Cambridge BBSRC DTP – Bioscience for Health sample projects

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

Rotation projects

Network development and dysfunction in a mouse model of autism

Department of Physiology, Development and Neuroscience (PDN)

Many synaptic defects have been identified in mouse models of autism based on known gene mutations. Yet little is known how these synaptic deficits alter the development of neuronal networks. In this project, we will culture early postnatal cortical neurons on 64-grid multi-electrode arrays (MEAs) to investigate how spontaneous network activity develops in wild-type cultures with high temporal precision and how this process is disrupted in the neurons with the autism-related mutations.

This project will address both basic science aims to understand network development and translational science aims to identify disease mechanisms and test potential new therapies. Student will have the opportunity to learn tissue culture, recording, and computational techniques.

Background in computer science and/or mathematics is preferred. Student with strong computational background will have opportunity to develop new methods for analysing network development.

Spinal cord function in the invertebrate chordate amphioxus

Department of Zoology

It is widely believed our chordate ancestors used their newly evolved longitudinal muscle blocks to swim. Whether this implied a gradual evolution of slow-twitch fibres followed by fast-twitch fibres is currently unknown, as it is the nature of the locomotor network coordinating them.

The modern amphioxus, living relative of these ancestral chordates, have both kinds of muscle fibres. They are powerful swimmers but nothing is known about the physiology that allows them to be so precise and fast. It is especially interesting that their symmetric undulatory swimming is produced by asymmetrically arranged myomeres. It has been recently proposed that inhibitory neurons, asymmetrically arranged, might compensate for this in a spinal cord full of excitatory neurons. This hypothesis is merely based in the expression of certain neurotransmitters in spinal cord neurons of amphioxus embryos. However, nothing is known about the postsynaptic effects of these neurons, and thus whether they are excitatory or inhibitory is currently pure speculation.

The rotation project proposed will address this question, in collaboration with the Parker lab, by investigating the electrophysiology of the amphioxus spinal cord. The swimming behaviour will be characterised by recording muscle activity using electromyograms, and intracellular recordings will be used to characterise the properties of specific cell classes underlying the behaviour. Thereafter, full repertoire of cell types in the same adult spinal cord will be characterized by immunohistochemistry (with antibodies against Gaba, Acht, Glut, …) in order to understand the kind of neurotransmitters utilized by those neurons identified in the electrophysiology assays as excitatory or inhibitory.

BBSRC Doctoral Training Partnerships

UNIVERSITY OF CAMBRIDGE

Executable modelling of breast cancer signalling pathways to identify novel therapeutic strategies

Department of Biochemistry

Cell fate decisions, such as proliferation and apoptosis are governed by intra and inter cellular signalling crosstalk. Dysregulation of signalling pathways can lead to cancer, and so numerous targeted drugs have been developed with the goal of inhibiting pathway activity. Cancer patients with varying genetic backgrounds respond differently to these drugs, and so understanding how these pathways interact is key both to knowing which pathways to target, but also which combinations of drugs to use for individual patients.

The PI3K/AKT/mTOR pathway regulates the cell cycle, and as such is one of the most mutated pathways in breast cancer patients. The current understanding of the pathway predicts that patients with genetic alterations activating the PI3K/AKT/mTOR pathway would be more responsive to mTOR inhibitors, however the analysis of clinical trials suggests this is not the case. To explain the resistance to PI3K/AKT/mTOR pathway inhibitors, Astrazeneca (AZ) has generated Reverse Phase Protein Array (RPPA) data for twenty-three breast cancer cell lines treated with four PI3K/AKT/mTOR pathway inhibitors.

The goal of this project is to build cell-specific network models of the PI3K/AKT/mTOR pathway, based on the RPPA data using the BMA tool www.biomodelanalyzer.org .

The student would work closely with the Fisher lab and a senior scientists at AZ. This study would help better understand the mechanisms of resistance to PI3K/AKT/mTOR pathway inhibitors, and identify novel combination treatments for breast cancer patients.

The diet dilemma: can you eat what you like and live happily ever after?

Babraham Institute

The discovery that ageing can be slowed by dietary intervention raises the prospect of extending lifespan and health-span through lifestyle change or long-term drug treatment.

Dietary restriction (DR) without malnutrition has beneficial health effects for model organisms as well as humans but forms an unattractive lifestyle choice. Finding more palatable alternatives to DR requires a better understanding of why and how organisms respond to food.

It is widely (and mistakenly) assumed that DR simply slows down metabolism leading directly to an increase in lifespan. Remarkably, we have recently shown that in yeast, a classic model organism for ageing that responds well to DR, simply changing but not restricting diet dramatically improves health-span, such that cells actually became fitter with age prior to death at a normal age! This means that life-span and health can be separated, so ageing cannot be the inevitable decline towards death that we culturally perceive. In fact lifespan extension by DR requires chromatin modifying enzymes, at least in lower eukaryotes, suggesting that DR instigates an epigenetic reprogramming event, leading to altered gene expression patterns that increase lifespan and promote healthy ageing.

We aim to determine the nature of these gene expression changes and how they positively impact the ageing cell.

The objectives of this placement are to determine the long term transcriptional response to DR in yeast, and to test how DR impacts the fitness of yeast exposed to changing food availability.

Techniques: Ageing cell isolation; RNAseq and bioinformatics; imaging flow cytometry.

