Project Details	
Project Code	NMH27Ex Piers
Title	Discovery and functional testing of Alzheimer's disease risk–resilience pathways in human iPSC microglia
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	Late onset Alzheimer's disease (LOAD) risk is shaped by microglial genes, particularly the TREM2 signalling axis. The coding mutation TREM2 R47H increases disease risk, while the coding mutation in the downstream signalling molecule PLCG2 P522R appears protective. This inverse relationship provides a powerful genetic entry point to identify pathways that drive vulnerability or resilience genome wide. This project will use computational methods to discover molecular pathways showing opposite patterns across risk- and protective-variant human iPSC-derived microglia. The student will prioritise pathways, perturb candidate genes, and test whether these alter microglial effects on neuronal functions relevant to LOAD pathogenesis.
Description	Late onset Alzheimer's disease (LOAD) is strongly influenced by genetic variants that alter microglial signalling, with the TREM2 pathway emerging as a central axis of risk and resilience (Feiten et al., 2026). The TREM2 R47H variant increases disease risk (Guerreiro et al., 2013), while PLCG2 P522R, which acts downstream within related microglial signalling networks, appears protective (Sims et al., 2017). This creates a powerful experimental opportunity to study risk and resilience within a shared signalling framework to identify agnostic pathways that push human microglia towards vulnerable or protective states. However, the molecular programmes that distinguish TREM2-axis risk from resilience in human microglia remain poorly understood, and it is not known whether these pathways can be manipulated to improve microglial support of neurons. This project will test the hypothesis that LOAD risk and protective variants produce opposing regulatory effects in human iPSC-derived microglia, and that selected resilience-associated pathways can be experimentally manipulated to improve neuron–microglia function. The project is deliberately staged to remain feasible, with data-led discovery to nominate pathways followed by a prioritisation framework to select candidates to be perturbed and subsequently functionally tested. Objective 1 will use data-led discovery to identify inverse risk–resilience pathways. The student will analyse our existing datasets from human iPSC-derived microglia carrying Alzheimer's-associated risk and protective variants. Rather than asking only which genes change in one genotype, the analysis will search for pathways showing opposite behaviour across a risk–resilience axis, i.e. pathways increased in risk-variant microglia but reduced in protective-variant microglia, or pathways reduced in risk but enhanced in resilience. The student will integrate differential molecular signatures with pathway enrichment, cell-type specificity and publicly available datasets. The output will be a ranked map of disease validated candidate risk–resilience pathways. Objective 2 will prioritise pathways for functional testing. To avoid an open-ended exploratory project, the student will develop a candidate prioritisation framework. Pathways will be ranked using criteria including

	strength of inverse risk–resilience signal, reproducibility across datasets, microglial relevance, genetic support, biological plausibility, feasibility for perturbation and potential impact on neuron–microglia function. From this framework, 1-2 high-priority pathways and 2-4 candidate genes will be selected for experimental validation. The student will have ownership over the scoring framework and final candidate selection, supported by supervisory input. Objective 3 will perturb prioritised genes in human iPSC-derived microglia. The student will use CRISPR editing approaches. Specifically, the student may use a CRISPRi approach to suppress a regulator associated with the risk state, activate a regulator using CRISPRa associated with the protective state, or test whether knockdown of a candidate gene shifts microglia towards a resilience-like molecular or cellular phenotype. Perturbations will first be assessed in 2D iPSC-microglia cultures using molecular, morphological and functional readouts. Objective 4 will functionally test the strongest candidates in neuron–microglia models. Validated perturbations will be taken into human iPSC-derived neuron–microglia co-cultures to assess microglial state, inflammatory response, neuronal stress, neurite integrity and cell viability. In collaboration with Dr Daniel Whitcomb at the University of Bristol, selected conditions will undergo electrophysiological assessment using patch-clamp analysis, to determine whether manipulating risk–resilience pathways alters neuronal excitability and synaptic function. The project provides clear student ownership while remaining realistic. The student will shape the analytical pipeline, define the risk–resilience scoring strategy, select candidate pathways, optimise perturbation conditions and decide which candidates progress to functional testing. The scope is intentionally controlled ensuring that the PhD remains achievable while still offering interdisciplinary training in bioinformatics, iPSC modelling, functional genomics and electrophysiology. By the end of the studentship, the project will identify microglial pathways that distinguish Alzheimer's risk from resilience and test whether these pathways can be manipulated to improve neuron–microglia function. This could reveal early mechanisms of disease vulnerability and nominate candidate therapeutic pathways for preserving protective microglial biology. References Feiten, A. F., Dahm, K., Schlepckow, K., van Lengerich, B., et al. (2026). TREM2 expression level is critical for microglial state, metabolic capacity and efficacy of TREM2 agonism. Nature Communications 2026 17:1, 17(1), 2002-. https://doi.org/10.1038/s41467-026-68706-8 Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., et al.. (2013). TREM2 Variants in Alzheimer's Disease . New England Journal of Medicine, 368(2), 117–127. https://doi.org/10.1056/NEJMOA1211851 Sims, R., van der Lee, S. J., Naj, A. C., Bellenguez, C., et al. (2017). Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nature Genetics, 49(9), 1373–1384. https://doi.org/10.1038/ng.3916
Can be completed part time?	Yes

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