NOTE: THE SCHOOL OF PHYSIOLOGY, PHARMACOLOGY AND NEUROSCIENCE (PPN) is being disbanded. Staff from this school have joined other schools within the **Faculty of Health & Life Sciences**. The projects offered by former members of PPN are listed by the school in which the project offered will be run.

PSYCHOLOGY & NEUROSCIENCE

Dr Tamara Boto and Dr Valentina Mosienko

Fuelling repair: how glial metabolism shapes brain recovery after trauma

Traumatic brain injury (TBI) is a major global health challenge, affecting an estimated 28 million people every year and remaining one of the leading causes of injury-related death and disability worldwide. Beyond its immediate impact, TBI often leaves survivors with long-term cognitive, emotional, and physical difficulties, and significantly increases the risk of developing dementia and other neurodegenerative diseases later in life. Despite decades of research into its underlying mechanisms, there are still no effective treatments that can significantly reduce the short- and long-term consequences of TBI. To prevent or even reverse brain damage following TBI, it is critical to understand underlying pathology driving the disease and translate these findings into innovative, targeted therapies.

This project aims to understand cell-specific metabolic changes following TBI and determine how these pathways can be manipulated to promote recovery after brain damage.

Carbohydrates are the preferred energy source in the brain. Neuronal metabolism largely depends on pyruvate generated from lactate, a glucose-derived metabolite primarily synthetised and released by non-neuronal cells likes astrocytes. However, neurons can utilise alternative energy substrates including lipids in pathophysiological conditions such as starvation or injury. Clinical and preclinical studies have revealed changes in both carbohydrate and lipid metabolism in the TBI. However, cell-specific perturbations in cellular metabolism and their effects on short- and long-term outcomes after TBI remain poorly understood.

Here, we will use a unique *Drosophila* model of TBI to dissect how biasing energy sources towards glucose or lipids in a cell-specific manner influences recovery. By subjecting flies to controlled TBI of varying intensities and genetically impairing glycolysis, lipid metabolism, or both in either glia or neurons, we will assess the resulting effects on fly survival, brain integrity, and metabolic homeostasis post-injury. The student will use state-of-the-art imaging techniques with fluorescent reporters *in vivo* to track brain metabolism as well as well stablished metabolic essays in brain samples *in vitro*.

This project tackles a novel approach, combining the expertise of the hosting labs in *Drosophila* neuroscience and TBI (Boto) and glial biology and metabolism (Mosienko) to understand fundamental mechanisms of brain repair and uncover new metabolic targets for therapeutic intervention in TBI. The student will acquire expertise in behavioural, molecular and brain imaging techniques, and will become part of the thriving neuroscience community in Bristol.

Contact:

Tamara Boto (tamara.boto@bristol.ac.uk)

Valentina Mosienko (valentina.mosienko@bristol.ac.uk)

Dr Robin Corey

Computational pharmacology of GPCRs

G protein-coupled receptors (GPCRs) are one of the largest families of membrane proteins and play a key role in cellular signal transduction. As such, they are the target of 30-40% of all pharmaceuticals, making them crucial in the treatment of various diseases, including cardiovascular disorders, cancer, and neurological conditions. We now have a wealth of structural information on a range of GPCRs, however a lot remains to be understood about their pharmacology and biology.

In the Corey lab, we use **computational molecular and AI modelling** to understand features relating to GPCR biology. We are keen to support a range of topics within this area including:

- **membrane microdomains:** these are important for GPCR signalling, and we're interested in the precise molecular features that lead to their formation and cause a given GPCR to segregate between them
- **receptor pharmacology:** what is the structural basis of receptor pharmacology? e.g. nitazenes/fentanyl at the μ-opioid receptor, psychedelic compounds such as psilocin at the serotonin receptors, and nucleotides at the P2Y receptors.
- **receptor dimerisation**: how well can modelling predict homo- and heterodimers between different receptor types? What is the role of specific lipids in this? How do these dimers contribute to GPCR signalling?

