UNIVERSITY OF LIVERPOOL

MRes in Advanced Biological Sciences

Research Projects
2023 -2024

Please read through the research project choices available below
and list your top 4 choices in order on your reply slip

Faculty of Health and Life Sciences

Project Title:	**Investigating the role of calmodulin in cardiac arrhythmia**
Project ID No:	1
Supervisor:	Dr Nordine Helassa
Pathway:	Cell Signalling;Chemical Biology;Structural Biology;
Type of Project:	Laboratory

Project Description: Long QT syndrome (LQTS) is an inherited conditions that disturb heart rhythm and can cause life threatening arrhythmias (e.g. sudden cardiac death). Recent studies have identified mutations in the major Ca2+ sensor calmodulin (CaM) that are associated with cardiac arrhythmia susceptibility suggesting that CaM dysfunction is a key driver of the molecular aetiology of the disease. However, the detailed molecular mechanism leading to irregular heartbeats in this condition remains unclear. This research project aims to determine the effect of the disease-associated mutations on calmodulin function. In particular, we will assess the mutant proteins stability and their interaction with key ion channels involved in cardiac muscle contraction. We will use a combination of biochemical techniques (recombinant protein expression/purification, protease digestion susceptibility, SDS-PAGE), advanced biophysical method (NMR, ITC, circular dichroism) and confocal microscopy (calcium imaging). Data obtained from this project will give us a better understanding of the role of calmodulin in cardiac arrhythmia and will open ways for therapeutic strategies.

Further Reading: [1] Prakash O et al. Calmodulin variant E140G associated with long QT syndrome impairs CaMKIIδ autophosphorylation and L-type calcium channel inactivation. J Biol Chem. 2022 Dec 8;299(1):102777. doi: 10.1016/j.jbc.2022.102777. [2] Prakash O et al. CPVT-associated calmodulin variants N53I and A102V dysregulate Ca2+ signalling via different mechanisms. J Cell Sci. 2022 Jan 15;135(2):jcs258796. doi: 10.1242/jcs.258796. [3] Chazin WJ, Johnson CN. Calmodulin Mutations Associated with Heart Arrhythmia: A Status Report. Int J Mol Sci. 2020 Feb 19;21(4):1418. doi: 10.3390/ijms21041418.

Project Title:	**Structure functional studies of human Methionine Adenosyltranferases upregulated in hepatocellular carcinoma**
Project ID No:	2
Supervisor:	Dr Svetlana Antonyuk
Pathway:	Structural Biology;Molecular Oncology;
Type of Project:	Laboratory

Project Description: Methionine Adenosyltranferases (MATs) are responsible for SAMe (S- Adenosylmethionine), the principal methyl donor in cells. Methylation plays a part in almost all aspects of gene expression control, from DNA to proteins and also RNA. The importance of these enzymes in human disease is highlighted by the upregulation of MATalpha2beta complex in human hepatocellular carcinoma (HSC) and many cancers, while mutations if MATalpha1 has been associated with a number of human diseases including persistent hypermethioninemia. MATalpha2 is validated as a therapeutic target for biomarker-directed clinical trials for the substantial patient population with MTAP-deleted cancers. Although MATalpha1 and MATalpha2 catalyze the same reaction, they differ in kinetic and regulatory properties and sensitivities to inhibitors of MAT (Lu, 2012). MATalpha2 forms the complex with its regulatory subunit MATbeta. It is known that trans-differentiation of HSCs is connected to phosphorylation of MATalpha2beta complex and its stabilisation (Romani et al, 2015), while mutations MATα2 residues (Y371F and T374V) cause prevention of induction of HSC activation observed by the WT protein. The project will determine if these mutations affect MATα2 structure, activity and MATαlpha2beta complex formation. The project is lab based and will require protein overexpression and purification, site directed mutagenesis, protein crystallisation and structural determination by protein crystallography, ELISA activity determination.

