Defining the neuronal autophagosome assembly site: spatiotemporal control ATG9A trafficking in human iPSC-derived neurons

Supervisory team:
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Project description:
Mammalian autophagosome assembly requires the coordinated supply of vesicles enriched for the essential autophagy transmembrane protein, ATG9A. Upon autophagy stimulation, ATG9A vesicles relocate from the peri-Golgi region to peripheral autophagosome assembly sites where ATG9A acts as a lipid scramblase to maintain lipid balance across the expanding autophagy isolation membrane. Little is known about the molecular control of this key membrane trafficking event, particularly how ATG9A trafficking is spatially coordinated in human neurons. In this PhD, you will generate gene edited human cell-lines (including iPSCs) expressing ATG9A endogenously tagged with markers for dynamic confocal imaging fluorescence microscopy of ATG9A (GFP; PA-GFP; Halo-tag) and biotinylation enzymes (e.g., APEX-2; Turbo-ID) for spatiotemporal proximity proteomics analysis of ATG9A interaction partners. Microfluidics will be used with human iPSC-derived cortical glutamatergic and midbrain dopaminergic neurons for regional targeting of treatments/manipulations, to understand better how ATG9A trafficking and autophagy are controlled in different compartments of these highly specialised cells. To untangle the roles of candidate regulatory pathway components, computational modelling of trafficking parameters will be used to describe ATG9A vesicle dynamics during neuronal autophagosome assembly. Modelling predictions will then be tested using knockdown/overexpression in human iPSC neurons.

This PhD project will be suitable for candidates with backgrounds and/or interests in mammalian neuronal cell biology, membrane trafficking, and/or gene editing. Candidates with experience of computational modelling of complex cellular pathways are also encouraged to apply. Advanced training will be provided in CRISPR genome editing, mammalian cell biology, iPSC neuronal differentiation, confocal fluorescence imaging, computational pathway modelling, and bioinformatics.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.