**University of Leicester**

**MIBTP studentship project 2026**

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| **First Supervisor** | Professor Flaviano Giorgini |
| **School/Department** | School of Biological and Biomedical Sciences, Division of Genetics and Genome Biology |
| **Email**  | fg36@le.ac.uk  |

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| **Second Supervisor** | Professor Don Jones |
| **School/Department** | School of Medical Sciences, Cancer Sciences |
| **Email**  | donald.jones@leicester.ac.uk  |

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| **Additional Supervisor** | Dr Mary Collier, University of Leicester |

**Section 2 – *Project Information***

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| **Project Title** | Unravelling the role of the kynurenine pathway in cellular development and physiology using transcriptomics and proteomics with CRISPR-edited induced pluripotent stem cell (IPSC) neurons and microglia |
| **Project Summary**  |
| Kynurenine pathway (KP) metabolites are neuroactive and associated withschizophrenia (SZ) and bipolar disorder (BD). How the KP contributes to theseconditions is not clear and requires elucidation. The enzyme kynurenine 3-monooxygenase (KMO) is the central regulator of KP metabolism, and itsfunction may underlie the pathway alterations in these disorders. KMO is amitochondrial protein expressed in neurons and microglia within the centralnervous system. A single nucleotide polymorphism (SNP) rs1053230 in the KMOgene encodes two KMO protein variants with either an arginine or cysteine atposition 452. This SNP is associated with differences in KMO expression andactivity, and cognition in patients with SZ and BD. We recently found that theKMO-Arg452 variant has reduced protein stability compared to KMO-Cys452, andKMO-Cys452 interacts with proteins associated with synaptic vesicle recyclingand synaptic organisation. Both KMO variants interact with microtubule systemproteins involved in mitochondrial transport.The PhD candidate will employ induced pluripotent stem cell (iPSC)-derivedneurons and microglia to investigate the effects of the KMO variants on severalmolecular metrics (e.g. subcellular localisation, protein stability, mitochondrialfunction, protein interaction partners), as well as in neuronal development andfunction via metrics relevant to SZ and BD. The work will involve transfectingthese cell types with siRNAs to knockdown KMO expression or synthetic mRNAsto specifically express the KMO variants with fluorescent tags for advancedmicroscopy, transcriptomics via RNAseq and proteomics via mass spectrometry.KMO-knockout neurons and microglia will be generated by CRISPR editing toinvestigate complete KMO loss of function and to serve as background forexpression of the KMO variants. This work will clarify the mechanismsunderlying cognitive dysfunction in these disorders and may benefit therapeuticinterventions for affected individuals.Techniques that will be undertaken during the projectThis project will involve the culturing and analysis of induced pluripotent stemcell (IPSC) derived neurons and microglia. These cells will be transfected withsynthetic mRNAs and siRNAs in order to overexpress and knockdown genes ofinterest. CRIPSR-Cas 9 gene editing will be performed to knockout a key gene inthe kynurenine pathway. The cells will be analysed by advanced microscopy,QPCR, immunoblotting, RNASeq transcriptomics and proteomics by massspectrometry. Bioinformatics analyses will be performed on the transcriptomicsand proteomics data obtained. |
| **References** |
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