Project 8:
Methylation changes underpinning cancer and other diseases

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Project description
The methylation of CpG sites in the human genome is established during embryogenesis and further moulded over the course of a lifetime, leading to a mosaic of different methylation states across cells, tissues and individuals. Methylation patterns are an important part of gene regulation, especially by silencing expression through hypermethylation. While some well-described methylation aberrations play a critical role in the development of some pediatric [1] and adult cancers [2], little is known about the general functional effect of specific methylation patterns in cancers or normal tissues, nor is there currently a general framework to distinguish between “driver” and “passenger” epimutations.

In this project, we seek to understand the functional consequence of both early and late established methylation patterns on cell transcriptome and behaviour, their relevance to the emergence of clonal expansions and disease, and specifically whether early methylation patterns may be informative for risk prediction. As part of this project, the fellow will need to develop a framework to distinguish relevant methylation changes with functional consequences (“drivers”) from those without (“passengers”).

This project combines the expertise and data sets on somatic methylation patterns from the Nangalia Group, access to large-scale data sets on cancers (e.g. TCGA) and normal tissues (e.g. SMaHT) from the Coorens Group, and the expertise on using genomics to study the origins of cancer and disease from both groups.

The fellow will be part of the Nangalia Group at the Wellcome Sanger Institute and the Coorens Group at EMBL-EBI, with mentorship, training and career development opportunities from both groups. Specifically, the fellow will acquire interdisciplinary skills spanning computational method development for the analysis of methylation patterns, integration across -omics datasets. As part of the project, the fellow will:

- Quantify hypermethylation events in large-scale cancer genome data sets in cancers without apparent drivers or single hits in tumour suppressor genes
- Evaluate the effect of fluctuating, mosaic methylation patterns on gene expression across disease and normal tissues
- Integrate various data sets to develop frameworks to predict functional effects epimutation drivers

[1] Coorens, T.H.H. *et al.* "Embryonal precursors of Wilms tumor." *Science* 366.6470 (2019): 1247-1251.
[2] Glodzik, D. *et al.* "Comprehensive molecular comparison of BRCA1 hypermethylated and BRCA1 mutated triple negative breast cancers." *Nature communications* 11.1 (2020): 3747.