From Flies to Human Cells: understanding astrocyte reactivity and dopaminergic modulation in brain injury

Project ID: 199

Supervisory team

Main supervisor: Dr Oscar Cordero Llana (University of Bristol)
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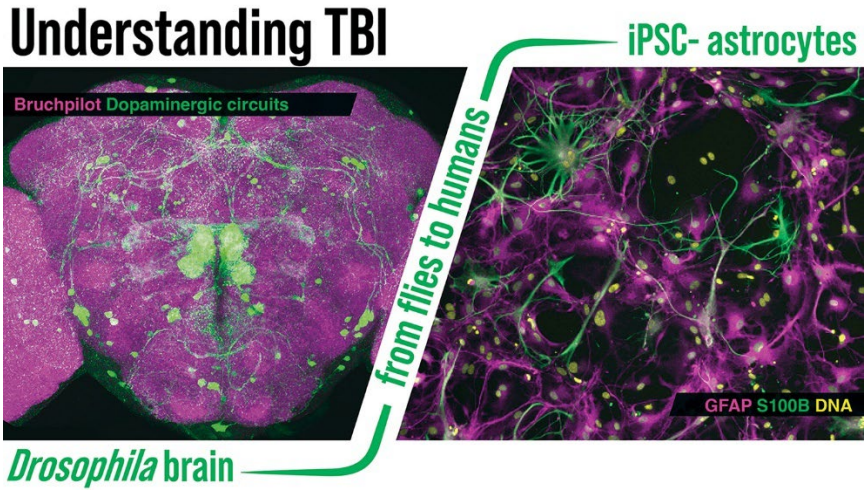
Collaborators: Dr Lucy Crompton (University of the West of England (UWE))

Host institution: University of Bristol

Project description: While neuroinflammation is an expected response of the organism to threats to the nervous system, exacerbated neuroinflammatory states are detrimental. This exacerbated response can result in prolonged inflammation well after the triggering event is resolved, in which case it is defined as chronic neuroinflammation, which has been associated with different neurodegenerative conditions even in the absence of infection, for example in Alzheimer's, Parkinson's or after Traumatic Brain Injury.Brain injury is a leading cause deterioration of health and wellbeing. The mechanisms of disease progression are virtually unknown, although we know that after the initial injury, inflammatory processes propagate intracranially, leading to persistent symptoms even years after the injury.



We propose to use an interdisciplinary approach to study the inflammatory processes triggered by brain injury focusing on dopaminergic modulation of astrocytes, using both Drosophila flies in vivo and human induced pluripotent stem cell (iPSC)-derived astrocytes in vitro. Understanding how astrocytes contribute to physiological changes in the brain in inflammatory conditions is a novel avenue of research; with emerging exciting evidence that astrocytes respond to inflammatory signals, produce cytokines, and display phagocytic activity both in insects and humans.Objective 1: To evaluate the damage induced by brain injury in dopaminergic circuits, performing morphological (analysis of neurodegeneration ex vivo) and physiological analysis (with newly developed dopamine fluorescent sensors and calcium reporters in vivo).Objective 2: To describe injury-induced inflammatory mechanisms. Analyzing the effect of brain injury in astrocyte number and activity, as well as the expression of dopamine receptors in different glial cells, both in TBI animals and in induced iPSC-derived reactive astrocytes.Objective 3: To assess if dopamine manipulation modulates neuropathology after brain injury. The student will use optogenetic techniques to manipulate dopaminergic neurons in flies, to assess the effect of dopamine modulation of astrocytes in vivo. To understand modulation

in human cells, the student will use iPCs to generate astrocytes and mimic inflammatory conditions in vitro. They will then characterise astrocyte reactivation in the presence of dopamine agonists and antagonists, to understand how inflammatory responses are modulated by dopamine.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.