Amyloid Transcription Block Survival - Deriving Functionally Active Peptide Inhibitors of Amyloidosis and Toxicity

Supervisory team:
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Project description:

The aim of this project is to develop peptides that can be used to effectively inhibit 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 and lead to the symptoms of the disease (Meade et al, Mol Neurodegen 2019: https://rdcu.be/bLohx; Meade et al NPJ Parkinson's disease 2020). The PhD program will focus the student on inhibiting this process building from a system that we have already demonstrated to work (Cheruvara et al, J.Biol.Chem 2015). Using a novel screening system that targets aS prior to any misfolding or aggregation, the student will screen large peptide libraries (>2 Million members) inside living bacterial cells using a 'Transcription Block Survival' (TBS) assay. In this assay, inhibitors will only become selected if DNA-binding activity is prevented, leading to a restoration of cell viability.

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. To achieve this the student will use the TBS 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 using biophysical, neuronal cell-based methods. The project will also involve work with Bristol University and the application of high-resolution NMR to probe structures and interactions of the peptides with aS, providing valuable structural biology expertise. Finally, by comparing endogenously produced peptides against externally added peptides, the student will begin to explore aspects of drug delivery, such as permeability and the ability to reach intracellular targets.

The composition of the supervisory team ensures comprehensive expertise in all facets of this interdisciplinary project. You will find a supportive and stimulating training environment, to guide you through the challenges and rewards of this project while gaining a wide range of skills that are translatable to many other systems.