PhD PROJECT PROPOSAL

## **PhD Project Title**

Topological Design of Novel Metallo Foldamer-Protein Hybrids for Applications in Light Harvesting and Luminescent Imaging

## **PhD Supervisory Team**

Principal Supervisor: Dr. Sarah Pike, s.j.pike@bham.ac.uk, School of Chemistry,

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## **Project Abstract**

Foldamers have been explored as mimics of biological helices, wherein this topology has been shown to dramatically modify various physical properties (including photophysical) compared to alternative topologies. Foldamers are constructed from non-biological building blocks/components, and as such present an opportunity to readily introduce non-biological features into the design including optical, electronic and magnetic properties. However, there are no reports of attempts of using foldamers to construct higher order structures inspired by Nature. This is despite Nature utilising higher order topology for almost all functions. One example is the generation of metal ion sites which are essential to the correct function of ~50% of proteins.

This PhD will design, prepare and evaluate higher order foldamer structures, based on the coiled coil assembly (i.e., the supercoiling of multiple helices). Light harvesting and medical diagnostic function, through the introduction of metal binding and the associated physical properties, is entirely dependent on the resulting topology of these higher order structures. Accordingly, structure-function relationships will be explored so as to establish the key design rules that govern the construction of increasingly complex topologies based on an entirely new class of foldamer-protein hybrid scaffolds.

## **Detailed Project Description**

Project Aim: This project will design and produce new molecules that self-assemble to create novel hybrid metallofoldamer-protein scaffolds capable of a diverse range of topologies by generating biomimetic coiled-coil structures from the assembly of stable synthetic foldamer-helices. These new higher order hybrid structures will possess tuneable (photo)physical properties and find wide-reaching applications as light harvesting constructs and as luminescent and magnetic probes for potential sensing and medical imaging purposes.

Background: Foldamers are synthetic helical oligomers that adopt stable secondary structures through mimicking the folding patterns of biological systems to generate structures of well-defined size and shape (Figure 1).1,2 Foldamers have been the subject of great interest due to their diverse range of applications in materials chemistry and supramolecular chemistry. However, despite the importance of biomimetic foldamers and their known ability to mimic the simple natural helical topologies, there are no reports on the development of higher order foldamer scaffolds that can mimic the sophisticated tertiary and quaternary topological structures found in biological systems. Given that the topology of the foldamer scaffold controls their (photo)physical properties and, in turn their function, accessing new to higher order topologies has the exciting potential to open up the field towards optimising existing applications or generating new applications with these novel structures (e.g., as light harvesters or medical diagnostics).



*Figure 1. Stable folded conformation of synthetic organic helical oligomer (foldamer) in the solid state. a) viewed side on, b) viewed from the N terminus.2*

De novo designed metallopeptide scaffolds that adopt topologically well-defined coiled-coil motifs (Figure 2) can be accessed through combining the fields of inorganic chemistry with synthetic biology (i.e. by incorporating metals into folded biological building blocks (peptides) to create new metallopeptide scaffolds).3,4 In recent years, de novo metallopeptide coiled-coil scaffolds, have found impressive applications as potential light harvesting constructs and MRI contrast agents.5-7 However, the fact that these existing metallopeptide coiled-coil scaffolds are made from biological building blocks, means that they are based on, and therefore limited, to biological topologies. Accordingly, existing systems are restricted to exhibiting a range of topologies, that historically have been limited by evolutionary-imposed constraints, and this severely hinders the optimisation of their performance and the accessibility of new topologies for innovative applications.

 As it is necessary to tune and improve the photophysical properties of these scaffolds in order to optimise their performance for applications beyond biology, including as light harvesters and luminescent or magnetic probes for medical purposes, it is vital that we are able to access new topologies that are not restricted to biomimetic systems with evolution-imposed constraints. Accordingly, we will create new hybrid metallofoldamer-protein systems that adopt higher order coiled coil assemblies which are able to adopt a range of novel topologies for generating new applications as highly efficient light harvesters or effective medical diagnostics tools.



