Project title
Origins, footprints and consequences of mutations in endometrial stem cells

Supervisors:
Tim Coorens, EMBL-EBI
Roser Vento-Tormo, Wellcome Sanger Institute

Project description
Cells of the endometrium continuously acquire somatic mutations throughout life. Some of these mutations alter the behaviour of a cell, confer a fitness advantage and are often associated with cancer ("driver mutations"). Uniquely, the endometrium has one of the highest rates of cells harbouring driver mutations of any human tissue studied, with approximately 90% of endometrial cells harbouring a driver at age 60. This high rate is likely a consequence of the monthly shedding and regrowth of the endometrium during reproductive life, and underpins the origin of endometrial cancer and endometriosis. Recently, the Vento-Tormo lab has identified stem cell niches in the human endometrium, the cell type in which key somatic driver mutations are acquired and passed on to a large part of the endometrium. However, it is unknown how endometrial stem cell dynamics changes over development, during ageing and under the influence of somatic mutations. Furthermore, our understanding of the precise manner in which mutations perturb cells into disease states remains poor.

Novel technologies, including high-resolution spatial genomics and computational advances including machine learning, now enable the joint study of mutations and gene expression to infer the effect of somatic mutations and the origins of disease. However, large, high-quality data sets and novel, robust algorithmic tools are required to answer these fundamental biological questions.

This project is a unique collaboration between the Vento-Tormo Lab (cellular multi-omics and cell-cell communication) at Sanger and the Coorens Lab (somatic evolution and phylogenetics) at EBI. Through combining high-resolution spatial transcriptomics data, advanced DNA sequencing methods and implementing cutting-edge computational tools and AI/machine learning to integrate multi-omics and predict the effect of somatic mutations, this project aims to understand how the endometrial epithelium changes during development and ageing, the effect of specific somatic driver mutations on the phenotype of endometrial (stem) cells and how cell-cell communication is perturbed by somatic mutations in the endometrium.

The fellow will be part of both the Vento-Tormo and Coorens labs and benefit from mentorship of both groups, the ability to develop interdisciplinary skills spanning the research areas of both groups. In particular, the fellow will:

- Apply cutting-edge technologies to generate genomic data from endometrium across ages, including spatial transcriptomics, laser capture microdissection and multi-omics
- Analyze and integrate these novel types of data to reconstruct the ancestry of endometrial cell clones, expression patterns and multi-omic profiles
- Design and implement novel algorithms and bioinformatic tools, including machine learning approaches, to infer the effect of somatic mutations on cell behaviour and cell-cell communication

- Interpret the biological changes of the endometrium during development and ageing, and study exactly how perturbation through somatic mutations changes the behaviour of cells and leads to endometrial cancer, endometriosis and other diseases

While this project focuses on the endometrium, the skills, approaches and techniques applied throughout this project are readily transferable to other settings of human tissues and disease.