Project Details	
Project Code	MRCNMH25Ex Witton
Title	Characterising a new neuroimmune pathway to treat Alzheimer's disease
Research Theme	Neuroscience & Mental Health
Summary	Microglia are brain-resident immune cells. Alongside conventional molecular signals, the latest research suggests that specific patterns of brain activity can control microglia function. We have found that a type of brain activity normally activated during cognition (called gamma oscillations) signals to microglia via a receptor subgroup, which may drive a neuroprotective response. Using a novel experimental assay developed by our lab, this project will uncover how this signalling works to reveal new drug targets for treating conditions where immune systems in the brain malfunction, such as in Alzheimer's disease.
Description	**BACKGROUND** Microglia are brain-resident immune cells that provide the main form of defence against neuropathology. It is well known that there is dynamic crosstalk between microglia and neuronal cells that 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, called 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 induce a homeostatic and neuroprotective immune response linked to enhanced microglia surveillance and phagocytosis that can clear pathological proteins (like amyloid-β) in mouse models of Alzheimer's disease (AD) (PMID: 27929004). This is important because impaired gamma oscillations and abnormal microglia function are cardinal 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 this end, we have developed a new model of GAINS in ex vivo mouse brain slices and have used it to discover that GAINS occurs via colony stimulating factor 1 receptors (CSF1R), which are expressed by microglia, and via nuclear factor kappa B (NFκB) pathway signalling (manuscript in prep.). Excitingly, molecular targets of CSF1Rs and NFκB overlap with signalling pathways linked to AD risk genes (PMID: 24951455, PMID: 29312321) and targets of AD medicines in clinical trial (e.g. NCT05744401). **QUESTION & AIMS** The scientific question at the heart of this project is "What are the specific cellular and molecular mechanisms underlying GAINS?" Building on our current data, 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) Identify molecular mediators of GAINS downstream of CSF1R signalling ex vivo. (2) Validate molecular mediators of GAINS in vivo.

	(3) Explore the role of astrocytes as a cellular source of GAINS-evoked CSF1. **PROJECT DESIGN** Objective 1 will be tackled using ex vivo models of GAINS developed in our lab. Gamma oscillations will be induced in mouse brain slices using pharmacology and optogenetic techniques and recorded using electrophysiology, whilst changes in the properties of fluorescence-tagged microglia (labelled using Alexa 488 isolectin B4) are measured using 2-photon microscopy (e.g. morphology, density, motility). Several molecular pathways link CSF1Rs to NFκB, including MAP kinase-ERK, protein kinase C, and PI3 kinase-Akt; (PMID: 35290551). We will test the role these pathways play in GAINS using commercially available inhibitors of molecules involved in each signalling pathway. For Objective 2, we will test whether GAINS is regulated by CSF1Rs and their downstream molecular targets in vivo. We will induce gamma oscillations in mice using optogenetics (mirroring our slice model) and via 40 Hz light stimulation that can drive GAINS in visual cortex (PMID: 3106275). Mice will be treated with antagonists for CSF1Rs (e.g. BLZ945) or inhibitors of their targets that block GAINS ex vivo (i.e. in Objective 1). We will also use acute in vivo 2-photon brain imaging in mice to measure microglia dynamics (e.g. motility, migration) during GAINS and when it is pharmacologically blocked. Astrocytes are cells that provide a key source of CSF1 in the brain (PMID: 34472465). 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 by inhibiting astrocyte metabolism using drugs (e.g. aminoadipic acid) or viral-genetic tools developed by co-supervisor Mosienko. **STUDENT OWNERSHIP** Our project objectives are not mutually exclusive, and thus different research lines 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 balance the focus of the project between these different types of experiment depending on their interests and prior experience. Similarly, the student can balance the focus between cellular/molecular signalling (Objectives 1 & 2) and astrocyte focussed (Objective 3) experiments in line with their interests. Additionally, whilst not an explicit focus of the project, co-supervisors Mosienko and Noble have significant molecular biology expertise to facilitate analysis of GAINS-driven changes in microglia and astrocyte gene and/or protein expression; this direction could also be facilitated by our team's active collaborations with Exeter's Complex Disease Epigenomics Group (https://www.epigenomicslab.com/) if this is of interest to the student. **OUTCOMES** The project will discover cellular and molecular mechanisms underlying a novel neuroimmune pathway that could be leveraged to treat neurodegenerative disorders characterised by aberrant gamma oscillations and disrupted neuroimmune function, like AD.

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