Further Reading: Panmanee J. et al FEBS DOI: 10.1111/febs.14790 (2019); Panmanee J., Antonyuk.S, Hasnain, S. Acta Cryst. D76, 594–607 (2020).

Project Title:	**Studying animal metabolism in relation to health and disease**
Project ID No:	3
Supervisor:	Prof Warwick Dunn
Pathway:	Animal Sciences;
Type of Project:	Laboratory

Project Description: Metabolites play many important roles in biological processes related to animal health and disease through metabolism, regulation (e.g. post-translational modifications) and signalling. The role of metabolites can be investigated applying targeted studies focused on a small number of metabolites or by applying untargeted metabolomics approaches which study 100-1000s of metabolites in biofluids, cell culture or tissues collected from animals/pets; this later strategy is analogous to transcriptomics and proteomics. In this project you will learn about and apply metabolomics to study an animal-based disease to identify disease biomarkers and/or identify metabolic processes associated with disease onset or progression. The project will operate in collaboration with the School of Veterinary Science at the University of Liverpool. During the project you will learn to extract metabolites from biological samples, to operate liquid chromatography-mass spectrometry instruments, to process complex metabolomics data and to perform statistical analysis of data.

Further Reading: Dunn WB, Broadhurst DI, Atherton HJ, Goodacre R, Griffin JL. Systems level studies of mammalian metabolomes: the roles of mass spectrometry and nuclear magnetic resonance spectroscopy. Chem Soc Rev. 2011 Jan;40(1):387-426. doi: 10.1039/b906712b.

Project Title:	**Determination of 3C-like protease-substrate specificity and reaction kinetic by proteomics**
Project ID No:	4
Supervisor:	Dr Edward Emmott
Pathway:	Microbiology;Functional and Comparative Genomics;
Type of Project:	Laboratory

Project Description: Positive-sense, single-stranded RNA viruses are responsible for many of the major diseases affecting humans worldwide, including coronavirus, poliovirus and norovirus. During the life cycle, they all express their entire genome as a polyprotein thus relying on a viral endopeptidase (3C-like protease) to release structural and non-structural proteins essential for viral replication within the host cells. However, it is known that some intracellular host proteins are also substrates to 3C-like proteases and these virus-host interactions play an important role in the course of the disease. In this project, we propose the development of mass spectrometry-based and fluorometric-based assays to determine both specificity and proteolysis kinetics of multiple host substrates in the presence 3C-like proteases. By understanding and quantifying the dynamics of these virus-host interactions, we can achieve an oriented prioritisation of potential intervention targets to control the virus disease.

Further Reading: https://www.nature.com/articles/s41467-021-25796-w

Project Title:	**Engineering more water-use efficient crops: functional genomics of CO2 fixation during Crassulacean acid metabolism**
Project ID No:	5
Supervisor:	Dr James Hartwell
Pathway:	Plant Sciences;Functional and Comparative Genomics;Post Genomic Sciences;Cell Signalling;Biotechnology;
Type of Project:	Laboratory

Project Description: The world is getting hotter and drier due to climate change, and the human population is growing rapidly. Furthermore, it has been predicted that we will need to increase crop yields by 50 - 70 % by 2050 in order to feed the predicted 9 - 10 billion people. This extra food production has to be achieved using the same land and the same or less fresh water relative to the water used by agriculture today. Achieving such dramatic advances in crop productivity to underpin human food security this century is widely regarded as a key global grand challenge that requires ground-breaking, innovative approaches that "think outside the box". Our research aims to leverage a naturally occurring super-charged adaptation of photosynthesis called Crassulacean acid metabolism (CAM). CAM can enhance plant water use efficiency well beyond that of any of today's major food crop species such as rice, wheat or maize. Through decoding genomes and transcriptomes, and undertaking functional genomics research in model CAM species in the genus Kalanchoë, our work is establishing the minimal parts list for engineering CAM into C3 crops to enhance water use efficiency and photosynthesis. This project will leverage our recent discoveries by exploring the genes involved in CAM using transgenic approaches to switch genes off or on. In particular, we seek to understand how the endogenous circadian clock signals to the CAM system to ensure dark and light specific biochemical steps happen at the correct time. This MRes project will allow the student to make a key contribution to our understanding of the genetic elements associated with CAM and its optimal temporal regulation. The student will also become accomplished in plant transformation and the techniques required for the detailed molecular, biochemical and physiological characterisation of the generated transgenic lines.

