Investigating the role of synuclein in Parkinson's neurons

Supervisors: Dr Liang-Fong Wong
Prof James Uney

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Neurodegenerative diseases are often characterised by accumulation of intracellular toxic proteins, oxidative stress and axonal swelling in diseased neurons. Defective axons can affect axonal transport of proteins critical for synapse function and contribute to pathological insult. In Parkinson's brains, dystrophic axons with degenerative bulbs and reductions in axonal motor protein levels are observed prior to phenotypic downregulation of dopamine and neuronal loss[1,2]; this reduction is greater in neurons containing α-synuclein inclusions[2]. This suggests that disruption of axonal transport may trigger die-back of dopaminergic axons leading to neurodegeneration and cell death.

α-synuclein missense and multiplication mutations have been suggested to cause neurodegeneration via impairment of exocytosis, axonal transport dysfunction and increase in autophagy processes. Furthermore α-synuclein has been shown to impair neurite outgrowth in neurons thereby exacerbating neuronal degeneration [3]. This project will investigate the interactions of α-synuclein (and its mutants) with axonal transport and autophagy proteins in neurons derived from induced pluripotent stem (iPS) cells from Parkinson's patients using neuron-specific lentiviral vectors to overexpress and/or inhibit α-synuclein expression (and its mutants). The effects of perturbing α-synuclein levels on neuronal function, in particular the effects on axonal growth and transport, will be measured using molecular, biochemical, state-of-the-art confocal and electrophysiological methods.

This project will provide mechanistic insight into the early events that occur during the development of Parkinson's disease and may lead to the development of new biomarkers and the identification of novel targets for therapeutic intervention. The student will have access to excellent supervision, expertise, resources and practical support in both laboratories and gain training in diverse techniques such as molecular biology, viral vectors, iPS and ES cell culture, neuron derivation and cell imaging.

References

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