Ordering the Disordered in Parkinson's disease to Derive Peptides Inhibitors of alpha-Synuclein Toxicity

Supervisory team:
Main supervisor: Prof Jody Mason (University of Bath)
Second supervisor: Prof Matthew Crump (University of Bristol)
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Host institution: University of Bath

Project description:
The student will develop peptides that can be used to effectively block formation of a toxic protein responsible for the pathology of Parkinson's disease (PD). The protein, known as alpha-synuclein (aS), self-associates inside dopamine producing cells in the brain to form toxic clumps known as Lewy bodies that interfere with normal brain function, leading to the symptoms of the disease. We will inhibit this process building from a system that we have demonstrated to work (Meade et al J Mol Biol 2021, 2022, Watt et al ACS Chem Neurosci 2022, Watt et al J Biol Chem 2022). Using a novel screening system that targets the natural folded state of aS, that is prior to misfolding and aggregation, the student will screen large peptide libraries (>2 Million members) inside living bacterial cells. In this assay, inhibitors are only selected if the very first step in aggregation is blocked, leading to a restoration of cell viability.

The student will use the screening assay to generate numerous inhibitory peptides to block the very first steps in the misfolding of aS. This will provide a wide range of sequences from which we can understand the mechanism of inhibition via biophysical, neuronal cell-based, and structural biology methods. Our overarching aim is to assign function to specific sequence elements within our newly generated inhibitors to demonstrate the principles of rational inhibitor design, ultimately improving the properties of future peptide generations. Finally, by comparing endogenously produced to externally added peptides, the student will begin to explore aspects of drug delivery, such as permeability to reach intracellular targets. The composition of the supervisory team ensures comprehensive expertise in all facets of this interdisciplinary project. The training environment will be highly supportive and stimulating, including ample opportunity for wider engagement with the scientific community. You will be guided through the challenges and rewards of this project while gaining a wide range of skills that are translatable to many other systems.

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.