Any chosen project would involve close collaboration with wet lab groups, with access to experimental data to validate and provide a broader biological context to the modelling data. Therefore, the project would suit a student who is interested in carrying our interdisciplinary research and learning how to integrate different types of modelling and experimental data to generate biological hypotheses and insights.

The project will involve learning and applying a range of cutting-edge computational methods, including both molecular modelling and AI-based modelling, which have emerged as powerful tools in the modelling of biomolecular structures and dynamics. Therefore, it would be a great opportunity for any student who is interested to give these different computational methods a try. In addition, there will be the opportunity to learn programming languages, such as Python. For a friendly and informal chat, drop me an email at robin.corey@bristol.ac.uk

Dr Carla Frare

Suspended animation: waking sleeping beauties.

Daily torpor is a remarkable short-term form of hibernation exhibited by many mammals including mice. In the face of environmental challenges (food scarcity or adverse weather) mice engage in an extreme physiological and behavioural strategy. They reduce their energy consumption by >90% by allowing their core temperature to fall to close to ambient, slowing their heart rate by 5-fold and becoming inert for 3-6 hours. The triggers and brain circuits generating torpor are a hot topic and we and others have developed strategies to generate "synthetic torpor", which can be triggered on demand. This state of near suspended animation and tissue protection is of great interest to fields as diverse as longevity, organ transplantation and long-distance space travel.

Just as fascinating, but much less studied, is the subsequent arousal from torpor. This rapid rewarming-reperfusion phase lasts around 30-60 minutes and restores core temperature and metabolic rate. This occurs without any deleterious consequences, such as reactive oxygen species damage, ATP dysregulation, or organ injury, associated with rewarming in both accidental and therapeutic hypothermia in humans causing morbidity and increasing mortality. Surprisingly, the mechanisms and neuronal circuits regulating arousal are not yet known.

The student will work with Frare, Ambler, and Pickering to identify the neurons activated during arousal from torpor by using a novel transgenic mouse line. Arousal neurons will be quantitatively mapped across candidate brain regions (locus coeruleus, raphe pallidus, tuberomammillary nucleus). Optogenetic activation or inhibition of these candidate regions will be used to assess their ability to trigger early arousal or lengthen torpor, respectively.
Contact: carla.frare@bristol.ac.uk

Professor Jonathan Hanley

Synaptic plasticity and microRNA-dependent regulation of translation.

Changes in synaptic strength underlie the formation of neural circuits during development and their modification in learning and memory processes. Furthermore, dysfunction of such systems is thought to underlie numerous neurological disorders such as Alzheimer's. Long-

term synaptic plasticity requires changes in the synthesis of synaptic proteins by the local, activity-dependent, microRNA (miRNA)-dependent regulation of translation. My laboratory is focussed on mechanisms for transducing plasticity stimuli (e.g. NMDA receptor stimulation) into changes in miRNA activity, particularly via Argonaute (Ago) phosphorylation and the regulation of protein-protein interactions in the RNA-induced silencing complex (RISC). We recently demonstrated that the interaction between Ago2 and RISC proteins including GW182 and DDX6 increase in response to LTD induction (Long-Term Depression, a process of synaptic weakening). This mechanism causes translational repression of proteins involved in the maintenance of synaptic function or the structure of dendritic spines, leading to functional changes including spine shrinkage.

A self-funded PhD or Masters by Research (MScR) project is available to study aspects of miRNA activity and RISC regulation, and their role in synaptic plasticity.

The project will involve training in the key techniques of cell biology research, including biochemical, molecular and cell imaging techniques to study the molecular mechanisms that underlie the regulation of the synaptic proteome by miRNA activity. In addition, we collaborate with electrophysiologists for analysing synaptic transmission, and behavioural neuroscientists for studying memory, providing additional opportunities for gaining experience in a range of neuroscience techniques. The project will be supervised by Prof. Jonathan Hanley, with collaborative input from other PIs in Bristol. For further information, please contact jon.hanley@bristol.ac.uk

We are looking for an enthusiastic and innovative student with a degree in neuroscience, biological science or medical science. Bristol is a centre for neuroscience and cell biology research, and the student will benefit from exposure to a wide range of cutting-edge research in this area. The city of Bristol is vibrant, cosmopolitan and culturally diverse, with good flight connections to European cities.

