| Project Details | |
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| Project Code | NMH27Br Grieve |
| Title | Gatekeepers of GPCR Signalling: Degradation Pathways in Health and Disease |
| Research Theme | Neuroscience & Mental Health |
| Project Type | Wet lab |
| Summary | Neuropsychiatric disorders remain among the greatest challenges in medicine, yet we still lack a detailed understanding of how changes at the molecular level contribute to altered brain function. This PhD project will uncover fundamental mechanisms controlling the life cycle of key neuronal signalling proteins and investigate how genetic variation influences these processes. Combining cutting-edge cell biology, functional genomics, biochemistry and human genetic approaches, the student will discover new regulators of neuronal signalling and explore their relevance to mental health. The project offers multidisciplinary training and the opportunity to make discoveries at the interface of molecular biology and human disease. |
| Description | G protein-coupled receptors (GPCRs) are the largest family of cell-surface signalling proteins and mediate communication between cells throughout the body and brain. Many neurotransmitter systems that underpin mental health, including dopamine and serotonin pathways, rely on GPCRs to regulate mood, motivation and emotional processing. Disruption of GPCR function has been implicated in numerous neuropsychiatric disorders, including depression, anxiety, schizophrenia and addiction, and GPCRs remain among the most important targets for therapeutic intervention.<br>Recent advances in human genetics have identified numerous disease-associated variants in GPCR genes. However, for many of these variants, it remains unclear how they alter receptor function and contribute to disease. While some mutations directly affect receptor signalling, many disrupt more fundamental aspects of receptor biology, including protein folding, intracellular trafficking and turnover. These processes form part of the cellular proteostasis network that ensures proteins are correctly produced, maintained and regulated throughout their lifetime. In neurons, where precise control of receptor abundance and localisation is essential for signalling, disruption of these pathways may have profound consequences for brain function.<br>This PhD project will investigate how GPCR proteostasis is controlled in neuronal systems and determine how genetic variation in GPCRs and their regulatory machinery influences receptor function and human disease risk. Using molecular biology, cell biology, biochemistry, functional genomics and human genetic approaches, the student will define the pathways that determine GPCR fate and work with genetic epidemiologists to establish whether these mechanisms are linked to neuropsychiatric outcomes in human populations.<br>Aim 1: Define how disease-associated GPCR mutations alter receptor proteostasis<br>The first aim will investigate how disease-associated GPCR variants influence receptor biology. The student will generate and characterise selected GPCR mutants identified through human disease genetics and |

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| | determine how these variants affect their proteostasis in neuronal models.<br>Diverse disease-associated GPCR mutations will be used as mechanistic tools to understand how genetic variation disrupts receptor proteostasis. Using advanced microscopy, quantitative cell biology and biochemical approaches, the project will determine how individual mutations alter receptor homeostasis and whether distinct variants converge on common regulatory pathways.<br>Aim 2: Identify cellular regulators of GPCR fate using functional genomics<br>The second aim will use functional genomics to discover the cellular pathways that regulate GPCR abundance and stability. The student will develop screening approaches capable of monitoring receptor fate in living cells and perform genetic screens to identify regulators of receptor homeostasis.<br>These studies are expected to uncover pathways involved in membrane protein quality control. Importantly, regulators identified through these screens will provide candidates for investigation in human genetic datasets. Working with genetic epidemiology collaborators, the student will examine whether variation in GPCR regulatory pathways is associated with neuropsychiatric traits and mental health outcomes.<br>This integration of functional genomics and population genetics will move beyond identifying cellular regulators to understanding their relevance in human disease. The project will remain flexible, allowing emerging discoveries to guide the prioritisation of pathways involved in receptor stability, signalling competence, or broader aspects of neuronal proteostasis.<br>Aim 3: Mechanistically dissect pathways controlling GPCR turnover<br>Candidate regulators identified through genetic screens will be validated and studied in detail to determine how they influence receptor fate. The student will combine cellular assays with biochemical reconstitution approaches to establish direct mechanistic links between candidate factors and GPCR regulation.<br>Studies may include defining protein-protein interactions, reconstructing regulatory pathways in simplified membrane systems and determining how disease-associated GPCR mutations alter recognition, processing and turnover by cellular quality-control machinery.<br>A major component of this aim will be integration with human genetics. Working closely with genetic epidemiologists, the student will investigate whether GPCRs and newly identified quality-control regulators contain genetic variants associated with altered risk of neuropsychiatric traits affecting mood, cognition and behaviour. This approach will enable mechanistic discoveries from cellular models to be triangulated with evidence from human populations, providing new insights into how disrupted GPCR proteostasis contributes to brain disease.<br>The project is designed to evolve as discoveries emerge, providing opportunities for students interested in cell biology, biochemistry, genomics, computational biology or therapeutic discovery. Students may pursue imaging-based studies of receptor trafficking, mechanistic studies of protein interactions, integration of functional discoveries with human |

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| | genetic datasets, or identification of pathways that could be manipulated to restore receptor function.<br>The student will be supported by an interdisciplinary supervisory team with expertise in biochemistry, cell biology, chemistry and human genetics. This environment will provide training across multiple disciplines and exposure to a diverse range of experimental and computational approaches.<br>By combining neuroscience, functional genomics, human genetics and mechanistic biochemistry, this project aims to uncover fundamental principles governing GPCR regulation in neurons. The findings will advance understanding of how genetic variation in receptors and their quality-control machinery influences neuronal signalling and mental health, while providing multidisciplinary training at the interface of cell biology, genetics and neuroscience. |
| Can be completed part time? | Yes |
| Supervisory Team | |
| Lead Supervisor | |
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