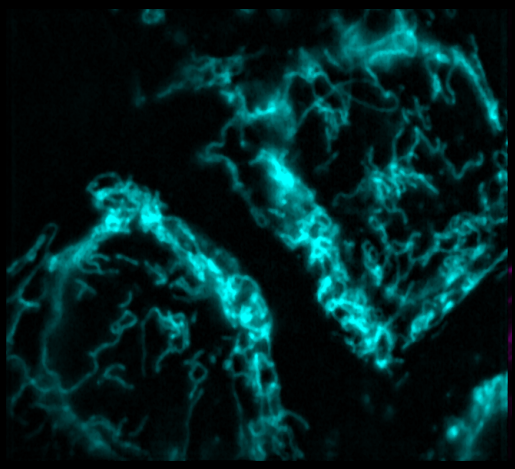
DETERMINING THE MOLECULAR UNDERPINNINGS OF NEURODEGENERATION

Cytoskeleton and Motors Lab @ Single Molecule Science

Problem: Neurodegeneration, mitochondria and microtubules

Neurodegeneration is a major public health crisis in Australia, with about 280,000 people living with Alzheimer's disease (AD) and ~100,000 people with Parkinson's disease (PD). While both diseases have been characterised at cellular, tissue and whole-organism scales since their first description, there are still no drugs that can prevent or cure either disease.

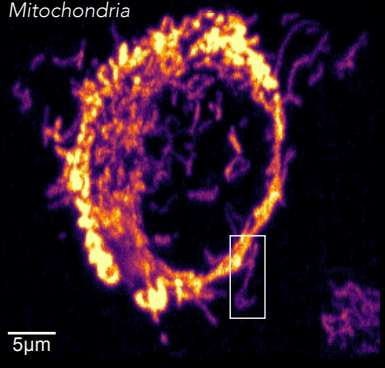
Microtubules are self-organising polymers that serve as tracks for transport of components essential for cell survival. In AD and PD neurons, there is extensive destabilisation of microtubules. Mitochondrial form is acutely linked to their function, with fragmentation of mitochondria correlated with damage and excessive ROS production. This phenotype of mitochondrial fragmentation is a common feature of neurodegeneration. In recent research from the Cytomotors Lab using fission yeast as a simple model system, we established that mitochondrial dynamics were dictated by their attachment to the underlying microtubules. In this research, we will address the question: Do altered microtubule dynamics in neurodegeneration result in the abnormal mitochondrial dynamics?

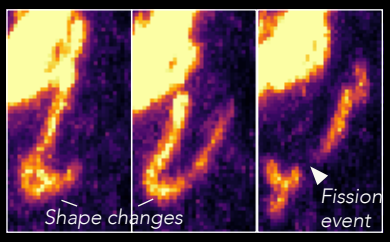


Mitochondria imaged using Structured Illumination Microscopy

Approach I: Live-cell imaging in cellular models of neurodegeneration

Lattice Light Sheet Microscopy (LLSM)
Mitochondria

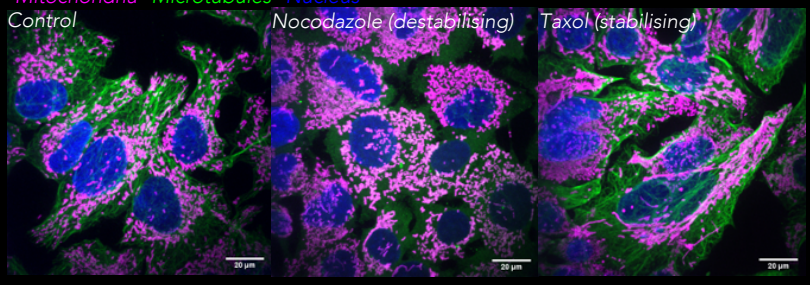




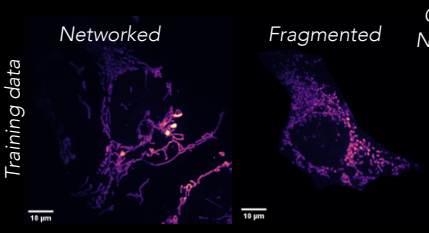
We will construct cell culture models of AD and PD to probe the link between microtubules and mitochondria. Cells will be imaged using state-of-the-art lattice light sheet microscopy (LLSM) which affords the ability to probe the fast spatio-temporal dynamics of mitochondria.

We will also explore the relationship between microtubules and mitochondria in these AD and PD models by simultaneously visualising the two entities upon perturbation of microtubule dynamics using microtubule stabilising and destabilising compounds.

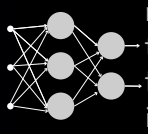
Mitochondria *Microtubules* *Nucleus*



Approach II: High-throughput screen and deep learning



Convolutional Neural Network (CNN)



To unravel the molecular link between microtubules and mitochondria, a targeted screen of microtubule-associated proteins (MAPs) which alter microtubule dynamics will first be conducted in AD and PD cell culture models of neurodegeneration. A CNN algorithm that classifies mitochondrial phenotypes in cells will be developed to automatically identify potential hits for further testing (in collaboration with Prof. Dukkipati, India). The hits produced in this screen that result in increased fusion will then be overexpressed in the background of AD and PD cells with an aim to restore mitochondrial form and function.

Contact us!

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We are committed to fostering a welcoming, respectful, and inclusive environment while we have fun doing our science. Learn more about us:
https://www.cytomotorslab.com/

UNSW is located on the unceded territory of the Bedegal (Kensington campus) who are the Traditional Custodians of the lands where our campus is situated.