Webpages:

https://hanleylab.site123.me

https://research-information.bris.ac.uk/en/persons/jonathan-g-hanley

Funding Notes:

If you are an International or UK student with your own funding, please email Professor Hanley directly jon.hanley@bristol.ac.uk

Prof James Hodge, Dr Sam Amin, Dr Edgar Buhl

Functional characterisation of novel models of neurodevelopmental disorders

Keywords:
Neuroscience, Physiology, Pharmacology, Behavioural Biology, Genetics, Cell biology, Biochemistry, Bioinformatics, Human genetics

Research into neurodevelopmental disorders offers an opportunity to engage in cutting-edge research focused on some of the most complex and underserved areas of medicine. We are studying several genes including CASK, CDKL5, DYRK1a, TSc and for mitochondrial

proteins with important neurodevelopmental functions and mutations that cause human diseases, which are poorly understood and treated. In this project you will use the power of *Drosophila* genetics to perform a functional screen of the different neurodevelopmental mutants in flies. The effect on brain development, synaptic plasticity, learning, circadian rhythms, sleep and epilepsy will be determined using mutants and assays in the Hodge lab. Mechanistic characterisation will be performed including at the level of gene expression, protein function, neuronal morphology, activity, proliferation and degeneration. The potential of the neurodevelopmental molecules as therapeutic targets will be explored using pharmacology.

This opportunity will you with the skills and knowledge necessary to make meaningful contributions to the field of neuroscience and disease research. The MRes will offer both theoretical training and hands-on lab experience. We will also provide real-world experience, ensuring you gain practical skills in setting up, delivering, and analysing clinical trials. This will provide you with a deep understanding of the challenges faced by affected individuals and their families. You will be supported by Dr Sam Amin with clinical aspects of the project and working with Public Patient Inclusion and Engagement groups (https://caskresearch.org/, https://curecdkl5.org.uk/ and https://www.dyrk1a.org/). For instance, to survey the prevalence of the different kinase mutations in the UK, their accompanying symptoms and current treatments as well as the research priorities of these different communities. They will also be the opportunity to learn how to engage with collaborative research, industry partners and pharmaceutical companies in this research area https://www.bristol.ac.uk/neuroscience/research/neurodevelopment/.

You will be trained in a range of techniques including bioinformatics, genetics and behavioural characterisation of mutants including, locomotion, seizure-activity, sleep, circadian activity and memory. e.g. using *Drosophila* activity monitors, video tracking and analysis software. Mechanistic studies may include imaging, optogenetics, electrophysiology and pharmacology. All techniques set up in the lab. Contact: james.hodge@bristol.ac.uk

Prof James Hodge & Dr Edgar Buhl

Modelling the interaction between genetic and lifestyle factors to Alzheimer disease progression

Keywords:
Neuroscience, Physiology, Pharmacology, Behavioural Biology, Genetics, Cell biology, Biochemistry, Bioinformatics, Human genetics

Genome and Epigenome Wide Association Studies (GWAS and EWAS) for Alzheimer's disease (AD) have identified several genes significantly associated with the disease. While, Whole Exome (WES) and Genome Sequencing (WGS) have identified rare mutations associated with AD. These ~200 genes confer an individual's risk of AD along with ~14 modifiable risk or lifestyle factors (e.g. social isolation, pollution, physical inactivity, alcohol, poor sleep, loss of hearing and sight) negatively effecting outcome, therefore by flipping them some of factors (better sleep, exercise, diet etc) can potentially decreasing risk. Understanding how these factors interact to confer risk of AD, is poorly understood and difficult to control for and study in human populations, with mammalian models being slow and expensive to make, age and study. To address this knowledge gap, we use the genetic tractable and short-lived fruit fly *Drosophila,* allowing us to quickly make and characterise

