Project Details	
Project Code	MRCNMH26Ex Oguro-Ando
Title	Neuronal Clues to Astrocytes: Uncovering Hidden Mechanisms in the Developing Brain
Research Theme	NMH
Project Type	Wet lab
Summary	How do neuronal signals drive astrocyte-mediated changes in brain development? This project will investigate the underlying cellular and molecular mechanisms by which neuronal JAKMIP1 influences astrocytes, a key type of brain glial cell, and how this neuron-astrocyte communication is disrupted in autism and related developmental conditions. With training in RNA sequencing, microscopy, and brain cell analysis, you will uncover how interactions between brain cells shape development and behaviour. This is a unique opportunity to work at the interface of molecular neuroscience, cell biology, and neurodevelopment.
Description	"How do neuron-derived signals fine-tune astrocyte function that shapes brain development?" Neurodevelopmental conditions such as autism spectrum disorder (ASD) are increasingly recognised as involving not just neurons, but also glial cells that support and shape brain development. Among these, astrocytes play key roles in maintaining synaptic function and circuit stability. Intriguingly, astrocytes often show abnormal morphology and signalling in ASD models – even when they are not directly affected by the underlying genetic mutation. This suggests that disrupted neuron-to-glia communication may contribute to the broader pathology of developmental disorders. This project focuses on JAKMIP1 (Janus kinase and microtubule-interacting protein 1), a scaffold protein highly enriched in neurons. JAKMIP1 regulates local mRNA translation and microtubule-based transport. Mice lacking JAKMIP1 display autism-relevant behaviours such as impaired social interaction, vocalisation deficits, and increased repetitive behaviours. Although JAKMIP1 is mainly expressed in neurons, recent findings show that astrocytes in JAKMIP1 knockout (KO) mice—despite expressing little or no JAKMIP1 themselves—exhibit reduced branching and altered STAT3 signalling. This provides strong evidence for non-cell-autonomous mechanisms, in which mutations in one cell type (neurons) indirectly affect the function of another (astrocytes). Key research question: How does neuronal JAKMIP1 regulate astrocyte morphology and signalling during brain development, and what secreted factors mediate this non-cell-autonomous influence? Objectives The student will pursue the following objectives, each designed to build skills in molecular neuroscience, cell biology, and neurodevelopmental disease research. 1. Modelling neuron-to-glia signalling in vitro • The student will prepare neuron-conditioned media from WT and JAKMIP1 KO mice and use them to stimulate primary mouse astrocyte cultures.

	• Morphological changes in astrocytes will be quantified using immunocytochemistry and Sholl analysis. • Phosphorylated STAT3 (pSTAT3) will be assessed to monitor pathway activation in response to neuronal signals. 2. Identifying the molecular signals • Using existing RNA-seq and proteomic datasets from JAKMIP1-deficient SH-SY5Y cells, the student will shortlist candidate secreted molecules (e.g. BDNF, IL-6, LCN2). • Recombinant versions of these factors will be tested individually and in combination on astrocyte cultures to determine their impact on morphology and STAT3 activation. • Inhibitor-based experiments will further clarify whether specific pathways are necessary or sufficient to mediate the effects. 3. Validating cell-type-specific expression and extending in vivo relevance • To investigate the cellular origin of candidate signals, the student will perform qPCR analysis on already-isolated neuronal and astrocyte RNA samples from WT and JAKMIP1 KO mouse brains (separated via MACS). • This will help determine whether dysregulated expression of key secreted factors (e.g. Bdnf, Il6, Lcn2) originates in neurons or astrocytes. • In the final phase, astrocytic phenotypes observed in the JAKMIP1 model will be compared to those from other neurodevelopmental disorder models (e.g. Sp4Y163X, Setd1a deletion), using available histological and gene expression datasets provided by MURIDAE Research Cluster. Student training and project ownership: This project offers comprehensive training across multiple disciplines: • Molecular biology: RNA isolation, qPCR, protein expression analysis • Cell biology: primary astrocyte culture, microscopy, morphology quantification • Bioinformatics: RNA-seq/proteomic data interpretation using R or Python • Experimental design: hypothesis testing using recombinant factors and inhibitors • Systems neuroscience: cross-model comparison of astrocyte phenotypes The student will be encouraged to take increasing ownership of the project, especially in the design and refinement of experiments based on initial findings. For example, they may choose to explore astrocyte responses in human iPSC-derived models or further investigate the role of specific signalling pathways in greater depth. They will benefit from close supervision by experts in glial biology and psychiatric genetics, and access unique resources including JAKMIP1 KO brain tissues, in-house omics data, and cross-institutional collaboration between the University of Exeter, Bristol and Cardiff University. Broader significance: This project addresses an emerging frontier in developmental neuroscience: how intercellular signalling—not just cell-autonomous gene function—shapes brain development. By uncovering how neuron-

	derived factors alter astrocyte function in JAKMIP1 deficiency, the student will contribute to a deeper understanding of neuron–glia interactions in health and disease. These insights may help identify novel therapeutic targets aimed at restoring glial function in autism and related conditions.
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