| Project Details | |
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| Project Code | NMH27Ex Flynn |
| Title | Turning off transcription factors to understand what happens first in neurodevelopmental disorders |
| Research Theme | Neuroscience & Mental Health |
| Project Type | Wet lab |
| Summary | What are the first things that go wrong in neurodevelopmental disorders? This project will use human stem cells to grow early brain cells, then rapidly switch off selected disease-linked transcription factors. By measuring the immediate effects on chromatin accessibility and gene activity, using advanced genomics approaches such as CUT&Tag and RNA-seq, we can uncover how disrupted gene control leads to neurodevelopmental disorders including intellectual disability, autism, epilepsy and speech impairment. The student will learn cutting-edge stem cell, genome editing and genomics methods while helping answer a fundamental question about how human brain development goes wrong. |
| Description | Neurodevelopmental disorders are a major cause of lifelong disability, with profound impacts on affected individuals, families and society. Many conditions involving learning, communication, behaviour, epilepsy risk and mental health are caused by variants in genes that control brain development. A particularly important group of these genes encode transcription factors, proteins that bind DNA and help determine which genes are switched on or off as the brain develops.<br>Pathogenic variants in transcription factors such as FOXG1, FOXP1, MEF2C, POU3F3, TCF4 and BCL11A cause or contribute to severe neurodevelopmental disorders that can include intellectual disability, autism, speech impairment, seizures and motor difficulties. Although these genes are established regulators of brain development, we still do not fully understand what happens first when they are disrupted in human neural cells. This is a major gap, because the earliest molecular changes are likely to reveal the most direct disease mechanisms.<br>A central challenge is that transcription factors act early and control many downstream genes. When a transcription factor is permanently mutated or deleted, cells may gradually change identity, activate compensatory pathways, or fail to develop normally. This makes it difficult to separate the direct effects of transcription factor loss from later consequences.<br>This project will address that problem using acute protein depletion. The student will engineer human induced pluripotent stem cells so that selected neurodevelopmental disorder-associated transcription factors can be rapidly switched off on demand. This provides a powerful way to watch the first molecular events unfold after loss of a disease-relevant protein, before cells have time to adapt.<br>The project will use an established human stem cell system that generates neural progenitor cells and forebrain neurons, cell types directly relevant to neurodevelopmental disorders. The student will prioritise one or two transcription factors such as FOXG1 and FOXP1, guided by known disease relevance, expression in the model system, DNA-binding information, enhancer activity and feasibility of genome editing. |

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| | The central research question is: how do neurodevelopmental disorder-associated transcription factors directly control gene regulation in human neural progenitors and neurons, and how does their acute loss lead to disease-relevant disruption of brain development?<br>Project Aims<br>Year 1<br>The student will be trained to grow human stem cells, turn them into neural progenitor cells and forebrain neurons, and edit their genomes using CRISPR. They will choose one or two lead transcription factors using published disease biology, expression data, DNA-binding information and existing enhancer maps. They will then engineer iPSC lines in which this factor can be rapidly switched off. The student will use these cells to map where the factor binds in the genome and which promoters and enhancers are active during normal neural development, using approaches such as CUT&Tag and chromatin accessibility profiling.<br>Year 2<br>The student will switch off the selected transcription factor in neural progenitors and neurons and measure what happens in the first few hours after its loss. This allows us to capture the earliest molecular events before cells have time to adapt or change identity. The student will measure changes in DNA accessibility, enhancer activity and gene expression using approaches such as CUT&Tag, RNA-seq and nascent transcriptomics, which measures newly made RNA. This will reveal whether acute loss of a disease-associated transcription factor disrupts specific neural gene programmes, alters promoter or enhancer function, or changes how key developmental genes are switched on.<br>Year 3<br>The student will integrate the genomic datasets to identify the genes and regulatory elements most vulnerable to transcription factor loss. They will ask whether affected regions are linked to autism, intellectual disability, epilepsy or related neurodevelopmental disorders. Selected regulatory elements may be tested using CRISPR perturbation, rescue after protein restoration, or comparison with known patient-associated variants. This will move the project from genome-wide discovery to a mechanistic understanding of how disruption of transcriptional control contributes to disease.<br>The student will receive broad training in stem cell biology, human neural differentiation, CRISPR genome editing, acute protein depletion, functional genomics and computational analysis. They will also have intellectual ownership, from selecting the final transcription factor candidates to designing the mechanistic experiments in the final year. This project offers an exciting opportunity to work at the interface of neuroscience, genomics and disease biology, using cutting-edge technologies to answer a fundamental question: how does disruption of transcriptional control lead to neurodevelopmental disorder?<br>Prospective applicants are encouraged to email the supervisory team for an informal discussion about the project and training environment. |
| Can be completed part time? | No |

| Supervisory Team | |
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| Lead Supervisor | |
| Name | Dr Sean Flynn |
| Affiliation | Exeter |
| College/Faculty | Faculty of Health & Life Sciences |
| Department/School | Clinical and Biomedical Sciences |
| Email Address | s.m.flynn@exeter.ac.uk |
| Co-Supervisor 1 | |
| Name | Dr Greg Ngo |
| Affiliation | Cardiff |
| College/Faculty | College of Biomedical and Life Sciences |
| Department/School | School of Medicine |
| Co-Supervisor 2 | |
| Name | Professor Brian Hendrich |
| Affiliation | Exeter |
| College/Faculty | Faculty of Health & Life Sciences |
| Department/School | Living Systems Institute/Biosciences |
| Co-Supervisor 3 | |
| Name | |
| Affiliation | |
| College/Faculty | |
| Department/School | |