

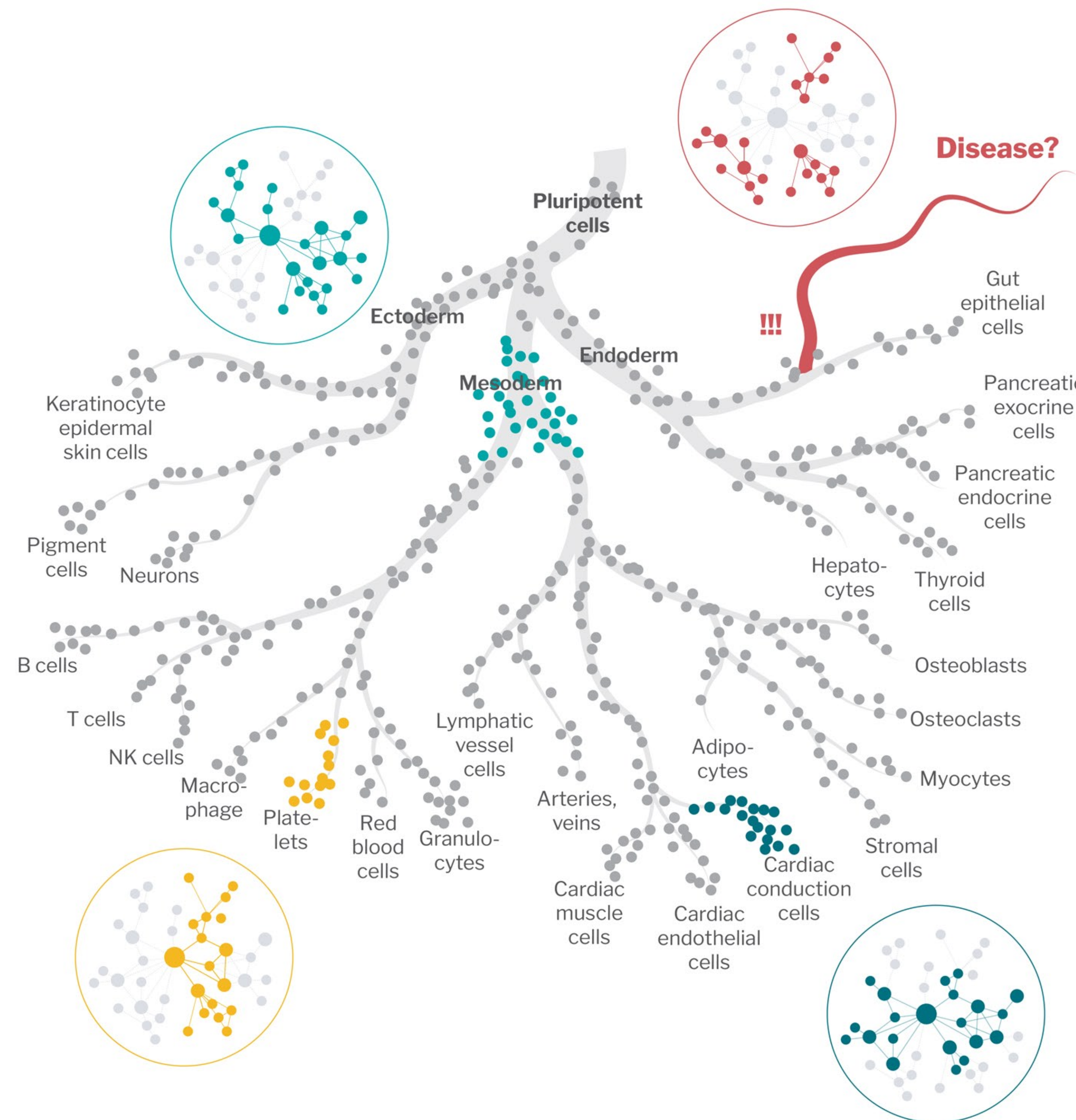
ROADdt: Gene Regulatory Network remodeling along disease development trajectories

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network science | gene regulatory networks | cell differentiation | scRNAseq

