PhD PROJECT PROPOSAL

PhD Project Title

Controlling peptide topology to access a new class of MRI contrast agents

PhD Supervisory Team

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Project Abstract

This project will use topological design to access a new and highly novel class of MRI contrast agents (CAs). Peptide CAs based for the first time on Cu(II), will challenge the existing dogma that this paramagnetic metal is unsuitable for use in MRI CAs. This project will explore the relationship between topological peptide design (parallel vs antiparallel, oligomeric state, homo vs heteroassembly), Cu(II) binding and MRI CA performance, so as to develop an entirely new class of MRI CAs.

Detailed Project Description

This PhD project will develop a new class of Cu(II) coiled coils for use as MRI contrast agents, challenging the existing, mistaken, belief, that Cu(II) is unsuitable. Evaluating a broad range of peptide designs with different topological features, will allow for the establishment of key structure activity relationships (SARs). Using the correct topological design, the most efficient Cu(II) coiled coil MRI contrast agent can be prepared.

Background: Nature relies heavily on exquisite control of topology. One class of key biological molecules, proteins, feature a single, or multiple, chains of amino acids which fold with a well-defined complex 3D topology of helixes, sheets, loops and turns. It is estimated that around 50% of proteins feature bound metal ions which are essential for function. The bound metal ions role can include electron transfer, catalysis, binding of small ligands like oxygen, play a structure role, or triggering topological changes.

Miniature artificial proteins, which are designed to assemble with well-defined topology based on small robust folded segments, provide many of the advantages of native proteins, but without many of their limitations (fragile, highly complex). The majority are based on coiled coils, formed by the supercoiling of two or more alpha-helixes. Metal complexes of these coiled coils (see Figure 1), depend on the correct topology; parallel vs antiparallel, number of strands (ie 2-8), twist of coiled coil, staggered vs aligned, assembly of homo or hetero structures etc.

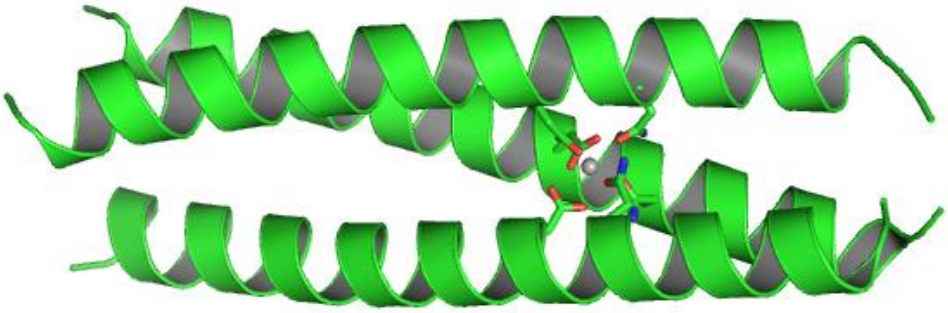

Figure 1. X-ray crystal structure of a designed parallel three-stranded homo lanthanide coiled coil.[5]

Almost all reported designed metallo coiled coils are biomimetic, attempting to reproduce the properties of native metal ion binding sites. However, though these provide important insight into Biology, they do not offer new function. The Peacock and Britton Groups have designed a coiled coil with the perfect topology for binding Gd(III) ions, the paramagnetic metal most widely used in clinical MRI contrast agents (CAs), and found them to display superior relaxivity (a measure of CA efficiency) than clinical Gd(III) CAs.[1-3] Thereby providing function beyond what Biology currently offers. Importantly the efficiency of the CA is highly dependent on the topology of the design, with linear translation of an otherwise identical metal binding site leading to a fourfold enhancement in relaxivity.[2]

We have recently established, for the first time, that Cu(II) coiled coils display extremely promising MRI relaxivity,[4] challenging the existing dogma, that Cu(II) is unsuitable for use in MRI CAs.

Project Objectives: This PhD project will explore this new class of Cu(II) coiled coils, and establish what are the key topological features which control MRI relaxivity, the measure of CA efficiency. This will be achieved by designing a library of coiled coils of differing oligomeric state, length, altered binding site location, parallel vs antiparallel, in an effort to establish the key structure “activity” relationships (SARs) by which new and improved designs can be accessed.

Outcomes and Methodology: The project is structured around the four goals listed below, and will be achieved by a combination of: automated peptide synthesis (CEM liberty Blue); HPLC purification; characterisation (MS, CD, UV-visible and fluorescence spectroscopy); and NMR evaluation (MRI relaxivity).

1) Synthesize a library of novel Cu(II) coiled coils with a range of different topologies

2) Evaluate MRI relaxivity and structures of above library
3) Establish key structure activity relationships
4) Design second generation Cu(II) coiled coils based on established SARs

Training and skills development: This project brings together expertise in peptide and protein design, synthesis and characterisation (Peacock) with MRI application and development (Britton). This powerful synergy will offer the student the opportunity to become expert in the broadest range of techniques and skills. Training and experience will be gained in MR imaging and relaxivity measurements, peptide design, synthesis and biophysical characterisation techniques (including, but not limited to, mass spectrometry, ultraviolet-visible, fluorescence and circular dichroism spectroscopy), as well as important keys skills relating to data analysis, problem solving and science writing/communication.

Suitability of the project for the CDT in Topological Design: The topology of designed coiled coils is essential to their structure and determines the identity and properties of the resulting metal binding site. The rational and predictable design of different topologies will generate a library of Cu(II) coiled coils. Key structure activity relationships (SARs) will be established between different topological design features and MRI relaxivity, in an effort to both improve upon, and, understand the mechanism by which this new class of Cu(II) MRI contrast agents function.

Research links with the supervising team: Dr. Peacock is a world-leader in the field of bioinorganic chemistry and metallo coiled coil design and has extensive experience in the design and synthesis of new topological architectures with tuneable physical properties. Dr Britton is a highly respected physical chemist and world-leader in applying MR imaging to understanding chemical processes.

Links with Research Strategies: This project strongly aligns with the School of Chemistry research sections (MSBC, for which Peacock is Head of Section) and I2S (Britton), as well its priority area “Health”. The research directly aligns with both the EPSRC Chemical Sciences and Engineering Grand Challenge: “Directed Assembly of Extended Structures with Targeted Properties” (for which Peacock is a Grand Challenge Leader for the “Controlling molecular self-assembly in biological and biomimetic systems”), and the EPSRC strategic priority “transforming health and healthcare…. through technological solutions”.

Candidate Background and Interests: Candidates should hold or expect to receive a good (1st or 2.1 UK or equivalent) degree in chemistry or related subject. Experience in bioinorganic chemistry, peptide design or physical chemistry is desirable but not essential.

References:

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[2] Berwick, M. R.; Slope, L. N.; Smith, C.; King, S. M.; Newton, S. L.; Gillis, R; Adams, G.; Rowe, A.; Harding, S.; Britton, M. M.; Peacock, A. F. A., *Chem. Sci.*, 2016, *7*, 2207

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[5] Slope, L. N.; Daubney, O. J.; Campbell, H.; White, S. A.; Peacock, A. F. A., *Angew. Chem. Int. Ed.*, 2021, *60*, 24473