Polyphenols as inhibitors of tau aggregation: protecting the ageing brain

Supervisory team:
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Project description:
Tau is a microtubule-associated protein that can misfold into toxic inclusions known to be key drivers in the pathology of Alzheimer’s disease. Recent studies at Bath have identified several polyphenol-based molecules that are known to be effective in modulating tau aggregation in vitro, but which lack the necessary cell penetrance, bioavailability, and potency to further develop the molecules into useful diagnostics or therapeutics. By using our initial hits as molecular scaffolds, the student will gain expertise in intracellular high-throughput screening using a small-molecule library to identify molecules that are capable of binding to tau and modulating amyloid formation and associated toxicity. Since the screen is undertaken inside living cells it has the additional benefit of being able to profile for compounds that can traverse biological membranes, that are themselves non-toxic, and that can abolish tau-associated toxicity that arises from misfolding and aggregation. Moreover, as the assay relies on correct protein folding and consequent fluorescence readout as a marker of success, the most effective compounds can be easily and rapidly identified and even quantitatively ranked according to the greatest levels of fluorescence. The student will be involved with all aspects of the project including solid-phase peptide synthesis, in vitro aggregation experiments, library screening assays in both bacterial (Mason, Bath) and mammalian systems (Williams, Bath), expertise in cell biology using primary neurons, and skills using in silico molecular docking simulations (Sessions, Bristol). The student will use the above techniques to create both a cellular and molecular understanding of how the most effective membrane penetrant polyphenols exert their effects; i.e. where within tau that they bind, the conformation and oligomeric state of tau that is populated, and how they exert their effect upon downstream markers of toxicity. The latter will help to couple neuronal cell context with the biophysics of inhibition and toxicity to provide a complete understanding of how the most effecting compounds work. We envisage that the most effective molecules will form precursors to drugs for tau-based diseases and as probes to monitor tau aggregation before symptoms present.
Figure 1. Fluorescence-based screen using the Tau-eGFP fusion. In the absence of inhibition, the Tau portion of the fusion aggregates rapidly and causes the entire Tau-eGFP fusion to misfold and aggregate (left). Therefore, no fluorescence is observed. However, inhibition of Tau aggregation enables eGFP to form its native green fluorescent structure (right). The green part of the ribbon diagram shows the structure of eGFP, with the yellow part a schematic representation of a non-aggregated form of Tau. The polyphenol scaffold is shown at the center of the figure. A 96-well plate is shown at the bottom of the figure. Compounds will be added to each well, followed by E. coli cells expressing the Tau-eGFP fusion. Negative (colorless) and positive (green) controls are shown in the columns on the edges of the plate. For negative controls, no test compounds are added to the wells. For positive controls, the wild-type tau-eGFP fusion is replaced with a fusion in which the Tau sequence is scrambled into a sequence previously shown not aggregate and enable fluorescence of the Tau-eGFP fusion.