Please find below the MSc by Research projects (start date of October 2019) available in the School of Physiology, Pharmacology and Neuroscience, University of Bristol. The MSc by Research projects involve 10 months of full time research in one of our state of the art laboratories followed by 2 months of writing up your thesis (submission deadline 2 years after start date). For more information including fees and how to apply please use the following link: http://www.bristol.ac.uk/study/postgraduate/2019/life-sciences/phd-physiology-pharmacology/. Loans are available for UK students (http://www.bristol.ac.uk/fees-funding/postgraduate/pg-loans/). If you are interested in one of the projects below or the project area of a particular research group, please feel free to contact the supervisor directly.
Approach – Avoidance foraging; a novel and ethiological rodent assay to evaluate anxiety-like behaviour and the brain networks that support it

Supervisors: Prof Richard Apps - R.Apps@bristol.ac.uk, Prof Bridget Lumb, Dr Charlotte Lawrenson & Dr Robert Drake - Robert.Drake@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

The Group:

This Masters by Research (MSc) is entirely laboratory based giving you the best possible experience of life as a researcher as well enough time to develop skills and techniques. You will be working in a cutting-edge in vivo neuroscience research laboratory using the latest technology and approaches in pre-clinical research. On-going work in the group includes collaboration with industry partners and medical professionals giving you the fullest possible experience of multidisciplinary research.

The Project:

A previous Masters project has developed and pharmacologically validated a novel anxiety assay called approach-avoidance foraging (AAF) in which animals collect food at increasing distances in an anxiogenic arena. We now wish to further this work and assess the ability of AAF to detect effects of atypical anxiolytics that offer clinical efficacy but often show little effects in pre-clinical assays typically used to assess anxiety (e.g. elevated plus maze). Findings from this work will support previous work from our laboratory and form the basis for submissions for publication offering you potential authorship from your Masters work. In addition, our group uses viral vectors to transduce brain networks and make selective manipulation using with opto- and chemogenetic approaches to reveal functional contributions to behaviour. On-going work is assessing the role of the medial prefrontal cortex in the regulation of survival functions including fear, anxiety and pain. There is opportunity to evaluate contributions of mPFC to the regulation of anxiety-like behaviour in the AAF assay and thus reveal brain networks that contribute to anxiety disorders in humans.

In this Masters you will get training and experience in:
* Small animal surgery
* Animals behaviour and assays
* Pharmacology and methods of peripheral and central drug delivery
* Viral vectors/opto-/chemogenetics

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Exploring the interaction between sleep and myelination

Supervisor: Dr Michele Bellesi - michele.bellesi@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

In order to function properly the brain needs myelin, an electrically insulating substance that surrounds nerve fibers. Myelin is continuously remodelled in the brain and sleep is one of key factors contributing to the formation and maintenance of myelin in the brain.

The objective of my research is to understand how sleep regulates myelination and whether we can promote myelin formation and maintenance by enhancing sleep. Recent research demonstrated that enhancing sleep is possible in both rodents and humans using non-invasive approaches.
This research will help clarify why sleep is beneficial to our health and whether sleep can be manipulated to enhance the capability of our brain to produce more myelin, particularly in the pathological context of debilitating neurological diseases, where myelin formation is crucial for the recovery process.

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**Dissecting principles of long-range neuronal connectivity in mammalian motor circuits**

**Supervisor: Dr Paul Chadderton - p.chadderton@bristol.ac.uk**

**School of Physiology, Pharmacology and Neuroscience**

Brain function relies upon specific patterns of wiring between individual neurons. Neurons connect via their axons to other cells in their vicinity (locally) and also to other brain regions (long-range). Both types of connection can be exquisitely precise, but we have much to learn about the logic of neuronal connectivity from one region to another. This issue is particularly pressing in the cerebellum (or ‘little brain’) which is composed of three discrete structures (cortex, nuclei and inferior olive) that are linked via long-range projections. The aim of this project is to map projection patterns of single cells from the cerebellar cortex to the nuclei using molecular tools (e.g. genetically encoded fluorescent proteins) [1,2] to determine the rules governing connectivity between these two regions [3].

