Project Details	
Project Code	MRCNMH26Ex Piers
Title	Risk vs. Protection: How Microglia Shape Neuronal Survival in Alzheimer's disease
Research Theme	NMH
Project Type	Wet lab
Summary	Genetic variants in TREM2 and PLCG2 alter microglial responses in Alzheimer's disease, but the consequences on neurons remain unclear. This project will use cutting-edge human stem cell models to compare microglia carrying pathogenic versus protective variants, to understand how altered gene regulation affects microglial states and influences neuronal health. The student will combine transcriptomics and functional co-culture assays to uncover how microglia shape neural circuits in disease. This interdisciplinary project offers training in stem cell biology, neuroimmunology, functional neuroscience, and computational biology within a vibrant cross-institutional environment.
Description	**BACKGROUND** TREM2 and PLCG2 are critical regulators of microglial activation and function, with genetic variants in both genes linked to Alzheimer's disease (AD) risk. Rare coding variants in these genes such as TREM2 R47H and PLCG2 P522R represent two ends of the pathogenic-protective spectrum. However, we lack a mechanistic understanding of how these variants alter microglial transcriptional states and how such states influence neurons, particularly in early disease. Emerging data suggest that microglia-neuron crosstalk is critical in synaptic maintenance and neuroprotection. This project will use genetically edited human iPSC-derived microglia to model TREM2 and PLCG2 variant effects and assess downstream consequences on neuronal health and function. **HYPOTHESIS & AIMS** We hypothesise that AD-associated TREM2 and PLCG2 variants induce distinct regulatory programs in microglia, altering their interaction with neurons and contributing to disease progression. Protective variants may enhance neuro-supportive phenotypes, while pathogenic ones may impair microglial regulation of synapses and neuronal viability. Specific aims Aim 1: Generate and characterise isogenic iPSC-derived microglia carrying TREM2 and PLCG2 variants. Aim 2: Map transcriptional and epigenetic changes induced by these variants. Aim 3: Assess how variant-bearing microglia affect neuronal health, synaptic function, and network activity in co-culture systems. Aim 4: Explore pharmacological modulation of variant-induced phenotypes using pathway-specific inhibitors. **PROJECT DESIGN** Aim 1 will involve the differentiation of isogenic iPSC lines carrying TREM2 or PLCG2 protective and pathogenic variants into microglia using a defined protocol. The resulting cells will be validated with flow cytometry, immunostaining, and qPCR transcriptomic profiling to confirm microglial identity.

	Aim 2 will generate RNA-seq to identify transcriptional differences between variant-expressing microglia and integrate previously generated epigenomic datasets from the same lines to examine how these variants modulate the gene regulatory landscape in the context of Alzheimer's disease risk. Aim 3 will focus on co-cultures of variant microglia and iPSC-derived cortical neurons to assess functional consequences on neuronal health. Neuronal morphology, synapse density, and electrophysiological activity will be monitored to compare the capacity of protective versus pathogenic microglia to support neuronal viability and network connectivity. Aim 4 will evaluate whether small-molecule modulators targeting variant-sensitive pathways can alter microglial behaviour in co-cultures. Functional plasticity will be assessed by determining whether pharmacological treatments can shift microglial phenotypes in both directions, from pathogenic toward protective states and vice versa. **STUDENT OWNERSHIP** The project is designed to support early and active student involvement. Data generated in Aims 1 and 2, profiling variant-specific transcriptional and epigenetic changes, will guide the student in shaping Aim 3. They will select the most relevant functional assays to assess microglia-neuron interactions. The student will also have the opportunity to choose small molecule modulators to explore in Aim 4, based on pathway insights. Structured mentorship and technical training will be provided by the supervisory team, but the student will be encouraged to make independent decisions and take intellectual ownership of the project's direction. Cross-institutional visits will enable them to acquire complementary expertise in calcium imaging and electrophysiology. **OUTCOMES** This project will provide new insights into how TREM2 and PLCG2 variants influence microglial states and their downstream impact on neuronal function in Alzheimer's disease. By identifying gene regulatory networks affected by these variants, the work will shed light on conserved pathways of microglial dysfunction. Modelling protective and pathogenic variants in a controlled isogenic system enables mechanistic discovery that extends beyond individual genotypes, offering broader insights into microglial regulation and its role in disease progression. In doing so, the project will inform potential therapeutic strategies to modulate microglial behaviour, with translational relevance for the wider Alzheimer's population. The findings are expected to support high-impact publications and advance drug discovery in neurodegeneration.

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