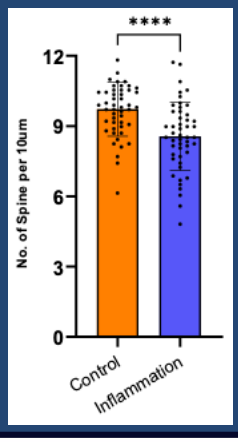
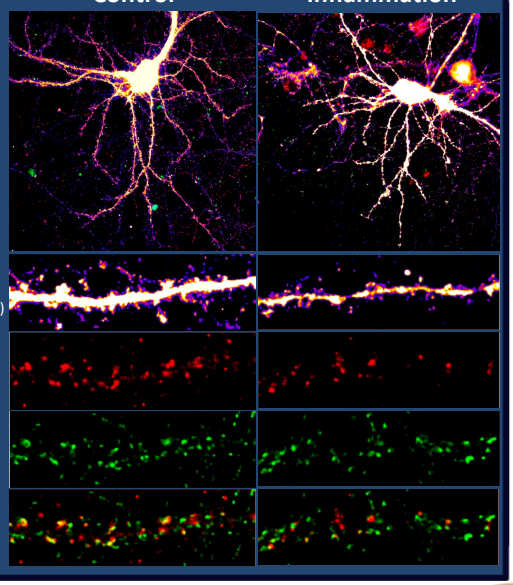
Centre for Neuroscience and Regenerative Medicine

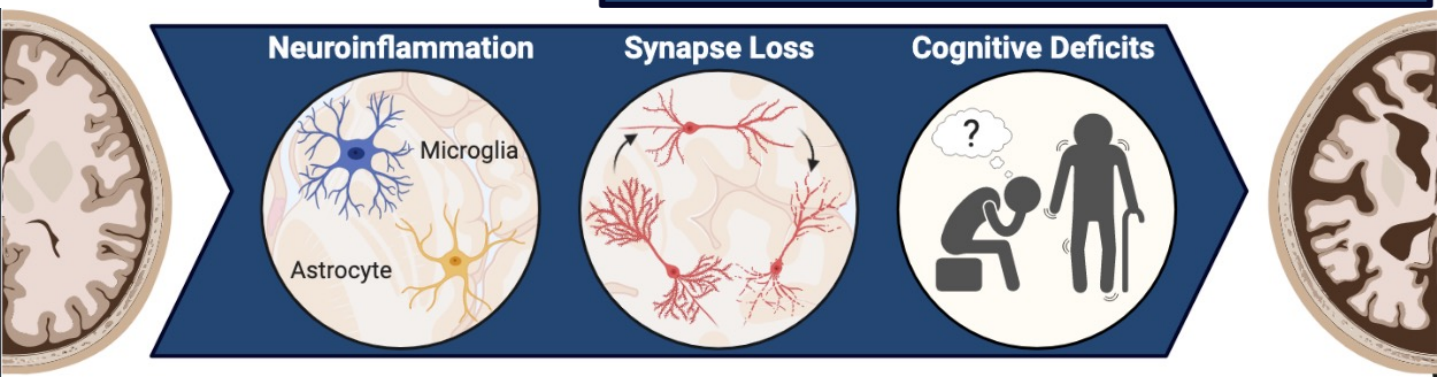
Project: Investigating mechanisms underlying neuroinflammation induced synapse loss in mouse models of Alzheimer's disease

Neuroinflammation and synapse loss are well defined early hallmarks of Alzheimer's disease (AD), and it is thought that one drives the other[1,2]. However, the exact mechanism remains elusive. This project will therefore investigate how, when and under what conditions microglia and astrocytes engobble synapses and if blocking these mechanisms[3] in Alzheimer's mice can prevent cognitive deficits. There are various parts to this project. We will use in-vitro models to elucidate the cytokines responsible for synapse loss, before conducting these experiments in-vivo. We then will utilize genetically modified mouse models of AD and viruses to see if blocking our proposed mechanism will improve memory deficits. This will lead to a better understating of AD.

Pro-inflammatory cytokines lead to synapse and spine loss in primary neuron cultures







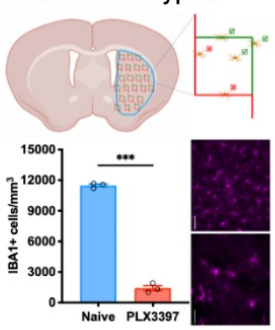
Models for this Project

- Genetically modified mice to model Alzheimers disease (J20, Apoe4KI)
- Stereotaxic brain surgery to inject inflammatory stimuli or treatments into the CNS
- Stereotaxic surgery to inject viruses into the CNS to label or knockout cells types
- Primary neuron and glial cell culture to study the effect of cytokines on synapses

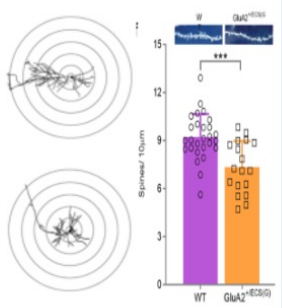
Techniques used for this Project

Behaviour tests to assess cognitive deficits (Barnes and Water maze, Fear conditioning, OFT)

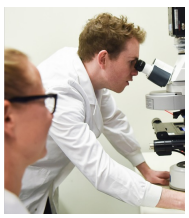
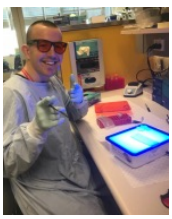
Microscopy and Stereology to quantify different cell types

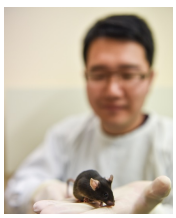
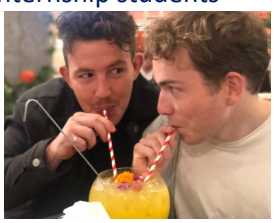


Microscopy and Neurolucida to quantify dendritic spines



Our Team – 4 Postdocs – 2 Research Assistants – 5 PhD students – 1 Honours student – 2 Internship students

1 - Wright, A. L., Zinn, R., Hohensinn, B., Konen, L. M., Beynon, S. B., Tan, R. P., ... & Vissel, B. (2013). Neuroinflammation and neuronal loss precede Aβ plaque deposition in the hAPP-J20 mouse model of Alzheimer's disease. PloS one, 8(4), e59586.
2 - Morris, G. P., Clark, I. A., Zinn, R., & Vissel, B. (2013). Microglia: a new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research. Neurobiology of learning and memory, 105, 40-53.
3 - Konen, L. M., Wright, A. L., Royle, G. A., Morris, G. P., Lau, B. K., Seow, P. W., ... & Vissel, B. (2020). A new mouse line with reduced GluA2 Q/R site RNA editing exhibits loss of dendritic spines, hippocampal CA1-neuron loss, learning and memory impairments and NMDA receptor-independent seizure vulnerability. Molecular brain, 13(1), 1-19.