Biosensing using arrays of de novo designed proteins

Supervisory team:
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Host institution: University of Bristol

CASE partner: Rosa Biotech

Project description:

In de novo protein design entirely new proteins structures and functions are built from scratch. This is basic science that tests our understanding of sequence-to-structure/function relationships of natural proteins. It also presents possibilities for generating protein structures not yet observed in nature (Woolfson et al., (2015) Curr Opin Struct Biol 33 16). In applied science, it offers routes to hyperstable proteins with functions not performed by natural proteins.

Over the past 5 – 10 years, protein designers have delivered increasingly complex stable de novo proteins that fold and assemble as prescribed. This has come through improvements in our understanding of sequence-to-structure relationships in proteins, advances in computational design methods, the reduced cost of synthetic peptides and genes, and increased speeds of high-throughput screening of protein libraries. These advances set new targets for the field of de novo protein design. One of these challenges is to make functional de novo proteins with potential applications in biotechnology and medicine.

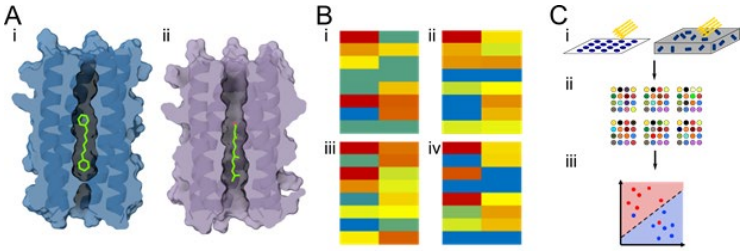

Figure 1- Figure: A: i. HB with a small-molecule dye, DPH, modelled into the pore. ii. X-ray crystal structure of an HB:farnesol complex. B: Fluorescent fingerprints for (i) a biomarker, cholesterol, (ii) an explosive precursor, hexamethyltetramine, (iii) a nerve-agent mimic, triisopropylphosphonate, and (iv) a peptide hormone, insulin. C, In Barrel Array Diagnostics And SenSing (BADASS): (i) Dye-loaded HBs immobilised on chips or in

Recently, the Woolfson group has discovered and developed an entirely new class of de novo proteins called alpha-helical barrels (aHBs; Thomson et al., (2014) Science 346 485). These have central cavities that recognise and bind small molecules, e.g. biomarkers of disease including cancers. aHBs resemble receptor proteins of the mammalian olfactory system. However, unlike these natural receptors, which are membrane proteins, aHBs are water soluble, hyperstable and easy to produce and manipulate. In collaboration with a University of Bristol spin-out company, Rosa Biotech, we are developing aHBs as components of a novel biosensor to mimic the sense of smell; essentially, we are trying to construct a biochemical nose from scratch. This is necessarily interdisciplinary science, as it has to bring together chemistry, structural biology and photophysics to make it work.

The proposed PhD project builds on our foregoing work and the academia-biotech collaboration. It aims to train the student at these interfaces specifically in rational and computational protein design, X-ray crystallography, and the development of diagnostic devices. In addition, the project brings in a new academic collaboration in chemical physics and spectroscopy through the Oliver group. In this way, the student will not only be able to design and characterise new proteins biochemically and structurally, they will also be able examine how these proteins interact with fluorescent dyes that Rosa Biotech uses in its innovative technology.