BBSRC Doctoral Training Partnerships

UNIVERSITY OF CAMBRIDGE

Cambridge BBSRC DTP – Industrial Biotechnology and Bioenergy sample projects

(Students are provided with a list of ~150 projects to select from, these are just a sample)

Rotation projects

Modelling the dynamics of systemic bacterial infection

Department of Veterinary Medicine

Salmonella enterica is a major cause of systemic bacterial disease in developing countries. We use experiments in mice to study the early dynamics of infection and its response to vaccination or antibiotic treatment. Over the last 10 years, we have gained unprecedented insight into host-pathogen interactions by combining genetic engineering of bacterial strains and mathematical models.

In this project, the student will analyse recent experimental data using state-of-the-art statistical tools developed in our group. The objective will be to quantify the timing and intensity of bacterial transfer among organs during the course of infection under different treatments.

Some programming skills and familiarity with the R environment are required, but there is room to accommodate a range of skillsets. This project can lead to a full PhD with the aim of developing similar models to other experimental systems using published and original data from international collaborators.

Synthetic patterning circuits

Department of Plant Sciences

Cell-free extracts are capable of driving high levels of transcription and translation in vitro. These provide a simple system for rapid testing of genetic circuits. Forms of genetic logic can be constructed from modular regulatory and signalling elements and implemented in cell free extracts. DNA circuitry will be immobilised on solid-state surfaces and assayed in fluid chambers. Feedback regulated patterning processes will be monitored by production of reporter genes.

The project will provide training in Synthetic Biology techniques including modular DNA assembly, advanced microscopy, quantitative imaging, circuit design and evaluation.

Chemically modified natural materials for sustainability

Department of Chemistry

This project will focus on chemical modification of natural materials that have low embodied energy and / or environmental impact. The ultimate goal is to use modified natural materials as alternatives to more traditional manufactured materials like concrete and steel for tall timber buildings. Chemical modification wood and grass-based natural materials show better macroscopic properties, which can be achieved by combining complex functional materials (aqueous natural polymers and dynamic shear-thinning gels) with natural long-fibre structural material such as timber or bamboo. Preservation and prevention of wood degradation for the built environment as well as in historical artifacts will be explore by structurally-modifying porous matrix materials such as wood. Physical properties of natural macromolecules located in the plant cell wall such as chitosan or cellulose can be modified through simple chemical modifications. These modifications will aim to lower the viscosity of the macromolecules enabling diffusion through the wood matrix. After impregnation, the material properties of the wood can be further tuned by external stimuli enabling network formation of the chemically-modified macromolecules by selectively turning on self-assembly. This would result in an improvement in the structural stability of the wood.

The rotation student will explore a variety of synthetic strategies and chemical functionalisation techniques as well as macromolecular self-assembly methods for the natural macromolecules. S/He will also learn synthetic and material characterisation techniques such as solid state NMR, UV-VIS, IR and rheology.

Development of a bacterial spore-based drug delivery system

Department of Chemical Engineering and Biotechnology

Bacterial spores are the most robust cells in nature. They are formed by a limited number of species in response to nutrient starvation, and remain locked in a dormant state until stimulated to return to life by certain small molecular germinants.

Preliminary work conducted in the Christie lab has indicated that the sporulation machinery can be modified to direct the developing spore to synthesise and deposit a range of macromolecular therapeutic molecules (insulin, human growth hormone, antibodies) into the spore core. Hypothetically, these fragile molecules can then be stored securely inside the spore under ambient conditions for perhaps thousands of years (!), removing the burden and costs associated with cold storage of biopharmaceuticals. Additionally, protection conferred by the spore offers the possibility of oral delivery for some of these drugs, circumventing numerous problems associated with parenteral administration.

The purpose of the proposed project is to continue to optimise the development of the spore delivery system, using principally molecular genetic and biochemical techniques to:

(i) extend the range of biopharmaceuticals that can be synthesised
(ii) assess the structure and function of therapeutic proteins released from disrupted spores.

Scope exists also to work on novel phage- and enzyme-based systems that are being developed to release the therapeutic payload upon triggering spore germination.

Investigation of off-pathway oligomer formation on the physical stability of therapeutic peptides

Department of Chemistry

Biologics – protein and peptide-based drugs – are fast becoming the most important therapeutic agents in the 21st Century. Their use is set to rise astronomically in the next ten years as they are shown to be efficacious against a very wide range of diseases states, including diabetes and cancer.

However, problems with the physical stability of therapeutic proteins and peptides prevents their development and use in numerous cases, despite their efficacy and activity in vivo. In these cases, the formation of soluble oligomers, and insoluble aggregates such as amyloid fibrils results in major issues of formulation and use.

In this project, a range of biophysical techniques will be used to investigate the conditions under which our model peptide system, GLP-1, forms on versus off-pathway oligomers, and their influence on the overall aggregation pathway will be assessed. The project will also use relatively straightforward modelling methods to understand mechanistic details of the aggregation processes.