You will join a dynamic and multidisciplinary team who apply a range of approaches (2-photon imaging, high density electrophysiological recording, patch clamp, computational modelling) to understand mechanisms of motor control and learning in the intact brain. During this project, there will be opportunities to collaborate with group members to gain experience of other in vivo techniques and to present your work at international conferences.

For more information, please contact Paul Chadderton (p.chadderton@bristol.ac.uk).

[http://www.neuralcircuitsinbehaviour.org](http://www.neuralcircuitsinbehaviour.org)

**References:**

**Sleep and affective behaviour: exploring the long-lasting effects of chronic sleep loss in adolescence**

**Supervisor: Dr Luisa de Vivo - luisa.devivo@bristol.ac.uk**

School of Physiology, Pharmacology and Neuroscience

Chronic insufficient sleep has become epidemic among adolescents worldwide and is as a serious health risk. Insufficient sleep is associated with higher risk of developing neuropsychiatric and behavioural disorders, such as anxiety and depression, that are the primary drivers of disability worldwide.

My group is studying how losing hours of sleep across adolescence affects, in the long-term, the morphology of neuronal connections (or synapses) in brain regions important for the control of behaviour and affective status. Altered size, density or molecular composition of synapses are a consistent structural finding in multiple neuropsychopathologies and underlie impaired neural circuit performance and impaired behaviour. By gaining insight into the underlying biological mechanisms linking chronic insufficient sleep to psychiatric disorders I aim to identify potential therapeutic targets to improve mental health.

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**The role of protein SUMOylation in Osteoarthritis – a link to Type-2 Diabetes?**

**Supervisor: Dr Chrissy Hammond - Chrissy.Hammond@bristol.ac.uk**

School of Physiology, Pharmacology and Neuroscience

Abstract: In an ageing population, age-associated diseases such as Type-2 Diabetes (T2D) and Osteoarthritis (OA) represent an increasing healthcare and socio-economic burden. Several studies have established that T2D sufferers are more likely to develop OA, suggesting either a causal link or shared risk factors for these diseases. Intriguingly, the post-translational modification, SUMOylation, has been suggested to be involved in both T2D and OA, and studies have demonstrated that exposure of different cell types to T2D dietary risk factors (e.g. saturated fatty acids) increased whole cell protein SUMOylation. Recent genetic association studies have implicated genes involved in the regulation of SUMOylation, such as SENP6, as potential osteoarthritis susceptibility genes but to date we have little understanding of the role they play in the skeletal system. Using zebrafish as an animal model we will test how modulation of SUMOylation affects skeletal cell behaviour in viva and test whether levels of SUMOylation are altered in other mutant lines which develop severe early onset osteoarthritis. We use zebrafish as they develop rapidly, are genetically amenable allowing us to readily generate genetic mutant and are translucent in the larval stages allowing us to follow cell behaviour in the living animal. As zebrafish develop in water, they can readily be drugged by application of compounds of interest to the water in which they are incubated.

In this project the student will use CRISPR-cas9 genome editing to knock out SENP6, they will use live imaging of zebrafish carrying transgenic reporters for chondrocytes, osteoblasts and osteoclasts to visualise the skeletal system. Using biochemical assays (in collaboration with Dr Tim Craig at UWE) they will test levels of SUMOylation in chondrocytes and osteoblasts from wild type and mutant fish at different stages of maturation. Finally using compounds that regulate SUMOylation we will test whether increasing add/or decreasing levels of SUMOylation can delay osteoarthritis progression in vivo.

For more information on the group see [www.fishosteoarthritis.com](http://www.fishosteoarthritis.com)
Testing whether pain underlies the altered behaviour of zebrafish osteoarthritis mutants

Supervisor: Dr Chrissy Hammond - Chrissy.Hammond@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