Further Reading: Susanna F Boxall, Nirja Kadu, Louisa V Dever, Jana Kneřová, Jade L Waller, Peter J D Gould and James Hartwell (2020) Kalanchoë PPC1 is Essential for Crassulacean Acid Metabolism and the Regulation of Core Circadian Clock and Guard Cell Signaling Genes. The Plant Cell, 32, 1136 – 1160. Susanna F Boxall, Louisa V Dever, Jana Kneřová, Peter D. Gould and James Hartwell (2017) Phosphorylation of Phosphoenolpyruvate Carboxylase Is Essential for Maximal and Sustained Dark CO2 Fixation and Core Circadian Clock Operation in the Obligate Crassulacean Acid Metabolism Species Kalanchoë fedtschenkoi. The Plant Cell 29, 2519-2536 James Hartwell, Louisa V Dever, Susanna F Boxall (2016) Emerging model systems for functional genomics analysis of Crassulacean acid metabolism. Current Opinion in Plant Biology 31, 100-108.

Project Title:	**How does the YB-1 oncoprotein control protein translation in hypoxic tumour cells**
Project ID No:	6
Supervisor:	Dr Niall Kenneth
Pathway:	Cell Signalling;Molecular Oncology;
Type of Project:	Laboratory

Project Description: As solid tumours expand, they rapidly outgrow the blood supply leaving portions of the tumour with significantly lower oxygen concentrations (hypoxia) than surrounding healthy tissue. In healthy cells prolonged hypoxia usually results in cell death, however cancerous cells can adapt to survive and thrive in the hypoxic environment. Tumour hypoxia is associated with increased tumour aggressiveness and negative clinical outcomes in cancer patients. Developing new strategies to treat advanced hypoxic tumours is therefore of great interest. One of the ways cancer cells thrive in hypoxic environments is by preferentially making (translating) protective proteins to ensure their survival. We are interested in how a cancer-causing protein called Y-box binding protein-1 (YB-1), specifically increases the production of proteins during tumour hypoxia to protect the cancerous cells. In this project the student will investigate how YB-1 is 'switched on' in hypoxic tumours and understand the consequences of 'switching it off'. We believe that the mechanisms of YB-1 activation uncovered in this proposal are likely to be sensitive to current, repurposed, and new types of drugs, and this work could provide a new way to both stratify and target YB-1-dependent translation in patient-specific tumours.

Further Reading: Ivanova, I. G., Park, C. V, Yemm, A. I. and Kenneth, N. S. (2018) PERK/eIF2α signaling inhibits HIF-induced gene expression during the unfolded protein response via YB1-dependent regulation of HIF1α translation. Nucleic Acids Res. 46, 3878–3890.Ivanova, I. G., Park, C. V. and Kenneth, N. S. (2019) Translating the Hypoxic Response—the Role of HIF Protein Translation in the Cellular Response to Low Oxygen. Cells. 5. Hunter, J. E., McHugh, O., Ecclestone, G. B., Child, F., Mearns, H., Robson, G., . . . Kenneth, N. S. (2022). Disruption of HIF1A translational control attenuates the HIF-dependent hypoxic response and solid tumour formation in vivo. bioRxiv, 2022.2011.2002.514731. doi:10.1101/2022.11.02.514731

