Project Details	
Project Code	MRCNMH25Ex Basson
Title	Understanding the social brain circuits affected in neurodevelopmental disorders.
Research Theme	Neuroscience & Mental Health
Summary	The Kdm5b gene is linked to a number of neurodevelopmental disorders, including ADHD, autism, bipolar disorder and intellectual disability. Using a unique mouse model, we recently identified a neurobiological mechanism that underlies socio-communicative deficits in this model and showed that taregtting this mechanism can restore normal function. The aim of this project is to use cutting-edge approaches to identify the brain regions and cell types that control these behaviours, study the brain circuits affected by Kdm5b deficiency and understand how treatments can restore normal function. This research will have important implications for understanding socio-communicative deficits in neurodevelopmental disorders.
Description	Background Mutations in genes encoding chromatin modifying and interacting proteins are frequent causes of neurodevelopmental disorders. Using a mouse model, we have been studying one of these, Kdm5b, which encodes a protein that regulates gene expression by modifying the structure of chromatin in the cell nucleus. Loss of function variants in this gene are associated with intellectual disability and autism spectrum disorders. Kdm5b-deficient pups exhibited striking socio-communicative deficits. By studying changes in gene expression, we have identified abnormal expression of a gene encoding an important neurotransmitter receptor in the developing brain and found that treatment of mice with a pharmacological compound that target this receptor can rescue the vocalisation deficits. These findings create an exciting opportunity to identify the brain regions, brain circuits and molecular mechanisms that control socio-communicative behaviours that are often abnormal in neurodevelopmental disorders. Research question We now need to find answers for a number of fundamental questions: 1) What brain regions and cell types control vocalisations in young mice and how does Kdm5b deficiency affect the activity of these cells and brain areas during behaviour? 2) How does treatment with pharmacological compounds restore normal brain function and behaviour? 3) How do these abnormal brain functions impact other behaviours during early postnatal development? Specific objectives are: 1. To identify the key brain regions activated during vocalisation behaviours and affected by Kdm5b deficiency, 2. To use state-of-the-art single cell sequencing, immunostaining and conditional gene deletion approaches to identify the cell types affected by Kdm5b deficiency, 3. To use a combination of imaging, molecular and electrophysiological assays to determine how treatments that can restore normal behaviour work and

	4. To develop and use new approaches to assess if Kdm5b deficiency affect other relevant behaviours during early postnatal stages. During year 1 and 2, the student will use reporters of neuronal activation to identify the brain regions and cell types activated during vocalising behaviours, identify those that are affected by Kdm5b activity and rescued by pharmacological treatment. During year 2 and 3, the student will use electrophysiological approaches to further characterise and identify abnormal brain circuits in Kdm5b mutants. During year 3, the student will work closely with the Isles laboratory and experts in the GW4 BioMed2 partner organisation the Mary Lyon Centre as part of the MRC National Mouse Genetics Network to determine how altered brain activity impact behavioural development. 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.
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