Developing better biopharmaceuticals using biomolecular simulation and design

Supervisory team:
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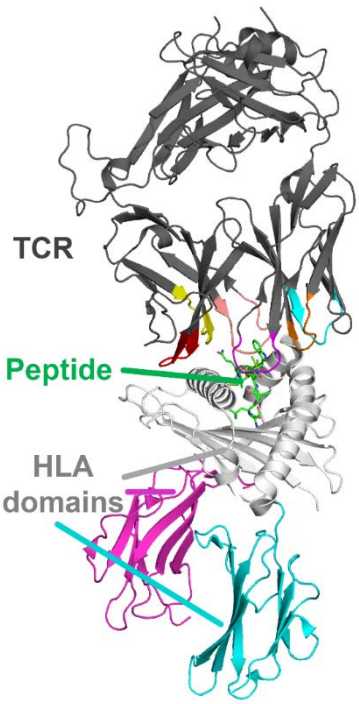
Host institution: University of Bristol
CASE partner: Immunocore Ltd

Project description:
Most biomolecular interactions are thought to increase the (local) rigidity of a complex and this is often exploited when designing new (small-molecule) drugs. However, for biopharmaceuticals, tuning the dynamics and flexibility of interactions is potentially a pathway to potent and specific 'biologic' drugs. We focus on the Human Leukocyte Antigen (HLA), which plays a crucial role in the adaptive immune system by presenting peptides for recognition by the αβ T cell receptor (TCR). The role that the peptide plays in TCR recognition is potentially crucial in determining the functional outcome of an immune response. Our recent work (in review) indicates that the recognition peptide is able to modulate the conformational dynamics of the HLA and that these changes are detected by the TCR, resulting in substantial changes in TCR-peptide-HLA binding affinity. Developing new biopharmaceuticals incorporating information on molecular dynamics is a new paradigm for the design of peptide-based drugs and opens up new opportunities for therapeutics.

Computational (molecular dynamics) simulation is ideally placed to explore and predict the potential of new peptide-based drugs. In particular, the use of enhanced sampling allows the exploration of very large effective time-scales key to accurately capturing the molecular dynamics of TCR-peptide-HLA binding and binding-free energy calculations can now accurately predict affinities. Using these approaches, combined with complementary experimental tools and comparison with extensive (structural and affinity) in-house data from the industrial partner, the project will develop the ability to rationally design peptide-based drugs for T cell activation.



The project is truly cross-disciplinary, incorporating new advances in computational simulation and in silico protein design, novel experimental techniques to complement the computational work, and the direct involvement of an ideal industrial partner. The student will be embedded in the Bristol Computational Biochemistry group (www.bristol.ac.uk/bcompb), ensuring fruitful interactions with other computational biochemists and ample computational resources. Notably, the student will further have the advantage of spending time in different research environments (Bristol, Bath and with the industrial partner, Immunocore). The training potential for the student is outstanding and will enable to the successful student to develop their career in the commercially relevant and growing (computational) biopharmaceutical area. We expect the student will attend and present at appropriate national and international conferences as well as interact extensively with industry to present work to stakeholders.