Project Details	
Project Code	MRCNMH24Ex Witton
Title	Characterising a novel neuroimmune pathway to treat neurodegenerative disease
Research Theme	Neuroscience & Mental Health
Summary	Microglia are brain-resident immune cells. Alongside conventional molecular signals, evidence suggests that specific patterns of brain activity can control microglia function. We have found that a type of brain activity activated during cognition (called gamma oscillations) signals to microglia via a receptor subgroup, which may drive a neuroprotective response. This project will uncover how this signalling works to reveal drug targets for neurodegenerative disease.
Description	Rationale Microglia are brain-resident immune cells that provide the main form of defence against neuropathology. There is dynamic crosstalk between microglia and neuronal cells that maintains brain homeostasis and coordinates neuroimmune responses. Recent studies have identified a novel 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 a feature of neurodegenerative diseases like AD, thereby raising the tantalising possibility that these diseases could be treated by triggering Gamma-Activity Induced Neuron-microglia Signalling (herein, GAINS). To this end, we have recently discovered that GAINS occurs via colony stimulating factor 1 receptors (CSF1Rs), which are expressed by microglia (manuscript in prep.). Excitingly, molecular targets of CSF1Rs overlap with signalling pathways linked to AD risk genes (PMID: 24951455) and targets of AD medicines in clinical trial (e.g. NCT05744401). Aims The aim of this project is to uncover the cellular and molecular mechanisms underlying GAINS. Linking our findings to data suggesting that the NF-κB pathway is also involved (e.g. PMID: 31871276), we hypothesise that GAINS is mediated via NF-κB activation directly downstream of CSF1R signalling. Objectives to test this hypothesis are: 1. Identify molecular mediators of GAINS downstream of CSF1Rs 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 optogenetics and recorded using electrophysiology, whilst changes in the properties of fluorescence-tagged microglia (by Alexa 488 isolectin B4) are measured using 2-photon microscopy (e.g. morphology, density, motility). Several molecular pathways link CSF1Rs to NF-κB, including PI3 kinase-Akt; phospholipase C-protein kinase C; and MAP kinase-ERK (PMID: 35290551). We will test the role these pathways

	play in GAINS using commercial inhibitors of molecules involved in each 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 a key cellular 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. Outcomes The project will discover cellular and molecular mechanisms underlying a novel homeostatic neuroimmune pathway that could be leveraged to treat neurodegenerative disorders like AD.
Supervisory Team	
Lead Supervisor	
Name	Dr Jonathan Witton
Affiliation	Exeter
College/Faculty	Faculty of Health and Life Sciences
Department/School	Department of Clinical and Biomedical Sciences
Email Address	j.witton@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Valentina Mosienko
Affiliation	Bristol
College/Faculty	Faculty of Life Sciences
Department/School	School of Physiology, Pharmacology & Neuroscience
Co-Supervisor 2	
Name	Professor Jonathan Brown
Affiliation	Exeter
College/Faculty	Faculty of Health and Life Sciences
Department/School	Department of Clinical and Biomedical Sciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	