


Single cell RNA-seq reveal alterations of transcriptional programs in hematopoietic stem cell upon aging

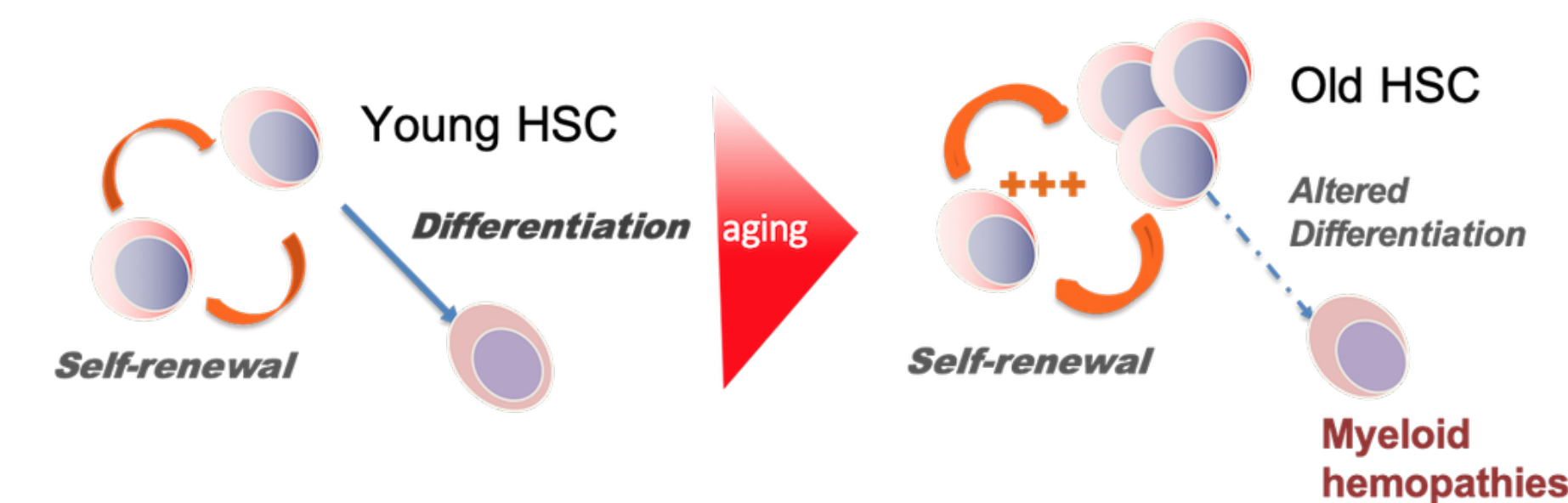
The hematopoietic stem cell aging

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Introduction

Hematopoietic stem cells (HSCs) represent a rare population of cells residing in the Bone Marrow (BM) at the top of hematopoietic hierarchy. A critical balance is maintained between self-renewal and lineage differentiation of HSCs to maintain hematopoietic homeostasis. With aging, this balance is altered with an increase of long term HSCs **self-renewal** and a **myeloid biased** differentiation, which favors the appearance of myeloid leukemias and anemias. My thesis project aims to understand molecular mechanisms that cause this aged-related disequilibrium in the mouse.



