Project 1: Spatial methylation barcodes to track clones in human tissues

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Project description

Over the course of development and adult life, our tissues are seeded and organised as a mosaic of distinct clonal cell populations, the organisation of which can be dysregulated by expansions in health or disease. Somatic mutations, identified by whole genome sequencing of single cells or clones have been used to reconstruct mutation-based phylogenetic trees and gain insights into human development and clonal dynamics over life [1,2]. The scale of work that can be done, however, is limited by the cost of whole genome sequencing individual cells.

We propose a novel and highly scalable approach to track clone sizes in human tissue, combining spatial genomics approaches with sequencing-based readouts of methylation. Our method builds upon the recent discovery that, in certain loci of the genome, complex methylation barcodes are laid down early in development [3]. The ability to read out these molecular barcodes will allow us to determine which cells descend from shared embryonic ancestors, and to spatially measure clone sizes within tissues. Initially, we will apply this initially to one organ, the liver, to see how clone sizes vary across the age range and differs between health and disease states. The liver is chosen for a number of reasons: first, it is relatively cellularly homogeneous, so that we can expect neighbouring cells to be related; second, large amounts of tissue are available, both as resections and explants; third, somatic mutations have been used to show clonal expansions in normal liver in conditions such as non-alcoholic fatty liver disease [4] and alpha-1-antitrypsin deficiency [5]; and fourth, we have access to tissues from rare liver conditions that we suspect are associated with clonal expansions, but in which clonal expansions have not been demonstrated.

This project is a unique collaboration between the Coorens Group at EMBL-EBI (somatic evolution and phylogenetics) and the Lee-Six Group at the Wellcome Sanger Institute (spatial genomics). The fellow will acquire interdisciplinary skills spanning experimental approaches for spatial methylation data generation, analysis of methylation data and epimutation calling, and the development of computational tools to resolve clones. In particular, the fellow will:

- Apply and if necessary, improve data generation methods for spatial methylation
- Analyse embryonic methylation patterns and determine the range of clone sizes in healthy liver across the age range
- Apply the method to detect clonal expansions in non-alcoholic fatty liver disease demonstrated previously
- Extend the method to screen hitherto uncharacterised liver conditions for clonal expansions
- Confirm these results using genome sequencing of laser capture microdissections

While this project focuses on liver, the skills, approaches and techniques applied throughout this project are readily applicable and transferrable to other tissues and disease states, if time allows and the fellow wishes to pursue this further.

[1] Coorens, T. H. H. *et al.* Extensive phylogenies of human development inferred from somatic mutations. *Nature* **597**, 387-392, doi:10.1038/s41586-021-03790-y (2021).
[2] Lee-Six, H. *et al.* Population dynamics of normal human blood inferred from somatic mutations. *Nature* **561**, 473-478, doi:10.1038/s41586-018-0497-0 (2018).
[3] Hackett, S.F. *et al*. In vivo lineage tracing across human tissues using methylation barcodes in the protocadherin gene cluster. *bioRxiv*, doi: 10.64898/2026.02.23.707349 (2026).
[4] Ng, S. W. K. *et al.* Convergent somatic mutations in metabolism genes in chronic liver disease. *Nature* **598**, 473-478, doi:10.1038/s41586-021-03974-6 (2021).
[5] Brzozowska, N *et al.* Selection for somatic escape variants in SERPINA1 in the liver of patients with alpha-1 antitrypsin deficiency. *Nature Genetics* **57**, 875-883, doi: 10.1038/s41588-025-02125-1 (2025).