Project Title:	**Sexual selection in insects**
Project ID No:	7
Supervisor:	Prof Zenobia Lewis
Pathway:	Evolution and Behavioural Biology;Host-Parasite Biology;Microbiology;
Type of Project:	Laboratory

Project Description: am very broadly interested in the evolutionary ecology of insect reproduction. I investigate 'traditional' questions in sexual selection, mainly using Lepidopteran and Dipteran model species. However, more recently, I have also become interested in how commensal microbes such as gut bacteria, can influence the reproductive behaviour of the host. For example, we have shown that gut microbes can disrupt the signals used in kin recognition in Drosophila flies. I am very flexible with respect to what students may wish to investigate, within the remit of my expertise.

Further Reading: https://www.nature.com/articles/ismej2013157; https://royalsocietypublishing.org/doi/full/10.1098/rsbl.2011.0544; https://royalsocietypublishing.org/doi/full/10.1098/rsbl.2010.0605

Project Title:	**Biosynthesis and Bioengineering of Molecular machines**
Project ID No:	8
Supervisor:	Prof Luning Liu
Pathway:	Biotechnology;Microbiology;Plant Sciences;Structural Biology;
Type of Project:	Laboratory

Project Description: To address the major grant challenges that we face nowadays, e.g. Climate change, sustainable energy, and human health, there is a pressing need for new biotechnological strategies and solutions. Molecular machines have captured the imagination of scientists and public alike for decades, given their remarkable biological roles in cells and clear potential to sustainably transform and enhance human life. In prokaryotic organisms, molecular machines, for example bacterial microcompartments and photosynthetic apparatus, play vital roles in related to photosynthesis, nitration assimilation, pathogenesis, and microbial ecology. This project is aimed at studying the molecular basis underlying the biogenesis and assembly of molecular machines of model bacterial systems including cyanobacteria, Salmonella, E. coli, using molecular biology, biochemistry, microscopy, and omics approaches. We will also use synthetic biology to engineer and reprogramme synthetic machines for metabolic enhancement, bioenergy production, drug delivery and molecular therapeutics. The knowledge and biological systems generated in this project will underpin the production and development of new nano-biomaterials for diverse biotechnological applications. Developing a protein shell as a novel drug delivery nanoplatform for cancer therapeutics Nanomedicine has benefited significantly from the development of nanotechnology in medical/pharmaceutical research. This is especially noteworthy in the generation of new systems for disease diagnosis and the delivery of therapeutics. Although several nanocarrier systems based on micelles, liposomes, inorganic/polymer nanoparticles (e.g. ferritins, virus-like particles) have been in development, these systems have substantial limitations including issues of poor biocompatibility, high toxicity, lack of site-specificity, low drug loading, and instability. We have recently invented a way to create new protein cages based on the polyhedral protein shells of bacterial microcompartments. This PhD project aims to explore this exciting opportunity and to evaluate the capacities of the engineered protein cages as carrier systems in site-specific delivery of therapeutic drugs in cancer treatment. The outcomes of this study will have broad implications in the development of therapeutic drug delivery in many disease areas and may also provide opportunities to address other medical needs and challenges in health care. This is truly a multidisciplinary project and will integrate a variety of experimental approaches in synthetic biology, biochemistry, microscopy, and cancer biology. It will offer excellent opportunities for the student to work at the interface between biology, medicine, chemistry, and synthetic engineering.

