Wellcome Trust Biomedical Vacation Scholarship projects

Biochemistry, Dr Minkoo Ahn: Rational engineering of the ribosome to modulate the proteome

The ribosome produces every protein found in all life forms with 99.99% precision. During translation it orchestrates crucial cellular processes such as folding and translocation into cell-membrane to guide nascent polypeptides to fold into their native structures, and the ribosome structure plays a vital role. Recently, we developed a novel engineering/structural biology platform to rationally engineer the ribosome and to study the structure and dynamics of nascent polypeptides (Ahn, 2022, Nat. Commun., https://www.nature.com/articles/s41467-022-31906-z ). There are many interesting aspects of the ribosome structure, particularly its narrow exit tunnel and outside surface, that are involved in translational and co-translational processes to be explored. As a part of this exciting journey students will join my lab and design new E. coli 70S ribosome variants based on bioinformatics analysis, and generate them using CRISPR/Cas9 gene editing. If time permits, they will continue exploring the proteome expressed by these engineered ribosomes using biochemistry, structural biology and proteomics analysis.

Cellular and Molecular Medicine, Dr Daniel Morse: Anti-pathogenic properties of environmental bacteria

The successful applicant will be sourcing environmental microorganisms and culturing them in the laboratory to explore their anti-pathogenic effects against common pathogenic bacteria. Techniques include microbial culture and isolation, solid culture contact-dependent exclusion assays, liquid culture inhibition assays, haemolysis assays, and Gram stain and PCR for sequencing to identify the environmental candidates.

Cellular and Molecular Medicine, Dr Maisem Laabei: Novel antimicrobial compounds to treat multi-drug resistant infections

Antimicrobial resistance (AMR) is one of the top 10 global health issues. Lack of novel drugs in the clinical pipeline are severely hampering treatment options and driving AMR. Staphylococcus aureus is a major human pathogen that causes a broad range of infections resulting in significant morbidity and mortality globally. Due to the constant threat of AMR, the WHO has placed S. aureus on the list of priority pathogens for which the development of antibiotics is urgently required. We have developed a novel polyamine-based compound that displays activity against major human bacterial pathogens including S. aureus. This project will further define the molecular activity of these compounds using a suite of molecular microbial methods. Here the student will employ basic and advanced molecular techniques to understand how this compound causes bacterial inhibition when used alone or in combination with clinically used antibiotics. The student will investigate whether our compound can restore sensitivity of resistant S. aureus to beta-lactam antibiotics. Here the student will optimise and run time-kill assays against a suite of multi-drug resistant S. aureus isolates and determine the outcome of antibiotic synergy. Next the student will use fluorescence microscopy and document the impact of polyamine treatment on bacteria which have been modified to express specific fluorescent proteins that are integral to macromolecular biosynthesis. Combined, this project will help characterise the mechanism of action and inform on the potential clinical utility of a novel antimicrobial compound.

Pharmacology, Physiology and Neuroscience, Professor Ingeborg Hers: Evaluation of the role of BTK in platelet function and thrombosis using chemical degraders

Platelets are small cells in the blood that play an important role in stopping a bleeding but when inappropriately activated also contribute to thrombosis and cardiovascular disease. Our present insights in the underlying mechanism by which platelets contribute to thrombosis heavily relied on the use of genetic animal models and small molecule inhibitors with associated drawbacks such as species differences and pharmacological non-specificity. We recently demonstrated that it is feasible to remove a protein from platelets using small heterobifunctional degraders called PROTACs (PROteolysis TArgeting Chimeras) which target proteins for ubiquitination leading to proteasomal degradation1. These are exciting findings as it is the first time that a human platelet 'knockout' has been generated. In this project, we will build on these findings and optimise the conditions for degradation of the tyrosine kinase BTK in whole blood. This will allow detailed evaluation of the role of BTK in human platelet function and thrombosis formation. The lab work will take place the Bristol Platelet Group in the Biomedical Sciences Building and will involve a wide range of techniques including platelet isolation, platelet extractions and sample generation, western blotting and in vitro platelet functional analysis (plate aggregation, flow cytometry and in vitro thrombosis).

1. Trory, J.S. et al. (2023). Chemical degradation of BTK/TEC as a novel approach to inhibit platelet function. Blood Adv 7, 1692-1696.

