**University of Leicester**

**MIBTP studentship project 2026**

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**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 with  schizophrenia (SZ) and bipolar disorder (BD). How the KP contributes to these  conditions is not clear and requires elucidation. The enzyme kynurenine 3-  monooxygenase (KMO) is the central regulator of KP metabolism, and its  function may underlie the pathway alterations in these disorders. KMO is a  mitochondrial protein expressed in neurons and microglia within the central  nervous system. A single nucleotide polymorphism (SNP) rs1053230 in the KMO  gene encodes two KMO protein variants with either an arginine or cysteine at  position 452. This SNP is associated with differences in KMO expression and  activity, and cognition in patients with SZ and BD. We recently found that the  KMO-Arg452 variant has reduced protein stability compared to KMO-Cys452, and  KMO-Cys452 interacts with proteins associated with synaptic vesicle recycling  and synaptic organisation. Both KMO variants interact with microtubule system  proteins involved in mitochondrial transport.  The PhD candidate will employ induced pluripotent stem cell (iPSC)-derived  neurons and microglia to investigate the effects of the KMO variants on several  molecular metrics (e.g. subcellular localisation, protein stability, mitochondrial  function, protein interaction partners), as well as in neuronal development and  function via metrics relevant to SZ and BD. The work will involve transfecting  these cell types with siRNAs to knockdown KMO expression or synthetic mRNAs  to specifically express the KMO variants with fluorescent tags for advanced  microscopy, transcriptomics via RNAseq and proteomics via mass spectrometry.  KMO-knockout neurons and microglia will be generated by CRISPR editing to  investigate complete KMO loss of function and to serve as background for  expression of the KMO variants. This work will clarify the mechanisms  underlying cognitive dysfunction in these disorders and may benefit therapeutic  interventions for affected individuals.  Techniques that will be undertaken during the project  This project will involve the culturing and analysis of induced pluripotent stem  cell (IPSC) derived neurons and microglia. These cells will be transfected with  synthetic mRNAs and siRNAs in order to overexpress and knockdown genes of  interest. CRIPSR-Cas 9 gene editing will be performed to knockout a key gene in  the kynurenine pathway. The cells will be analysed by advanced microscopy,  QPCR, immunoblotting, RNASeq transcriptomics and proteomics by mass  spectrometry. Bioinformatics analyses will be performed on the transcriptomics  and proteomics data obtained. | |
| **References** | |
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