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**PhD project title**: Exploring the role of the kynurenine pathway in ageing

University of Registration: Leicester

**Project outline**

1. Project outline describing the scientific rationale of the project

Altered metabolic flux in the kynurenine pathway (KP) of tryptophan degradation has been closely linked to pathogenesis of several neurodegenerative disorders. Indeed, increased levels of neurotoxic metabolites relative to neuroprotective metabolites in the KP is associated with progression of Huntington’s and Alzheimer’s diseases, and normalising this balance by targeting key enzymes in the pathway ameliorates disease-associated phenotypes in model organisms. Some work has also linked the KP to ageing in humans and model systems, though the mechanism(s) underlying these effects are unclear. Inhibition of the rate-limiting KP enzyme tryptophan 2,3-dioxygenase extends lifespan in *C. elegans* and *Drosophila* (Oxenkrug, *J Neural Transm* 2010; van der Goo et al., *PNAS* 2012) and several studies have observed altered KP metabolites during ageing in mice and humans (e.g. Braidy et al., *FEBS J* 2011; de Bie et al., *J Neurochem* 2016). Notably, metabolites of the KP have been found to cross-link eye lens proteins, and levels of kynurenine-modified proteins increase with age and cataract severity (Rakete and Nagaraj, *J Biol Chem* 2016). We have recently described alterations in mitochondrial function in flies with perturbed KP metabolism (Maddison and Giorgini, unpublished), which could further impact ageing processes.

This project seeks to explore the role of the KP in ageing in the fruit fly *Drosophila melanogaster*. Key regulatory enzymes of the KP will be targeted by genetic, pharmacological, and nutritional approaches, while several parameters will be monitored in the flies, including: levels of key KP metabolites, lifespan, behaviour (negative geotaxis and circadian rhythms), mitochondrial function/morphology, oxidative stress, and other factors. Correlations will be drawn between alterations in lifespan/behaviour with KP metabolism and the functional readouts. Key time points and manipulations will be further explored by determining alterations in global gene expression by RNASeq, which will provide insight into the molecular mechanisms underlying the phenotypes observed. Interesting gene candidates identified by these analyses will then be further explored by genetic approaches in the flies, using key readouts mentioned above. In total, this work will elucidate the role of KP metabolism in *Drosophila* ageing, which will likely have relevance to humans.
Relevant BBSRC Strategic Research Priority:  
World Class Underpinning Bioscience

Techniques that will be undertaken during the project.

*Drosophila* genetics

Confocal and electron microscopy

Mitochondrial respirometry

mRNA and protein quantification (QPCR and immunoblotting)

Behavioural analyses (negative geotaxis and circadian rhythms)

Differential gene expression analyses (RNASeq)

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