BBSRC Doctoral Training Partnerships

UNIVERSITY OF CAMBRIDGE

PhD projects

Developing small peptide inhibitors of RAMP-GPCR interactions

Department of Pharmacology

Receptor activity-modifying proteins (RAMPs) are single pass transmembrane (TM) proteins initially identified by their ability to determine the pharmacology of the calcitonin receptor-like receptor (CLR), a family B G protein-coupled receptor (GPCR). It is now known that RAMPs can interact with a much wider range of GPCRs including family A and family C GPCRs. RAMPs influence receptor expression at the cell surface, trafficking, ligand binding and G protein coupling. Thus the GPCR-RAMP interface offers opportunities for drug targeting, illustrated by examples of drugs developed for migraine.

In this PhD project we propose to design novel single span peptides that block RAMP-GPCR interactions. Mammalian cells express three different RAMPs, but they all share the same structure: the N-terminal domain modulates ligand binding whereas the short C-terminal intracellular domain has no known function; the TM domain is thought to facilitate the interaction with GPCRs, and it is this domain that we will target for interference. Using short peptides that we will design based on the TM helix we propose to block RAMP-GPCR interactions.

Our goal is develop peptides that target all three RAMPs. Initially we will extend our RAMP2 screens (in the rotation project) to other GPCRs and then develop new peptides that interfere with RAMP1- and RAMP3-GPCR interactions. Further, we envisage extending the use of these peptides to block recruitment of other GPCR accessory proteins such as β-arrestin proteins. The ability to block individual signalling pathways will provide critical data to aid our on-going efforts to computational model RAMP-mediated agonist bias. Thus the project is multi-disciplinary, combining peptide chemistry, cell biology and in silico modelling. The focus can be adapted to suit the student's background and interests.

Somite rotation in the invertebrate chordate amphioxus

Department of Zoology

Somites are a defining characteristic of vertebrates and their derivatives include some of the most notable vertebrate innovations such as the vertebrae. Amphioxus is the most basal invertebrate chordate having somites, however it lacks most of the somite derivatives that represent vertebrate innovations. In Zebrafish and Xenopus the rotation of the somites during development is essential for generating compartments within somites, which are the developmental source of vertebrae, swimming muscles and dermis.

We recently discovered that somites in amphioxus also rotate 90 degrees to align to the notochord, just as described in Xenopus and Zebrafish. This process has been never described in amphioxus before. Hence, the objective of the PhD project will be to characterize this process from a morphogenetic point of view.

The rotation project is expected to clarify the morphological aspects of the somite rotation in amphioxus and to determine the developmental timepoint for further gene expression analyses.

The PhD project will continue by investigating key genes involved in this process at this precise developmental timepoint. One approach to be used will be to perform differential expression analyses using RNA-seq libraries prepared from treated and untreated embryos around the time of somite rotation. This will allow identifying those genes that appear to be strongly regulated by Notch and to further analyze them by whole mount in situ hybridization (WMISH) in treated and untreated embryos. Thereafter, the expression patterns will be compared to those described for Xenopus and Zebrafish during somite rotation.

The mechanism of indole signalling in Escherichia coli

Department of Genetics

We have formulated a novel hypothesis for a unified mechanism of indole signalling. It is based in our published work on the properties of indole and brings together a number of previously unconnected observations on the effects of indole and other proton ionophores on E. coli cells.

Making the cytoplasmic membrane permeable to protons should result in a flow of protons into the cytoplasm with a corresponding fall in pH. We propose that in the lower part of the indole effective concentration range (0-3 mM), the effect of low-level permeabilisation of the membrane to protons is cytoplasm acidification. At the upper end of the concentration range (3-5 mM) we propose that higher membrane permeability reduces the transmembrane electrical potential and that this inhibits cell division and growth. We have shown previously that although 0-2 mM indole has little effect on the transmembrane potential, the potential starts to fall rapidly as the indole concentration increases through the range 3-5 mM.

The project will test the main assertions of the model as follows:

1. Assertion 1: The effects of indole on cell physiology are concentration-dependent. In the range 0-2 mM indole decreases intracellular pH while 3-5 mM reduces membrane potential.
2. Assertion 2: The effects of indole on cell physiology are due primarily to the conduction of protons across the cytoplasmic membrane.
3. Assertion 3: The biological effects of indole (induction of xenobiotic exporters, inhibition of growth and cell division) are due to concentration-dependant effects on cell physiology.

Characterising embryonic stem cell-derived tenocytes and defining the changing role of scleraxis during tendon development

Animal Health Trust (AHT)

To aid adult tendon regeneration and reduce the frequency of re-injury novel strategies are being developed which use stem cells that have the potential to differentiate into tenocytes. However, during normal adult tendon repair there is already a substantial influx of tenocytes which produce scar tissue. It is therefore important to design cell therapies that can mimic fetal tenocytes and recapitulate scar-less regeneration.

We have shown that equine ESCs differentiate into tenocytes following their injection into the injured horse tendon. Using an in vitro 3D culture system to generate artificial tendons, we have identified transforming growth factor beta 3 and mechanical force as key drivers of differentiation. However, whether ESC-derived tenocytes represent adult or fetal cells is unknown.

In this PhD the student will exploit new ways of working by performing global gene expression analyses on ESC-derived, adult and fetal tenocytes. Bioinformatics approaches will be used to determine the developmental stage that ESC-tenocytes represent. Global gene expression analyses will also be performed on cells that are engineered to have knocked down scleraxis levels to identify genes that are downstream of scleraxis regulation. Our synthetic cell culture system to generate artificial tendons will be used and the student will have the opportunity to refine this model by employing bioengineering techniques to apply forces to the tendons to better mimic the in vivo situation.

The results of this project will provide novel information to inform future experimental and clinical studies on the application of cell based-therapies for modulating tendon regeneration.