Project outline

1. Project outline describing the scientific rationale of the project

**Background:** Fragment-based drug design (FBDD) has shown increasingly delivered important new drugs for challenging pharmaceutical targets. Fragments possess a number of attractive features, from having low molecular weights to be more polar and soluble than larger “drug-like” compounds; these characteristics are often thought to translate into compounds with favourable physical properties, pharmacokinetics/bioavailability, and ADME/toxicology properties. NMR has become a preferred method for identifying fragments that bind to a protein or nucleic acid target of interest. FBDD is based on screening of thousands of compounds against a selected biological target. Ligand-observed NMR experiments are governed by chemical exchange. In general, ligand binding to a macromolecule translates into shortened relaxation time of the complex relative to the free ligand. Once fragments bind have been identified, the objective is then to design potential “drug-like” compounds by either growing the fragment, linking fragments together, or merging fragments onto existing scaffolds for the target. Crucially, identifying the binding pockets and 3D information on the fragments has traditionally been done by X-ray Crystallography. Data from industry (ZoBio; a small pharmaceutical company with expertise in FBDD and partner in the project) indicate that in as much as 50% of the cases, the X-ray crystallography data are (partially) wrong or incomplete at best, likely resulting from non-native conditions, such as crystal packing and low temperature. NMR spectroscopy studies the systems under much more native system and the combined NMR and X-ray data together yield a much better route to FBDD.

**Objective:** to develop both experimental NMR and computational approaches for FBDD that increase both accuracy and reliability as well as the speed of throughput.

We will target the process of lead optimization for improving drug-like properties of the hit and work on integration of small-molecule (NMR-assisted) 3D structure and docking procedures.

**Context:** Prof. Vuister is a member of the Department of Molecular and Cell Biology of the UoL and is a core member of the recently founded Leicester Institute of Structural and Chemical Biology (LISCB) centre of excellence, which has structure-based drug design as one of its core themes. Very recently, Prof. Vuister was awarded a continuation of his BBSRC grant, which aims to capture the structural variability inherently present in proteins from readily available NMR data. In addition, MRC funded the continuation of his Collaborative Computational Project for NMR (CCPN) partnership grant. This project
develops computational NMR technology. Both these two projects will greatly reinforce the studentship.

Within LICSB, one MRC and two BBSRC iCase PhD students and several other PhD students engage with related drug discovery focussed research projects, thus providing the ideal environment and support. Additionally, LICSB-PI Prof. Carr has established a very strong track record in knowledge-based drug discovery supported by strategic, long-term research partnerships with UCB-Celltech, the drug discovery charity Medical Research Council Technology (MRCT) and he is also the co-lead for a new, multi-centre, structure-based drug-discovery initiative to support CRUK, thus providing additional relevant context to the project. I would propose he acts as a co-PI on the project.

**Relevance to BBSRC and Approvals**

1. **How does this project fit within the remit of the BBSRC?**

   The project engages the student with an exiting and highly relevant technological and scientific environment, allowing him/her to explore his/her knowledge, strengths and weaknesses training him/her with the skills required to tackle the future biosciences research challenges. The high quality training in all areas provided to the student will develop his/her skills considerably and contribute to BBSRC’s strategic aim to maintain world-class UK bioscience by supporting the best people and best ideas.

2. **Select the relevant BBSRC Strategic Research Priority:**
   - World Class Underpinning Bioscience

3. **How does the project comply with BBSRC’s requirement for multidisciplinarity and new ways of working?**

   The project advances interdisciplinary research, applying experimental and computational techniques to the next challenges in Biosciences, in line with the BBSRC’s Bioscience in Health strategic priority.

4. **Please list the techniques that will be undertaken during the project.**

   - Protein expression, purification and characterization
   - High-resolution multidimensional heteronuclear NMR Spectroscopy
   - Ligand screening using various biophysical techniques
   - Scientific software development and data analysis