**University of Leicester**

**BBSRC MIBTP Studentship Project 2024-5 entry.**

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| **Project Reference** |  |

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**Section 2 – *Project Information***

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| **Project Title** | Understanding control of genome folding by cohesin |
| **Project Summary**  |
| Our basic goal is to understand how chromatin structure influences gene regulation. Chromatin is generally repressive in nature but its structure is manipulated by cells in a regulated way to determine which genes are potentially transcriptionally active and which genes remain repressed in a given cell type. This regulation depends on interactions between DNA sequence-specific transcription factors, chromatin enzymes and chromatin. The structural subunit of chromatin is the nucleosome core, which contains 147 bp of DNA wrapped 1.7 times around a central histone octamer composed of two molecules each of the four core histones (H2A, H2B, H3 and H4). Generally, nucleosomes are regularly spaced along the DNA, like beads on a string. Gene activation involves the recruitment of a set of factors to a promoter in response to appropriate signals, ultimately resulting in the formation of an initiation complex by RNA polymerase II (Pol II) and transcription. These events occur in the presence of nucleosomes, which are compact structures capable of blocking transcription at every step. To circumvent and regulate this chromatin block, eukaryotic cells possess dedicated enzymes, including ATP-dependent chromatin remodeling machines, histone modifying complexes and histone chaperones. These remodeling machines use ATP to move nucleosomes along or off DNA, or to exchange histone variants between nucleosomes. The histone modifying complexes contain enzymes which modify the histones post-translationally to alter their DNA-binding properties and to mark them for recognition by other complexes, which have activating or repressive roles. Histone-modifying enzymes include histone acetylases (HATs), deacetylases (HDACs), methylases and kinases. Histone chaperones mediate histone transfer reactions that occur during transcription and DNA replication (e.g. Asf1 and the CAF-1 complex). In addition, the genome is spatially organised to allow for DNA-based processes. Key to this organisation is the cohesin complex which organises thegenome by reeling chromatin into loops which grow in size until stopped by CTCF. The enzymes that regulate chromatin modification and structure are central to epigenetics. Many human diseases have been linked to chromatin remodeling enzymes and epigenetic modifications. For example, aberrant regulation of the HAT p300 leads to aggressive forms of squamous carcinoma. A full understanding of the structure and mechanism of functions of chromatin structure, enzymes and modifications is therefore vital and enables new strategies in pharmacological targeting. Our aim is to dissect the machinery of such chromatin regulators and elucidate their contributions to gene regulation.Our current efforts are focused on elucidating the structure and function of cohesin and its regulators, chromatin modifiers, ATP-dependent chromatin remodeling complexes and histone chaperones. We have made significant progress towards understanding a number of these key chromatin regulators. The major aim of this PhD project is to build on these key insights. We will use structural biology approaches including cryoEM and biochemical studies of key chromatin regulatory complexes including Cohesin and its regulators.Techniques that will be undertaken during the projectStructural biochemistry, protein expression in various expression systems including E. coli, Insect cells, affinity and ion-exchange protein purification, radioactivity-based activity assays, Complexes will be reconstituted and imaged in the Midlands Regional cryoEM facility, the ESRF Synchrotron (France) or at the eBIC facility at the Diamond Light Source (UK) |
| **References** |
| 1. García-Nieto A., Patel A., Li Y., Oldenkamp R., Feletto L., Graham J.J., Willems L., Muir K.W., Panne D.\* & Rowland B.D.\* Structural basis of centromeric cohesion protection. Nature Struct Mol Biol (2023). \* co-correspondence; Journal Cover.2. Ibrahim Z. Wang T., Destaing O., T. Schalch et al. Panne D. Structural insights into p300 regulation and acetylation-dependent genome organisation Nature Commun13, 7759 (2022).3. Li Y., Haarhuis J., Cacciatore A.S., Willems L., TeunissenH., Muir K.W., de Wit E., Rowland, B.D. & Panne D. (2020) The structural basis for cohesin-CTCF anchored loops. Nature 578, 472–476.4. Muir K.W., Li Y., Weiss F., Panne D. (2020) The structure of the cohesin ATPase elucidates the mechanism of SMC-kleisin ring opening. Nature Struct Mol Biol 27: 233-239.5. Ortega E., Rengachari S., Ibrahim Z., Hoghoughi N., Gaucher J., Holehouse A.S., Khochbin S., Panne D. (2018) Transcription factor dimerization activates the p300 acetyltransferase. Nature 562: 538–544.6. Sauer P., Timm J., Sitbon D., Ochsenbein F., Almouzni. G, Panne D. (2017) Insights into the molecular architecture and histone H3-H4 deposition mechanism of the Chromatin assembly factor 1., eLife, doi:10.7554/eLife.23474 |

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