novel AD models based on the candidate AD risk loci and mutations. Likewise, we can carefully control the environment and lifestyle of large cohorts of genetically identical populations and make longitudinal measurements. We have obtained transgenic mutant lines for the closest *Drosophila* orthologues of AD risk genes which will be screened in fruit flies for AD relevant phenotypes under different conditions. We can target expression of mutants to the cells and tissues they are normally expressed using promoters and RNAi transgenes. The effect on lifespan will be measured using longevity assays and survival curve analysis as well as in the eye to assess neurodegeneration, all assays set up in the lab. Cognitive decline can be measured using olfactory-shock conditioning memory assays which are routinely used in the lab. The effect of the AD risk gene mutations on circadian rhythms and sleep will be assessed by expressing the candidates in clock and sleep neurons and monitoring circadian rhythms and sleep. Mechanistic insight will be provided by measuring neurodegeneration, neuronal excitability and enhancement and suppression of human Tau and amyloid-β phenotypes, and therapeutic potential by measuring pharmacological reversal of AD phenotypes. As a team we can quickly test novel hypotheses on gene by environment interactions on AD progression. Contact: james.hodge@bristol.ac.uk

Dr Valentina Mosienko

Astrocyte mechanisms in depression

Depression is the most common mental health illness affecting about 20% of the population at least once in their lifetime. Depression has been proposed to be a result of a decreased level of brain monoamines such as serotonin. In turn, therapeutic effects of most prescribed antidepressants are ascribed to their ability to elevate brain serotonin. However, there is growing evidence suggesting that mechanisms in depression and of antidepressants rely on signalling pathways independent of serotonin.

During this project, you will investigate effects of chronic stress and antidepressant treatment on the most common glial cell type in the brain called astrocytes. Astrocytes are implicated in depression: number of astrocytes is reduced in amygdala, hippocampus and prefrontal cortex in brain samples from both depressed patients and animal models of depression – astrocyte phenotype that can be reversed by a treatment with an antidepressant.

As part of this project, you will dissect brain area specific and serotonin-independent changes to astrocyte morphology, number and signalling as a response to stress and antidepressant treatment in a mouse model.

You will be embedded within a multidisciplinary and dynamic team of researchers that employ animal models, *in vitro* and *in vivo* voltammetry and imaging, and RNAseq to investigate the role of astrocyte signalling pathways in stress response, depression, and antidepressant treatment. You will have ample opportunities to grow in areas of behaviour, molecular and cellular neuroscience, as well as to collaborate with bioinformaticians, present your work at a conference, and contribute to publishing a research paper.

Please, do not hesitate to get in touch with me valentina.mosienko@bristol.ac.uk if you would like to further discuss this exciting project.

Dr. A Teschemacher

Title: Do nanoplastic particles in the brain affect the metabolic function of astrocytes?

Contact: Anja.Teschemacher@bristol.ac.uk

Keywords: Neuroscience; Nutrition; Cell biology; Toxicology

Levels of micro- and nano-plastic particles have been rising in our environment over the past decades and are now increasingly confirmed within the human brain. Alarm has been raised over suggestions that cellular metabolism may be affected by their presence, but the impact on brain energy handling and neuronal resilience is not understood. The potential correlation between incidence of neurodegenerative disorders such as Alzheimer's Disease and environmental plastic load urgently calls for further research into this matter.

This project will investigate the impact of embedded plastics on the metabolic activity of astrocytes and their ability to support neurones. A range of in vitro assays, including live cell confocal imaging on primary cell cultures, will be used.

Dr Daniel Whitcomb

Title: The molecular mechanisms of transcranial focused ultrasound neuromodulation

Abstract: Neurodegenerative diseases – such as Alzheimer's disease – affect great numbers of people globally, and yet we are still without significant efficacious therapeutic interventions. One novel treatment area receiving increasing interest is neuromodulation through brain stimulation. This has been particularly effective within the context of Parkinson's disease, where symptoms of the disease are mitigated by deep brain stimulation. However, the mechanisms underlying the effects of brain stimulation – and how best to leverage them for therapeutic effect in neurodegenerative disease – are largely unknown.

