**University of Leicester**

**Future 50 PhD Scholarship**

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| **Project Reference** | MCB Schlach |

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**Section 2 – *Project Information***

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| **Project Title** | PR-DUB-chromatin interactions in cancer | |
| **Project Highlights:** | 1. | Misregulation or loss of the PR-DUB complex is a hallmark of many cancers |
| 2. | This project addresses the molecular mechanism of how PR-DUB interacts with chromatin. |
| 3. | Our close collaboration with clinicians will inform the approach and enable speedy translation of the findings into the clinic. |
| **Project Summary** | | |
| BRCA1-associated protein 1 (BAP1) is a tumour suppressor protein that antagonizes the silencing activity of polycomb complexes. Its loss is associated with development of malignant mesothelioma, uveal and cutaneous melanoma and other forms of cancer. Together with ASXL1, BAP1 forms the PR-DUB complex and removes the ubiquitin modifications deposited by the polycomb repressive complex 1 (PRC1) from histone H2A. ASLX1 is a critical regulator of BAP1 activity in cancer cells. Besides the N-terminus, which interacts with BAP1, ASXL1 features a PHD domain of unknown function at its C-terminus. In most BAP1-associated cancers, loss of BAP1 has been linked to tumour progression. However, myeloid tumours have been shown to be driven by a C-terminal truncation of ASXL1, which was observed to increase BAP1 activity and is therefore proposed to act as a gain-of-function mutation in these cancers. However, the molecular mechanism driving BAP1 activation is not understood.  In this project we will reconstitute PR-DUB full-length and cancer-associated truncations of ASXL1 and investigate their interaction and activity on ubiquitinated nucleosomes. For this, we will synthesize ubiquitinated histones, perform deubiquitination assays and use structural approaches including cryo-EM to understand how PR-DUB is regulated. In collaboration with Epicypher, we will further aim to determine if the PHD domain of ASXL1 binds to specific histone modifications. To investigate the significance of nucleosome recognition in proliferation of malignant mesothelioma and other cancers caused by BAP1 we will further transduce cell lines with specific PR-DUB mutants to establish how the biochemical mechanisms are driving tumorigenesis.  The student joining this project 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 a collaboration between the Leicester Cancer Research Centre and LISCB/MCB, which leverages our expertise in biochemistry and high-resolution structural methods to understand the fundamental biology of disease processes. Our studies will provide insight into the molecular mechanism of ASXL1 and is well positioned to inform future therapeutic approaches to treat myeloid tumours. | | |