The degenerative joint condition osteoarthritis affects more than 10 million people in the UK and is the most common form of disability. While the major pathology of osteoarthritis is progressive loss of articular cartilage and an increase to subchondral bone, the symptom with the biggest effect on patients is joint pain. Osteoarthritis was, for a long time, believed to be a natural consequence of ageing and joint wear and tear. In the last decade it has been shown that there is a strong genetic component of osteoarthritis which accounts for between 40 and 60% of susceptibility and it is believed that around 100 genes may be involved. Zebrafish are frequently used as an animal model, as they are highly genetically amenable and they show well conserved physiology with higher vertebrates. Zebrafish, like mammals show increasing signs of osteoarthritis as they age. The Hammond lab have generated 12 stable mutant lines carrying mutations in osteoarthritis susceptibility genes. All of the lines show premature onset of osteoarthritis in the jaw and spine, with loss of cartilage and formation of bony spurs called osteophytes. The fish also show altered jaw movement and swim behaviour, however it is currently unclear whether this altered behaviour is due to physical constraints on the joint, or to pain leading to avoidance of certain types of motion. This project (working in collaboration with Dr Lynne Sneddon in Liverpool) will test whether zebrafish with osteoarthritis have joint pain, by testing whether analgesia affects jaw movement and swim behaviour and cortisol levels.

Zebrafish have been shown to exhibit aversive behaviour in response to painful stimuli such as heat and cold shock or following the induction of a minor wound, which can be prevented by providing analgesia to the fish. Agents that block peripheral pain sensation, such as lidocaine, and agents blocking central pain, e.g. opioids, have been demonstrated to be effective. In this project video tracking assays will be developed to test behaviour of larvae and adult fish. The onset of altered behaviour in osteoarthritis mutants will be characterised. We will then design analgesia dosing regimen (by testing their effects on aversive behaviour) and test whether blockade of peripheral and/or central pain leads to a reversion to normal behaviour.

For more information on the group see www.fishosteoarthritis.com

Maturing stem cell-derived cardiomyocytes to provide improved models of arrhythmia

Supervisors: Dr Stephen Harmer: s.c.harmer@bristol.ac.uk (+44 (0) 117 331 1543)
http://www.bristol.ac.uk/phys-pharm/people/stephen-c-harmer/overview.html
Prof. Jules Hancox: jules.hancox@bristol.ac.uk (+44 (0) 117 331 2292)
http://www.bristol.ac.uk/phys-pharm/people/jules-c-hancox/overview.html

School of Physiology, Pharmacology and Neuroscience

Introduction: Cardiac arrhythmias are a major cause of morbidity and mortality. Arrhythmias occur when the normal flow of electricity in the heart becomes disordered. In human ventricular and atrial cardiomyocytes (CMs) the action potential (AP) is coordinated by ion channels, exchangers and transporters which act to depolarise and repolarise in a timely manner. The main repolarising currents are the transient outward potassium current (Ito), the rapid and slow delayed-rectifier potassium currents (Ikr and IKs), and the inwardly rectifying potassium current (IK1). The sum of these currents acts to provide a ‘repolarisation reserve’ ². This reserve is important because if one current is diminished then other currents can compensate which prevents excessive AP prolongation and reduces the chance of arrhythmic events. The critical role of these currents in repolarisation is exemplified by the fact that mutations in the pore forming alpha-subunits
that compose $I_{Ks}$, $I_{K1}$ and $I_{Ks}$ cause long QT syndrome and short QT syndrome (LQTS and SQTS). In detail, mutations in KCNQ1 and KCNE1, which encode for the alpha and beta subunits of $I_{Ks}$ respectively, cause long QT syndrome types 1 and 5 (LQT1 and 5) $^2$.

Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) provide a unique model system for investigating disease mechanisms that underlie arrhythmic disorders and have been used to model LQT1 $^4$. As a research model, hiPSC-CMs have a number of advantages in that they are human (and patient specific) in origin, provide an alternative to using cardiomyocytes derived from animals, are genetically editable, and can provide a near renewable supply of cells. However, in comparison to adult cardiomyocytes, hiPSC-CMs are structurally immature and exhibit a late foetal phenotype $^2$, hiPSC-CMs are also electrophysiologically immature and possess greatly reduced levels of the inwardly rectifying potassium current ($I_{K1}$) that normally underlies the ‘resting potential’ in CMs $^6,8$. In addition, in contrast to the findings of the first hiPSC-CM based models of LQT1 $^4$, we have found that the kinetics and expression of $I_{Ks}$ in hiPSC-CMs is highly variable. Our view, and that of others $^1,2,10$, is that the electrophysiological immaturity and diminished repolarisation reserve found in hiPSC-CMs (due to reduced $I_{K1}$ and $I_{Ks}$) severely hampers their current utility as a model system in which to study the long QT syndrome.

