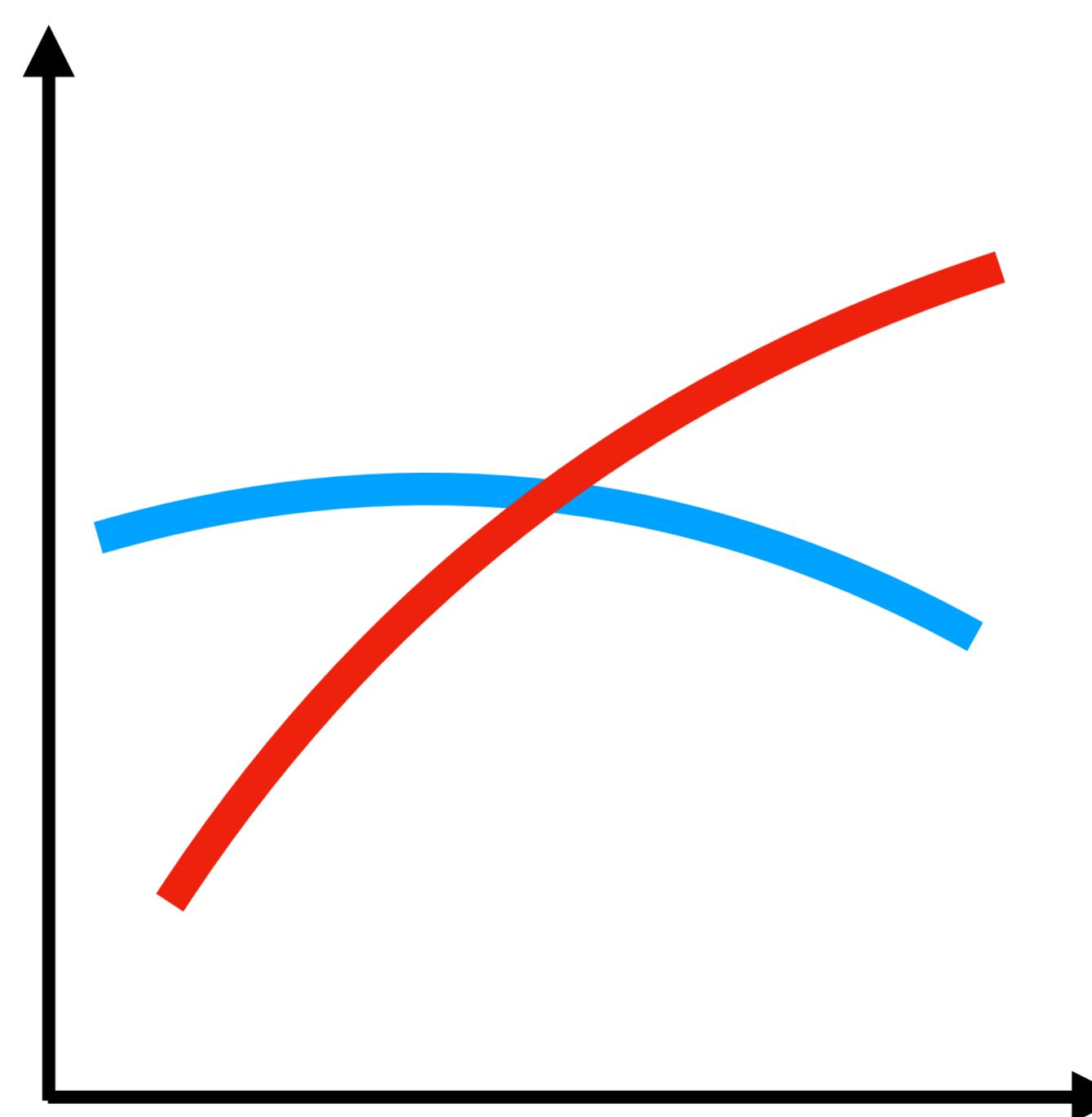
No differential



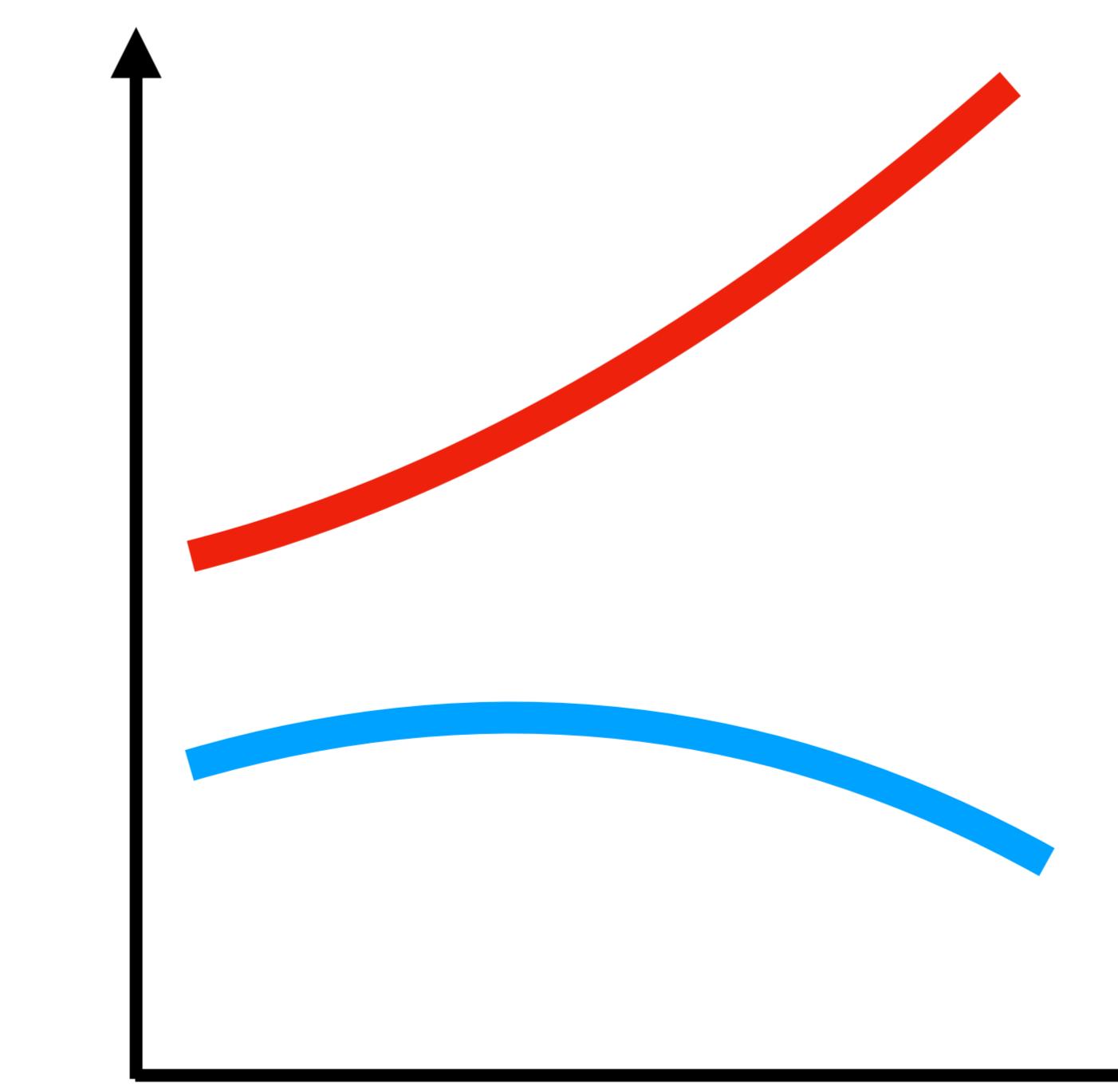
Mean only



Trend only

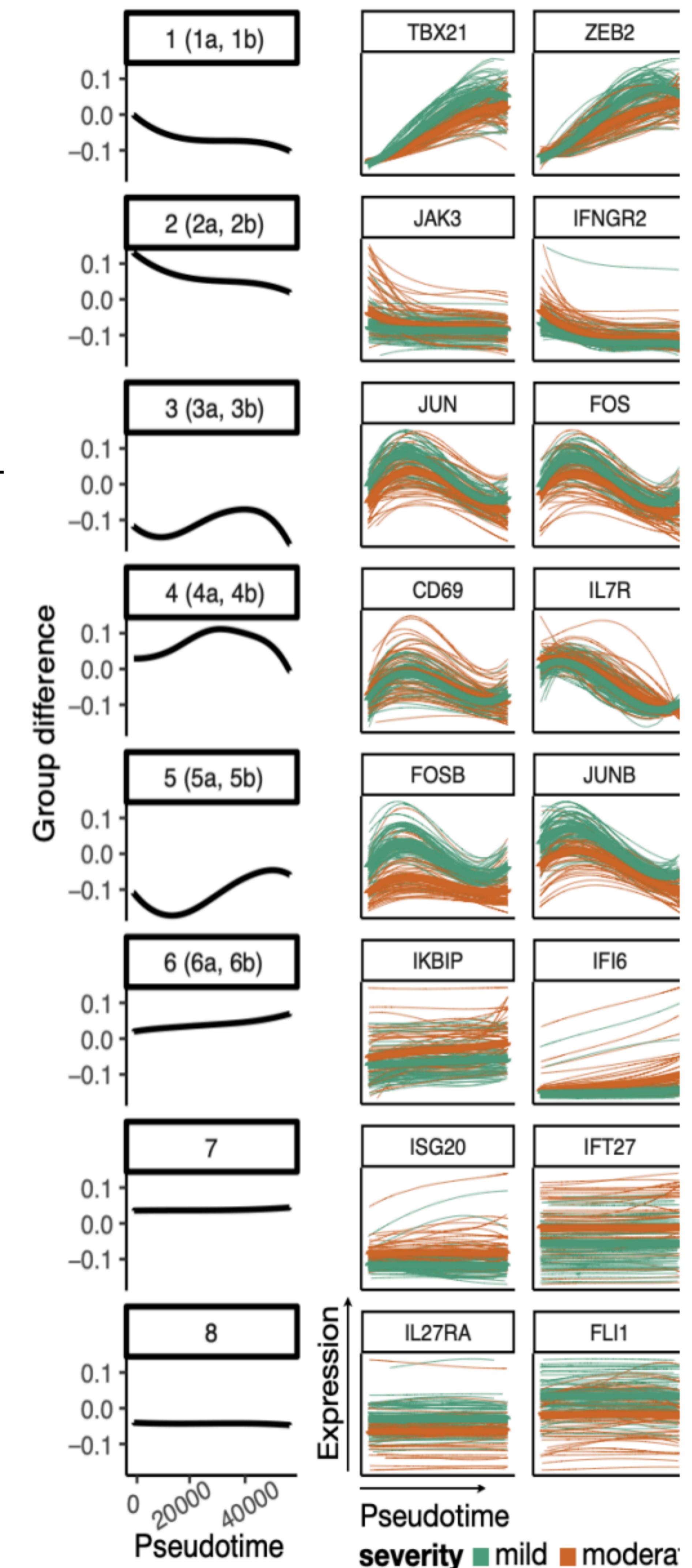
