Universität Basel

Research Project

Allen Discovery Center for Cell Lineage Renewal

Third-party funded project

Project title Allen Discovery Center for Cell Lineage Renewal
Principal Investigator(s) Schier, Alexander ;
Co-Investigator(s) Scheiwiller, Marcel ;
Organisation / Research unit
Departement Biozentrum / Cell and Developmental Biology (Schier)
Department
Departement Biozentrum
Project start 01.10.2021
Probable end 30.09.2024
Status Active

Multicellular organisms develop by way of a lineage tree, a series of cell divisions and molecular changes that give rise to cell types, tissues and organs. Despite their fundamental relevance to development, our knowledge of cell lineages and their determinants remains fragmentary, and fundamental questions remain unanswered: What are the molecular and cellular programs that drive cells to acquire specific fates? How do these vary within an individual, between individuals, and across species? What are the cell lineage motifs that underlie consistencies and differences in form and function? In its first phase, our Center has established novel paradigms for recording cell lineage and cell states. We can introduce heritable and cumulative changes into the genome to record the lineage relationship between cells (scGESTALT; MEMOIR). We can measure the transcriptional and epigenetic states of cells and reconstruct the molecular trajectories underlying cell type differentiation (sci-seq). We can measure transcriptomes and lineage markers in tissues and reconstruct the spatiotemporal unfolding of development (seqFISH; sci-Space). In C. elegans , we have used such information to define developmental principles such as multilineage priming. In C. elegans , Drosophila , zebrafish and mouse, we have used our datasets to define cellular diversity and regulators of cell type differentiation. We now have the methodological foundation to address fundamental questions in developmental biology at the scale of the entire vertebrate embryo.ă ă In order to reveal developmental rules that are shared and divergent across individuals and species, we propose to map (Aim 1), model (Aim 2) and manipulate (Aim 3) embryogenesis. We will focus on zebrafish and mouse embryogenesis, because these are well-established and accessible model systems in which we have laid the requisite groundwork.ă ă In Aim 1 , we will use genomic and imaging approaches to generate high-resolution maps of natural zebrafish and mouse embryogenesis and of stem cell-derived synthetic mouse embryogenesis. Maps will include cell lineage, gene expression, chromatin accessibility data and signaling activity and will be complemented by live imaging of cell movements.ă ă In Aim 2 , we will integrate these datasets to generate a consensus scaffold of the molecular trajectories and lineage structures of embryogenesis, together with statistical models that seek to explain developmental processes in terms of rates of cell division and probabilistic differentiation. In a complementary approach, we will develop lineage motif analysis, a framework for extracting the key recurrent programs of cell lineage histories in relation to time, space and molecular state. We will then apply both the consensus model and lineage motif analysis to investigate different kinds of developmental variation: interclonal, interindividual and interspecies. We will make our tools, datasets, models and insights available to the community through a navigable ‘virtual embryo’.ă ă In Aim 3 , we will functionally test model predictions and address how genetic, embryological or environmental manipulations affect cell fate decisions, lineage variation and developmental robustness. We will

manipulate key parameters of development such as the activity of lineage regulators and intercellular interactions, cell number and proliferation rates in different lineages, and environmental and metabolic conditions. The observed phenotypic consequences will shed light on the mechanisms underlying developmental robustness and variation.

Financed by

Foundations and Associations

Add publication

Add documents

Specify cooperation partners