*Figure 2. a) Coiled-coil scaffold incorporating lanthanide ions,5 b) de novo coiled-coil lanthanide design for potential MRI imaging and luminescence purposes.7*

*Project Outline:* In this project, we will address the current limitations associated with the lack of higher order foldamer scaffolds and the biologically restricted topologies of existing de novo metallopeptide scaffolds by creating a new class of hybrid metallofoldamer-protein systems that adopt the coiled coil motif which have the potential to adopt non-natural topologies. These hybrid metallofoldamer-protein scaffolds will be made from synthetic building blocks (foldamers and metals) and will be able to be readily modified, at the molecular level, so that the (photo)physical and magnetic properties of the system can be easily tuned in order to optimise their performance as light harvesting constructs and luminescent or magnetic probes and sensors for medical diagnostics.

Through systematic variation of the molecular structure of the synthetic building blocks (i.e., type of metal) we will systematically tune the size and shape of the coiled-coil scaffold. In this way, we will access new topologies in order to achieve molecular control over the (photo)physical and magnetic properties of the system. Accordingly, during the course of the project, a diverse range of libraries of metallofoldamer-protein coiled-coil whose novel topologies will permit optimization of their performance as a new class of light harvesting system and luminescent or magnetic probe for medical diagnostic purposes.

*Objectives:*

1. To create a new class of topological molecules based on coiled-coil systems incorporating hybrid metallofoldamer-protein scaffolds and fully characterize them using standard and advanced analytical and spectroscopic techniques.
2. To generate libraries of these new topological metallofoldamer-peptide scaffolds wherein fundamental structural features (e.g. type of metal) are systematically varied to provide a broad scope of substrates and a vast library of hybrid scaffolds.
3. To optimise the photophysical or magnetic properties of the new class of topological molecules based on hybrid metallofoldamer-protein scaffolds and establish structure-activity and function relationships on the influence of key structural features (e.g. foldamer length, foldamer building block and/or type of metal) on their performance as light harvesting systems and as luminescent or magnetic probes for imaging applications.

*Methodology:* Each of the objectives of the project require a combination of organic chemistry synthesis and advanced analytical study to generate the new hybrid metallofoldamer-protein scaffolds and to assess their stability and performance as light harvesting systems and as luminescent or magnetic probes. This work will be carried out under the supervision of Drs. Pike and Peacock in the Department of Chemistry.

Training and skills to be developed over the PhD: The candidate will develop a range of standard and advanced organic and biological chemistry synthetic skills. The candidate will also develop a wide-range of analytical skills and techniques over the course of the PhD including, UV/vis, circular dichroism (CD) spectroscopy, mass spectrometry, infrared spectroscopy, and NMR spectroscopy (including 1H and 13C NMR and 2D-correlation techniques) and single-crystal X-ray diffraction analysis. The candidate will develop a multi-disciplinary skillset with expertise in organic, biological and inorganic chemistry design, synthesis and characterisation (including crucially elucidating 3-dimensional structure), as well as cultivating important keys skills relating to science communication and developing the ability to tackle tasks through problem-based thinking and analysis. Upon completion of the PhD, the candidate will be equipped with the necessary skills to pursue a future career in academia or industry.

*Candidate Background and Interests:* Candidates should have an interest in or experience of synthetic organic and/or inorganic chemistry. Candidates should hold or expect to receive a good (1st or 2.1 UK or equivalent) degree in chemistry or a chemical sciences related subject.

**References:**

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[4] H. R. Marsden, A. Kros, Angew. Chem. Int. Ed., 2010, 49, 2988-3005.

[5] Slope, L. N.; Daubney, O. J.; Campbell, H.; White, S. A.; Peacock, A. F. A. (2021) Location dependent lanthanide selectivity engineered into structurally characterized designed coiled coils, Angew Chem., 2021, 60,24473-24477.