**University of Leicester**

**Chemistry GTA Studentship Project 2022**

**Section 1 – *Supervisor Information***

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| **First Supervisor (Name and Title)** | Dr. Richard Doveston |
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**Section 2 – *Project Information***

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| **Project Title** | A Bespoke Screening Platform for Discovering Protein Molecular Glues as Novel Therapeutic Agents |
| **Project Highlights:** | 1. | Interdisciplinary chemical biology |
| 2. | Novel drug discovery technology |
| 3. | New concepts in medicinal chemistry |
| **Project Overview**  |
| The need for new medicines that work through novel and unorthodox mechanisms is more striking than ever because of increased resistance to existing drugs such as antibiotics and cancer therapies. In this project we will develop a drug discovery platform that can specifically identify and profile a highly novel drug class with huge potential: protein-protein interaction (PPI) stabilisers, or ‘molecular glues’. Using molecular glues to stabilise protein-protein interactions has the potential to be a highly effective strategy across a multitude of, as yet, unexplored drug targets. Despite the potential, there is a distinct lack of R&D programmes dedicated to molecular glue discovery within the pharmaceutical sector. One reason for this is that PPI stabilisation does not adhere to the classical rules of drug discovery. Therefore, existing high-throughput discovery methodologies lack the versatility and sensitivity to identify relevant ‘hit’ molecules that feed the developmental pipeline.This project will directly address this issue by developing a high-throughput screening platform specifically geared toward identifying molecular glues. The Doveston group has recently developed a high-throughput fluorescence-based approach to detect molecules that bind at the interface between two interacting proteins. Such molecules are the ideal starting points for optimisation into potent and selective molecular glues. We now want to further develop this technology into a versatile ‘PPI Interface Modulation Screen’ (PIMS).PIMS will uniquely combine biorthogonal chemical reactions and biophysical analytical techniques to identify molecules that bind at PPI interfaces, and assess their activity in a simultaneous manner. This approach is advantageous because molecules can be profiled according to binding and activity in order to prioritise hits for follow-up validation. It avoids inadvertent disregard, or complete oversight, of promising starting points for optimisation that may show non-classical profiles i.e. high activity but low affinity binding, or high affinity binding but low activity. The PIMS technology has the potential to kick start pharmaceutical R&D programmes dedicated to the discovery of novel molecular glue medicines. Given the vast scope of potential PPI targets, this presents a unique opportunity to develop treatments for diseases that present the biggest challenges to our society today and in the future.  |
| **Methodology**  |
| As a developmental case study we will focus on the PPIs of an important hub protein called 14-3-3. 14-3-3 binds to a range of binding partners in order to modulate their activity. It is an ideal test bed because many of the interactions can be stabilised by molecular glues. In addition, 14-3-3 PPIs are an emerging class of drug targets in their own right. The project will be carried out in four phases:**Phase 1:** Refine target-guided synthesis methodology as a means to ‘capture’ novel ligands that bind in proximity to PPI interfaces.**Phase 2:** Optimise a fluorescence-based thiol quantification assay developed in the Doveston group to detect interface ligand binding in a high-throughput manner. **Phase 3:** Develop the PIMS technology that quantifies ligand binding and qualitatively profiles biological activity by hybridising the thiol quantification assay with fluorescence polarisation methodology.**Phase 4:** Demonstrate the potential impact of PIMS by screening bespoke libraries and commercial compound collections against the 14-3-3 interaction with the estrogen receptor α. |

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| **References** | *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.*Discovering Protein-Protein Interaction Stabilisers by Native Mass Spectrometry*, J. Bellamy-Carter, M. Mohata, M. Falcicchio, J. Basran, Y. Higuchi, R.G. Doveston, A. C. Leney, *Chem. Sci.* **2021**, 12, 10724-20731. |