

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

### **Supervisory team:**

**Main supervisor:** Prof Jody Mason (University of Bath)

**Second supervisor:** Dr Robert Williams (University of Bath)

Dr Richard Sessions (University of Bristol)

**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 (Cheruvvara et al, J.Biol.Chem 2015). Using a novel screening system that targets the natural 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 computational 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.