We have recently reported that ultrasound - best known as a medical diagnostic imaging tool – has significant neuromodulation effects on neurons. This builds on a growing literature in humans and animal models showing that when ultrasound is directed across the skull into the brain, it modulates brain activity. Surprisingly, despite these well-described effects, little is known about the underlying intracellular signalling mechanisms responsible.

This project will therefore investigate the cellular and molecular mechanisms responsible for the neuromodulatory effects of ultrasound stimulation. We will use a combination of acute rodent brain tissue and *in vivo* rodent brain stimulation to characterise signal cascades and protein-protein interactions that mediate the changes

to neural function elicited by ultrasound stimulation. This work will be crucial in characterising the effects of ultrasound stimulation, enabling effective application of the approach in novel therapeutic interventions for neurological conditions.

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BRISTOL MEDICAL SCHOOL

Professor Ingeborg Hers

Targeted Protein Degradation: A New Frontier in Platelet Biology and Drug Discovery

Supervisors: Prof Ingeborg Hers, Prof Varinder Aggarwal and Dr Robin Corey.

Blood clots drive life-threatening conditions such as heart attacks and strokes. Although current antithrombotic drugs (e.g., COX inhibitors, P2Y12 antagonists) reduce the risk of recurrent clots, they also increase bleeding because they broadly disrupt haemostasis. New strategies are required to prevent thrombosis while preserving normal platelet function, but progress is limited by the anuclear nature of human platelets, which prevents the use of standard genetic approaches. Our group has recently demonstrated for the first time that Proteolysis Targeting Chimeras (PROTACs) can degrade intracellular proteins in human platelets, creating new opportunities for target discovery. Unlike inhibitors that transiently block activity, PROTACs harness the ubiquitin–proteasome system to eliminate proteins entirely, removing both catalytic and structural functions. Students on this project will be working in a multidisciplinary environment and design and test PROTACs while gaining experience across chemistry, molecular modelling, cell biology and cell signalling. Experimental techniques will include platelet isolation, flow cytometry, plate and light aggregometry, adhesion/spreading assays, confocal microscopy, western blotting, TR-FRET and biophysical assays. This project will explore the role of platelet kinases, to support development of next-generation, safer anti-thrombotic therapies. Contact: i.hers@bristol.ac.uk

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Dr Cherrie Kong

Localisation of inositol trisphosphate receptors (IP_3R) in cardiac ventricular myocytes

Supervised by: Cherrie Kong

Ca^{2+} release during cardiac excitation-contraction coupling (ECC) is mediated by ryanodine receptors (RyRs) located at the sarcoplasmic reticulum (SR). The inositol trisphosphate receptor (IP_3R) is another SR Ca^{2+} channel. Although the IP_3 pathway is known to be upregulated in heart failure, the impact of IP_3 and IP_3R activity on ECC is not well understood. It has been proposed that activated IP_3R may interact with RyR to promote Ca^{2+} "leak" at diastole and disrupt ECC, however the feasibility of this idea depends on the proximity of IP_3R to RyR and/or the presence of a mediator, such as Ca^{2+}/calmodulin-dependent kinase 2 (CaMKII).

This project aims to clarify how IP_3 regulates ECC by investigating the distribution of IP_3R, RyR and CaMKII in cardiomyocytes. Contact Cherrie Kong (cherrie.kong@bristol.ac.uk) for more details.

Investigating β-adrenergic regulation of cardiac L-type Ca^{2+} channels using molecular dynamics approaches.

Supervised by: Robin Corey and Cherrie Kong

The L-type Ca^{2+} channel ($Ca_{V1.2}$) provides the trigger current (I_{Ca}) for Ca^{2+} release during cardiac excitation-contraction coupling. I_{Ca} is stimulated by β-adrenergic signalling and is a key point of control in health and disease. While transient β-adrenergic activation during the fight-or-flight response increases cardiac output, chronic activation is associated with disease.