Pharmacology, Physiology and Neuroscience, Dr Michael Ambler: Mapping the hypothalamic control of torpor

Torpor is a remarkable hypothermic, hypometabolic state engaged by a variety of species including mice in response to food scarcity or a cold environment. We are interested in the neural control of torpor, with the aim to identify conserved mechanisms that might represent powerful targets for future clinical applications. The preoptic area of the hypothalamus contains neurons that are active during fasting-induced torpor in the mouse. Using targeted recombination in active populations (TRAP), we have shown that targeted reactivation of those same neurons in fed mice recapitulates key features of torpor(1, 2). This project aims to further characterise the location of the key neurons within this area that drive the physiological changes. The group have performed many viral vector injections into this area, driving expression of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs(3)). In some animals, subsequent chemoactivation of transfected neurons triggered torpor ('hits'), while in others it did not 'misses).

Psychological Science, Dr Charlotte Crisp: Chronotype and cognition: does the timing of psychological interventions matter?

Background: Performance on cognitive tasks depends on the time-of-day and individual chronotype. This is called the 'synchrony effect' i.e., late chronotypes ('night owls') perform better in the evening and early chronotypes ('morning larks') in the morning (at their 'optimal time-of-day'). However, it is unknown whether this synchrony effect is important for completing psychological interventions which require similar cognitions. It could be that individuals are more engaged and learn better at optimal times-of-day meaning the intervention is more effective at this time. Aims: The student will be working on pre-collected data from the MILESTONE study. This is a Randomised Controlled Trial testing the

effect of an online psychological intervention (Cognitive Bias Modification) on the neural correlates of emotion processing (using fMRI) in patients with depression that have just started taking SSRI medication. The aim of the proposed project is to 1) understand the chronotype distribution in this sample, 2) test whether chronotype is related to the time-of-day the online intervention was completed, and 3) investigate whether the effectiveness of the intervention (learning) is improved when completed at a time-of-day synchronised to chronotype (synchrony effect). Student development: The student will be able to work on the data immediately and will be involved with data cleaning, statistical analysis and writing up the findings. They will join TARG research group at University of Bristol – a large group interested in cognition, mental health, tobacco and alcohol and intervention design. They will be able to join lab meetings, paper feedback sessions and develop their interests.

The project can be completed in person at the University of Bristol or remotely online. Ideally the student would have familiarity with using basic scripts in R and running statistics e.g., using SPSS.

Psychological Science, Dr Edwin Dalmaijer: How do food preferences and dislike impact stomach physiology?

The stomach influences our behaviour: its activity is modulated during periods of disgust, and when it is settled pharmacologically our disgust-avoidance behaviour is reduced. In this project, we aim to specifically look at disgust for unfamiliar foods in young children. Stomach physiology will be measured using electrogastrography, and we will teach you how to use this technique and how to analyse the generated data. Applicants should have an affinity with human physiology, children, and data. Programming skills are a plus, but not required.

Psychological Science, Professor Nick Scott-Samuel and Professor Ute Leonards: The effect of visual context on search performance across neurodiverse populations

Many university learning environments seem unsuitable for sustained concentration. Architectural choices appear to be based on fashion, rather than considerations of visual stress, with glare, periodic patterns and high contrasts – typically unpleasant visual stimuli – a recurring feature. A recent report of students' experiences suggests that sensory stressors disproportionally affect people with neurodiverse conditions (e.g. ASC, ADHC, Dyslexia, Dyscalculia, Dyspraxia, Tourette's, OCC, depression), preventing them from performing to their full potential or even causing them to fail. The same holds true for migraineurs. But what affects whom and under which conditions in real world environments remains unknown. We propose to start to tackle this issue by investigating how task-irrelevant surrounds covering large areas of the visual periphery impact performance within the central visual field. We will use a visual search task, displayed on a high-resolution projector for large visual field coverage. Both search task difficulty and surrounding appearance can be manipulated to reveal which visual patterns have the largest effect on performance. Performance should drop and reaction times increase for difficult search tasks with more distracting / visually stressful surrounds, and we predict that these effects will be more pronounced in people with neurodiverse conditions and/or migraine. Our data will inform design decisions for lecture theatres, seminar rooms etc. and contribute towards the ongoing debate about inclusivity in higher education. Furthermore, there is no reason why those data could not generalise well beyond university teaching spaces into the contemporary built environment.