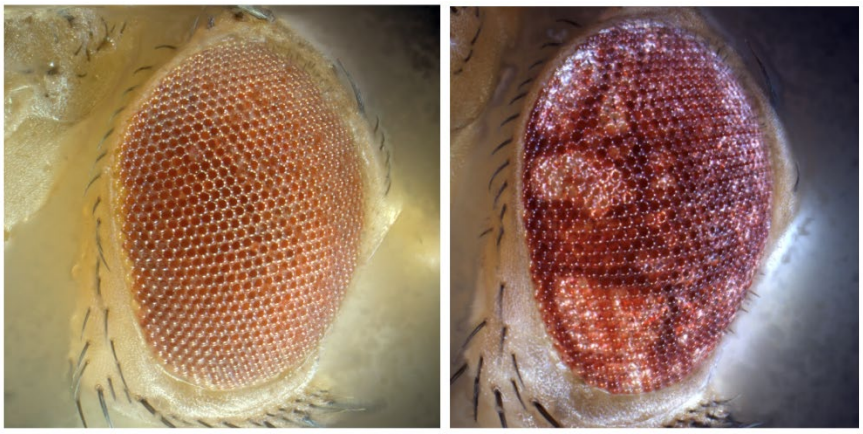
Drosophila models for mechanistic analysis of Huntingtin function in neurodegeneration

Supervisory team:
Main supervisor: Dr Owen M Peters (Cardiff University)
Second supervisor: Dr Michael Taylor (Cardiff University)
Dr Wynand van der Goes Van Naters (Cardiff University), Prof Anne Rosser (Cardiff University)

Host institution: Cardiff University

Project description:
Background: Huntington's Disease (HD) is a devastating neurodegenerative disorder caused by expansion of the "CAG repeat" in the Huntingtin (HTT) gene, which produces a mutant form of the Huntingtin protein (mHTT). This mutation triggers progressive neuronal loss in the brain, resulting in cognitive and behavioural decline, motor dysfunction, and ultimately death. Despite extensive research, no disease-modifying treatments are currently available. HD genetics is relatively well-described, but a major barrier to identifying of new therapeutic targets is the incomplete understanding of the underlying mechanisms leading to neurodegeneration. This is due in large part to the multifunctional activity of HTT.



The Drosophila eye is a well-established system for understanding development and cell death. *In healthy flies (left), the compound eye is composed of approximately 700 well organised ommatidia. Expression of mutant Huntingtin (mHTT) in the fly eye results in degeneration and cell death. This PhD project aims to establish how genetic and molecular interactions between HTT and transcription factors contributes to degeneration.*

System: The classic model organism, the fruit fly Drosophila melanogaster, has a long and proud history of informing human biology, proving a powerful approach for uncovering the molecular underpinnings of complex diseases. Drosophila offers a sophisticated genetic toolkit and its eye photoreceptors are a well-characterised system for analysing mHTT-induced loss of neurons. Strikingly, using these tools, we have recently established that interfering with function of transcription factors implicated in neural development can suppress this mHTT effect.

Aim: Elucidate the genetic and molecular interactions between transcription factors and HTT, and how this interplay may promote or suppress neurodegeneration.

Experimental Approach: You will use diverse techniques from genetics and neurosciences. In vivo genetic analysis in Drosophila with its incisive range of techniques has many advantages for gaining rapid insight. Separating effects of mHTT during neural development and on neurodegeneration is currently of much interest in HD research. The Drosophila system is well-placed to unpick this: gene function can be controlled in a highly specific temporal and spatial manner, enabling you to test how factors modify mHTT-induced neuron loss in the fly eye. You will assess

contributions during both developmental and adult stages. Moreover, any new potential factors identified in clinical HD research will be brought to this fly eye system, which acts as an “in vivo test tube”, to rapidly test their function. Factors found to strongly modify mHTT-induced degeneration will be taken forwards for electrophysiological and further molecular characterisation.

Outcomes: This project has the potential to expand our understanding of the molecular events driving pathology in HD. Identifying genetic modifiers of mHTT neurotoxicity may pave the way for the development of novel strategies to attenuate neurodegeneration in HD. Furthermore, understanding the role of developmental processes in HD may reveal new insights into the early stages of the disease, offering opportunities for earlier intervention.

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.