Universität Basel

Research Project

Single-cell genomic reconstruction of retina developmental disorders

Third-party funded project

Project title Single-cell genomic reconstruction of retina developmental disorders
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Organisation / Research unit
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Department
Project start 01.06.2019
Probable end 31.05.2023
Status Completed

Innovative methods to recapitulate human retina development from pluripotent stem cells create new and exciting opportunities to explore the human visual system in controlled culture environments. In parallel, new single-cell sequencing technologies are revolutionizing our ability to analyze cell composition and differentiation in complex tissues. In this proposal, we will use single-cell genomics to reconstruct human retina organoid development, dissect network alterations that lead to human retina malformations, and develop novel corrective therapies for monogenic retina developmental disorders. Our project will be advanced through the following specific aims: Aim 1. Lineage tracing with single-cell transcriptomics in retina organoids: We will develop an inducible cell barcoding system to trace cell lineages at different time points during retina organoid development. We will use this method to label individual retinal progenitor cells, trace their output and lineage trees with high-throughput scRNA-seq, and quantify lineage transition probabilities between cell types. Aim 2: High-throughput reconstructions of retinal malformations: Leber Congenital Amaurosis (LCA) is a class of retinopathies that lead to disrupted photoreceptor function and can result in blindness at birth. We will use CRISPR/Cas9 editing to generate isogenic iPSC lines that contain genetic mutations for various LCA subtypes. We will generate retinal organoids from these iPSC lines and use single-cell transcriptomics and imaging to identify perturbed cell states. Aim 3: Gene targeting for cell-type specific corrective therapy: We will use cell subtype-specific viral vectors to deliver correct versions of mutated genes, or directly correct mutated genes using targeted editing, in retina organoids derived from patients with LCA. We will analyze the effects of corrective therapy using lineage-coupled and spatially resolved whole organoid reconstructions. This project provides an exciting and quantitative direction to study human retinogenesis. We will work as a team of scientists to build high-resolution and multi-scale models of normal and malformed retina development by measuring lineages and gene expression in thousands of single cells from healthy and mutant organoids. Our interdisciplinary project will illuminate mechanisms underlying a particular class of retinal malformations that can result in debilitating blindness, and we will make substantial progress towards practical solutions for patient-specific gene therapy for these disorders. Our general strategy is to work towards integrated, high-throughput, spatially resolved single-cell genomic reconstructions of patient-specific retina developmental disorders. We believe that this project, and our overall strategy, will have an enormous impact on the development and assessment of clinical therapies aimed at treating human blindness.

Financed by
Swiss National Science Foundation (SNSF)

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