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**PhD Project Commencing October 2024**

**(Closing date: 14 March 2024)**

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**Genetic approaches for rational development of animal models**

**of complex I-linked mitochondrial disease**

Mutations in mitochondrial complex I genes are common causes of primary mitochondrial neuromuscular diseases such as Leigh syndrome. However, there are few animal models available for them, with most studies focussing on just one, deletion of subunit NDUFS4, which has a complicated and multifaceted impact on the enzyme.

This project aims to develop a series of new models with specific, well-defined functional complex I defects. Using point mutations, we will create ‘clean’ models with decreased enzyme activity, but with the structure, biogenesis and stability unaffected. The models will be applied to determine mitochondrial, cellular and physiological outcomes, to better understand how complex I dysfunctions cause diseases.

First, we will define a rational set of candidate mutations and evaluate them using *Paracoccus denitrificans*, a high-throughput bacterial model system. Enzyme function and integrity will be evaluated to identify a suitable set of variants with increasing severity.

Second, selected variants will be transferred into *Drosophila* and confirmed in cultured cells, then successful variants created *in vivo* using cutting-edge genetic engineering approaches to deliver a unique series of *Drosophila* strains with varying levels of complex I function. The strains will be phenotypically characterised (alone and/or in combination), to determine their physiological impacts, with emphasis on tissue-specific requirements.

Finally, successful mutations will be assessed in mammalian cell lines, enabling development of new mouse models in future work.

The project will provide high-level training in molecular biology, genetic engineering and biological techniques and experience of multi-scale approaches to mitochondrial biology and disease mechanisms.

**Keywords**

General: disease model, enzyme, genetics, mitochondria, mutagenesis

More specific: complex I, *Drosophila*, mitochondrial diseases, respiratory chain

**References**

1. Jarman, O. D., Biner, O., Wright, J. J. & Hirst, J. (2021) Paracoccus denitrificans: a genetically tractable model system for studying respiratory complex I. *Sci. Rep.* **11**, 10143. doi:10.1038/s41598-021-89575-9
2. Agip, A.-N. A., Chung, I., Sanchez-Martinez, A., Whitworth, A. J. & Hirst, J. (2023) Cryo-EM structures of mitochondrial respiratory complex I from *Drosophila* melanogaster. *eLife* **12**, e84424. doi:10.7554/eLife.84424
3. van de Wal, M. A. E. et al. (2022) *Ndufs4* knockout mouse models of Leigh syndrome: pathophysiology and intervention. *Brain* **145**, 45-63. doi:10.1093/brain/awab426

**Subject areas**

Genetics, Genetic Engineering, Molecular Biology, Biochemistry

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