Further Reading: https://academic.oup.com/plcell/advance-article/doi/10.1093/plcell/koac348/6873962?login=false https://ami-journals.onlinelibrary.wiley.com/doi/10.1111/1751-7915.13740
https://www.cell.com/trends/microbiology/pdf/S0966-842X(21)00259-6.pdf
https://www.nature.com/articles/s41467-022-30608-w
https://pubs.acs.org/doi/10.1021/acssynbio.1c00311
https://pubs.acs.org/doi/10.1021/acs.biomac.2c00781
https://journals.asm.org/doi/10.1128/mbio.03629-21

Project Title:	**Biosynthesis and Bioengineering of Molecular machines**
Project ID No:	9
Supervisor:	Prof Luning Liu
Pathway:	Biotechnology;Microbiology;Structural Biology;
Type of Project:	Laboratory

Project Description: To address the major grant challenges that we face nowadays, e.g. Climate change, sustainable energy, and human health, there is a pressing need for new biotechnological strategies and solutions. Molecular machines have captured the imagination of scientists and public alike for decades, given their remarkable biological roles in cells and clear potential to sustainably transform and enhance human life. In prokaryotic organisms, molecular machines, for example bacterial microcompartments and photosynthetic apparatus, play vital roles in related to photosynthesis, nitration assimilation, pathogenesis, and microbial ecology. This project is aimed at studying the molecular basis underlying the biogenesis and assembly of molecular machines of model bacterial systems including cyanobacteria, Salmonella, E. coli, using molecular biology, biochemistry, microscopy, and omics approaches. We will also use synthetic biology to engineer and reprogramme synthetic machines for metabolic enhancement, bioenergy production, drug delivery and molecular therapeutics. The knowledge and biological systems generated in this project will underpin the production and development of new nano-biomaterials for diverse biotechnological applications.

Further Reading: https://academic.oup.com/plcell/advance-article/doi/10.1093/plcell/koac348/6873962?login=false https://ami-journals.onlinelibrary.wiley.com/doi/10.1111/1751-7915.13740
https://www.cell.com/trends/microbiology/pdf/S0966-842X(21)00259-6.pdf
https://www.nature.com/articles/s41467-022-30608-w
https://pubs.acs.org/doi/10.1021/acssynbio.1c00311
https://pubs.acs.org/doi/10.1021/acs.biomac.2c00781
https://journals.asm.org/doi/10.1128/mbio.03629-21

Project Title:	**Why do cancers cells re-express meiotic SYCP1 protein and how can use this in the clinic**
Project ID No:	10
Supervisor:	Dr Urszula McClurg
Pathway:	Biotechnology;Cell Signalling;Molecular Oncology;
Type of Project:	Laboratory

Project Description: The aim of meiosis is to generate gametes by recombining the chromosomes and reducing the genome from diploid to haploid. However, in mitosis haploid genome and recombination have catastrophic, oncogenic outcomes. Consequently, the process of somatic cell division requires the accurate and specific silencing of meiotic genes when cells transition to mitosis. Interestingly, failure of this silencing occurs in approximately 15% of human cancer patients who re-express the meiotic SYCP1 protein. We find that SYCP1 re-expression is induced by common chemotherapy treatments causing DNA damage induction. The process of meiotic recombination involves similar mechanisms to DNA double strand break repair (DSBR) and due to this similarity SYCP1 re-activation in cancer cells may contribute to genome instability. In this project you will investigation potential mechanisms driving SYCP1 re-expression in cancer. You will investigate the biology of SYCP1 re-expression in cancer, the effect it has on cellular physiology and response to chemotherapeutics. Consequently, by the end of the year graduating candidate will have a sound understanding and practice in laboratory approaches including immufluorescence, immunopathology, Western blotting, cloning, molecular physiology and pharmacology.

Further Reading: Sou IF, .., Tee W-W, McClurg UL. 2021. Meiosis initiation: a story of two sexes in all creatures great and small. Biochemical Journal, 478(20), 3791-3805. https://portlandpress.com/biochemj/article/478/20/3791/230041/Meiosis-initiation-astory-of-two-sexes-in-all Sandhu S, …, McClurg UL. 2021. A pseudo-meiotic centrosomal function of TEX12 in cancer. BioRxiv, https://doi.org/10.1101/509869 (In press in Communications Biology) https://www.biorxiv.org/content/10.1101/509869v2

