Project Details	
Project Code	NMH27Ca Smith
Title	Silent Architects: Uncovering How Astrocytes Shape Brain Health
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	Astrocytes are central regulators of brain function, controlling neuronal activity, metabolism, extracellular matrix organisation and resilience to disease. However, many astrocyte-enriched genes remain poorly understood. This PhD project will investigate novel astrocyte genes and signalling pathways identified through transcriptomic analyses. Using Drosophila genetics, advanced imaging and molecular neuroscience, the student will determine how these genes regulate astrocyte function and influence neuronal physiology and neurodegeneration. Based at Cardiff University, the student will join the highly collaborative Cardiff University, GW4 and UK Dementia Research Institute (UK DRI) research communities, receiving outstanding multidisciplinary training.
Description	Astrocytes are essential regulators of brain function, controlling neurotransmitter recycling, ion homeostasis, metabolism, synaptic activity and neuronal function. These diverse functions depend on their molecular programs and their highly elaborate morphology, which enables astrocytes to contact thousands of synapses, blood vessels, neighbouring glia and neurons. Remodelling of astrocyte molecular programs and functions is increasingly recognised as a determinant of neuronal circuit function, yet the genes that mediate essential astrocyte functions remain to be fully understood. Understanding how astrocyte gene networks control key astrocyte functions is therefore an open challenge in neuroscience, with important implications for brain health and neurodegenerative disease. Recent transcriptomic studies from the Khakh laboratory have identified astrocyte-enriched genes, many of which possess conserved orthologues in animal models but have not been functionally characterised. Preliminary pathway analyses across brain regions of the mouse suggest ~825 genes participate in core signalling networks regulating receptor tyrosine kinase signalling, extracellular matrix organisation, mitochondrial function, lipid metabolism and cell-cell communication. This project will exploit these datasets to move from gene discovery to mechanistic understanding by identifying the genes from these 825 that regulate astrocyte functions that influence brain function using fruit flies (Drosophila). Drosophila provides an ideal model because astrocyte-like glia perform conserved functions in neurotransmitter uptake, metabolic support, calcium signalling and neuron-glia communication, while the extensive genetic toolkit enables rapid cell-type-specific manipulation and in vivo functional screening that would be difficult to achieve in mammalian systems. The central hypothesis is that astrocyte genes regulate evolutionarily conserved astrocyte functions, which in turn determine astrocyte physiology, neuronal circuit function and susceptibility to neurodegeneration. Aim 1. Functional screening of conserved astrocyte genes The student will prioritise conserved astrocyte genes identified from transcriptomic datasets based on Drosophila orthologues and available genetic reagents. Using astrocyte-specific GAL4 drivers, candidate genes

	will be knocked down by RNAi (or disrupted using CRISPR where appropriate) and screened using robust behavioural assays including locomotor performance, longevity, sleep and other measures of nervous system function. This scalable primary screen will identify genes whose disruption produces reproducible behavioural phenotypes in flies and prioritise candidates for mechanistic investigation. Student ownership: The student will help prioritise the candidate 825 genes, optimise the screening strategy, establish hit-selection criteria and select genes for downstream investigation. Aim 2. Determine how candidate genes regulate astrocytes Genes identified in Aim 1 will undergo detailed cellular analysis to determine how they regulate astrocyte function and morphology. Using high-resolution confocal microscopy and quantitative morphometric analysis, the student will measure astrocyte process complexity, branching, territory size and interactions with neighbouring neurons. These studies will build upon established positive-control models established in the Khakh lab. For example, knockdown of ezrin or the AD risk gene FERMT2 causes profound disruption of astrocyte morphology, providing a benchmark for identifying novel regulators of astrocyte morphology. In terms of benchmarks for astrocyte functions, the Khakh and other labs have shown that loss of Kir4.1 potassium channels and Glt1 glutamate and GAT3 GABA transporters strongly affect ion and neurotransmitter homeostasis and neuronal function. Immunohistochemistry will be used to assess expression of proteins for the targeted genes. Phenotypes emerging from gene knockouts will then be supported by astrocyte functional studies by examining calcium signalling, mitochondrial organisation, oxidative stress, lipid metabolism and neuron-glia communication using genetically encoded reporters, live imaging and molecular approaches. Together, these studies will determine how alterations in core astrocyte genes influence astrocyte physiology and ultimately behavioural outputs. Student ownership: The student will optimise imaging pipelines, develop quantitative analyses and determine which functional assays best explain behavioural phenotypes. Aim 3. Define signaling networks controlling astrocytes and brain function The final aim will integrate individual genes into conserved signalling networks using genetic epistasis, pathway reporters and rescue experiments. Rather than studying genes in isolation, the student will determine how prioritized genes interact to regulate astrocyte function. Preliminary analyses indicate that candidate genes are enriched in pathways including EGFR, Notch, Hippo, extracellular matrix and mitochondrial metabolic signalling, providing clear mechanistic hypotheses for testing. Finally, conserved pathways regulating astrocytes will be examined in Drosophila models of Alzheimer's disease and related neurodegenerative disorders to determine whether preserving astrocyte morphology is beneficial for neuronal resilience – as has been shown by the Khakh lab for mouse models of Alzheimer’s disease. Where

	appropriate, human transgenes will be used to test functional conservation and strengthen translational relevance. Student ownership: The student will design epistasis experiments, prioritise signalling pathways and disease models, and develop an integrated mechanistic framework linking astrocyte gene networks, morphology, brain function and neurodegeneration.
Can be completed part time?	No
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