Project Details	
Project Code	MRCNMH26Ex Phillips
Title	Explaining the elusive first step in neurodegenerative diseases by solving the structures of disordered proteins in physiological environments
Research Theme	NMH
Project Type	Wet lab
Summary	Neurodegenerative diseases, such as Parkinson's disease, are strongly linked to the aggregation of intrinsically disordered proteins (IDPs). However, the precise triggers and mechanisms driving this process remain unclear without molecular structural detail. Determination of 3d protein structure has advanced recently (2024 Nobel Prize for AlphaFold) but only explains folded proteins. IDPs are a major frontier because they are exquisitely sensitive to environmental conditions, dramatically changing their molecular structure in response to stimuli and cellular trafficking. Here, we will determine IDP structures in their native physiological environments to explain their influence on the formation of toxic aggregates and neuronal cell death.
Description	**Opportunity:** Alpha-synuclein in an intrinsically disordered protein (IDP) central to neurodegenerative diseases including Parkinson's, dementia, and Multiple System Atrophy. Expressed in presynaptic terminals, alpha-synuclein mediates critical functions through conformational plasticity and forms neurotoxic Lewy bodies though largely unresolved mechanisms. Moreover, IDP conformational ensembles are highly dynamic and exquisitely sensitive to environmental conditions. This prevents conventional structural elucidation and thus hinders attempts to understand structure:function relationships underpinning their biological role. Hydrogen/deuterium-exchange mass spectrometry (HDX-MS) when measured with millisecond time resolution can overcome these limitations and enable the characterization of alpha-synuclein's behaviour within biologically relevant contexts providing critical insight into its native structure-function relationship. This project will ultimately yield an experimentally grounded model of alpha-synuclein under biologically relevant conditions, enabling the development of a more realistic structure-function relationship to accelerate research into Synucleinopathies and deliver previously unattainable neurobiological insights. More broadly, these efforts will demonstrate a robust and insightful approach for structural elucidation of IDPs, and facilitate the development of a powerful condition-aware interpretive framework for HDX-MS. **Background:** The intrinsically disordered protein (IDP) alpha-synuclein is central to synucleinopathies, a class of neurodegenerative diseases including Parkinson's, Lewy body dementia, and Multiple System Atrophy which affect a growing population globally. While alpha-synuclein has been extensively studied, its physiological functions and pathological behaviour remain challenging to meaningfully evaluate. Alpha-synuclein exists as an ensemble of structures that is functionally dependent on it cellular environment. Consequently, conventional structural biology methods and even AI-based tools like AlphaFold, offer little insight into its behaviour within a biologically relevant context. This lack of

	meaningful structural insights has stifled efforts to unravel the mechanisms driving aggregation and toxicity, identify biomarkers of disease progression, and ultimately develop suitable therapeutics against synucleinopathies (Zacharopoulou JACS 2025). Hydrogen-deuterium exchange mass spectrometry (HDX-MS) is a uniquely powerful tool for probing the structural dynamics of IDPs like alpha-synuclein. By measuring regional variations in the rate of backbone amide proton transfers in a deuterium rich buffer, HDX-MS can identify transient structural features. Critically, HDX-MS studies are amenable to physiologically relevant conditions including cellular mimics and lysates, making it ideal for capturing the conformational ensemble of alpha-synuclein under native condition (Seetaloo Anal. Chem. 2022). HDX-MS data can be leveraged using ensemble reweighting strategies wherein populations of structures generated by molecular dynamics (MD) simulations are adjusted to optimize agreement with experimental data and reveal the most probable conformations under specified conditions. Although widely utilized, the utility of this approach for modelling IDPs like alpha-synuclein within a biologically relevant context has traditionally been critically limited by data quality. This work seeks to leverage the globally unique 1 ms time-resolved approach developed in the Phillips lab to generate high-precision rigorously parameterized HDX-MS data, that can be integrated into existing ensemble reweighting pipelines, to generate atomistic models of alpha-synuclein that are both experimentally grounded and biologically relevant. This will directly support efforts to probe the structural basis of synucleinopathies, delivering previously unattainable neurological insights and laying the foundation for therapeutic targeting and meaningful biomarker discovery. **Experimental Design / Aim:** The student will use HDX-MS to probe alpha-synuclein's conformational ensemble within compositionally distinct cellular mimics that replicate the complexities of its native environment. Then they will build towards endogenous protein measurements via addition of physiological extracts (blood plasma; neuronal extracts such as synaptosomes and lysosomes) complete with endogenous partners. This will build on the neuronal stem cell culture expertise of the Bhinge group, enabling the relevant cell line development of alpha-synuclein familial mutants, cell extracts and sample generation for orthogonal studies (e.g. cross-linking mass spectrometry). By incorporating well-established controls into the Phillips lab's robust millisecond HDX-MS workflow, we will chemically parameterize solution conditions allowing for more rigorous condition-aware data comparisons and unambiguous evaluation of HDX behaviour within these complex environments. These data can then be used to constrain molecular dynamics driven ensemble reweighting to elucidate the protein's native conformational ensemble under the precise physiological conditions studied. By replicating this approach across familial mutants of alpha-synuclein (e.g. A53E; A30P), we hope to explain previously unresolved structural determinants of Parkinson's pathophysiology.

	Skills and Training: The prospective student will work closely with a cross-departmental interdisciplinary supervisory team at the Living Systems Institute, University of Exeter: Dr Jonathan Phillips (Biosciences) and Dr Akshay Bhinge (Clinical and Biomedical Sciences). This project will provide opportunities for the student to develop well-rounded skills: including stem cell biology techniques, biochemistry, high resolution mass spectrometry, microfluidics, statistical data analysis, computational modelling and strong written and oral communication. Once trained in the fundamental aspects for sample generation and mass spectrometry analysis, the student will be highly autonomous and responsible for driving the project and expected to present and pro-actively discuss their findings with the team and externally at scientific meetings. Each supervisory team member will provide the student with access to complementary expertise important for guiding the student's project and career progression.
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