Project Details	
Project Code	MRCNMH26Ba Mason
Title	Selective Dephosphorylation of α-Synuclein in Parkinson's Using PhosTAC Peptides
Research Theme	NMH
Project Type	Wet lab
Summary	Phosphorylation of the protein α-synuclein at serine 129 (pS129) is a defining feature of Parkinson's disease and related conditions. This project will explore an innovative therapeutic strategy: designing PhosTAC peptides — bifunctional molecules that bring the cell's own phosphatases into contact with α-synuclein, allowing selective removal of the harmful phosphate at pS129. The student will use peptide library screening to discover candidate molecules, followed by biophysical and cellular assays to measure how they interact with α-synuclein. Advanced techniques such as NMR spectroscopy will then be applied to reveal how PhosTACs remodel α-synuclein's structure at the atomic level. This is an interdisciplinary project at the interface of peptide drug design, structural biology, and neurodegeneration research. The student will gain cutting-edge skills across chemical biology and neuroscience, contributing to the development of a novel class of therapeutic molecules for Parkinson's disease.
Description	**Background:** Alpha-synuclein (αSyn) plays a central role in Parkinson's disease and related synucleinopathies. In these disorders, αSyn misfolds and aggregates into toxic fibrils, disrupting cellular function and contributing to neurodegeneration. A key post-translational modification that drives this process is phosphorylation at serine 129 (pS129): while only ~4% of αSyn is phosphorylated at this site under physiological conditions, over 90% of αSyn found in Lewy bodies is pS129-modified. This strongly implicates pS129 in pathological aggregation and spread, yet its exact mechanistic role remains unresolved. Most approaches to modulate pS129 have focused on inhibiting upstream kinases such as PLK2, but this strategy can have broad off-target effects due to the many cellular substrates regulated by these enzymes. This project explores an innovative alternative: developing a PhosTAC, in the form of a bifunctional constrained peptide designed to recruit endogenous phosphatase activity specifically to pS129-αSyn. This will enable targeted site-specific dephosphorylation without global enzyme inhibition. The approach draws inspiration from PROTACs and molecular glues but applies the concept to control phosphorylation status instead of protein abundance. A key capabililty is our ability to create uniquely phosphoylated recombinant pS129-αSyn. Key Research Question: Can we design, optimise and validate a selective PhosTAC that removes pS129 in cells, thereby modulating αSyn structure, aggregation and toxicity? If successful, this would provide a powerful tool for probing the biological consequences of pS129 and lay the groundwork for a novel therapeutic strategy targeting αSyn at the post-translational level. **Specific Objectives:** Objective 1: Develop and validate tools for site-specific pS129 generation and detection

	The student will build on the group's established pipeline for producing recombinant αSyn site-specifically phosphorylated at S129 by co-expression with PLK2. They will confirm modification by mass spectrometry, HSQC NMR (S129/E130 chemical shifts) and western blotting with pS129-specific antibodies. They will also compare S129D mutants and WT controls to benchmark specificity in downstream assays. This will provide high-quality, defined protein for all subsequent experiments. Objective 2: Design and synthesise candidate PhosTAC peptides The student will design a series of bifunctional constrained peptides that combine: i) a library-derived, helix-constrained αSyn targeting sequence that selectively binds near S129; ii) a flexible linker; and iii) a motif known to recruit endogenous phosphatases (e.g. PP1 or PP2A recognition sequences). They will apply solid-phase peptide synthesis (SPPS) and incorporate library-derived constraints identified during screening (e.g. i+4 or i+7 cyclisation) to optimise structural stability and binding orientation. Initial designs will build on pilot binding data and structure–activity relationships. Objective 3: Biophysical and cellular validation of PhosTAC–αSyn engagement The student will characterise binding affinity and specificity by ITC, CD and NMR where feasible. They will test whether candidate PhosTACs form stable complexes with pS129-αSyn and can recruit phosphatase activity in vitro (using established activity assays and pull-downs). In parallel, they will introduce labelled versions (FAM/RhoB) to quantify uptake in neuronal cell models by FACS and fluorescence microscopy. Objective 4: Functional readouts of dephosphorylation and aggregation The student will apply western blotting with pS129-specific antibodies to assess dephosphorylation in neuronal cells expressing αSyn, alongside controls (WT, S129D). They will examine how PhosTAC treatment affects αSyn aggregation under lipid-induced and agitation-induced conditions, using TEM, aggregation kinetics assays and CD. Functional impact will be tested in SH-SY5Y and other neuronal lines, with MTT viability assays and measurement of downstream pathways regulated by αSyn. Hits will also be tested for serum stability and lack of off-target effects in non-neuronal control lines. **Ownership and Student Development** The project is designed to provide the student with strong interdisciplinary training in protein biochemistry, peptide design, biophysics, cell biology and chemical biology. The student will take ownership of PhosTAC design and synthesis, with freedom to steer the choice of targeting motifs, linkers and phosphatase-binding elements. They will optimise experimental conditions for functional tests and can explore more advanced delivery strategies or in vivo validation in the later stages of the project if progress permits. This work sits at the interface of fundamental mechanism and translational therapeutic development, offering rich opportunities for

	the student to build expertise across molecular design, disease biology and next-generation targeted intervention.
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