**University of Leicester**

**Future 50 PhD Scholarship**

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| **Project Reference** | MCB Tellier |

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| **First Supervisor** | Dr Michael Tellier | | |
| **School/Department** | Department of Molecular and Cell Biology | | |
| **Email** | [michael.tellier@path.ox.ac.uk](mailto:michael.tellier@path.ox.ac.uk) (Leicester from Feb 2022) | **Telephone Ext** |  |

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| **Second Supervisor** | Prof. John Schwabe | | |
| **School/Department** | Leicester Institute of Structural and Chemical Biology, Department of Molecular and Cell Biology | | |
| **Email** | john.schwabe@le.ac.uk | **Telephone Ext** |  |

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| **Additional Supervisor** | Dr Amanda Chaplin, Institute of Structural and Chemical Biology, Department of Molecular and Cell Biology, ac853@leicester.ac.uk |

**Section 2 – *Project Information***

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| **Project Title** | CTDP1, a phosphatase at the intersection of transcription and DNA repair | |
| **Project Highlights:** | 1. | Quick targeted degradation of CTDP1 to investigate its functions in transcription and pre-mRNA splicing. |
| 2. | Investigation of CTDP1 phosphatase activity in DNA repair-associated transcription. |
| 3. | Determination of the complete 3D structure of CTDP1. |
| **Project Summary** | | |
| CTDP1 is an essential protein phosphatase required for development and whose mutation is associated with developmental disease. CTDP1 is also essential for proliferation of cancer cells, making CTDP1 a potential therapeutic target. CTDP1 is composed of a phosphatase domain and a BRCT domain, which serves as a scaffold for protein complexes involved in DNA repair. CTDP1 phosphatase activity is associated with regulation of transcription by RNA polymerase (pol) II and exit from mitosis while the BRCT domain is linked to DNA inter-strand crosslinks (ICLs) repair. Interestingly, CTDP1 interacts with splicing factors but it remains unknown whether CTDP1 acts in pre-mRNA splicing. As CTDP1 is involved in cell cycle regulation, knockdown and knockout approaches promote cell cycle defects, which can affect the interpretations of transcriptional and DNA repair results due to secondary effects.  To avoid secondary effects from cell cycle defects, we will use a targeted degradation approach (dTAG) to quickly degrade CTDP1 in a cell line with inducible localized DNA double strand breaks (DSBs). The cellular targets of CTDP1 will be determined by using phosphoproteomics -/+ degradation of CTDP1 (collaboration: Marjorie Fournier, University of Oxford). In addition to pol II phosphorylation, identified targets of interest will be confirmed by western blots. We will investigate the functions of CTDP1 in transcription and pre-mRNA splicing by using POINT-seq, a nascent transcription technique that provides co-transcriptional splicing. CTDP1 genomic localization and pol II phosphorylation following CTDP1 degradation will be obtained by CUT&RUN.  CTDP1 knockdown sensitizes cancer cells to different DNA-damaging treatments inducing DSBs. As *de novo* transcription occurs on DSB sites to generate non-coding RNAs required for DNA repair, we will determine in collaboration with Dr Chaplin whether CTDP1 activity regulates DNA repair and transcription around DSBs following induction of localized DSBs. In collaboration with Prof. Schwabe’s group, we will determine the complete 3D structure of CTDP1, as only two small regions have been resolved. The structure of CTDP1 will be critical for the development of specific small molecule inhibitors and/or PROTACs/molecular glues to inhibit or degrade CTDP1 in cancer cells.  **This project will address CTDP1 suitability as a therapeutic target in cancer.** | | |