Project Details	
Project Code	MRCNMH26Ex Witton
Title	Unlocking a new neuroimmune strategy to treat Alzheimer's disease
Research Theme	NMH
Project Type	Wet lab
Summary	Microglia are the brain's resident immune cells. The latest research suggests that, alongside conventional molecular signals, microglia function is also influenced by certain patterns of brain activity. Our team has found that a type of brain activity linked to cognition – called gamma oscillations – can regulate microglia through a particular receptor subtype, potentially triggering a neuroprotective response (DOI: bioRxiv 10.1101/2025.03.03.641001). Using a novel experimental assay developed by our lab, this project will uncover how this brain-immune signalling works to identify new therapeutic targets for Alzheimer's disease and other neurological disorders involving malfunction of the brain's immune system.
Description	**BACKGROUND** Microglia are brain-resident immune cells that provide the main form of defence against neuropathology. It is well known that dynamic crosstalk between microglia and neuronal cells maintains brain homeostasis and coordinates neuroimmune responses. Recent studies, however, have identified a new form of neuron-microglia communication driven by rhythmic neuronal activity. Communication between neurons generates rhythmic patterns of electrical brain activity, known as neuronal oscillations. Studies have revealed that neuronal oscillations around 40 Hz – called gamma oscillations – generate a signal that regulates microglia function (PMID: 31076275). Specifically, gamma oscillations promote a homeostatic and neuroprotective microglial response linked to enhanced surveillance and phagocytosis that can clear pathological proteins (such as amyloid-β) in mouse models of Alzheimer's disease (AD) (PMID: 27929004). This is important because impaired gamma activity and microglial dysfunction are hallmark features of neurodegenerative diseases like AD, thereby raising the tantalising possibility that these diseases could be treated by triggering Gamma-Activity Induced Neuron-microglia Signalling (hereinafter, GAINS). However, very little is known about how GAINS works due to a lack of tractable models of this phenomenon. To address this, we have developed a novel model of GAINS in ex vivo mouse brain slices and have used it to discover that GAINS operates through colony stimulating factor 1 receptors (CSF1Rs), which are expressed by microglia, and via nuclear factor kappa B (NFκB) pathway signalling (DOI: bioRxiv 10.1101/2025.03.01.641001). Excitingly, molecular targets of CSF1Rs and NFκB intersect with signalling pathways linked to AD risk genes (PMID: 24951455, PMID: 29312321), resilience to disease (PMID: 40311610), and targets of AD medicines in clinical trial (e.g. NCT05744401), highlighting the translational potential of this research. **QUESTION & AIMS** The scientific question at the heart of this project is: What are the specific cellular and molecular mechanisms by which gamma-frequency neuronal activity modulates microglial function? Building on our recent findings (DOI: bioRxiv 10.1101/2025.03.01.641001), we hypothesise that

	GAINS is mediated by factors downstream of microglial CSF1Rs that converge on NFκB pathway activation. Objectives to test this hypothesis are: (1) Define molecular mediators of GAINS downstream of CSF1R signalling ex vivo. (2) Validate the role of candidate mediators of GAINS in vivo. (3) Explore the role of astrocytes as a source of gamma activity-evoked CSF1 and their contribution to GAINS. PROJECT DESIGN Objective 1 will be tackled using an established ex vivo GAINS model developed by our lab. Gamma oscillations will be induced in mouse brain slices using pharmacology and optogenetic techniques and monitored using electrophysiology, while the responses of fluorescence-tagged microglia (labelled using Alexa 488 isolectin B4) are measured using 2-photon microscopy (e.g. changes in morphology, density, motility). To dissect the intracellular pathways linking CSF1R activation to NFκB, we will apply well-validated, selective pharmacological inhibitors targeting candidate molecular cascades, including MAP kinase-ERK, protein kinase C, and PI3 kinase-Akt (PMID: 35290551). For Objective 2, we will confirm the relevance of CSF1Rs and their downstream molecular targets in GAINS in vivo. We will induce gamma oscillations in mice using optogenetics (mirroring our slice model) and via patterned 40 Hz visual stimulation known to evoke GAINS in visual cortex (PMID: 3106275). Mice will be treated with CSF1R antagonists (e.g. BLZ945) or inhibitors of their targets that block GAINS ex vivo (i.e. in Objective 1). We will also employ acute in vivo 2-photon brain imaging in mice to visualise microglia dynamics (e.g. motility, migration) during GAINS and where it is pharmacologically blocked. Astrocytes are a key source of CSF1 in the brain (PMID: 34472465), making them prime candidates as an upstream regulator of GAINS. Objective 3 will leverage our ex vivo assay to test the role of astrocytes in GAINS. Specifically, we will disrupt astrocyte function during GAINS in brain slices using pharmacological inhibitors of astrocyte metabolism (e.g. aminoadipic acid) or viral-genetic tools currently employed by co-supervisor Mosienko. **STUDENT OWNERSHIP** Our project objectives are complementary rather than sequential, meaning different research strands can run in parallel and be tailored to the student's interests. As the project incorporates both ex vivo (Objectives 1 & 3) and in vivo (Objective 2) models, the student can choose to emphasise one or both approaches depending on their preferences. Similarly, the student can balance the focus between cellular/molecular signalling (Objectives 1 & 2) and astrocyte-focused (Objective 3) experiments in line with their interests. Additionally, while not an explicit focus, co-supervisors Mosienko and Noble bring extensive molecular biology expertise, which offers opportunities to explore GAINS-related changes in gene and/or protein expression in microglia and astrocytes. This direction can also be supported by our team's active collaborations with Exeter's Complex Disease Epigenomics Group

	(https://www.epigenomicslab.com/), should the student wish to develop skills in this area. **OUTCOMES** The project will uncover cellular and molecular mechanisms underlying a novel neuroimmune pathway that could be leveraged to treat neurodegenerative disorders characterised by aberrant gamma activity and disrupted neuroimmune function, such as AD.
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