**University of Leicester**

**BBSRC MIBTP Studentship Project 2025-6 entry.**

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| **First Supervisor** | Dr. Hanna Kwon (she/her)  |
| **School/Department** | Molecular and Cell Biology  |
| **Email**  | hk295@le.ac.uk <https://le.ac.uk/people/hanna-kwon>  |

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| **Second Supervisor** | Prof. Andrew Hudson  |
| **School/Department** | Chemistry |
| **Email**  | ah242@le.ac.uk  |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | Unravelling the Mechanisms of Heme Delivery and Its Role in Cancer Biology  |
| **Project Summary**  |
| Heme is a vital small molecule involved in the function of numerous proteins. It plays key roles, such as binding oxygen in globins and facilitating electron transfer in cytochromes. Heme is synthesised in the mitochondria, however, we do not know the mechanism by which heme is transported to various cell compartments where it can be incorporated into different proteins. Since free heme is toxic, chaperone proteins that weakly bind and transport heme are essential for this process. Recently, a number of chaperone proteins, such as GAPDH, FLVCR1b, PGRMC1/2, etc., have been identified as important players in the heme delivery system, but the detailed molecular mechanisms behind heme transport pathways remains unclear.  In this PhD project, you will explore the mechanisms of intracellular heme delivery, focusing on how heme chaperones regulate the homeostasis of enzymes that are often overexpressed in cancer cells, namely the heme dioxygenases. Key questions include whether the suspected heme chaperones (named above) play a general role in intracellular heme delivery to dioxygenases, how they mediate heme binding and transfer, and how their interaction properties influence cellular heme transport.  You will: - Measure the heme-binding properties of wild-type and mutant heme chaperone proteins using isothermal calorimetry and UV-visible spectroscopy. - Evaluate the interaction of these chaperones with apo-heme dioxygenases and their ability to transfer heme using novel fluorescence techniques developed in the Kwon/Hudson laboratories. - Solve the structures of heme chaperone complexes and their interactions with the dioxygenases using cryo-electron microscopy (cryoEM), X-ray crystallography, and complementary spectroscopy techniques.  This project offers an exciting opportunity to deepen our understanding of a fundamental cellular process and its implications for cancer biology. The insights gained will not only shed light on the regulation and activation of heme dioxygenases but could also lead to novel therapeutic strategies for cancer and other diseases.  As a PhD student, you will gain a diverse set of interdisciplinary skills spanning structural biology, chemical biology, and biophysics.Techniques that will be undertaken during the projectMolecular Biology (cloning & mutagenesis) Protein expression and purification  Enzyme kinetics Confocal and fluorescent microscopy Protein crystallisation  Structure determination (X-ray crystallography & cryo-EM)  |
| **References** |
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