| Project Details | |
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| Project Code | MRCNMH24Ex Basson |
| Title | Using multidisciplinary approaches to understand and develop treatments for neurodevelopmental disorders |
| Research Theme | Neuroscience & Mental Health |
| Summary | We recently identified a new neurodevelopmental disorder characterised by intellectual disability and psychiatric symptoms, similar to other severe neurodevelopmental orders we study. The aim of this project is to use learning and memory tasks, sophisticated single cell sequencing, chromatin, bioinformatic and molecular approaches in a new mouse model to understand the causes of this disorder and develop and test novel treatments. |
| Description | Background: A primary goal of our research is to understand how brain development is regulated at the level of chromatin. Mutations in genes encoding chromatin modifying and interacting proteins are frequent causes of neurodevelopmental disorders. Sid Banka's group (Manchester) has identified a new neurodevelopmental syndrome caused by mutation of the RLF (Rearranged L-myc fusion) gene. Children with this disorder exhibit moderate to severe intellectual disability and other debilitating psychiatric symptoms for which there currently are no suitable treatment. Research question: The function of RLF in brain development is not known. Preliminary data suggest that RLF regulates DNA methylation and histone 3 lysine 4 methylation (H3K4me), a modification found at important gene regulatory elements. Dysregulation of H3K4me has been implicated in other similar disorders, as well as in schizophrenia. Our long-term aim is to understand how chromatin dysregulation cause these disorders and if targeting the epigenetic machinery responsible for H3K4me represents a useful therapeutic approach. The Basson laboratory has developed a new mouse line that carries a disease-causing Rlf variant. The aim of this project is to use this in vivo model to ask how Rlf mutation disrupts brain development, affect chromatin structure and gene expression and result in abnormal behaviours and learning and memory deficits. Specific objectives are: 1. To identify the key brain regions and developmental processes affected by Rlf mutation, 2. To use state-of-the-art next generation sequencing approaches (RNA-seq, ChIP-seq, ATAC-seq, Nanopore long-read sequencing and spatial transcriptomics), together with bioinformatic analyses to identify the neurodevelopmental genes and chromatin mechanisms regulated by RLF, 3) To use a combination of these molecular approaches and behavioural studies to evaluate potential targeted therapies for this condition. During year 1, the student will work closely with a post-doctoral scientist with expertise in brain development to investigate brain structure, cell specification, growth, migration and differentiation. They will liaise with Adam Jackson (Academic Clinical Fellow in Clinical Genetics) and Sid Banka in Manchester to develop a deep understanding of the clinical and genetic features of this new chromatin disorder to inform the experimental design. During year 2, the student will work with another post-doctoral research fellow with expertise in advanced sequencing approaches to identify neurodevelopmental genes regulated by RLF, and the effects of RLF mutation on chromatin structure. During year 3, the student will |

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| | determine if treatment of the mouse model with an FDA-approved compound that target these epigenetic mechanisms can rescue specific phenotypes. At this stage, the experimental design and read-outs of this project will be developed by the student, with input from the supervisors, clinical and pharmaceutical collaborators. The student will gain expertise in a range of cutting-edge in vivo and data science skills, including the first stages of translational research with pre-clinical models and a proficiency in data handling that are highly desirable and transferable to many careers. The student will take ownership of experimental design from the start (see below). Once the core objectives outlined above have been met, the student will have the opportunity to shape the remaining time of their PhD by pursuing areas of research that suit their interests. For instance, they may perform neurophysiology, behavioural studies, or cutting-edge chromatin and next generation sequencing experiments. Human iPSCs models are available in Manchester, providing an opportunity to expand the work into appropriate human model systems if appropriate. |
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