Towards new biologic drugs: In silico design of T-cell receptor affinity and specificity with biomolecular simulation

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

Project description:
When designing traditional small-molecule drugs, the molecular design principles are usually straightforward: optimize a (typically rigid) scaffold by increasing atomic interactions with a specific protein target to achieve high binding affinity. For biopharmaceuticals, however, the detailed dynamics and flexibility of interactions requires careful fine-tuning to develop 'biologic' drugs that are both potent and specific. This project will focus on the use of detailed modelling and dynamics simulation to understand and optimize the interactions between the αβ T-cell receptors (TCRs) and Human Leukocyte Antigens (HLA) that present specific peptides (derived from intracellular proteins), or pHLAs. Immunocore, the industrial partner for the project, has demonstrated how soluble TCRs that target specific pHLAs can be developed into cancer-cell killing biologic drugs. Our recent work with Immunocore, using atomistically detailed computer simulations (molecular dynamics), has identified that the dynamic interactions between TCRs and pHLAs govern both the affinity and specificity of TCRs. This knowledge can be exploited for designing new biopharmaceuticals that target specific cancers as well as infectious and autoimmune diseases.

Computational (in silico) approaches are widely recognized as essential to accelerate the drug development process. Using our current knowledge on how TCR-pHLA dynamics inform on affinity and specificity, this project will replicate experimental workflows that develop initial TCR hits into lead drugs. This will involve development, testing and evaluation of these in silico workflows. Combining rapid computational protein redesign with TCR-pHLA molecular dynamics simulation in-silico designed variants will be evaluated experimentally. This will demonstrate a new paradigm: developing new biopharmaceuticals by incorporating information from molecular dynamics simulations.

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 close involvement of the ideal industrial partner. The student will be embedded in the active biomolecular design and simulation community in Bristol (e.g. Bristol Biodesign Institute; Bristol Computational Biochemistry group), 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). The extensive training will enable the successful student to develop their career in the commercially relevant and growing (computational) biopharmaceutical area.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.