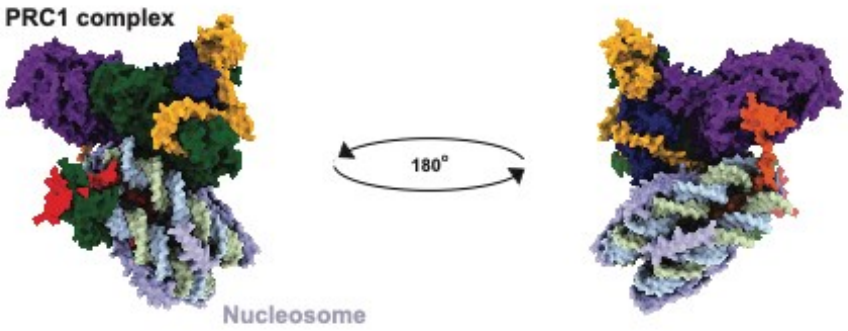

Edinburgh Doctoral College Scholarship, Project Overview

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Discovering molecular mechanisms of disease in incurable childhood brain tumours

Altering the regulatory processes that control chromatin function is a central disease mechanism in cancer. This is particularly true in childhood cancers, where chromatin disruption is pervasive and often the defining feature of disease. As such, understanding how altered chromatin regulation drives tumour development is essential if we are to understand disease biology and design effective therapeutics. We have discovered that a specific subclass of gene silencing chromatin regulatory complex, known as PRC1, is functionally essential in two childhood brain tumours – Diffuse Midline Glioma (DMG) and Atypical Teratoid/Rhabdoid Tumours (ATRT) [1,2]. In DMG and ATRT the function of PRC1 is co-opted to mediate aberrant gene silencing, which is essential for cancer cell growth and survival. However, we do not yet understand how PRC1 functions at a molecular level, meaning we do not understand how this aberrant gene silencing occurs. If we are to discover the mechanisms underlying development of these tumours, we need to understand PRC1 function.

By combining biochemical and biophysical approaches this project will discover how PRC1 complexes interact with and alter chromatin structure, to mediate this aberrant silencing. Purified, endogenous and recombinant complexes will be analysed using in-depth proteomics approaches (mass spectrometry) to characterise both their composition and structure. Purified complexes will also be used in atomic-force microscopy (AFM) imaging to unravel their binding geometry and effects on nucleosome and chromatin structure [3-5]. In addition, stretching single chromatin arrays in magnetic tweezers will inform on the forces that govern compaction [5-6] and how PRC1 modulates accessibility of the genetic code. Collectively, these experiments will provide new insights that will illuminate important molecular mechanisms; highlighting how PRC1 complexes enact disease associated gene silencing. These will represent important steps towards designing therapies for these two incurable brain tumours.

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