There is a clear consensus that the immature phenotype of hiPSC-CMs hinders their utility in disease modelling. Excitingly, a number of methods have recently been published (for example $^{11,12}$) that enable significant and accelerated structural and functional maturation of hiPSC-CMs. However, it is not yet known if these maturation protocols act to enhance $I_{Ks}$ expression or promote an improved level of repolarisation reserve.

**Project Aims and Objectives:** To explore whether recently reported maturation protocols, when applied singly or in combination, can act to enhance the expression of $I_{Ks}$ in hiPSC-CMs. If robust expression of $I_{Ks}$ in hiPSC-CMs can be engineered this will provide an improved model for characterising the disease mechanisms that underlie the long QT syndrome.

**Techniques to be used:** Work will be conducted in the Harmer and Hancox laboratories and the project will benefit from the combined technical expertise of both groups. Methods to be used will include:

- Culture of hiPSCs and differentiation into hiPSC-CMs.
- Quantitative real-time polymerase chain reaction (qPCR).
- Western blotting.
- Immunostaining and Confocal Laser Scanning Microscopy.
- Patch-clamp electrophysiology- whole-cell patch-clamp (WCPC) and perforated-WCPC.


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**The underlying mechanism by which hypoxia regulates platelet hyperactivity**

**Supervisor:** Prof Ingeborg Hers - i.hers@bris.ac.uk

School of Physiology, Pharmacology and Neuroscience

Platelets are small blood cells that are not only important in hemostasis but also contribute to thrombosis. Conversely, ischemic conditions such as myocardial infarction, peripheral artery disease and stroke are associated with platelet hyperactivity and reduced effectiveness of anti-platelet drugs. Recent studies showed an altered platelet protein profile in patients and animal models with ischemic disease and in platelets left under in vitro hypoxic conditions$^1,2$. These alterations coincided with increased platelet
activity. The underlying mechanism by which hypoxia can regulate platelet function however is still largely unknown. We previously showed that enhanced signalling through the PI3kinase and ERK pathways leads to platelet hyperactivity\(^3\). Here we hypothesise that hypoxia induces an alteration in platelet signalling pathways, resulting in platelet hyperactivity upon reoxygenation and reduced responsiveness to anti-platelet drugs. In this project the student will evaluate the effect of hypoxia on (i) intracellular signalling pathways and platelet function, and (ii) the effectiveness of anti-platelet drugs. This will be tested by using a hypoxia chamber incubating human blood/platelets under normoxic (21% \(O_2\)) or hypoxic (5% \(O_2\)) conditions. Platelet function will be assessed using a range of approaches, all well established in the Hers lab. The student will be trained in phlebotomy, platelet isolation and a range of functional essays including platelet aggregation, integrin activation, granule secretion, \(Ca^{2+}\) mobilisation and \textit{in vitro} thrombosis. Techniques such as immunoprecipitation, western blotting, confocal microscopy, plate-reader based essays, FACS analysis and use of flow chambers.


\section*{Protein SUMOylation as a regulatory mechanism underlying platelet hyperactivity}

\textbf{Supervisor: Prof Ingeborg Hers – i.hers@bristol.ac.uk}

\textbf{School of Physiology, Pharmacology and Neuroscience}

Platelet hyperactivity contributes to cardiovascular disease and increased risk of thrombosis in patients with conditions such as obesity and diabetes. The underlying mechanism that causes hyperactivity is still largely unknown but believed to be the results of the extracellular environment leading to intrinsic molecular changes. Many of these conditions are associated with increased levels of reactive oxygen species which can regulate posttranslational processes such as protein SUMOylation. This involves the covalent addition of is a small ubiquitin-like modifier (SUMO) peptide, which can modify protein localisation, activity and protein-protein interactions. We have recently demonstrated enhanced levels of platelet protein sumoylation under conditions of increased platelet activation and we therefore hypothesise that protein SUMOylation contributes to platelet hyperactivity. In this project, we will evaluate protein SUMOylation in human platelets using biochemical approaches, including immunoprecipitation/western blotting, and evaluate the effect of regulating platelet SUMOylation levels on platelet function and compare this to patients with obesity/diabetes. The student will be trained in a wide range of techniques including phlebotomy, platelet isolation, platelet aggregation, immunoprecipitation, western blotting, confocal microscopy, FACS analysis and in vitro thrombosis assays.

