Project Title: "Predicting Cell State from Chromatin Architecture to Understand Cancer Initiation and Progression"

Main Supervisor: Alice Sherrard

Research Group: Chromatin Regulation

Chromatin structure regulates gene expression and underlies cell identity. Mutations in chromatin regulators are frequently observed in cancer, leading to alterations in chromatin structure, genomic interactions, and modifications. For example, changes in nuclear morphology and chromatin organisation are common diagnostic indicators of cancer. Newly developed structural imaging approaches offer an opportunity to significantly advance our ability to detect structural aberrations in chromatin and therefore have potential to define new mechanisms of cancer development.

Our lab investigates how chromatin structure is regulated to drive cell fate transitions during mammalian development and cancer. We have developed innovative tools that combine 3D electron microscopy (EM) with nanogold labelling to visualise chromatin ultrastructure *in situ* and link it to molecular regulators and functions. Using these tools, we have uncovered previously unrecognised structural properties of chromatin that distinguish distinct stages of cell differentiation and epigenetic remodelling. Importantly, we have identified structural signatures that define unique states of pluripotency, providing a platform to define mechanisms that regulate cell fate transitions in development, and their relevance to cancer. Our overall goal is to define the mechanisms that shape chromatin structure during cell differentiation, determine how aberrant chromatin remodelling in cancer reconfigures genome structure and function, and understand how signals from the tumour microenvironment impact chromatin regulation.

In this project, the student will first work with established collaborators to generate an AI model to identify stages of differentiation from developmental and de-differentiation (induced pluripotency stem cells, iPSC) time courses of chromatin structure we have already generated. Next, the student will generate electron tomography datasets of established cancer models that capture defined stages of cancer initiation and progression and test the ability of their model to predict these stages. Finally, the student will investigate the mechanisms that drive chromatin structural changes using a combination of CRISPR mutagenesis and genomics (ChIP-seq, ATAC-seq). Integrating genomic profiling and high-resolution EM will generate a comprehensive, multi-scale model of pluripotency is established and how its dysregulation contributes to oncogenesis.

We are seeking an ambitious, motivated, and creative researcher to join the Chromatin Regulation Group. The student will receive cutting-edge training in chromatin biology in cancer at a leading global Cancer Research Institute, applying techniques in light and electron microscopy, image analysis, computational modelling, and genomics. Candidates with a strong academic track record and experience in chromatin biology, bioinformatics, or cancer research are highly encouraged to apply.