**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | Unlocking fundamental principles of chromatin signalling |
| **Project Summary** | |
| We are looking for a highly motivated PhD student to join our efforts to understand epigenetic mechanisms that regulate the function of eukaryotic genomes. The structure of chromatin and the associated chromatin effector complexes are key factors in the regulation of transcription and genome maintenance, repair and replication. Our goal is to understand the molecular processes that regulate the activity of these multi-protein complexes and how they interact with nucleosomes to drive biological function. This unique project aims to reveal the molecular mechanisms underpinning histone ubiquitination.  The genomes of eukaryotic organisms are covered by histone proteins, which act as a signalling platform that forms an integral part of the regulation and protection of the genome. The signals consist of post-translational modifications on histones for which there are "writer" and "eraser" enzymes as well as reader proteins that specifically bind the marks. Histone ubiquitination is a key modification that is involved in signalling on chromatin to coordinate many different processes including transcription elongation, silencing and DNA repair. We are particularly interested in understanding the structure and function of the H2B ubiquitin ligase complex. In this project, we will use biochemistry, structural biology techniques, genome analysis and cell biology to understand the mechanism of this ubiquitous and highly conserved histone modification. You will get a lot of hands-on experience in the laboratory and develop the skills to uncover fundamental biological processes. Most importantly, it is an exciting intellectual opportunity to enter a fast-moving, competitive field.  This project is part of an international collaborative effort that leverages our expertise in high-resolution structural and will use cryo-EM to visualize the molecular machinery involved in ubiquitination. We will establish structure-function relationships by combining the structural insights with biochemistry and genetic analyses. This work will uncover principles that govern eukaryotic genome regulation and will thereby aid in the development of therapeutic approaches.  Techniques that will be undertaken during the project:  Cloning, protein expression and purification, reconstitution of protein-nucleosome complexes, enzyme kinetics, NMR, X-ray crystallography and cryo-EM. CD, ITC and other biophysical techniques.  BBSRC Strategic Research Priority: Understanding the Rules of Life - Structural Biology | |
| **References** | |
| Bailey, L.T., Northall, S.J., and Schalch, T. (2021). Breakers and amplifiers in chromatin circuitry: acetylation and ubiquitination control the heterochromatin machinery. Current Opinion in Structural Biology 71, 156–163.  Stirpe, A., Guidotti, N., Northall, S., Kilic, S., Hainard, A., Vadas, O., Fierz, B., and Schalch, T. (2020). SUV39 SET domains mediate crosstalk of heterochromatic histone marks. BioRxiv 2020.06.30.177071. | |