\section*{Developing \textit{Drosophila} as a model to study the molecular and behavioural changes underlying Parkinson’s disease}

\textbf{Supervisor: Dr James Hodge – james.hodge@bristol.ac.uk}

http://www.bristol.ac.uk/phys-pharm-neuro/people-new/hodge/
School of Physiology, Pharmacology and Neuroscience

The general lab interest is how neural circuit activity underlies behaviour including circadian rhythms, sleep, memory and movement. We study this using *Drosophila* molecular genetics, behavioural paradigms, electrophysiology, imaging and optogenetics. We wish to elucidate the fundamental biological mechanisms underlying behaviour and elucidate how they are affected by ageing, drugs and diseases such as Alzheimer’s, Parkinson’s, Down’s and schizophrenia.

Parkinson’s disease (PD) is the 2nd most common neurodegenerative disease and involves dopamine (DA) neurodegeneration leading to motor and non-motor symptoms. Recent Genome Wide Association Studies (GWAS) for PD have identified ~50 risk loci (Chang et al., 2017). To gain molecular insight into how these genes may lead to PD pathology we will perform an in vivo screen of already available stocks of *Drosophila* that mis-express the fly orthologues of these risk loci and human PD genes. These transgenes will be expressed in all neurons, all glia or DA neurons and the effect on lifespan, locomotion, circadian rhythm and sleep compared, while neurodegenerative effects will initially quickly be screened in the eye. Genes that yield PD relevant phenotypes will be further characterized for memory defects. Behavioural phenotypes will be further mapped to the most defined populations of cells using the large number of promoters readily available in flies. This will allow for instance the determination of progressive neurodegeneration of subsets of DA neurons mapped to PD relevant behaviours, this is possible in flies as they have only 200 DA neurons in their 150000-neuron brain and live around 60 days. The most promising candidates will be characterised using electrophysiology, optogenetics and mitochondrial live imaging for changes in dynamics and mitophagy (Julienne et al., 2017).


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**Cortical-midbrain interactions and their contribution to pain chronification in rodents**

**Supervisors:** Prof Bridget Lumb – B.M.Lumb@bristol.ac.uk  
Dr Robert Drake - RobertDrake@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

The Group:
This Masters by Research (MSc) is entirely laboratory based giving you the best possible experience of life as a researcher as well sufficient time to develop skills and techniques. You will be working in a cutting-edge in vivo neuroscience research laboratory using the latest technology and approaches in pre-clinical research. On-going work in the group includes collaboration with industry partners and medical professionals giving you the fullest possible experience of multidisciplinary research.

The Project:
The medial prefrontal cortex has been implicated as an important locus in the transition to and maintenance of chronic pain in human patients. However, our understanding of the functional contributions that the mPFC makes to sensory and/or affective aspects of the pain state remains limited, and pre-clinical investigation is required to reveal neurophysiological mechanism that may for basis for novel and effective therapeutics.
This project will study alterations to interactions between the mPFC and the midbrain periaqueductal grey, the latter forming an important source of descending control of spinal pain processing which is known to be an important determinate of chronic pain in humans and animals. You will use viral vectors to transduce brain networks and make selective manipulation using opto- and chemogenetic approaches to reveal functional effects in pain behaviour and their casual contribution to the pain phenotype. This work will be conducted alongside acute and chronic electrophysiology, including in behaving animals, to deduce underlying neurophysiological mechanism.

In this Masters you will get training and experience in:
- Small animal surgery
- Viral vectors/opto-/chemogenetics
- Animal models and behaviour - including sensory and affective testing
- Acute and chronic electrophysiology.

Neural mechanisms of the effects of social interactions on the pain experience

Supervisors: Prof Bridget Lumb - b.m.lumb@bristol.ac.uk
Dr Susanne Quadflieg, Dr Jon Brooks & Dr Robert Drake

Schools of Physiology, Pharmacology and Neuroscience & School of Experimental Psychology,

The Group:
This project is a collaboration between two Schools in the Faculty of Life Sciences and is entirely laboratory based giving you the best possible experience of life as a researcher as well enough time to develop skills and techniques. You will be working in a cutting-edge in vivo neuroscience research laboratory using the latest technology and approaches in pre-clinical research. On-going work in the group includes collaboration with industry partners and medical professionals giving you the fullest possible experience of multidisciplinary research.