Recent studies have challenged the long-held view that β-adrenergic stimulation of I_{Ca} involved direct $Ca_{v1.2}$ phosphorylation. Instead, phosphorylation of Ras associated with diabetes (Rad), a small GTP-binding protein, disrupts its inhibition of $Ca_{V1.2}$ activity. The localisation of Rad in close proximity to $Ca_{v1.2}$ is likely to be important to its function. This local interaction could be affected by other molecules such as phosphatidylinositol 4,5-bisphosphate (PIP_2), caveolin-3 (Cav-3) or cholesterol, which have been implicated in aggregating proteins. Cav-3, in particular, has been shown to be involved in the β-adrenergic effect of I_{Ca}.

In this study, computational methods in simulating and predicting protein-protein and protein-lipid interactions will clarify the interplay between Cav-3, Rad and $Ca_{V1.2}$. Immunocytochemical and Ca^{2+} imaging studies will also be carried out to clarify protein distribution and the effect of β-adrenergic stimulation on Ca^{2+} influx. Contacts: robin.corey@bristol.ac.uk and cherrie.kong@bristol.ac.uk

Professor Stuart Mundell

Platelet biology and clinical use of antiplatelet drugs in patients with acute coronary syndromes

Platelets are essential to the prevention of bleeding when blood vessels are damaged. However, when platelets activate too much or at the wrong time and place the result is thrombosis, leading to heart attacks and stroke. Research in the laboratory of Professor Mundell aims to understand the complex mechanisms that regulate platelet activation, from a molecular to a systems level. Current research, in collaboration with clinicians and industry is focussed upon characterizing the mode of action and therapeutic use of drugs that inhibit platelet activity and their use in patients with acute coronary syndromes.

Hyperactivity of platelets in acute coronary syndrome (ACS) patients is well-documented although the molecular basis of phenotypic changes in platelet functionality is unclear. Changes in platelet surface receptor expression, including the platelet P2Y12 receptor (P2Y12R), may increase platelet reactivity in ACS patients. The P2Y12R, which is blocked by antiplatelet drugs like ticagrelor used in the treatment of ACS, possesses a high degree of agonist-independent activity. Increases in P2Y12R expression increase levels of agonist-independent receptor activity. Whether pathophysiological increases in P2Y12R expression influence platelet reactivity and thrombotic risk is unknown. Further how drugs like ticagrelor which reduce agonist-independent activity work at a molecular level is also unknown. This project has two main strands. First how does patient pathology alter patterns of platelet surface receptor expression with focus upon P2Y12R expression/agonist-independent activity. These patient-based studies ultimately aim to link the pathophysiological significance of changes in platelet receptor expression to increases in platelet reactivity. This has the translational potential to further tailor patient pharmacotherapy. Second key regions/residues that regulate constitutive receptor activity and inverse agonist action at the P2Y12R will be defined. Such fundamental insights into P2Y12R pharmacology will provide the basis to refine pharmacotherapy at this receptor in the treatment of ACS. Contact: s.j.mundell@bristol.ac.uk

BIOCHEMISTRY AND CELLULAR AND MOLECULAR MEDICINE

Professor Chrissy Hammond

Mending broken bones: testing novel injectable hydrogels in zebrafish fractures

In this project working in our lab in collaboration with the Armstrong lab, you would be testing whether new formulations of injectable hydrogels can improve fracture repair using the zebrafish model system. Zebrafish maintain translucency of some skeletal tissues though life, meaning we can watch cell behaviour dynamically in the living fish using fluorescent reporter lines. You would be testing how immune and skeletal cells respond to and interact with functionalized biomaterials and whether they can improve repair outcomes. chrissy.hammond@bristol.ac.uk

What doesn't break you makes you stronger: the role of mechanical loading on bone shapes through life

In this collaboration working in collaboration with the Rayfield lab you would be testing how mechanical loading shapes bones through life during development, into ageing and in disease states. Making use of our extensive biodatabank of zebrafish 3D CT scans, you will build models of the skeleton and using computational modelling test how we expect them to mechanically perform, then validate this using live imaging assays in the living fish using fluorescent reporter lines that label cell responding to load and testing how this affects cell behaviour. chrissy.hammond@bristol.ac.uk