**University of Leicester**

**BBSRC MIBTP Studentship Project 2024-5 entry.**

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| **Project Reference** |  |

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**Section 2 – *Project Information***

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| **Project Title** | *Molecular Glues as Novel Tools for Tackling Big Challenges in Human Health*  |
| **Project Summary**  |
| **Background:** The need for new medicines is greater than ever because of an ageing population and the complex clinical challenges brought about by drug resistance and/or side effects. These problems are particularly acute in the oncology and neurodegeneration therapeutic areas, and this a significant negative impact on society and the economy. As a result, the focus of drug discovery has shifted in recent years away from classical enzyme inhibitors (e.g. kinase inhibitors) to even more challenging targets. Protein-protein interactions (PPI), and in particular inhibitors of these interactions, are at the forefront of this revolution: venetoclax has recently become the first PPI inhibitor approved for the treatment of chronic lymphocytic leukaemia.However, PPI inhibition alone does not fully exploit the potential scope and power of PPIs as drug targets.   Using drugs that act as **molecular glues**, to **stabilise** the interaction between proteins, is a highly novel therapeutic strategy that can greatly expand the number, effectiveness and precision of available treatments. This project will build on exciting discoveries in our labs. We have found that covalent, or irreversible, molecular glues that target specific interactions of an important family of ‘hub’ proteins called 14-3-3 is a highly effective strategy for PPI stabilisation that could address a range of disease states including cancer and neurodegeneration.   **Project Aim:** The aim of the project will be to optimise and refine this therapeutic approach. This will be achieved by studying the role of cysteine amino acids in 14-3-3 proteins. Cysteine is crucial because its nucleophilic properties make it the ideal site for covalent protein modification. In addition, gain of cysteine mutations to 14-3-3 is significant in neurological diseases.  We will take an interdisciplinary chemical biology approach to develop more efficacious and selective molecular glues. Ultimately, we aim to deliver new chemical tools for to help further our understanding of disease, and drugs that can be translated into clinical use.         **Methodology and Training:** The project will be interdisciplinary in nature, combining elements of chemical biology, cellular biology, and structural biology. It will provide excellent training for students who are motivated to go to pursue careers in the fields of drug development, molecular diagnostics, or medical R&D.  **Techniques that will be undertaken during the project**This project bridges the interface between biology and chemistry by integrating cellular biology, structural biology and chemical biology approaches to develop novel molecular glues. The glues will facilitate the emergence of stabilising protein-protein interactions as a new tool for studying and exploiting the physiological roles of protein-protein interactions.  |
| **References** |
| **References:** *Tracking the mechanism of covalent molecular glue stabilization using native mass spectrometry*, [Carlo J. A. Verhoef](https://pubs.rsc.org/en/results?searchtext=Author%3ACarlo%20J.%20A.%20Verhoef),   [Danielle F. Kay](https://pubs.rsc.org/en/results?searchtext=Author%3ADanielle%20F.%20Kay), [Lars van Dijck](https://pubs.rsc.org/en/results?searchtext=Author%3ALars%20van%20Dijck),  [Richard G. Doveston](https://pubs.rsc.org/en/results?searchtext=Author%3ARichard%20G.%20Doveston), [Luc Brunsveld](https://pubs.rsc.org/en/results?searchtext=Author%3ALuc%20Brunsveld),  [Aneika C. Leney](https://pubs.rsc.org/en/results?searchtext=Author%3AAneika%20C.%20Leney)  and  [Peter J. Cossar](https://pubs.rsc.org/en/results?searchtext=Author%3APeter%20J.%20Cossar), *Chem. Sci.* **2023**, 14, 6756-6762. *Contemporary Biophysical Approaches for Studying 14-3-3 Protein-Protein Interactions*, B. Thurairajah, A. R. Hudson, R. G. Doveston, *Front. Mol. Bioscience*, **2022**, 9:1043673.  *Cooperative Stabilisation of 14-3-3 Protein-Protein Interactions via Covalent Protein Modification*, M. Falcicchio, J. A. Ward, S. Y. Chothia, J. Basran, A. Mohindra, S. Macip, P. Roversi, R. G. Doveston, *Chem. Sci.* **2021**, 12, 12985-12992.  |

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