Techniques that will be used will include several fluorescence-based methods, DLS, FT-IR, AFM, far-UV CD, AF4, UPLC and possibly mass spectrometry. The peptide will be provided by Medimmune, however, there will also be the opportunity for the student to undertake peptide synthesis themselves within the Department if they so wish, in order to address important issues on peptide purity and aggregation.

The student will be based in the Chemistry Department but have lots of opportunity to work with key teams at MedImmune including those of Dr dos Santos and Dr Lindo.

PhD projects

Engineering E. coli export pipes: a new platform technology for the synthesis and one-step secretion of therapeutic proteins

Department of Pathology

E. coli has long been the bacterial workhorse of the biopharmaceutical industry, used for production of important therapeutics including insulin (Eli-Lilly) and Roferon-A (Hoffman-LaRoche).

Current processes involve purification of recombinant proteins that are trapped inside the E. coli cell, either in the cytoplasm or in the periplasm. This approach has several limitations, in particular, the need for extensive downstream processing to remove extraneous bacterial proteins and other macromolecules, including the potent immunostimulant lipid A.

One potential way to simplify the process would be to engineer E. coli to secrete newly synthesised recombinant proteins directly into the extracellular environment, an approach that has strong potential as an enabling tool for efficient production of biopharmaceutical proteins.

One natural E. coli export pathway that could be exploited for one-step secretion of therapeutic proteins is the flagellar Type III Secretion System (fT3SS). Flagella are complex rotary nanomotors for bacterial motility. Remarkably, these cell-surface structures are essentially self-assembling, with thousands of structural subunits being exported out of the cell by a dedicated fT3SS located at the base of each flagellum.

The aim of the proposed project is to engineer E. coli to optimize the function of flagella as export pipes for one-step secretion of recombinant therapeutic proteins from their site of synthesis to the extracellular environment.

The project will employ synthetic biology techniques to:

(i) construct bespoke expression vectors for high-level production of recombinant therapeutic proteins that are targeted specifically to the fT3SS
(ii) streamline flagella to improve their function as gated export channels.

Development of RNA-based regulatory elements for whole cell biosensors

Department of Pathology

Whole-cell biosensors are based on living cells that produce a detectable responses to target analytes, for example the Arsenic Biosensor Collaboration is engineering Bacillus subtilis to visually report concentrations of arsenic in water samples [1,2]. Such biosensors may be constructed by transforming cells with synthetic genetic circuits that define sensing, processing and reporting functions.

In order for such sensors to be useful in the field, these sensors should be able to provide simple-to-interpret human-readable outputs and should be robust to environmental perturbation. For example, arsenic concentration in drinking water should be determined independent of variations in temperature and other metal ions and be reported as a simple binary output (e.g. "toxic" vs "safe").

We are currently developing genetic signal-processing tools to achieve this, based for example on protein transcription factors and non-coding RNA regulators (including CRISPR-Cas9). RNA-based regulatory components are particularly appealing for such tools because response-times may be reduced and properties such as specificity and affinity may be more easily tuned.

The aim of this project is to build and characterise genetic signal-control mechanisms that would control for environmental perturbations to whole-cell biosensors.

Cell wall architecture - the role of proteoglycans

Department of Biochemistry

Plant cell walls constitute most available renewable carbon and can be used for building construction, energy, animal feed and human food. The architecture of secondary cell walls-the way the components interact-determines the properties and digestibility of the plant material.

This PhD project will investigate an abundant class of proteoglycans in cell walls. We have evidence for an exciting, unexpected role of these proteins.

To determine their role in secondary cell wall function, bioinformatics will identify candidate genes, Arabidopsis mutants will be genetically screened, and proteoglycans in stem cell walls will studied. Material and saccharification properties of the stem cell walls of the mutants will be used to determine the function of these proteoglycans.

Factors affecting the physical stability of therapeutic peptides

Department of Chemistry

The physical instability of peptides and proteins is an enormous problem for many pharmaceutical and biotech companies. In particular, despite the fact that biologics (biological agents used as therapeutic drugs, e.g., peptide hormones, monoclonal antibodies etc), are increasingly important in targeting many different disease states, their clinical use is still greatly restricted by problems in their physical instability. For therapeutic peptides, long-term physical stability in terms of aggregation, remains a challenging issue.

This project will study the different factors that affect the physical stability of modified (e.g., lipidated) and non-modified peptides in order to understand the factors that affect aggregation processes. Many different biophysical techniques will be used to study the system, including kinetic approaches and also some computational modelling of different kinetic pathways.

The project will be able to assess some of the following factors:

1. Effect of chemical modification
2. On-pathway (fibril formation) versus off-pathway (formation of large oligomeric structures) processes.
3. The effect of the methods of peptide synthesis, purification, storage etc.
4. The effect of freeze drying, surfaces, pressure, and other processing steps.

Although this is a project that has great potential impact in terms of developing methods for preventing/limiting peptide/protein aggregation in vitro, this will be a fundamental study of peptide aggregation whose main aim is to understand the phenomenon at an atomic/molecular level.