**University of Leicester**

**Future 50 PhD Scholarship**

|  |  |
| --- | --- |
| **Project Reference** | RI LISCB Hudson |

|  |  |  |  |
| --- | --- | --- | --- |
| **First Supervisor** | Andrew Hudson | | |
| **School/Department** | Chemistry | | |
| **Email** | [ah242@leicester.ac.uk](mailto:ah242@leicester.ac.uk) | **Telephone Ext** |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Second Supervisor** | James Hodgkinson | | |
| **School/Department** | Chemistry | | |
| **Email** | jthodgkinson@leicester.ac.uk | **Telephone Ext** |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Second Supervisor** | Fred Muskett | | |
| **School/Department** | Molecular & Cellular Biology | | |
| **Email** | fwm1@leicester.ac.uk | **Telephone Ext** |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Second Supervisor** | Rebecca Hawker | | |
| **School/Department** | Chemistry | | |
| **Email** | r.hawker@leicester.ac.uk | **Telephone Ext** |  |

**Section 2 – *Project Information***

|  |  |  |
| --- | --- | --- |
| **Project Title** | Using synthetic chemistry and NMR to identify the ligand–substitution chemistry of haem in cells | |
| **Project Highlights:** | 1. | Two approaches will be used to learn about the transfer of haem molecules between protein-binding partners: one involving synthetic organometallic chemistry and the other involving protein NMR. |
| 2. | Synthetic variants of the tetrapyrrole ligand in haem will be prepared that can be photo-crosslinked to a transient protein-binding partner. |
| 3. | The effect of different haem-protein interactions on the secondary structure of a protein, and its ability to either bind to DNA or form heterodimers with other proteins, will be determined using NMR. |
| **Project Summary** | | |
| Haem is a small organic molecule containing iron at the centre. No eukaryote has ever been identified that can survive without heme. Thousands of different proteins are known in which a heme molecule is an integral component, and these are responsible for processes such as oxygen transport, electron transfer, respiration, metabolism of drugs, and all kinds of catalysis across the whole of the biological world. It is an amazing feat of Nature that such a simple molecule is pivotal to such a wide range of cellular biology, but it has emerged recently that this is just the tip of a much bigger iceberg. The recent literature describes an entirely new portfolio of other, more complicated, biological processes that are characterised by weaker (or transient) interactions between heme and protein ligands. In these examples, the heme group is not pivotal to the functional activity of the protein but is required intermittently to modulate protein behaviour via reversible binding to the side chains of certain amino acid residues (usually cysteines and histidines). Mechanisms for these interactions can be explained using the models for ligand-transfer reactions in transition metal complexes. In this case, the sites of ligand transfer are the axial positions in the heme (Fe-protoporphyrin IX) complex.  This project aims to uncover details about these ligand substitution reactions taking place in cells. Free molecules of haem are toxic and, therefore, molecules of haem must be chaperoned in cells by components (most-likely proteins) that reversibly bind onto the vacant axial coordinate sites. We wish to identify these proteins and characterise these binding interactions in the context of ligand-substitution chemistry.  We will also characterise the interactions between haem and proteins whose activity is modulated by haem binding. Important questions concern the location of the haem-binding site in these proteins, and the nature of any rearrangement in the secondary structure of the protein induced by haem binding.  Applicants for this PhD need to have an interest in synthetic organic chemistry and nuclear magnetic resonance (NMR) spectroscopy. The student will synthesise variants of the haem that can be photo-crosslinked to a transient protein-binding partner. The environment in the cell will be recapitulated *in vitro* using cellular extracts, and we will identify protein partners that interact most frequently with haem. We will subsequently characterise the binding interaction between haem and protein partners by NMR spectroscopy. We will also study the interactions between haem and proteins whose activities are known to be modulated.  Gallio, A. E.; Fung, S. S. P.; Cammack-Najera, A.; Hudson, A. J.; Raven, E. L. Understanding the Logistics for the Distribution of Haem in Cells. *JACS* Au 2021 <https://doi.org/10.1021/jacsau.1c00288>  Leung, G. C. H.; Fung, S. S. P.; Gallio, A. E.; Blore, R.; Alibhai, D.; Raven, E. L.; Hudson, A. J. Unravelling the mechanisms controlling haem supply and demand. *P Natl Acad Sci USA 2021*, 118, e2104008118; <https://doi.org/10.1073/pnas.2104008118> | | |