The Project:
Feelings of pain are a familiar and inevitable facet of human life. Regardless of their physical origin, most pains converge on a similar “unpleasant sensory and emotional experience associated with actual or potential tissue damage”. Different types of pain also tend to share similar consequences: they usually reduce people’s quality of life, increase the incidence of absence from work, and/or increase the use of healthcare resources. In light of the above, pain has long been considered a prevalent health condition that can result in severe personal and economic costs.
Aiming to reduce these costs, many physicians, neuroscientists, and psychologists have tried to identify treatments that can support effective pain management. Thanks to their efforts there remains little doubt today that both biological as well as psychosocial factors play an important role in alleviating or reducing pain. As a result, contemporary pain interventions typically combine pharmacological approaches with social support sessions. The actual interplay between relevant biological and psychosocial factors in pain management, however, remains poorly understood. To overcome this lack of clarity, this project aims to investigate whether a basic psychosocial intervention (i.e., the exposure to social company) can elicit a well-understood biological mechanism (neurochemical release e.g. oxytocin) to produce pain relief. To do so, it aims to develop a dedicated animal model that can be used to examine whether there is a causal relationship between the release of neuroactive substances such as oxytocin during exposure to social company and the subsequent relief of pain.

In this Masters you will get training and experience in:
- Small animal surgery
- Animals behaviour and assays
- Pharmacology and methods of peripheral and central drug delivery
- Viral vectors/opto-/chemogenetics
Can we improve patient outcomes by providing a more personalized approach to antiplatelet therapies?

Supervisor: Professor Stuart Mundell - S.J.Mundell@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

Heart attacks occur when a blockage called a thrombosis develops in the blood vessels of the heart which is a major cause of morbidity and mortality. Platelets play a central role in the development of arterial thrombosis in heart disease, responding to a variety of extracellular stimuli and agonists to undergo a rapid aggregation response, leading to a rapidly growing thrombus. Central amongst these agonists are TxA2 and ADP which operate through G protein-coupled receptors (GPCRs) on the platelet surface: TP for TxA2 and P2Y1 and P2Y12 for ADP. Current therapeutic strategies for the treatment of arterial thrombosis are largely based on these well characterized receptor systems with aspirin (which reduces TXA2 generation) and P2Y12 antagonists commonly used effective anti-platelet agents with their combination, termed dual antiplatelet therapy (DAPT). Although DAPT offers synergistic benefits in preventing thrombus formation not all patients benefit to the same extent with a marked inter-individual variability in the extent of platelet inhibition. The variability of response to DAPT results in a significant proportion of patients demonstrating either high or low platelet reactivity with an associated risk of thrombotic or bleeding events, respectively. To date, platelet function testing has achieved predominantly negative results in reducing adverse events secondary to DAPT therapy although studies have largely focussed on the entire patient population rather than those at either end of the platelet reactivity spectrum.

Project aims:

1) to characterize platelet receptor biology in coronary intervention patients experiencing high and low platelet reactivity and assess the effectiveness of DAPT on these patients.

2) characterize the usefulness of existing methods to assess the effect of anti-platelet agents on platelet function.

3) develop novel methods of platelet function assessment that may facilitate tailoring of therapy with a reduction in adverse clinical events.

In order to undertake this programme of research you will be supported by an established network of clinical (Bristol Heart Institute) collaborators. This grouping will provide you with both the logistical support and access to patient samples from ongoing clinical trials at the University Hospitals Bristol NHS Foundation Trust. You will receive training in a wide variety of relevant techniques ranging from advanced fluorescent single cell imaging microscopy through to the measurement of cell signalling pathways.

Please do contact me at S.J.Mundell@bristol.ac.uk if you would like further information about this exciting opportunity.