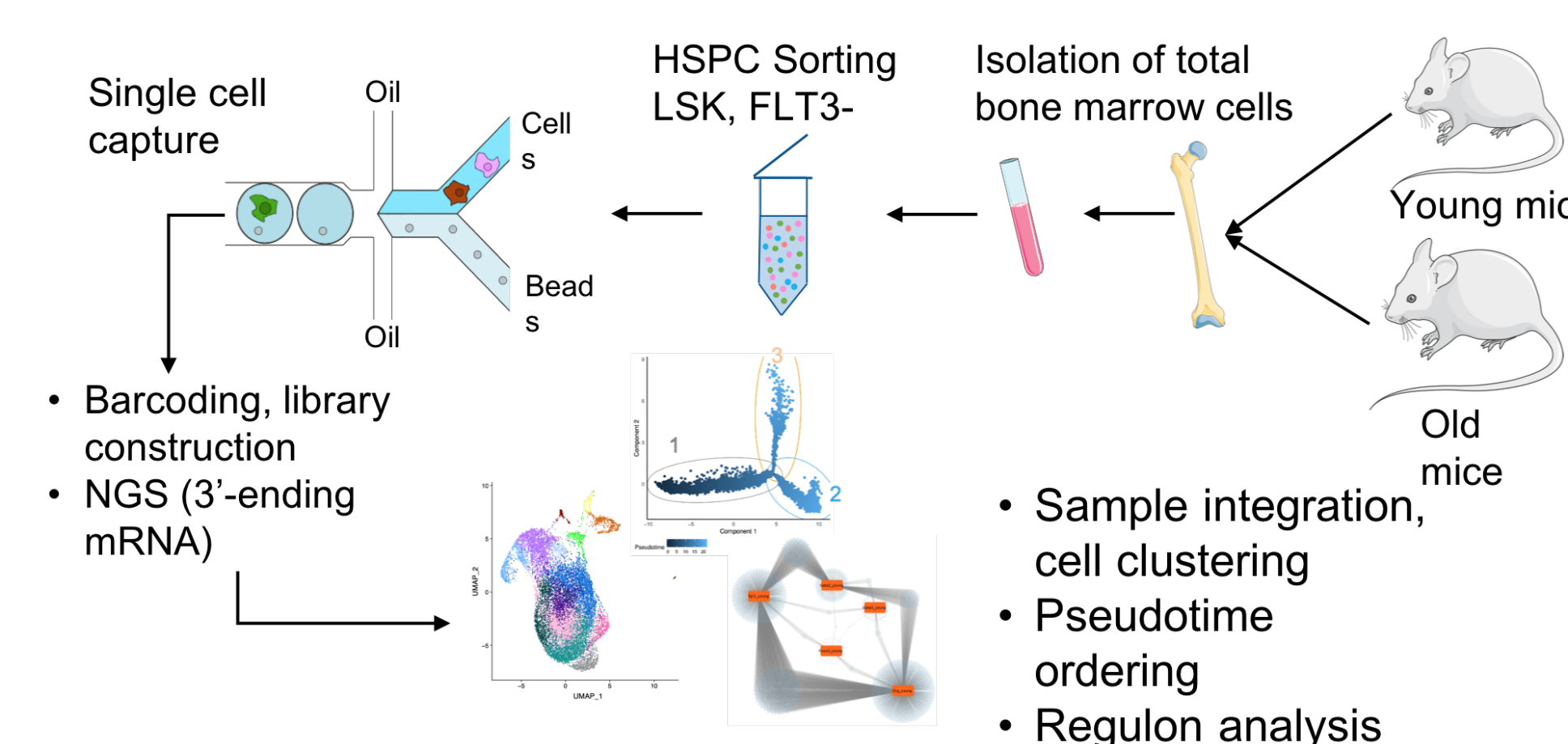
Aging of mouse HSC pool

Objectives

1. Characterize aging of early hematopoiesis in term of subpopulation and intrinsic changes of hematopoietic stem and progenitor cells (HSPCs).
2. Analyze the early differentiation process in young and old HSPCs to find its main actors (transcription factors).
3. Build a logical regulatory graph of transcription factors to modelize HSC aging.

