Project Details	
Project Code	MRC21NMHBa Mason
Title	Tightening the Noose on Parkinson's disease: Harnessing Lasso Peptides as Inhibitors of alpha-Synuclein Toxicity
Research Theme	Neuroscience & Mental Health
Summary	Starting from an initial hit sequence, we will screen small ultra-stable lasso peptide libraries, to identify members that block alpha-synuclein (αS) toxicity associated with Parkinson's disease. These highly structured molecules can resist breakdown, penetrate biological membranes, and are target selective. We will inhibit αS-associated toxicity using a powerful screen that searches millions of lassos inside live cells to identify those that restore viability.
Description	Alpha-synuclein (αS) is the major constituent of Lewy bodies and a pathogenic hallmark of all synucleinopathies, including Parkinson's disease (Meade et al, Mol Neurodegen 2019; Meade et al NPJ Parkinson's disease 2020). Building upon our expertise in this area, we will target αS using library-derived peptides via two highly novel elements: i) Grafting a peptide shown to bind αS and reverse toxicity (Cheruvara et al, 2015) into a short and highly structured lasso-peptide drug scaffold. Lassos are poorly exploited, yet harbor enormous potential to serve as a small rigid scaffold for drug design towards an entirely new drug class that is stable and specific, with the potential to transform PD treatment. ii) Use an intracellular peptide screening platform that targets αS upstream of misfolding. We will combine a novel assay we have developed, and our initial lead peptide, and graft it into the lasso loop for library design. We will scramble key residues required for effective binding, and use intracellular screening to search vast (>2M) libraries inside living cells. A key assay novelty is that only lassos which target monomeric αS and block toxicity via complete loss of aggregation will be identified. Mason's group is at the forefront of research in this area, where the student will create libraries, identify those that halt αS misfolding and toxicity and characterize peptide leads via a range of biophysical techniques (CD, ThT aggregation assays, Electron microscopy, crosslinking) to demonstrate efficacy. With Williams the student will move peptides into primary neuronal cells to demonstrate cell permeability, non-toxicity, and efficacy in synaptically active neurons. With Crump the student will utilize high-resolution NMR to identify key structures to identify the precise mechanism and residues by which αS and lasso interact, moving the project towards refinement by rational design. This interdisciplinary approach will generate high impact publications, IP, and potentially novel preclinical PD drug leads. The proposal is collaborative, involving experts in peptide library screening and biochemistry (Mason), cellular neuroscience (Williams), and atomic resolution structural information (Crump) of the most effective molecules. The approach is novel and timely – protein-protein interactions (PPIs) are rapidly becoming validated as drug targets that are intractable to small molecules. This results from shallow binding grooves and broad interacting surfaces. Our recent work has generated serum stable cell-penetrant peptides that enter cells to inhibit both Activator Protein-1 transcriptional activity and cell proliferation (Baxter et al, ACS Chem Biol 2017). The lasso-approach to αS offers the potential

	for high target affinity and selectivity, using the same proteogenic residues that confer PPI specificity, while retaining stability and solubility akin to small molecule therapeutics, opening the door towards a generalized approach that could in future be applied to a wide number of other protein targets implicated in neurological disease.
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