Cryo-EM and High-resolution structural studies of cardiac thin filaments

Supervisors: Dr Danielle Paul - Danielle.paul@bristol.ac.uk
Dr Rebecca Richardson - rebecca.richardson@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

To understand how mutations in the thin filament regulatory protein troponin cause familial hypertrophic cardiomyopathy (HCM) it is important to know the structure of the cardiac thin filament. Techniques for the genetic manipulation of the zebrafish are well established and it has become a major model for the study of human cardiac disease. Our lab isolates zebrafish thin filaments from adult fish and are working to
create a zebrafish model with mutations which cause HCM in humans. We study the 3D structure using Cryo-Electron Microscopy (EM), where the thin filaments are preserved in a frozen hydrated state. Using transmission EM and single particle analysis we can reconstruct a 3D map of the filament. We now want to study the structure of these filaments in situ and our goal for this project is to look at frozen hydrated cardiomyocytes from zebrafish. After freezing the myocytes, we will perform cryo-sectioning and tomography of the to elucidate the ultrastructure. Some of the techniques that will be learnt in this project include; microdissection, EM and Cryo-EM sample preparation, EM and Cryo-EM imaging, image processing and 3D molecular fitting.

**Figure 1.** (a) A negatively stained transmission electron microscopy image of a gold fish thin filament. (b) A 3D reconstruction revealing the location and shape of the regulatory protein troponin. (c) The known atomic structures are docked into the electron density map and non-crystallised regions modelled. (d) A transgenic zebrafish larvae expressing GFP in the cardiomyocytes of the heart.

References:


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**Bioengineering platelets for Blood Transfusions**

Supervisors: Professor Alastair Poole - A.Poole@bristol.ac.uk and Professor Ingeborg Hers - I.Hers@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

Platelets are essential elements of the blood responsible for primary haemostasis. It is clear, however, that their role is much wider than just this, playing a critical element in aspects of angiogenesis, wound healing, tissue regeneration, tumour growth and metastasis and inflammation. Their loss or dysfunction can therefore impact in a variety of pathophysiological conditions. In humans, a low platelet count (thrombocytopenia) can result from either increased loss (destruction or traumatic) or decreased generation of platelets. In either case therapeutic strategies need to include mechanisms to increase the generation of platelets in the body, and/or to administer exogenous platelets by transfusion. Our current lack of understanding of the molecular and cellular mechanisms of platelet generation are a significant hindrance to achieving these therapeutic strategies efficiently. We have recently made significant progress challenging the current understanding of platelet production from their precursor cells, megakaryocytes, **in vivo** however, using state-of-the-art intravital microscopy and electron microscopy ([http://www.lifescience-alliance.org/content/1/2/e201800061](http://www.lifescience-alliance.org/content/1/2/e201800061)).

Additionally, we have made a breakthrough in generating platelets **in vitro** in a novel microfluidic system. This already produces significant numbers of functional platelets from their precursor megakaryocytes, which is extremely encouraging. A significant bioengineering challenge lies ahead now to optimize the features of this flow system to enhance the numbers and functionality of the platelets that are produced. The work will involve a significant amount of detailed live cell fluorescence microscopy, electron microscopy, some cellular biochemistry and flow channel engineering. The project will use both human and mouse-derived stem cells, engineered to generate megakaryocytes as precursors for platelet production.
The value of the study will be to uncover novel determinants of platelet production in humans, which will provide insight into the causes of thrombocytopenia and pave the way for efficient generation of platelets in vitro for blood transfusion purposes. These are major goals for the whole field at present and would make a major advance in our understanding of fundamental mechanisms, but also provide a significant step on the way to clinical transfusion of bioengineered platelets.

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**Using Zebrafish to Study Heart Disease and Tissue Regeneration**

**Supervisor:** Dr Beck Richardson - rebecca.richardson@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

**Our Main Interests and Skills:**

- *In vivo* animal models
- Live imaging and sophisticated microscopy
- Inflammation
- Tissue repair and regeneration (skin and heart)
- Heart disease models (heart attack, heart failure, arrhythmias)
- Cell-cell communication
- CRISPR technology