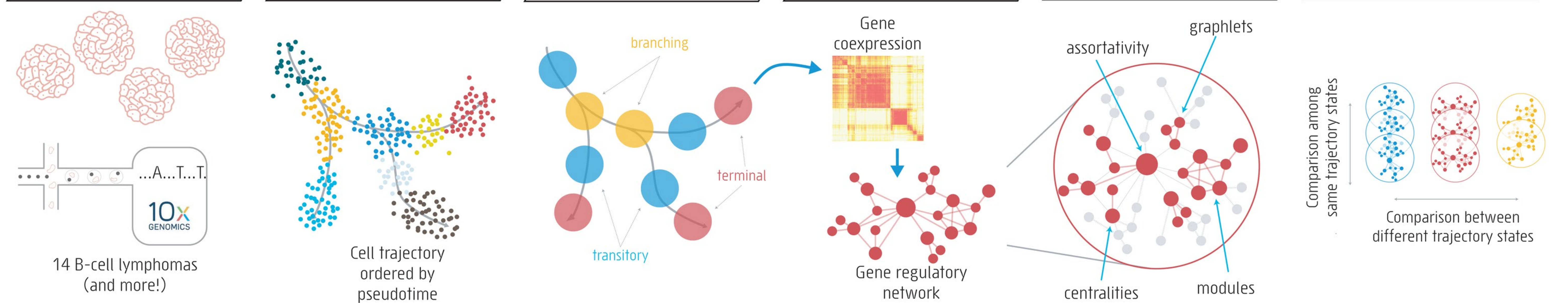
Background

- + There are over 200 different cell types in the human body. Gene regulatory networks govern the differentiation and maintenance to make this all possible.
- + In the process of cell differentiation, gene regulatory networks remodel to change the gene expression program in order to support different cell types / conditions.
- + Several diseases are characterized by the departure from normal cell differentiation trajectories to errant gene expression programs.
- + In order to understand the conditions resulting in disease, we must understand the underlying gene regulatory networks governing the gene expression program.
- + Network science has shown numerous relationships between the structure of networks and the dynamic processes that act on them.
- + I aim to understand the fundamental architecture of gene regulatory networks associated with disease

