Project title: "Defining the mechanisms that establish heterochromatin and promote silencing of tumour suppressor genes using electron microscopy"
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Research group: Chromatin Regulation in Cancer

The genome is broadly organised into heterochromatin ("silent") and euchromatin ("active") compartments. Disruption of heterochromatin can change cell identity, and mutations in heterochromatin regulators are frequently observed in cancer. For example, copy number amplifications in SETDB1, an enzyme that deposits the repressive histone modification H3K9me2/3, are found in lung, breast, liver, and skin cancers, among others. These mutations can lead to aberrant silencing of tumour suppressor genes (TSGs) and endogenous retroviral elements (ERVs), thereby promoting tumorigenesis. Understanding how heterochromatin is established and maintained is therefore critical to understanding the mechanisms that promote cancer. Emerging structural imaging approaches offer an opportunity to significantly advance current understanding of the dynamic, multi-step processes that drive heterochromatin formation and maintenance.

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 subclasses of heterochromatin, the function and molecular regulation of which may be important in cancer and will be explored in this project. Our 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 combine EM with nanogold labelling to map distinct chromatin structural configurations to specific classes of heterochromatin that are marked by known epigenetic regulators. Next, they will dissect the functional and temporal dynamics of heterochromatin assembly by labelling ERV elements in a time-course following SETDB1 overexpression. These experiments will utilise copy number amplifications and loss of function mutations observed in cancer and define how chromatin structure regulates gene silencing. Finally, using CRISPR, the student will deplete key heterochromatin regulators and define their roles in establishing silent chromatin compartments. Integrating genomic profiling and high-resolution EM will generate a comprehensive, multi-scale model of how heterochromatin is assembled and how its dysregulation contributes to oncogenesis.

We are seeking an ambitious, motivated, and creative researcher to join the Chromatin Regulation in Cancer 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, genome editing, and genomics. Candidates with a strong academic track record and experience in chromatin biology, microscopy, or cancer research are highly encouraged to apply.