**University of Leicester**

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

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**Section 2 – *Project Information***

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| **Project Title** | Developing novel proximity-inducing molecules to modulate post-translational modifications   |
| **Project Summary**  |
| Proteins are not static building blocks of life but modified by chemical transformations know as post-translational modifications (PTMs). PTMs and their dysregulation have been linked to diseases including age-related diseases and even ageing itself.1 The vast protein diversity within organisms combined with the wide diversity of potential PTMs makes studying specific PTMs on individual proteins and their biological role/function a real challenge. To date, researchers attempt to achieve this by incorporating PTMs or PTM mimics into a selected protein of interest using genetic modifications or synthetic chemistry.2,3 However, although important, these strategies have real limitations. For example, incorporation of the PTM or PTM mimic requires bespoke genetic or synthetic chemical modifications. Additionally, the synthetic modifications are not compatible with endogenous proteins in their native environment, and genetic approaches require severe perturbations of the organism itself (incorporation of non-natural amino acids and modified enzymes).   In this studentship, as a novel approach to studying PTMs on endogenous proteins you will design, synthesise and biologically validate novel proximity-inducing molecules. Proximity-inducing molecules, or heterobifunctional molecules, are molecules encompassing two differing ligands (two different protein-binding partners), connected via a linker component. We hypothesise that by designing novel proximity-inducing molecules that can artificially induce a close proximity between a selected protein of interest and a PTM-altering enzyme this will result in the highly selective modification of the PTM on the protein of interest. We will be able modify specific PTMs on selected endogenous proteins in their native cellular environment and potentially in vivo with high selectivity and temporal control by simple addition of the proximity-inducing molecule. Hence, researchers will be able to study the effects of specific PTMs on selected proteins by a facile approach in real time and determine their significance and role on a particular biological function or disease.  Techniques in organic synthesis will be required to prepare novel proximity-inducing molecules differing in linker lengths, as the linker can be crucial for an effective artificially induced close proximity between the selected protein of interest and the PTM-modifying enzyme. These proximity-inducing molecules will be characterised and their purity determined using analytical techniques such as NMR, mass spectrometry and HPLC. Once characterised, the proximity-inducing molecules will be assayed in cells for their ability to modulate the specific PTM of study on the selected protein of interest. This will require techniques in cell culture, Immunoprecipitation (IP), western blotting and biological mass spectrometry to determine if the PTM has been successfully modified by the proximity-inducing molecule.  Techniques that will be undertaken during the project* Techniques in synthetic organic chemistry
* Analytical techniques including mass spectrometry, NMR spectrometry and HPLC
* Techniques in cell culture, immunoprecipitation, western blotting and biological mass spectrometry
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| **References** |
| 1. Q. Zhong, X. Xiao, Y. Qiu, Z. Xu, C. Chen, B. Chong, X. Zhao, S. Hai, S. Li, Z.  An, L Dai, 2023, Protein posttranslational modifications in health and diseases: Functions, regulatory mechanisms, and therapeutic implications*. MedComm*, 4(3), p.e261. 2. O. Harel and M. Jbara, 2022, Posttranslational Chemical Mutagenesis Methods to Insert Posttranslational Modifications into Recombinant Proteins. *Molecules*, 27(14), p.4389. 3. W. Niu and J. Guo, 2023, Co‐translational Installation of Posttranslational Modifications by Non‐canonical Amino Acid Mutagenesis. *ChemBioChem*, 24(9), p.e202300039.  |