Methods

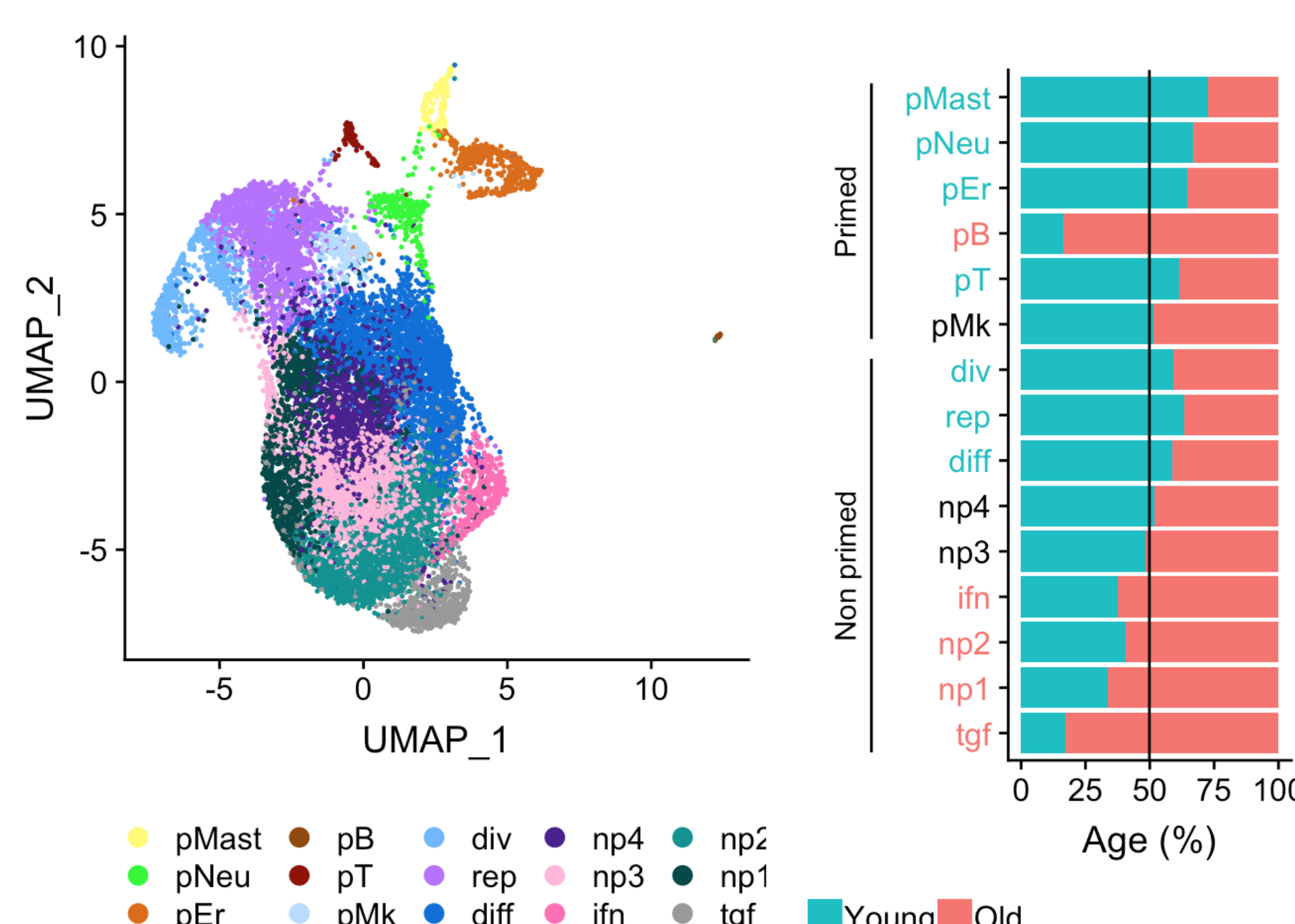
We generated single cell RNA-seq data from pools of young and old HSPCs, isolated from mouse BMs. We used Seurat ([Stuart et al. 2018](#)) and Monocle ([Qiu et al. 2017](#)) R packages to repectively cluster the cells and order them along their differentiation process. We also analyse regulon activities with pyScenic ([Aibar et al. 2017](#)) to identify transcription factor activity changes upon aging.



