Project Details	
Project Code	MRC23NMHCa Smith
Title	The Contribution of Mitochondrial Dysfunction to Alzheimer's disease
Research Theme	Neuroscience and Mental Health
Summary	Alzheimer's disease (AD) is associated with increased oxidative stress and mitochondrial dysfunction in the brain. The Redox system that helps detoxify neurons is decreased in AD patients and likely contributes to symptoms and neurodegeneration. The PhD student will manipulate Redox and mitochondrial regulating genes in Drosophila and iPSC neuron models of AD to find new potential therapeutic targets.
Description	Alzheimer's Disease (AD) likely manifests through a combination of genetic inheritance and environmental factors. Currently, the biggest risk factor for developing AD is age. Neurons are terminally differentiated and must be maintained throughout our entire lifetimes. However, during ageing levels of oxidative stress, in the form of reactive oxygen species (ROS) accumulate, which leads to oxidation of proteins/lipids, induces DNA damage and may eventually trigger neurodegeneration. Mitochondria are also compromised and produce less ATP. Antioxidant mechanisms which usually protect neurons are decreased with age, and decreased to an even greater extent in the AD patient brain. We have recently found that the AD risk gene WWOX is key regulator of metabolism, redox and mitochondrial health and that metabolism shifts are associated with amyloid beta (AB) protein aggregation and anticipate that other risk gene will be involved in metabolic regulation. Dysregulation of the metabolism and redox is largely understudied in the context of age-dependent neurodegeneration. The focus of this PhD studentship is to determine the mechanism of how redox and metabolism changes manifest in a number of AD models. Aim 1) Deciphering the molecular mechanism of redox and metabolism changes in AD. We will investigate 20 genes related to redox and metabolism pathways that may be contributing to neurodegenerative phenotypes in an AB Drosophila model of AD, chosen from a recent RNA-sequencing experiment. Transgenic RNAi expressing lines against uncovered genes will be driven specifically in neurons for knockdown and genetically encoded fluorescent genetic reporter technology used to measure ROS and mitochondrial dysfunction. To complement this the PhD student will further analyze lifespan, basic behaviour, memory and sleep (through co-supervision with JH) in gene knockdown models. We will also determine if altering redox homeostasis or metabolism plays a role in AB aggregation in the brains of the flies. *Student input - The select enzymes will be chosen from our previous RNA Seq data sets collected on AD models. The student can steer the project here to focus on different metabolic pathways that they find interesting e.g b-oxidation or glycolysis etc. Aim 2) Metabolomic and Lipidomic changes associated with several AD Drosophila models The student will then have specific 'big data' training for metabolomic and lipid profiling as brain samples from models are sent for mass spectrometry (UK DRI at Imperial). This analysis will be to generate novel yet complementary OMIC data sets to the previous RNA sequencing experiments to determine the molecular outcome of enzymatic changes that we find the AB and risk gene models. *Student input - metabolite and lipid changes

	will need to be verified through the use of lipid reporters or ELISA and the student will steer the project to find and optimise specific assays for the most promising candidates. Aim 3) Measure mitochondrial dysfunction associated AD risk genes. We will use existing iPSCs resources within the UK DRI to assay mitochondrial dysfunction (metabolism and ROS) associated with AD risk gene knock out or knockdown. The student will learn to differentiate these lines into cortical neurons and perform several relevant assays to measure metabolic and mitochondrial dysfunction (achieved under the co-supervision of NCR). Importantly the vast majority of genes in the redox and metabolism pathways are highly conserved between Drosophila and humans and candidate enzymes and metabolites investigated in previous years will further be examined in iPSC lines. *student input -i) Choosing the most relevant cellular model based off Drosophila in vivo findings ii) There are plenty of analysis methods and tools available for in vitro work and the student will be encouraged to develop different techniques and methodologies to measure cell specific changes.
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