

Local control of protein translation in neuronal dendrites during synaptic plasticity

Supervisory team:

Main supervisor: Dr Jonathan Hanley (University of Bristol)

Second supervisor: Dr Cian O'Donnell (University of Bristol)

Host institution: University of Bristol

Project description:

Long-term synaptic plasticity underlies learning and memory by tuning neural circuitry. A major process that underlies synaptic plasticity is the morphological modification of dendritic spines, which house the postsynaptic machinery. Recent studies show that numerous microRNAs (miRNAs) modulate the local translation of proteins that control spine morphology in response to stimulation. MiRNAs are small endogenous RNAs that mediate silencing of mRNA targets by associating with Argonaute (Ago) proteins in the RNA-induced silencing complex (RISC). Neuronal-specific miRNAs regulate various aspects of neuronal function and have important roles in brain disorders such as Alzheimer's, Parkinson's, ASD and others. A key question is how "local" is this control of translation, i.e., does gene silencing spread along the dendrite to neighbouring unstimulated synapses, and if so, how is this regulated? This is important because dominant theories of Hebbian learning assume that plasticity is synapse-specific, even though emerging evidence suggests otherwise. This research could therefore make a significant contribution to our knowledge of how learning works in the brain. Recent work from Hanley's lab has defined mechanisms for rapidly increasing miRNA-mediated gene silencing in response to NMDA receptor stimulation. Our hypothesis, to be tested in this project, is that these mechanisms regulate RISC activity close to the stimulated spine to modulate local miRNA-dependent translation and hence influence the morphology of a small number of neighbouring spines. The main experimental approach will be single-spine stimulation by glutamate uncaging, followed by confocal imaging techniques to define sites of nascent translation of specific proteins, and morphological changes of the stimulated and neighbouring unstimulated spines. The project will also investigate the mechanisms that mediate local control of translation by using molecular replacement approaches to introduce mutations in Ago2 or other RISC proteins. In tandem with the experiments, a set of molecular-level computer simulation models will be developed to test our hypotheses. These simulations will be used to dissect parts of the system that are not experimentally dissociable, such as diffusion of miRNA and signalling factors, or how spine geometry restricts protein translation in localised spatial compartments. This project will be carried out under the expert supervision of Dr. Jonathan Hanley (neuronal cell biology) and Dr. Cian O'Donnell (computational biology). The cell imaging and image analysis will be carried out in the state-of-the-art Wolfson Bioimaging Facility at the University of Bristol, with the expert assistance of their technical team.