**University of Leicester**

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

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| **Project Reference** |  |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | Nuclear and transcriptional dysregulations during cellular senescence |
| **Project Summary** | |
| Cellular senescence, which is characterised by a proliferation arrest, is a driver of ageing (1). Several stresses can induce cellular senescence, including persistent DNA damage, telomere dysfunction, and oncogene activation. We previously found that a deregulation of expression of long non-coding (lnc)RNAs can also promote cellular senescence, due to sustained DNA damage from transcription/replication conflicts (2). Interestingly, we found that during cellular senescence, a subgroup of lncRNAs located next to DNA replication initiation regions are getting activated and resulting in DNA damage and transcription/replication conflicts. These results indicate that the activation of this subgroup of lncRNAs could play a role in the promotion and/or maintenance of cellular senescence.  The project is therefore to elucidate in a fibroblast cell culture model the regulation and the role played by this subgroup of lncRNAs in cellular senescence. This will include several interconnected lines of enquiries:   1. When are these lncRNAs activated? Is it before or after cellular senescence? 2. How are these lncRNAs getting activated? Are they expression regulated by one or more cellular stresses? 3. Are these lncRNAs consistently promoting DNA damage via transcription/replication conflicts? 4. How is their activation related to other changes in the nucleus during cellular senescence, such as 3D genome organization, RNA polymerase II activity, and nucleosome packaging? 5. In the cascade of dysregulations occurring in the nucleus leading to cellular senescence, where is the activation of these lncRNAs located?   This project will equip the candidate with a unique combination of expertise in cutting-edge experimental approaches and data analyses.  **Techniques that will be undertaken during the project:**   * Genomics and transcriptomic approaches * Bioinformatics analyses * Proteomics * Live-cell imaging / super-resolution microscopy (3) * Cell culture * CRISPR/Cas9 genome editing * Standard molecular biology techniques (cloning, co-immunoprecipitation …) | |
| **References** | |
| 1. Di Micco R et al. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nature Reviews Molecular Cell Biology, 2020. 2. Nojima T\*, **Tellier M\***, et al. Deregulated Expression of Mammalian lncRNA through Loss of SPT6 Induces R-Loop Formation, Replication Stress, and Cellular Senescence. Molecular Cell, 2018. 3. Grigoryan A et al, LaminA/C regulates epigenetic and chromatin architecture changes upon aging of hematopoietic stem cells. Genome Biology, 2018. | |

**To apply please refer to**

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