Our lab is interested in modelling different aspects of heart disease and tissue repair/regeneration using zebrafish as a model. We are particularly interested in the inflammatory response to tissue injury and the roles this may play in promoting regeneration of damaged organs. The inflammatory response to an acute or ischaemic injury (such as a heart attack) is an inevitable and necessary part of the repair process but directly drives subsequent fibrosis and scar formation in mammals. Adult zebrafish, by contrast, deposit scar tissue following tissue injury but later resolve it entirely allowing for complete regeneration of organs such as the skin and heart. Our studies show that subtle changes in different immune cells are required for scar removal and tissue regeneration in zebrafish, but we still don’t fully understand how this is controlled. We have several projects currently available in the lab including: investigating how ageing effects immune cells and tissue repair and regeneration; live imaging the movement of immune cells into the heart; determining which genes are involved in controlling immune cell behaviour during regeneration; using CRISPR technology to introduce specific cardiovascular disease-causing mutations; deciphering the ways cells communicate during repair and regeneration. If you are interested in doing any of these projects for a MSc by Research or would like to hear more or visit the lab, please get in touch.

Immune cells (green) and scar tissue (red) in a zebrafish heart.
How does motivational state influence cognitive function in rodents?

Supervisor: Professor Emma Robinson - Emma.S.J.Robinson@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

The majority of studies in rodents use either food or water restriction to motivate the animals to perform a specific behavioural task. Whilst the motivational drive generated by these states improves training performance and the number of trials animals will complete within a given session, they may also be a confounding factor when considering the primary outcome of the task. This project will investigate how changing motivational states in animals alters their performance in different, well established tasks of cognition.

The student will look at the effects of different feeding conditions and water restriction schedules on initial acquisition of the task as well as subsequent performance measures associated with specific cognitive domains. The project will also look at whether motivational state interacts with drug-induced changes in cognition using amphetamine treatment. The project will provide training in animal behavioural studies and a range of in vivo skills.

Cystic fibrosis: restoring ion transport with small molecules

Supervisor: Prof David N. Sheppard - D.N.Sheppard@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

Cystic fibrosis (CF) is caused by dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR), a unique ATP-binding cassette transporter that functions as an ATP-gated anion channel, playing a pivotal role in salt and water movement across epithelial tissues (1). To date more than 2,000 mutations have been identified in the CFTR gene, but most are very rare and not all cause disease (1, 2). The most common cause of CF, the F508del mutation, disrupts CFTR transport to and stability at the plasma membrane and interferes with channel gating (2). To overcome these defects, small molecules have been developed called CFTR correctors and potentiators, which rescue the plasma membrane expression and function of F508del-CFTR (3). Other small molecules restore ion transport to CF cells by activating different anion channels expressed in these cells or functioning as artificial anion channels and transporters (4). An MSc by Research project with our group would explore how rare CF mutations cause CFTR dysfunction and small molecules restore ion transport to CF cells by rescuing or bypassing faulty CFTR proteins (5-8).


Modulation of Brain Energy Metabolism by Astrocytic G-protein-coupled Receptors

Supervisor: Anja Teschemacher - Anja.Teschemacher@bristol.ac.uk

School of Physiology, Pharmacology and Neuroscience

It has been becoming increasingly clear that ‘neuro’science research must consider the roles of non-neuronal cells in the central nervous system if integrated brain function is to be understood. We have by now come to
appreciate that astrocytes, the most abundant type of glia cells in the brain, play fundamental roles in neurotransmission, not only by fuelling the underlying cellular processes and by removing waste products, but also by integrating, amplifying, and modulating neuronal signals (Verkhratsky et al., 2015). Astrocytes handle glucose intake across the blood-brain barrier, contain the glycogen stores of the brain and, following glycolysis, release lactate into the extracellular space. This lactate may support neuronal function in states of increased energy demand, for example during memory formation (Alberini et al., 2017). However, beyond energy supply, recent evidence has suggested that lactate also acts as extracellular signalling molecule, for example in context of central arousal to salient stimuli, or in autonomic control (Tang et al., 2014; Teschemacher et al., 2015; Mosienko et al., 2015; Mosienko et al., 2018).

Whilst lacking in electrical excitability, astrocytes express a plethora of G-protein-coupled receptors and highly complex intracellular signalling cascades of which we currently have only limited understanding. Over the recent decade, molecular and imaging tools suitable for investigating these have been developed. This research project will use astrocytes in dissociated and slice cultures, viral vector transgenesis, confocal imaging and biosensor electrode measurements to study the effects of GPCR activation on lactate production and release.

Key references: