Project Details	
Project Code	MRC23NMHCa Wilkinson
Title	Linking microRNA dynamics to mental health: Assessing the contribution of brain expressed miRNAs to the increased risk for psychiatric disorder in 22q11.2DS subjects.
Research Theme	Neuroscience and Mental Health
Summary	A large proportion of people with 22q11.2DS, a syndrome where a segment of DNA and associated genes are missing from chromosome 22, will fall ill with some form of psychiatric disorder. We suspect this increased risk for psychopathology is due to abnormalities in the brain metabolism of microRNAs. We will test this idea using patient-derived human neurons in partnership with Takeda who will provide support and a training secondment at the company in Tokyo, Japan.
Description	Genetic factors, in tandem with life events, make a key contribution to mental health and variations in the genetic code can increase susceptibility to falling ill across a range of psychiatric disorders, including depression, anxiety and psychosis. Some of the most damaging genetic effects are seen in 22q11.2DS (also known as DiGeorge syndrome or velocardiofacial syndrome) in which a stretch of DNA and associated genes is missing on chromosome 22. These individuals present with a variety of physical and psychological challenges. Subjects with 22q11.2DS often develop psychiatric symptoms, with some reports indicating penetrance in as much as 75-90% of the population with approximately 15-25% being diagnosed with schizophrenia. The markedly high penetrance of 22q11.2DS for psychiatric disorder has led to much research into pathogenic mechanisms that may mediate the increased risk, the rationale being that understanding the biological basis of the psychopathology of 22q11.2DS may reveal mechanisms of common relevance to psychiatric disorder and also targets for therapeutic intervention. In this project we will use human induced pluripotent stem cell (iPSC)-derived neurons to address the hypothesis that abnormalities in the metabolism of microRNAs (miRNAs) in brain contribute to the increased risk for psychiatric disorder in 22q11.2DS. miRNAs are small single stranded bits of RNA between 19-24 nucleotides long that impact on gene function by interacting with mRNA during transcription, in the majority of cases by inhibiting mRNA. We strongly suspect a significant contribution of miRNAs to the 22q11.2DS phenotype due to the presence of the gene DGCR8 (DiGeorge Critical Region 8) in the deleted interval (DGCR8 is a master controller of miRNA biosynthesis), the enrichment of miRNAs risk variants in recent psychiatric genetics case-control association studies and the finding that reduced DGCR8 can mimic 22q11.2DS phenotypes. The student will gain skills, experience and ownership across a wide range of unique assets and cutting-edge experimental approaches and tools. These will include utilisation of banked 22q11.2DS and control iPSC, training in cell culture methods to differentiate neurons from human iPSC, miRNA profiling using bespoke sequencing methods, training in the most up-to-date bioinformatic approaches, CRISPR-mediated genome editing, manipulation of miRNAs (e.g. expression of shRNA or miRSponges) and functional analysis using multi-electrode arrays. In all cases, the relevant methodologies are established in the home laboratory and the student

	will be supported in their training and in developing an increasing independence by the Wilkinson/Harwood research group. The work will be in collaboration with Takeda Pharmaceutical Company Limited and will take advantage of the ongoing Cardiff-Takeda Drug Discovery Partnership led by Lawrence Wilkinson with Adrian Harwood as co-PI, offering access to Takeda expertise and experimental tools as well as a secondment to Takeda in Tokyo during the PhD. The student will have full input to the experimental designs to include; miRNA profiling of 22q11.2DS patient iPSC-derived neurons (using bespoke sequencing methods to overcome the short read lengths) followed by a bioinformatic analysis to link differently expressed miRNAs to their target mRNAs including an enrichment analysis for known risk gene variants. This will identify the key regulatory miRNA associated with psychiatric symptoms. To confirm the contribution of low dosage DGCR8 specifically to the pattern of miRNA changes in 22q11.2DS cells we will CRISPR-engineer DGCR8 heterozygous cells for comparison. In a final set of experiments we will increase candidate disease-relevant miRNAs by expression of small hairpin RNA (shRNA) or decrease them by expression of miRSponges and examine effects on gene expression and neuronal function.
Supervisory Team	
Lead Supervisor	
Name	Prof Lawrence Wilkinson
Affiliation	Cardiff
College/Faculty	Biomedical and Life Sciences
Department/School	Medicine
Email Address	wilkinsonl@cardiff.ac.uk
Co-Supervisor 1	
Name	Professor Adrian Harwood
Affiliation	Cardiff
College/Faculty	Biomedical and Life Sciences
Department/School	Biosciences
Co-Supervisor 2	
Name	Dr Peter Maycox
Affiliation	Other
College/Faculty	
Department/School	
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	