Project Details	
Project Code	MRC22NMHCa Smith
Title	Metabolic ageing signatures in Alzheimer's disease models
Research Theme	Neuroscience & Mental Health
Summary	Age is currently the biggest risk factor for developing Alzheimer's disease. It is not well understood how ageing impacts hallmark Tau and amyloid pathology in the brain and neuronal function. The PhD student will investigate how age related shifts in mitochondrial and peroxisomal metabolism impact the behavior and neurodegeneration seen in Drosophila models of Alzheimer's disease. The student will learn cutting edge imaging techniques and bioinformatic approaches.
Description	The number of people with dementia in the UK is forecast to increase to 1,000,000 by 2025 and 1,590,000 by 2040 and this trend is echoed globally. Over the age of 65 the risk of developing Alzheimer's disease (AD) increases almost exponentially with age. The molecular mechanisms controlling age-related risk are not well understood. Dysfunction of energy generating organelle, the mitochondrion in neurons with age is well established, and growing evidence attributes this decline to loss of mitochondrial DNA (mtDNA) integrity. Oxidative stress and metabolism shifts due to mitochondrial failure may drive increased amyloidogenic processing, contributing to pathology and may lead to irreversibly lipid oxidation and cellular damage. There is also growing evidence that the metabolic process of β-oxidation, which starts in the peroxisome compartment of cells is severally effected in AD. This process is essential to fuel oxidative phosphorylation in the mitochondria. The PhD student will therefore investigate whether improving peroxisomal and mitochondrial function in model systems may delay AD related changes. Aim 1: The student will first learn to use the fruit fly Drosophila to determine the effect of inducing mtDNA mutations (to levels usually seen in human neurons at approximately 60 years of age), on the pathology and behavioural phenotypes of Drosophila AD models. Both 'humanised' Tau (mutant and wild-type) and amyloid beta 42 (AB) transgenic models will be used throughout. Somatic mtDNA mutations will be induced by expressing APOBEC1 'mitochondrial mutator' (recently gifted to the lab) only in neurons. Preliminary data shows expression in wild type animals causes a significant shortening of lifespan. The student will perform genetic crosses to look at the effect of mitochondrial mutations on the hallmark phenotypes found in AD fly models (both male and females), namely: lifespan, behaviour, Tau / AB pathology in the fly brain, electrophysiology, neurodegeneration and sleep profiles. We also have a large tool set to enable us to determine mitochondrial and peroxisomal health in vivo at different ages using cutting edge clonal imaging techniques and a sequencing system to detect the amount and type of mtDNA mutations present. Aim 2: The PhD student will have the opportunity to learn how to generate and analyse large bioinformatic data sets. Dissected brain samples from our AD models with and without premature mitochondrial aging will be processed for untargeted lipidomic and metabolomic analysis and dysregulated species mapped into molecular pathways. Using these data, we will then genetically inhibit or overexpress several select candidate enzymes using

	commercially available Drosophila libruaries, with the aim of improving AD phenotypes in flies that maybe specifically related to Tau or AB. Aim 3: The student will also have the opportunity to investigate a defined lipid pathway relevant to AD. Cortical accumulation of saturated very long chain fatty acids (VLCFAs), substrates for peroxisomal β-oxidation, are increased in AD patient brains and animal models. Peroxisomal function is tightly linked to mitochondrial function since the product of β-oxidation, acetyl-CoA, is required to fuel Krebs Cycle and ultimately generate ATP. Our preliminary data shows that increasing levels of the VLCFA transporter ACDB5 allows for greater β-oxidation in vitro and could therefore be a therapeutic target. The student will investigate whether enhanced peroxisome lipid transportation in vivo will improve AD phenotypes, as defined in Aim 1. This will require molecular cloning techniques to produce a new' humanised' transgenic animal expressing ACDB5, which would be of interest to the Drosophila and metabolism communities. Age is currently the biggest risk factor for developing AD. Understanding the mechanisms behind this process may open-the-door to therapeutics targeted to alter a particular metabolic or lipidomic pathway.
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