Project Title:	**Understanding the evolution of meiotic DNA anchorage during recombination and its impact on species fitness**
Project ID No:	11
Supervisor:	Dr Urszula McClurg
Pathway:	Biotechnology;Cell Signalling;Molecular Oncology;Animal Sciences;Evolution and Behavioural Biology;Functional and Comparative Genomics;
Type of Project:	Laboratory

Project Description: Genetic diversity in nature, is the basis of evolutionary change. Furthermore, evolution is the basis of survival and adaptation and when harnessed it supports agriculture. In eukaryotes genetic diversity is achieved through a specialised process of cell division known as meiosis. During meiosis haploid gametes are generated through homologous recombination of DNA resulting in a new, unique DNA pattern combined from paternal and maternal lines. To perform genome rearrangements between homologous chromosomes meiotic cells generate a unique multiproteinaceus structure known as the synaptonemal complex. However, how this structure, and consequently the chromosomes that it pulls together, is anchored within the cell during these highly choreographed chromosome movements remained unclear. We recently discovered that in animals, similarly to yeast, fungi and plants, synaptonemal complex is structurally linked to the microtubule organising centres. We hypothesise that this provides a critical level of stability, which facilitates homologous recombination and consequently, genome diversification. We have generated a new tool to test this hypothesis which provides a unique opportunity to test the impact of synaptonemal complex – microtubule organising centre structural link on fertility, genome diversification and consequently evolution. This project will provide the student with training in genetics, genomics, biochemistry, structural biology and cell biology.

Further Reading: Sou IF, .., Tee W-W, McClurg UL. 2021. Meiosis initiation: a story of two sexes in all creatures great and small. Biochemical Journal, 478(20), 3791-3805. https://portlandpress.com/biochemj/article/478/20/3791/230041/Meiosis-initiation-astory-of-two-sexes-in-all Sandhu S, …, McClurg UL. 2021. A pseudo-meiotic centrosomal function of TEX12 in cancer. BioRxiv, https://doi.org/10.1101/509869 (In press in Communications Biology) https://www.biorxiv.org/content/10.1101/509869v2

Project Title:	**Is meiotic TEX12 a novel regulator of centrosome amplifications in cancer?**
Project ID No:	12
Supervisor:	Dr Urszula McClurg
Pathway:	Cell Signalling;Molecular Oncology;Biotechnology;
Type of Project:	Laboratory

Project Description: The aim of meiosis is to generate gametes by recombining the chromosomes and reducing the genome from diploid to haploid. However, in mitosis haploid genome and recombination have catastrophic, oncogenic outcomes. Consequently, the process of somatic cell division requires the accurate and specific silencing of meiotic genes when cells transition to mitosis. Interestingly, failure of silencing occurs in approximately 10% of human cancer patients who re-express the meiotic TEX12 protein. We find that TEX12 reexpression induces centrosome amplification, a common feature of cancers, and consequently genome instability. In meiosis spindle is formed by multiple microtubule organising centres resulting in unevenly distributed cell division. This spindle formation is akin to multiple cancers where centrosomes are amplified and aneuploidy is common. Consequently, TEX12 re-activation in cancer cells may contribute to centrosome amplifications by promoting meiotic like spindle. In this project you will investigate the biology of TEX12 re-expression in cancer, the effect it has on cellular physiology and centrosomes. Consequently, by the end of the year graduating candidate will have a sound understanding and practice in immufluorescence, immunopathology, Western blotting, cloning and molecular physiology.

