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**PhD Project Commencing October 2023**

**(Closing date: 5 January 2023)**

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**Investigating mitochondrial quality control and turnover in**

***Drosophila* models of neurodegeneration**

The mitochondrial genome (mtDNA) in animals encodes 13 subunits of the respiratory chain and ATP synthase, along with the tRNAs and rRNAs necessary for their production. Mutations in mtDNA can give rise to devastating mitochondrial diseases, and have been implicated as a driving force in the ageing process, with high levels of mtDNA mutations being found in various neurodegenerative disorders such as Parkinson’s and Alzheimer’s diseases. Until recently, modelling specific mitochondrial diseases has been hampered by very limited methods for manipulating mtDNA. Recent developments in the field have identified new methods to manipulate and even engineer the mitochondrial genome [1]. Our groups recently developed a new mtDNA mutator system by targeting the cytidine deaminase APOBEC1 to mitochondria in *Drosophila* [2]. The “mito-APOBEC1” flies generate high level of somatic mtDNA mutations which severely limit mitochondrial function, organismal vitality and lifespan. This model can now be used to investigate the impact of mtDNA mutations on cellular homeostatic processes and the mechanisms which mitigate the accumulation of mtDNA mutations such as mitophagy and other quality control measures. In addition, the project will adapt emerging technologies to develop additional fly models of mtDNA dysfunction, including both untargeted and targeted approaches using previously established TALE or zinc-finger targeting moieties [3]. This project will contribute to our ongoing programmes that will shed light on the pathogenic mechanisms of mtDNA mutations, and help develop much needed new models for mitochondrial diseases, ultimately, providing new insights that inform therapeutic strategies.

**Keywords**

General:

Mitochondria, Genome Engineering, mtDNA

More specific:

Mitochondrial diseases, base editors

**References**

[1] [Mitochondrial genome engineering coming-of-age.](https://pubmed.ncbi.nlm.nih.gov/35599021/)

Barrera-Paez JD, Moraes CT.Trends Genet. 2022 Aug;38(8):869-880. doi: 10.1016/j.tig.2022.04.011. Epub 2022 May 19. PMID: 35599021

[2] [Mitochondrially-targeted APOBEC1 is a potent mtDNA mutator affecting mitochondrial function and organismal fitness in Drosophila.](https://pubmed.ncbi.nlm.nih.gov/31337756/)

Andreazza S, Samstag CL, Sanchez-Martinez A, Fernandez-Vizarra E, Gomez-Duran A, Lee JJ, Tufi R, Hipp MJ, Schmidt EK, Nicholls TJ, Gammage PA, Chinnery PF, Minczuk M, Pallanck LJ, Kennedy SR, Whitworth AJ. Nat Commun. 2019 Jul 23;10(1):3280. doi: 10.1038/s41467-019-10857-y. PMID: 31337756

[3] [In vivo mitochondrial base editing via adeno-associated viral delivery to mouse post-mitotic tissue.](https://pubmed.ncbi.nlm.nih.gov/35136065/)

Silva-Pinheiro P, Nash PA, Van Haute L, Mutti CD, Turner K, Minczuk M. Nat Commun. 2022 Feb 8;13(1):750. doi: 10.1038/s41467-022-28358-w. PMID: 35136065

**Subject areas**

Biochemistry, Genetic Engineering, Genetics, Molecular Biology, Molecular Genetics, Neuroscience

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