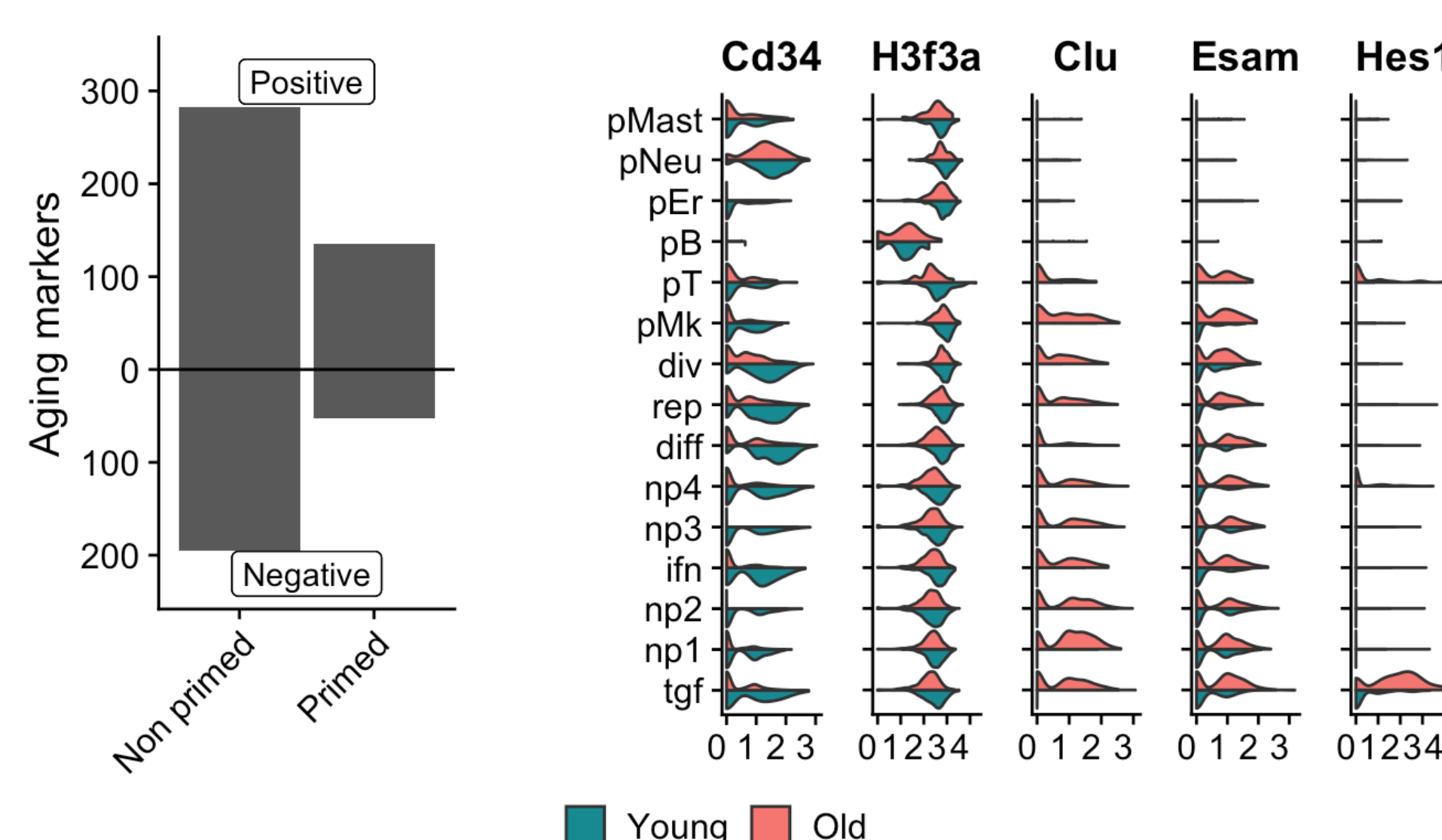
Overview of the analysis

Results

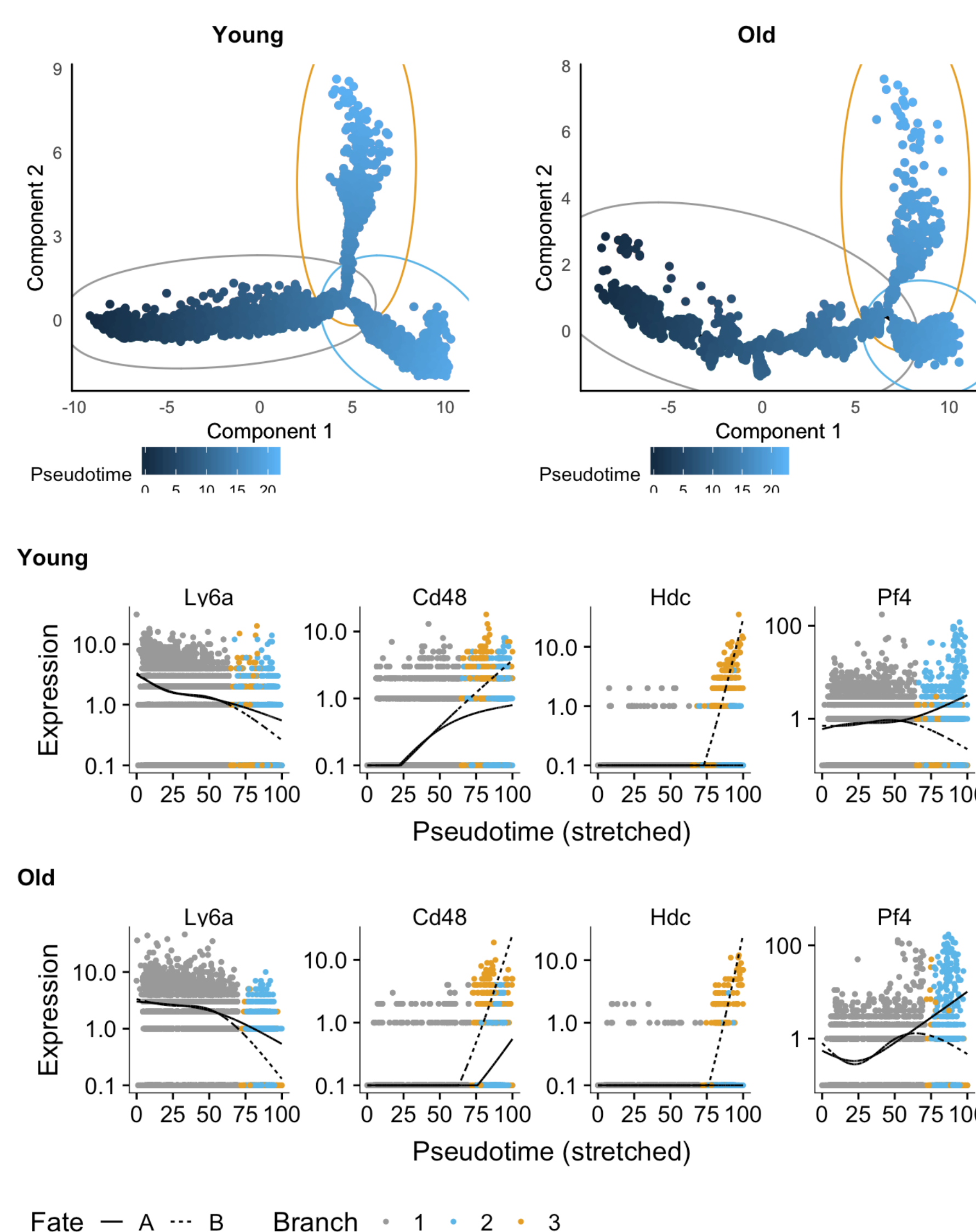
Clustering resulted in 15 clusters divided in lineage primed and non primed cluster and a Global shift of HSCs to the more immature clusters is observed:



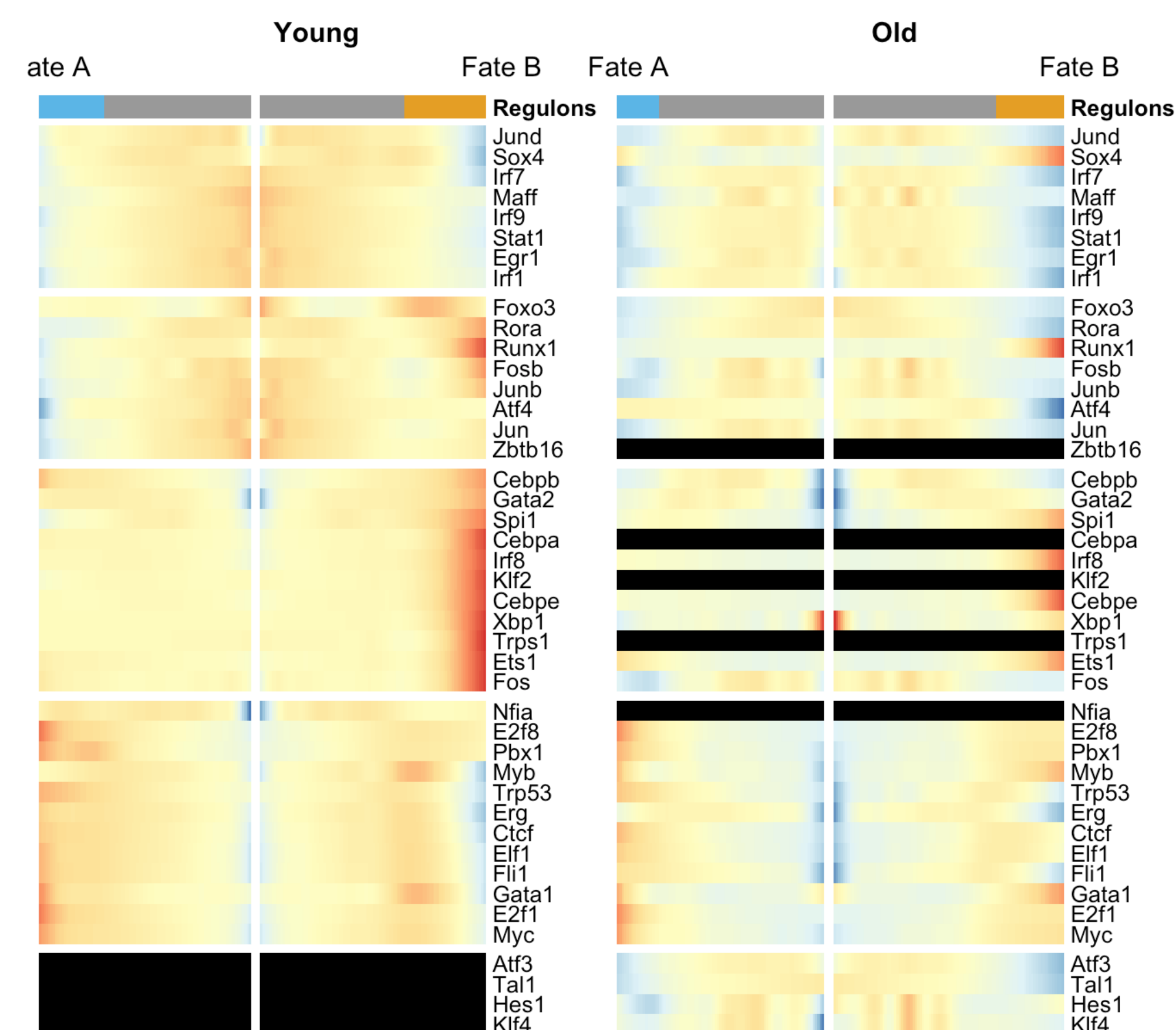
Aging markers were recovered mainly in non primed clusters:



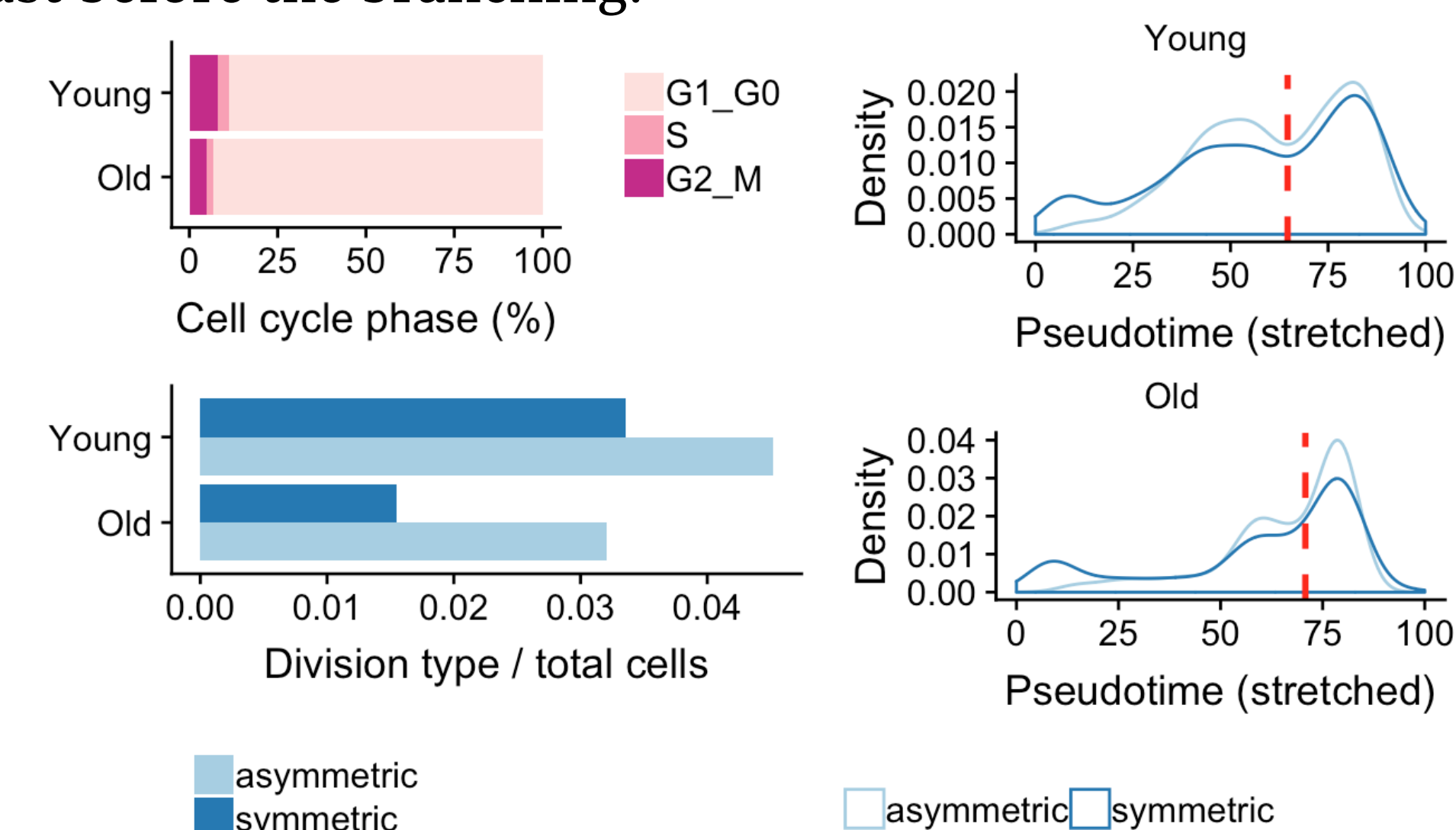
HSPC differentiation trajectory show a branching between a mast and a megakaryocyte-erythroid fate conserved with aging:



Regulons activities fit the differentiation process. however these transcription programs are strongly altered upon aging:

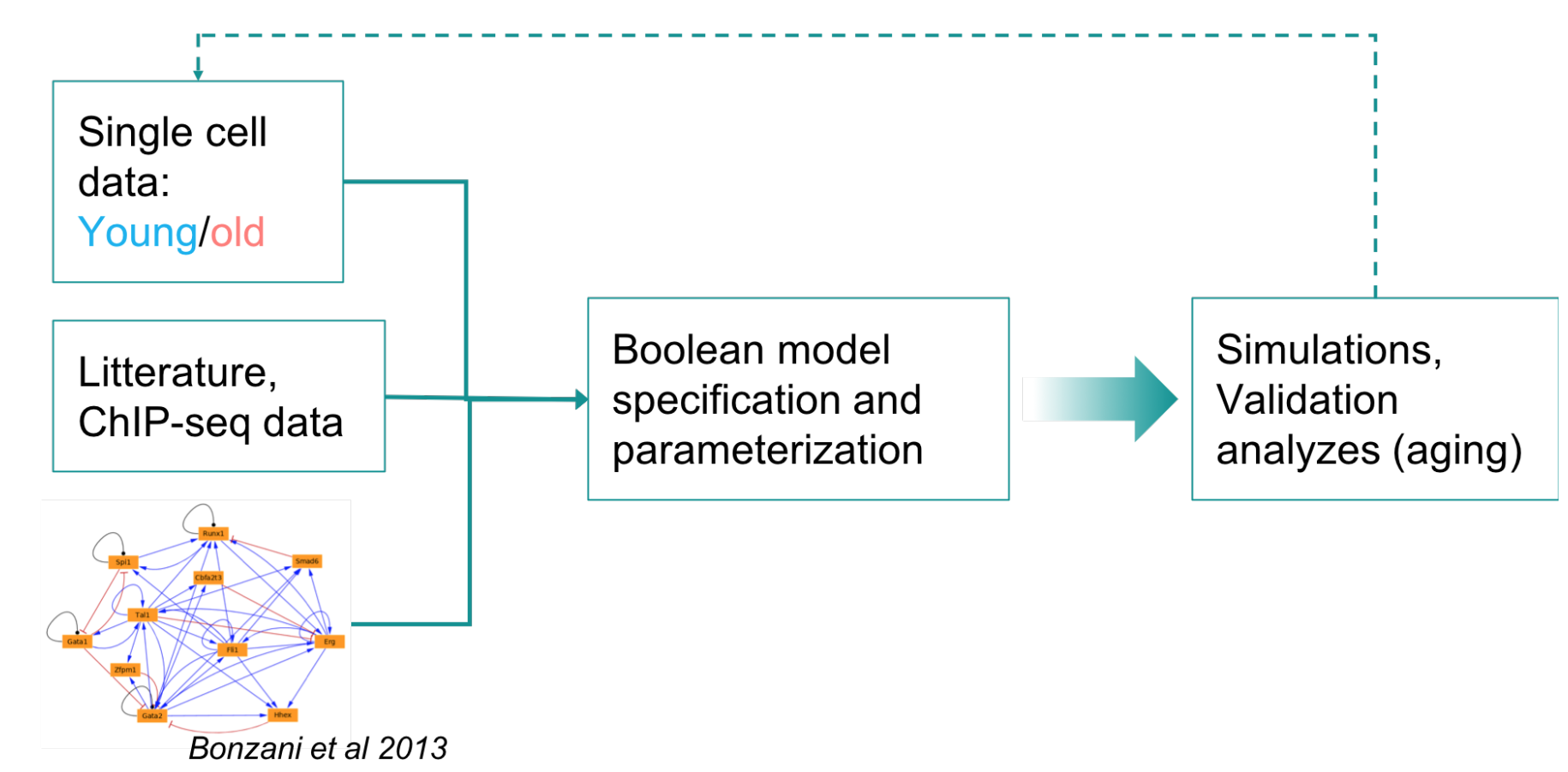


Old HSCs cycle less than young ones. Both asymmetric and symmetric divisions are mainly distributed after the branching in the old trajectory contrary to the young one where a consistent pool of dividing cell is located just before the branching:



Perspectives

Build a Boolean model centered on transcription factors controlling the molecular mechanisms that cause hematopoietic stem cell aging. To this aim, we will complete and specify existing models in the context of aging, by integrating our scRNA analysis results.



Modeling strategy

References

- Aibar, Sara, Carmen Bravo González-Blas, Thomas Moerman, Hana Imrichova, Gert Hulselmans, Florian Rambow, Jean-Christophe Marine, et al. 2017. "SCENIC: Single-Cell Regulatory Network Inference and Clustering." *Nature Methods* 14 (11). Nature Publishing Group: 1083.
- Qiu, Xiaojie, Qi Mao, Ying Tang, Li Wang, Raghav Chawla, Hannah A Pliner, and Cole Trapnell. 2017. "Reversed Graph Embedding Resolves Complex Single-Cell Trajectories." *Nature Methods* 14 (10). Nature Publishing Group: 979.
- Stuart, Tim, Andrew Butler, Paul Hoffman, Christoph Hafemeister, Efthymia Papalexi, William M Mauck III, Marlon Stoeckius, Peter Smibert, and Rahul Satija. 2018. "Comprehensive Integration of Single Cell Data." *bioRxiv*. <https://doi.org/10.1101/460147>.