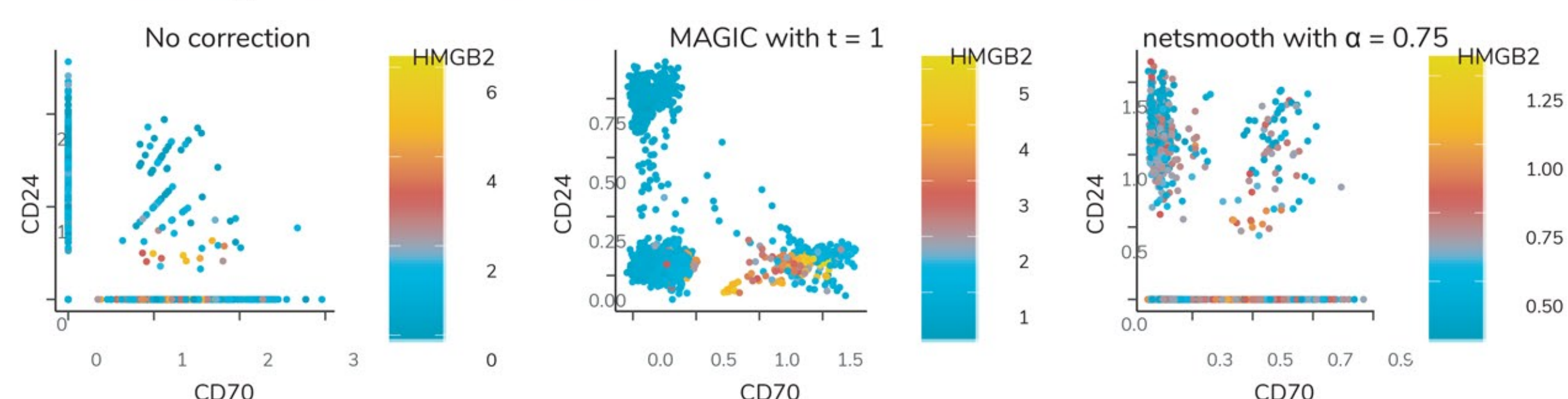


Outcomes

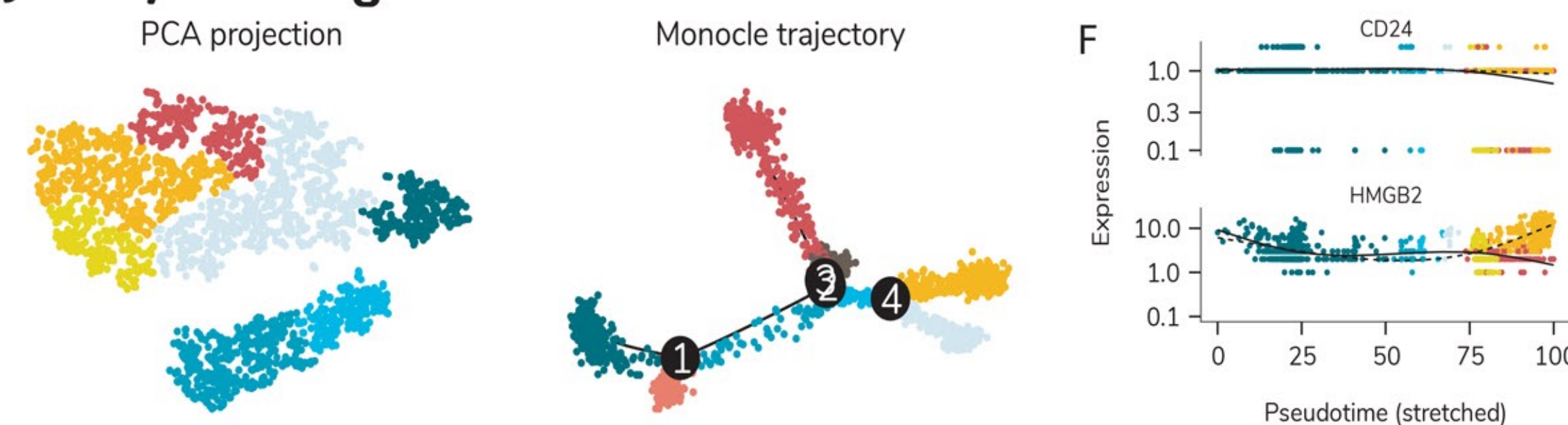
- + Gain better understanding of the dynamics on and remodeling of gene regulatory networks
- + Find general principles that also applicable to other differentiation processes
- + Identify key factors for egress towards diseased states and return to healthy states
- + Identify potential therapeutic targets
- + Guide strategies for personalized medicine
- + Prediction for disease course



