**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | Novel NMR-technologies for the assessment and quantification of allosteric- and dynamic effects affecting protein-drug interactions; application to cancer drug targets. |
| **Project Summary**  |
| **Background**. There is an urgent and unmet need for new drugs to treat major human diseases, including many types of cancer. Structure-based drug discovery, design and development (SBD3) has been developed as a major translational research focus at Leicester and NMR-based methods are instrumental to characterise complexes formed between target proteins and potential drug-like molecules. In the SBD3 approach, structural data drive the rational modifications to obtain optimised molecules with better properties and which bind with higher-affinity. However, this process largely ignores the effects of dynamics and allostery in the target proteins, thereby too often resulting in failure to progress the process.  **Aim of the research**. Nuclear Magnetic Resonance (NMR) is an experimental technique exquisitely suitable to probe and quantify dynamic effects suitable to assess and quantify dynamical processes affecting small molecule (drug) binding to proteins. Hence, in this project we will employ and develop a suite of NMR experiments that, when combined with computational procedures such as MD and docking and AI, yields a powerful experimental toolkit. We aim to use these NMR techniques for a systematic analysis of the influence of the dynamical aspects of protein-mediated interactions for the SBD3 processes. **Approach**. We plan to study three cancer-relevant drug targets. By systematically examining a series of protein-small molecule complexes or protein-protein complexes for the effects, extend and changes of the protein dynamical processes, we aim to establish its influence on the progression towards tighter,  better or allosteric binders. The three systems are: The members of the BCL-2 family of proteins and their effectors, responsible for programmed cell death. The RAS binding domain (RBD) of human BRAF that mediates a crucial step in the activation of serine/threonine BRAF kinase which functions in the MAPK signalling pathway. The programmed Cell Death 4 (PDCD4) protein that regulates synthesis by binding to the translation initiation factor eIF4A; loss PDCD4 is observed in various cancers and correlates with poor prognosis. Techniques that will be undertaken during the project:* Advanced biomolecular NMR spectroscopy, including unique equipment at the Birmingham national NMR facility
* Advanced data analysis, including AI, using the tools of the CCPN Analysis programme suite (developed by Prof. Vuister’s research group)
* Molecular dynamics modelling.

BBSRC Strategic Research Priority: Understanding the Rules of Life - Structural Biology |
| **References** |
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