**University of Leicester**

**Future 50 PhD Scholarship**

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| **Project Reference** | RI LISCB Hall |

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| **First Supervisor** | Dr. Gareth Hall | | |
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| **Additional Supervisor** | Dr. Christine Prosser  Group Leader, UCB |

**Section 2 – *Project Information***

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| **Project Title** | **Pioneering use of bovine knob domains for an antibody-assisted structure-based drug discovery approach to identify small molecule hits against proteins involved in chronic inflammatory diseases.** | |
| **Project Highlights:** | 1. | Innovative antibody-assisted drug discovery |
| 2. | Targeting cytokines involved in inflammatory conditions |
| 3. | Industrial Collaboration with UCB |
| **Project Summary** | | |
| The project will focus on pioneering the application of innovative antibody-assisted drug discovery (A2D2) approaches for a selection of proteins shown to be key drivers of chronic inflammatory conditions and respiratory diseases, such as IL-4, IL-5 and IL-13. This will involve the generation of diverse panels of high affinity antibodies and nanobodies against cytokines demonstrated to be fully validated inflammatory drug targets, to allow the identification, characterisation and exploitation of new opportunities for drug discovery. This project would be an opportunity to further capitalise on the expertise developed within our research group and allow us to investigate the use of bovine knob domain nanobodies, as an alternative to single chain antibodies (VHHs), to understand how these smaller modalities access different epitopes, stabilising novel target protein conformations and allowing us to access regulatory sites. Fundamentally, this will improve the probability of obtaining structural data to facilitate the identification of functional, small molecule hits. Complex structures obtained for a selected portfolio of antibodies and nanobodies bound to target proteins will provide an essential foundation for both structure-based design and fragment-based screening approaches to obtain small molecule modulators of activity, providing a novel and potentially more effective route to develop small molecule therapeutics.  The aim of this project is to identify new opportunities for inflammatory drug discovery, which could be progressed to produce new candidate small molecule therapeutics. The planned work will include a number of attractive and tractable targets for the proposed project, including, but not limited to, cytokines involved in chronic inflammatory conditions. The PhD project will provide thorough research training in many aspects of protein science, structural biology and functional assays, and to give the student first-hand experience of drug discovery in collaboration with the biotechnology company UCB Biopharma.  References:   1. Kang-Pettinger, T., at al., (2022) Identification, binding and structural characterisation of a diverse panel of single domain anti-PD-L1 antibodies inhibitory of PD-1 and CD80. Accepted to J. Biol. Chem. 2022. 2. Macpherson, A. (2021) The allosteric modulation of complement C5 by knob domain peptides. eLife. 10:e63586. 3. Hall, G., et al., (2016) Structure of a potential therapeutic antibody bound to IL-16:  mechanistic insights and new therapeutic opportunities. J. Biol. Chem. 291, 16840-16848. 4. Macpherson, A. (2020) Isolation of antigen-specific, disulphide-rich knob domain peptides from bovine antibodies. PLOS Biology. 5. Gandhi, N.A., et al., (2015) Targeting key proximal drivers of type 2 inflammation in disease. Nat. Rev. Drug Discov. 15, 35-50. 6. Lawson, A.D.G. (2012) Antibody-enabled small-molecule drug discovery. Nat. Rev. Drug Discov. 11, 519-525. | | |