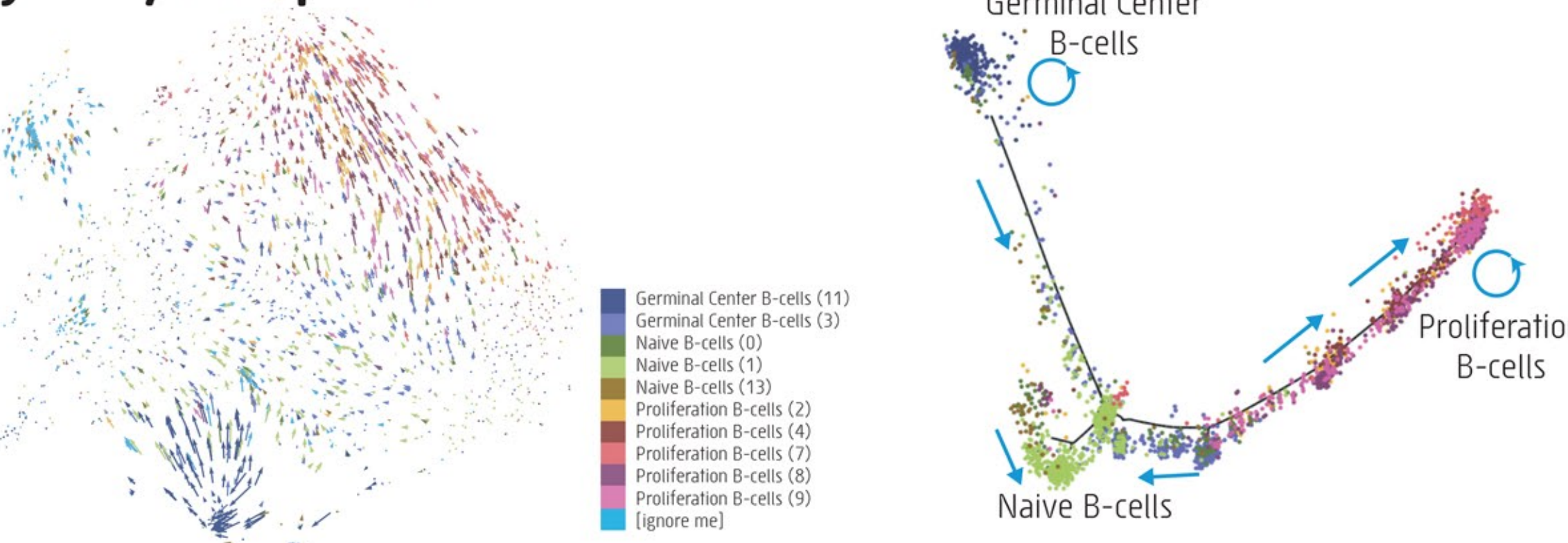
Denoising / Zero correction



Trajectory Building

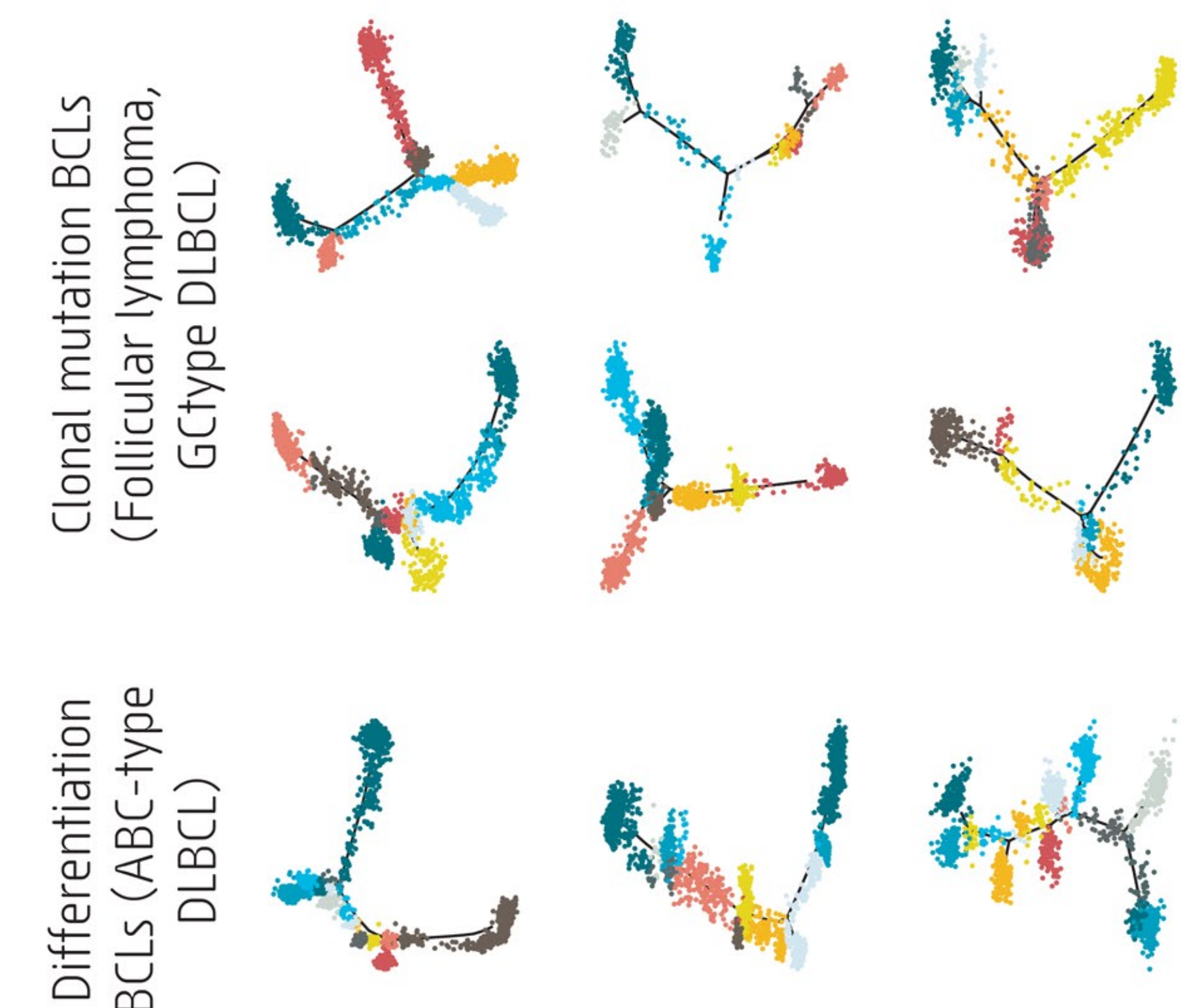


Trajectory Interpretation



Trajectory Gymnastics

+ By flipping, rotating, and stretching, trajectories can be grouped by the BCL subtype.



+ We are working on a mathematically rigorous way to quantify this!

1. Huang, S., Eichler, G., Bar-Yam, Y. & Ingber, D. E. Cell Fates as High-Dimensional Attractor States of a Complex Gene Regulatory Network. *Phys. Rev. Lett.* 94, 128701 (2005).
 2. Trapnell, C. et al. The dynamics and regulators of cell fate decisions are revealed by pseudotemporal ordering of single cells. *Nat. Biotechnol.* 32, 381-386 (2014).
 3. La Manno, G. et al. RNA velocity of single cells. *Nature* 560, 494-498 (2018).

4. van Dijk, D. et al. Recovering Gene Interactions from Single-Cell Data Using Data Diffusion. *Cell* (2018). doi:10.1016/j.cell.2018.05.061
 5. Ronen, J. & Ahalin, A. netSmooth: Network-smoothing based imputation for single cell RNA-seq. *F1000Res.* 7, 8 (2018).
 6. Huynh-Thu, V. A., Irrthum, A., Wehenkel, L. & Geurts, P. Inferring regulatory networks from expression data using tree-based methods. *PLoS One* 5, (2010).