Project Details	
Project Code	NMH27Ca Heurich
Title	Towards Precision Psychiatry: Early Detection and Intervention in Schizophrenia
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	Schizophrenia affects around 1% of the population and remains one of the most challenging mental health disorders to predict and treat. Increasing evidence suggests that changes in the immune system may contribute to disease development long before symptoms become severe. This project will investigate how immune pathways influence brain function in schizophrenia and whether they can be used to identify people at risk earlier. You will receive interdisciplinary training in neuroscience, immunology, molecular biology and computational modelling to undertake research aimed at improving diagnosis, prevention and personalised treatment of schizophrenia.
Description	Schizophrenia is a severe mental health disorder affecting approximately 1% of the population worldwide and is a leading cause of long-term disability. Although symptoms typically emerge in late adolescence or early adulthood, biological changes are thought to begin many years before diagnosis. Early intervention can substantially improve outcomes; however, there are currently no objective biological markers available to identify individuals at risk or to guide personalised treatment strategies. Increasing evidence suggests that dysregulation of the immune system, particularly the complement pathway, contributes to the development of schizophrenia. Genetic studies have identified complement component C4, and specifically the C4A isoform, as one of the strongest molecular risk factors associated with schizophrenia. Our recent clinical studies further indicate increased complement activation in individuals at clinical high risk for psychosis and in patients with schizophrenia, suggesting that complement dysregulation may be involved early in disease progression. The complement system is best known for its role in immune defence, but it also plays important roles in brain development and the elimination of synaptic connections. Excessive complement activity has been implicated in abnormal synaptic pruning, a process increasingly linked to schizophrenia. Despite strong evidence linking C4A to disease susceptibility, the biological mechanisms through which it contributes to schizophrenia remain poorly understood. Key Research Question How does complement component C4A contribute to the development of schizophrenia, and can a C4A biomarker support earlier diagnosis, patient stratification and targeted for future personalised interventions? To address this question, the project will combine molecular biology, neuroscience, immunology and computational approaches to investigate the role of C4A in cellular processes relevant to schizophrenia and evaluate its potential as both a biomarker and therapeutic target. Aim We aim to determine how complement component C4A contributes to schizophrenia pathophysiology and to evaluate its potential as a

	biomarker and therapeutic target for improved patient stratification, early intervention and precision psychiatry approaches. Objectives Objective 1: Characterise complement activation associated with schizophrenia. The student will investigate complement pathway activity and quantify biomarkers of C4A and C4 activation, using established assays. This work will build on existing clinical findings and provide an understanding of how complement dysregulation relates to schizophrenia risk and symptom development. Objective 2: Investigate molecular mechanisms of C4A activation. The student will examine how the complement enzyme C1s interacts with and activates C4A compared with its isotype C4B. Using biochemical and biophysical approaches, including functional assays and protein interaction studies, the project will determine how alterations in this pathway may contribute to disease-relevant biological processes. Objective 3: Develop and characterise molecular tools to study C4A function The student will built on our recently developed novel inhibitors and use computational modelling approaches to selectively modulate C4A activation. These tools will enable mechanistic investigation of the pathway and provide insight into whether C4A represents a viable target for future therapeutic intervention. Objective 4: Determine the impact of C4A on neuronal complement activity. Using cellular models relevant to neurobiology, the student will evaluate how altered C4A activation affects complement deposition, opsonisation on neurons. This work will investigate mechanisms that may contribute to altered neural connectivity in schizophrenia. Objective 5: Investigate complement-mediated phagocytic processes relevant to synaptic pruning. The student will assess how changes in C4A activity influence phagocytic uptake of complement-opsonised synaptic targets. These experiments will explore mechanisms linked to excessive synaptic pruning, one of the leading hypotheses explaining how immune dysfunction may contribute to schizophrenia pathophysiology. Objective 6: Evaluate the translational potential of C4A as a biomarker. The final phase of the project will integrate molecular and cellular findings to assess the potential of C4A-related biomarkers for patient stratification and personalised approaches to schizophrenia treatment. This objective aligns directly with the GW4 Neuroscience and Mental Health theme of developing new methods for personalised assessment and early intervention. Student Ownership and Project Development A major strength of this project is the opportunity for the student to shape its direction. While the core objectives provide a strong framework, several areas will be driven by the student's interests and emerging findings. For example, the student will have the opportunity to: • Explore additional schizophrenia-relevant biomarkers identified during the project.

	• Develop new computational or bioinformatic approaches for analysing complement-associated datasets. • Expand investigations into specific cellular pathways implicated by experimental results. • Contribute to the design of novel molecular probes or complementary therapeutic strategies. • Develop translational research questions linking laboratory findings to clinical cohorts and patient stratification approaches. The interdisciplinary nature of the project will allow the student to develop expertise across neuroscience, immunology, biomarker discovery and precision psychiatry, while making intellectual contributions that shape the future direction of the work. As the project progresses, there will be substantial flexibility to pursue promising discoveries arising from the student's experimental findings, providing a highly independent and rewarding doctoral research experience.
Can be completed part time?	Yes
Supervisory Team	
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