Investigating novel therapies for Huntington's disease

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Huntington's disease is a neurodegenerative disease caused by the abnormal expansion of the polyglutamine (polyQ) tract of the huntingtin protein and characterized by a progressive loss of motor and cognitive functions. Although huntingtin is ubiquitously expressed in all cells, its essential role in maintaining neuronal functions and providing neuroprotection means that the mutation selectively affects neuronal cells. Not only is the mutated form of the protein (mHtt) unable to perform much of the functions of wildtype huntingtin as it is highly prone to misfolding and aggregation, it is also highly toxic for neurons: it dysregulates glutamate receptors, leading to excessive calcium signaling, and increasing mitochondrial sensitivity to calcium, promoting oxidative stress. Both of these downstream effects lead to activation of cell death pathways. To date, treatment options for Huntington's patients are very limited and restricted to symptomatic treatment.

The nematode *Caenorhabditis elegans*, modified to express fluorescently tagged polyQ tracts of different lengths, provides a useful animal model for studying Huntington's disease because of its high genetic and physiological similarity to humans and its short lifecycle. Usually, agar 2D chemotaxis assays are used to evaluate its motor ability. However, this technique does not reflect the worms' natural 3D habitat. By mimicking *C. elegans*' environment, the outcomes of a new Pluronic gel-based burrowing assay technique reflect *C. elegans*' locomotory function more accurately than the classical chemotaxis assay.

Recently, four novel drugs have been identified which would have the potential to preventative treatment to Huntington's patients. Activator-3

and amentoflavone have recently been shown to upregulate autophagy, the mechanism by which cellular components are degraded. In doing so, both drugs would help to clear cells of the toxic protein products of the *mHTT* gene. They do so through the activation of the AMP-activated protein kinase (AMPK) pathway, a pathway already exploited by the antidiabetic drug metformin. Additionally, diethyl maleate (DEM) and isoprenol have been shown to increase cells' tolerance to oxidative stress. DEM does this, counterintuitively, by depleting glutathione levels, the major cellular antioxidant species, which leads to activation of genes involved in longevity (FoxO and Nrf2). Isoprenol directly prevents intracellular reactive oxygen species through activation of these same two genes.

Tying into the University's Health and Wellbeing research theme, this project aims to evaluate whether exposure to Activator-3, amentoflavone, DEM and isoprenol improves motor function in *C. elegans* using a Pluronic gel-based burrowing assay. Together, these drugs may slow the clinical onset and progression of Huntington's by targeting its cause and major downstream effects. I selected this topic for my research project in the first summer as it could represent exciting progress into providing long-term treatment for one of the most widespread yet poorly understood genetic disorders. Neuropathology is an area of science I hope to specialize in, and this project puts into practice techniques I have learnt during my course.