Project Details	
Project Code	MRCNMH24Ex Clifton
Title	The synapse in schizophrenia: molecular impacts of genetic variation
Research Theme	Neuroscience & Mental Health
Summary	To improve treatments for schizophrenia there is a need to better understand the biology impacted by genetic mutations conferring risk to the disorder. This project will aim to investigate the effects of high-risk genetic variants on synapses and their molecular constituents. We will make use of cell-specific RNA sequencing and large-scale patient genomic data to quantify these effects and predict biological vulnerability in the brain.
Description	Recent years have seen genomics research unearth hundreds of genes associated with risk for schizophrenia, yet these discoveries have not yet translated to the development of new treatments. To reach a point where we can improve treatments, there is a need to refine when and where genetic risk converges on vulnerable biological systems, taking into account the dynamic and compartmentalised nature of cellular processes over development. Time- and spatially-sensitive synaptic events utilise local translation of gene transcripts to rapidly produce selected proteins. Such events include plasticity, neurite outgrowth and synapse maturation, all of which have been implicated in schizophrenia risk through genetic and functional studies, highlighting the importance of studying synaptic dynamics driven by local translation. Modelling the developmental effects of risk variants in genes important for synaptic function may reveal critical periods of vulnerability in the synaptic translatome and targets for intervention. New findings from exome sequencing have revealed a small group of 10 genes containing a genome-wide excess of highly penetrant coding mutations in patients with schizophrenia. This greatly increases the feasibility of studying relevant pathology in model organisms. This project will focus on modelling the effects of missense variants in the NMDA receptor subunit gene, GRIN2A, to investigate the role of the local synaptic translatome in conferring risk to schizophrenia during brain development, taking advantage of the most recent techniques for ribosome profiling and single-cell transcriptomics. Working with the GW4 BioMed2 Associate Partner the MRC Mary Lyon Centre, a new mouse line has been generated modelling a GRIN2A missense variant found in patients with schizophrenia. The student will use cortical tissue from this mouse line to test the hypothesis that the mutation exerts pathogenic effects through disruption to locally translated synaptic transcripts, using the following objectives: • Profile changes in ribosome-associated transcripts at the synaptosome caused by the Grin2a variant. By crossing the mouse line with a RiboTag strain, cell-specific ribosomes will be tagged for immunoprecipitation and RNA isolation. RNA from different stages of postnatal brain development will be sequenced and analysed. • Identify cell type specific changes using single-cell transcriptional sequencing. Informed by the first objective, the student will choose one developmental stage to obtain cortical cells for dissociation and sequencing using 10X Genomics. The student will determine genotype effects and prioritise cell types based on susceptibility of differentially expressed genes to schizophrenia risk. • Use human genomics

	and developmental transcriptomes to predict when and where human gene expression dynamics may be most susceptible to alterations observed in the mouse model. Through collaborators at the Lieber Institute for Brain Development (Baltimore) and data available at Exeter, we will compare new mouse transcriptomes with expression dynamics from human dorsolateral prefrontal cortex, hippocampus and caudate nucleus, including foetal, single-cell and methylation datasets. In addition to the provision of training in these interdisciplinary techniques by the supervisory team, the student will be encouraged to develop their project by taking advantage of links with other academic institutions in the UK and abroad, either through conference meetings or a short research visit. This will allow them to begin establishing a network of collaborators and a wider awareness of current work in the field.
Supervisory Team	
Lead Supervisor	
Name	Dr Nicholas Clifton
Affiliation	Exeter
College/Faculty	Faculty of Health and Life Sciences
Department/School	Complex Disease Epigenetics Group
Email Address	N.clifton@exeter.ac.uk
Co-Supervisor 1	
Name	Professor Anthony Isles
Affiliation	Cardiff
College/Faculty	Division of Psychological Medicine and Clinical Neurosciences
Department/School	Cardiff Centre for Neuropsychiatric Genetics and Genomics
Co-Supervisor 2	
Name	Dr Elliott Rees
Affiliation	Cardiff
College/Faculty	Division of Psychological Medicine and Clinical Neurosciences
Department/School	Cardiff Centre for Neuropsychiatric Genetics and Genomics
Co-Supervisor 3	
Name	Professor Jonathan Mill
Affiliation	Exeter
College/Faculty	Faculty of Health and Life Sciences
Department/School	Complex Disease Epigenetics Group