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Exploring human pluripotent stem cell heterogeneity using a multi-scale imaging and informatics pipeline

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Understanding how human pluripotent stem cells (hPSCs) make cell fate decisions is central to both normal embryological development as well as therapeutic stem cell applications, such as generating uniform differentiated cell populations from induced pluripotent stem cells (iPSCs). Since human embryonic stem cells were first isolated, various directed-differentiation protocols have been developed by empirically adding or removing inductive signals to the differentiating cell population in order to progressively enrich specific cell subsets that will yield the cell of interest. This approach fails to achieve the degree of spatiotemporal regulation found *in vivo* and as a result, current directed differentiation protocols are inefficient and highly variable. Due to complex tissue-level effects, population-based assays are inadequate to fully understand the pluripotent state, let alone differentiation. This complexity is multi-factorial: the cell population is heterogeneous in morphology and gene expression, and the cellular microenvironment is multidimensional. We have developed an *in situ* multi-scale imaging system that captures high content single-cell information of hPSCs across long length scales. This platform integrates an automated robotic microscopy system with an analysis pipeline that allows us to study relationships between cellular location within a colony and single-cellular properties, long-range interactions between different cell phenotypes, and between colony-wide features such as size, shape, and texture, and the properties of their constituent cells. In order to understand genetic network dynamics in hPSCs *in situ* across long length scales we are developing computational algorithms to integrate and analyze single cell single-molecule mRNA FISH data into this multi-scale imaging and informatics pipeline.

Biography

Paul H. Lerou completed his MD degree from Jefferson Medical College and subsequently trained in pediatrics and neonatology at Boston Children's Hospital, Harvard Medical School (HMS). He did his postdoctoral work in the laboratory of George Q. Daley on human pluripotent stem cell derivation. He is currently an attending neonatologist at Brigham & Women's Hospital and assistant professor in pediatrics at HMS. His lab studies fundamental pluripotent stem cell biology and aims to apply this to the development of improved *in vitro* models of human disease using induced pluripotent stem cells.

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