Cell-type and functional characterisation of novel tau isoforms in health and dementia

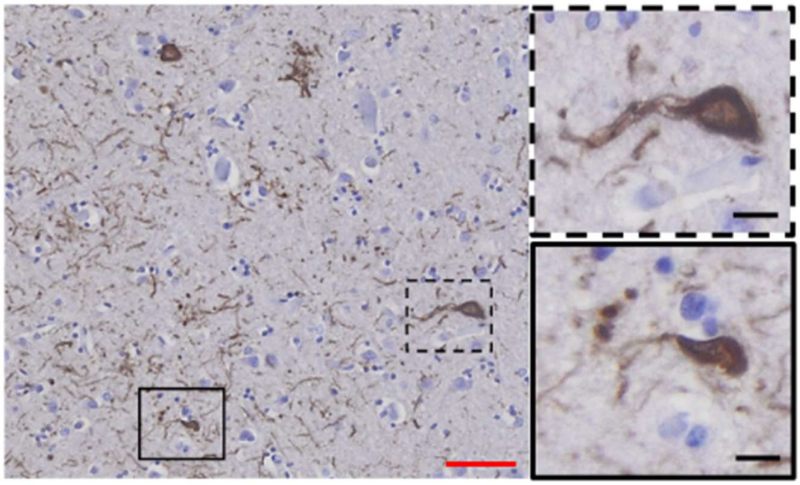
Project ID: 3501

Supervisory team

Main supervisor: Prof Wendy Noble (University of Exeter)
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Other supervisors: Dr Clemence Bernard(University of Exeter), Dr Rosie Bamford (University of Exeter)

Collaborators: Professor Selina Wray (University College London)

Host institution: University of Exeter



Project description: The tau protein, encoded by the MAPT gene, has many functions that are fundamental to maintaining neuron health during development and in adulthood. This includes binding to and stabilising the neuronal cytoskeleton and regulating axonal transport to position proteins where they are needed within the cell. Tau proteins are heavily modified in diseases such as Alzheimer's disease (AD) and frontotemporal dementia (FTD), with loss of their physiological functions as well as acquired neurotoxic properties contributing to disease progression. There are six major tau isoforms in adult human brain, because of developmentally regulated splicing of the MAPT gene. Abnormal MAPT splicing leads to some forms of dementia. Advances in genetic sequencing approaches led our team to identify previously uncharacterised MAPT isoforms in human cortex. However, their cell-type localisation, biological functions, and links with dementia currently remain unknown. This multi-disciplinary project will address fundamental questions about the tau proteins generated by these novel isoforms under physiological and disease conditions, testing the hypothesis that the novel MAPT isoforms generate functional tau proteins with altered functions, that contribute to dementia. The student will use a variety of approaches to examine the expression and localisation of MAPT isoforms in healthy and diseased human postmortem brain and to determine if there are patterns of isoforms that are co-expressed and that could contribute to dementia mechanisms. This includes using BaseScope duplex assays, which combine MAPT isoform-specific probes with cell-type markers, to determine the expression and cell-type specific localisation of the novel MAPT isoforms. The student will use similar approaches to study the expression of isoforms during early development using cultured human iPSC-neurons. They will next examine the ability of the newly identified MAPT isoforms to produce tau proteins in cultured cells. To achieve this goal, the novel tau isoforms will be expressed in cell lines lacking endogenous tau and protein production will be confirmed using biochemical and immunocytochemical approaches. They will examine the function of tau proteins in the cultured cells using a variety of assays that will be selected based on predicted properties of the MAPT isoforms/tau

proteins. Ultimately, this work will broaden our knowledge of tau proteins and may inform future strategies to combat dementia and promote healthy ageing.

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.