Further Reading: Cancer and meiotic gene expression: Two sides of the same coin? IF Sou, G Hamer, WW Tee, G Vader, UL McClurg Current Topics in Developmental Biology 2022//7/29
https://www.researchgate.net/publication/362339575_Cancer_and_meiotic_gene_expression_Two_sides_of_the_same_coin Sou IF, .., Tee W-W, McClurg UL. 2021. Meiosis initiation: a story of two sexes in all creatures great and small. Biochemical Journal, 478(20), 3791-3805.
https://portlandpress.com/biochemj/article/478/20/3791/230041/Meiosis-initiation-astory-of-two-sexes-in-all Sandhu S, …, McClurg UL. 2021. Centrosome dysfunction associated with somatic expression of the synaptonemal complex protein TEX12. Communications Biology 4(131) https://www.nature.com/articles/s42003-021-02887-4

Project Title:	**Investigating the role of chromatin in regulation of co-transcriptional RNA quality control**
Project ID No:	13
Supervisor:	Dr Manolis Papamichos
Pathway:	Cell Signalling;Functional and Comparative Genomics;
Type of Project:	Laboratory

Project Description: Transcription, the first step in gene expression, underpins life. Elimination of aberrant transcripts is vital for proper gene expression and of paramount importance to cellular homeostasis. In eukaryotes, nuclear RNA surveillance and quality control mechanisms monitor mRNA biogenesis co-transcriptionally and terminate transcription prematurely for degradation of the nascent RNA transcript. While the RNA degradation pathway has been characterized in molecular detail, the mechanisms regulating abortion of transcription are poorly understood. This knowledge gap will be investigated in this project. Eukaryotic transcription takes place in the context of the condensed yet highly dynamic chromatin nucleoprotein structure. Chromatin regulation is critical for proper transcription and dysregulated epigenome contributes to human disease. However, the role of chromatin in co-transcriptional RNA quality control remains elusive. We have uncovered a novel role for chromatin controlling co-transcriptional RNA surveillance. This project will test the hypothesis that chromatin acts as a molecular switch that dictates whether RNA Polymerase II will either progress into productive elongation or be removed. Employing a powerful combination of functional genetics and cutting-edge genomics and transcriptomics assays in the model organism budding yeast and in human cells, this project will investigate how chromatin coordinates transcription with RNA quality control. The project provides excellent training in Chromatin and RNA biology and opportunities to learn and use state-of the-art Oxford Nanopore Technologies for long-read sequencing. Illuminating the unexpected role of chromatin in RNA quality control, this project will reveal novel concepts in gene regulation, with the potential of creating innovative approaches in clinical intervention.

Further Reading: 3. Luzzi S, Szachnowski U, Greener S, Schumacher K, Fulton S, Han KH, Darke J, Piccinno R, Lafon A, Pugh BF, Devys D, Tora L, Morillon A and Papamichos-Chronakis M (2021). Chromatin remodelling by INO80 at promoter proximal pause sites promotes premature termination of mRNA synthesis. bioRxiv https://doi.org/10.1101/2020.03.02.973685 ; 4. Prendergast L, McClurg UL, Hristova R, Berlinguer-Palmini R, Greener S, Veitch K, Hernandez I, Pasero P, Rico D, Higgins JMG, Gospodinov A, and Papamichos-Chronakis M. (2020). Resolution of R-loops by INO80 promotes DNA replication and maintains cancer cell proliferation and viability. Nature Communications, 2020 Sep 10;11(1):4534.

Project Title:	**Investigating the role of the INO80 chromatin remodeler in oncogenic transcription in cancer: Mechanism and function in acute myeloid leukemia.**
Project ID No:	14
Supervisor:	Dr Manolis Papamichos
Pathway:	Cell Signalling;Molecular Oncology;Functional and Comparative Genomics;
Type of Project:	Laboratory

