Project Details	
Project Code	NMH27Br D'Andrea
Title	Mapping the biology of complex brain disorders: uncovering molecular pathways and identifying potential drug targets
Research Theme	Neuroscience & Mental Health
Project Type	Dry lab
Summary	Developing medicines to treat brain disorders such as schizophrenia has proven extremely difficult, with many new drugs failing in late-stage clinical trials. Research has shown that drugs which target genes convincingly linked to disease by genetic studies are significantly more likely to be successful. However, the optimal strategy for choosing novel drug targets based on genetic studies is not yet clear. In this project, we will combine disease genetics with information on which genes are active in different brain cell-types to identify biological processes disrupted in brain disorders and prioritise novel target genes for potential future drug development.
Description	Drug development has proven extremely challenging for complex brain disorders such as autism, schizophrenia and Alzheimer's disease, leading many companies to scale back or abandon work on CNS conditions. A major contributing factor has been the high failure rate of compounds in late phase trials, which reflects our currently poor understanding of disease biology: failing compounds have been shown to perform the biological action for which they were designed, but this activity has no efficacy in treating disease. Genetic studies can provide invaluable insight into the genes and biological processes disrupted in disease, and it has been estimated that the selection of targets with strong genetic support could more than double success rates in drug development. In this project, the student will use genetic and bioinformatic analyses of molecular neuroscience data (primarily single cell transcriptomics) to address a key unsolved question: which brain regions, cell-types and molecular pathways are disrupted in genetically complex brain disorders, and how can we best utilise this information to prioritise potential novel therapeutic targets? The project builds upon existing work informed by the supervisors' experience of performing drug target prioritisation for a multinational pharmaceutical company. In carrying out this research, the student will be exposed to recent advances in molecular and cellular neuroscience and will gain experience in the processing and analysis of next-generation sequencing data, statistical genetics and relevant bioinformatic techniques. The student will work through a series of primary objectives: 1) set up pipeline for the QC, processing and analysis of literature-derived scRNAseq datasets. 2) apply this pipeline to transcriptomic data for the adult human brain, identifying region and cell-type specific patterns of gene expression. 3) Interrogate the output from 2) using statistical genetic (common/rare variant association enrichment tests) and bioinformatic techniques (including structured Gene Ontology analyses) to identify regions, cell-types and molecular processes disrupted in brain disorders. 4) Integrate disease-genetic and functional data to prioritise potential target genes for drug development.

	In working through the above objectives, the student will focus on schizophrenia, for which the genetic data is relatively well-powered. This will serve as training in the computational techniques and over-arching research methodology. Once complete, the student will have the freedom to steer the project in the direction that most interests them: interrogating genetic data for other conditions in order to perform a cross-disorder analysis; drawing upon scRNAseq datasets with a more detailed focus on specific cell-types (e.g. glia, blood-brain barrier) that are relevant to a disorder of particular interest to them; or expanding the analysis to look at neurodevelopmental cell-types.
Can be completed part time?	No
Supervisory Team	
Lead Supervisor	
Name	Dr Daniel D'Andrea
Affiliation	Bristol
College/Faculty	Faculty of Science and Engineering
Department/School	School of Engineering Mathematics and Technology
Email Address	daniel.dandrea@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Andrew Pocklington
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	Division of Psychological Medicine and Clinical Neuroscience, School of Medicine
Co-Supervisor 2	
Name	
Affiliation	
College/Faculty	
Department/School	
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	