
Mapping the Pairwise Choices Leading from Pluripotency to Human Bone, Heart, and Other Mesoderm Cell Types.

Journal: Cell

Publication Year: 2016

Authors: Kyle M Loh, Angela Chen, Pang Wei Koh, Tianda Z Deng, Rahul Sinha, Jonathan M Tsai, Amira A Barkal, Kimberle Y Shen, Rajan Jain, Rachel M Morganti, Ng Shyh-Chang, Nathaniel B Fernhoff, Benson M George, Gerlinde Wernig, Rachel E A Salomon, Zhenghao Chen, Hannes Vogel, Jonathan A Epstein, Anshul Kundaje, William S Talbot, Philip A Beachy, Lay Teng Ang, Irving L Weissman

PubMed link: 27419872

Funding Grants: San Jose State University Stem Cell Internships for Laboratory-based Learning (SJSU SCILL), Identification and isolation of transplantable human hematopoietic stem cells from pluripotent cell lines; two steps from primitive hematopoiesis to transplantable definitive cells, and non-toxic conditioning of hosts for hematopoietic stem cell transp..., SCILL- Stem Cell Internships in Laboratory-based Learning

Public Summary:

Stem-cell differentiation to desired lineages requires navigating alternating developmental paths that often lead to unwanted cell types. Hence, comprehensive developmental roadmaps are crucial to channel stem-cell differentiation toward desired fates. To this end, here, we map bifurcating lineage choices leading from pluripotency to 12 human mesodermal lineages, including bone, muscle, and heart. We defined the extrinsic signals controlling each binary lineage decision, enabling us to logically block differentiation toward unwanted fates and rapidly steer pluripotent stem cells toward 80%-99% pure human mesodermal lineages at most branchpoints. This strategy enabled the generation of human bone and heart progenitors that could engraft in respective in vivo models. Mapping stepwise chromatin and single-cell gene expression changes in mesoderm development uncovered somite segmentation, a previously unobservable human embryonic event transiently marked by HOPX expression. Collectively, this roadmap enables navigation of mesodermal development to produce transplantable human tissue progenitors and uncover developmental processes. VIDEO ABSTRACT.

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