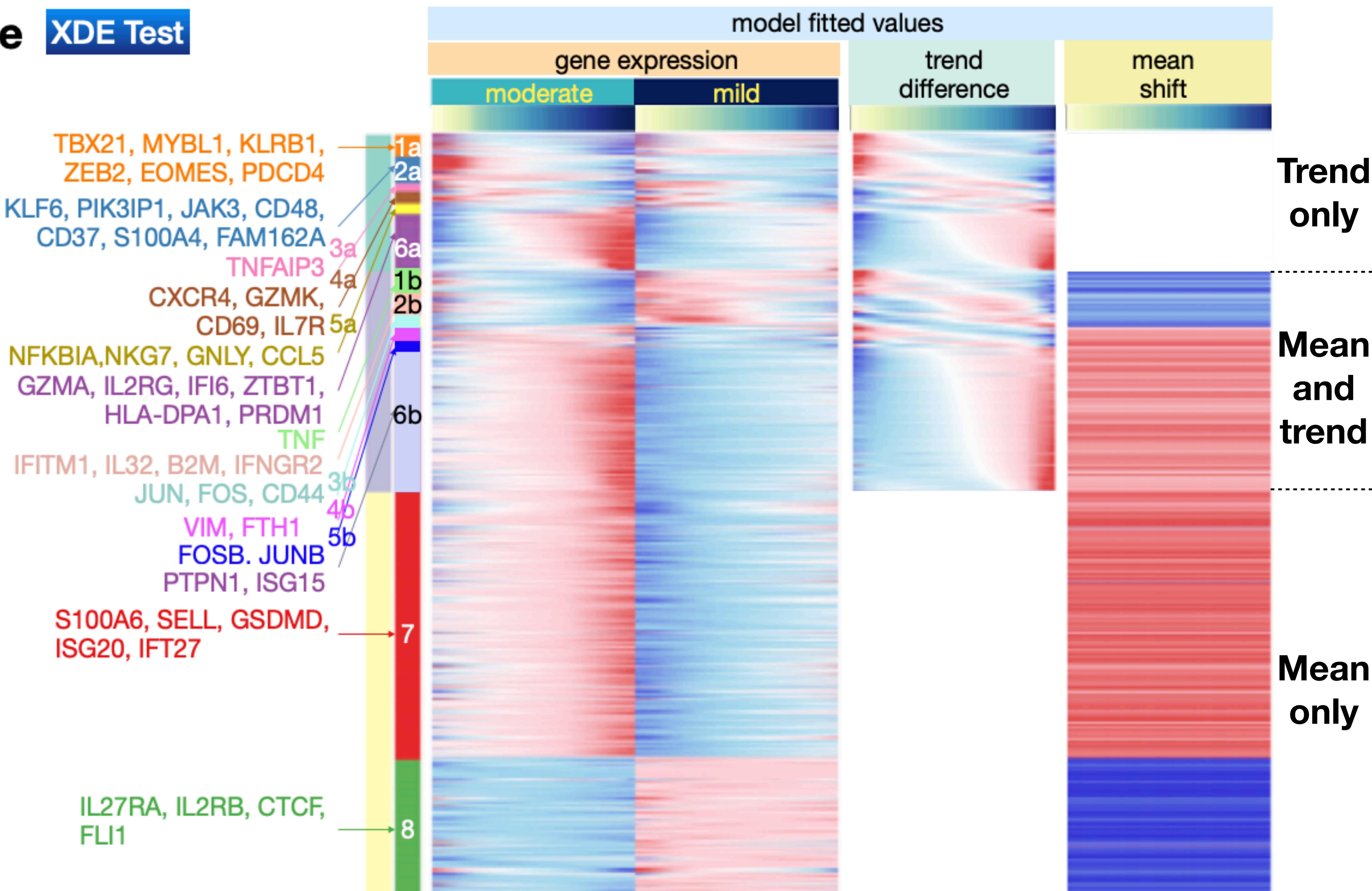


Mean and trend



Work in progress 3: multi-sample analysis

e XDE Test



CD8 T cells in moderate COVID-19 patients are programmed to be less functional effector-like and more terminally differentiated

Acknowledgement

Duke University

Changxin Wan

Johns Hopkins University

Hongkai Ji, PhD
Wenpin Hou, PhD

University of Pennsylvania

E Johns Wherry, PhD
Zeyu Chen, PhD

Thank you!