

## Mitochondrial protein and protein-biomolecular interactions probed with novel bile acid-based compounds

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Mitochondrial dysfunction is a well-recognised hallmark of ageing and age-related diseases [1] such as Parkinson's Disease (PD) and Alzheimer's Disease (AD). Uncovering the structural and functional role of mitochondrial proteins and their interactions with other biomolecules is an important step in characterising the mechanisms driving mitochondrial dysfunction in disease. Such detailed molecular characterisation may enable the development of new therapies. Such new therapies are being explored, using bile acids (BAs). Emerging studies indicate the potential utility of BAs as a treatment for neurodegenerative disease [2], by exerting anti-apoptotic effects [3]. Bile acids have been used to treat liver disease for centuries and are currently still used to treat pulmonary biliary cholangitis.

In our laboratory, we are using a target-based drug discovery approach to investigate the capacity for novel BA compounds to mitigate mitochondrial dysfunction in PD, AD and other age-related diseases. A key aspect of this approach is validating potential compounds and their respective targets through protein-ligand complex structure determination and using these compounds in fluorescence-based functional assays to investigate the role of these proteins in apoptosis and mitochondrial dysfunction. As well as mitochondrial dysfunction, there is a growing body of evidence for the role of gut dysbiosis in neurodegenerative disease [4-7]. Using batch and gut fermentation, as well as secondary analysis by gas chromatography and NMR metabolite profiling, BAs that positively modulate gut microbiome profiles in disease models can be investigated for their role in redressing gut dysbiosis.

My research aims to investigate novel BAs as therapeutic agents in AD through two mechanisms of intervention: the mitochondria and the gut microbiome, using an integrated approach involving crystallography, functional assays, and fermentation studies. The latest results of these efforts will be presented.

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