Project Description: Acute myeloid leukemia (AML) is a lethal, heterogeneous, aggressive cancer of the blood and bone marrow. Despite extensive investigation our current understanding of AML pathology and progression remain limited, impeding the development of effective treatments and resulting in dismal survival rates. Elucidating novel molecular pathways involved in AML proliferation can identify new targets for therapeutic treatments and empower the swift translation of fundamental discoveries into improved outcomes. This question will be addressed in this project. One of the major obstacles to effective AML treatment is the presence of oncogenes such as c-Myc. Oncogenes regulate cell growth and division, and when mutated or highly expressed contribute to cancer by inducing transcription and abnormal gene expression. Oncogene activation increases formation of co-transcriptional RNA-DNA hybrids known as R-loops. However, the role and regulation of R-loops in oncogenic transcription is unclear. We have shown that the ATP-dependent chromatin remodelling INO80 complex promotes resolution of R-loops to enable cancer cell proliferation. Our data suggest a role for INO80 in AML that is associated with oncogene-induced R-loops, poor outcome, and therapy resistance. This project aims to investigate the hypothesis that R-loop resolution by INO80 promotes oncogenic transcription, ensuring unlimited growth. Using both AML cell lines and patient-derived samples and employing a powerful combination of genomics, functional genetics and cell biology state-of-the-art assays we will characterize the role of INO80 in AML and elucidate the R-loop-associated transcriptional mechanisms of INO80. Our studies will provide molecular insight into pathways essential for AML and potentially other oncogene-driven cancers.

Further Reading: 4. Prendergast L, McClurg UL, Hristova R, Berlinguer-Palmini R, Greener S, Veitch K, Hernandez I, Pasero P, Rico D, Higgins JMG, Gospodinov A, and Papamichos-Chronakis M. (2020). Resolution of R-loops by INO80 promotes DNA replication and maintains cancer cell proliferation and viability. Nature Communications, 2020 Sep 10;11(1):4534.; 5. Poli J, Gasser SM, and Papamichos-Chronakis M. (2017). The INO80 remodeller in transcription, replication and repair. Philos Trans R Soc Lond B Biol Sci. 2017 Oct 5;372(1731).

Project Title:	**Investigating the role of the INO80 chromatin remodeler in resolving transcription-replication conflicts in cancer: Mechanism and function in acute myeloid leukemia.**
Project ID No:	15
Supervisor:	Dr Manolis Papamichos
Pathway:	Functional and Comparative Genomics;Cell Signalling;Molecular Oncology;
Type of Project:	Laboratory

Project Description: Acute myeloid leukemia (AML) is a lethal, heterogeneous, aggressive cancer of the blood and bone marrow. Despite extensive investigation our current understanding of AML pathology and progression remain limited, impeding the development of effective treatments and resulting in dismal survival rates. Elucidating novel molecular pathways involved in AML growth and viability can identify new targets for therapeutic treatments and empower the swift translation of fundamental discoveries into improved outcomes. This question will be addressed in this project. Targeting DNA replication stress is an emerging field in translational cancer research. Conflicts between oncogene-induced transcription and DNA replication can cause replication stress and DNA damage, creating opportunities for novel therapeutics. We have shown that the ATP-dependent chromatin remodelling INO80 complex promotes resolution of genotoxic co-transcriptional RNA-DNA hybrids known as R-loops to counteract transcription-replication conflicts and enable cancer cell proliferation. Our data indicate a role for INO80 in AML growth that is associated with poor outcome and therapy resistance. This proposal aims to investigate the hypothesis that R-loop resolution by INO80 coordinates oncogenic transcription with DNA replication to prevent DNA damage and ensure unlimited growth. Using both AML cell lines and patient-derived samples and employing a powerful combination of genomics, functional genetics and cell biology state-of-the-art assays we will characterize the role of INO80 in AML and elucidate the R-loop-associated transcriptional mechanisms of INO80 that prevent replication stress. Our studies will provide molecular insight into pathways essential for AML and potentially other oncogene-driven cancers.

Further Reading: 4. Prendergast L, McClurg UL, Hristova R, Berlinguer-Palmini R, Greener S, Veitch K, Hernandez I, Pasero P, Rico D, Higgins JMG, Gospodinov A, and Papamichos-Chronakis M. (2020). Resolution of R-loops by INO80 promotes DNA replication and maintains cancer cell proliferation and viability. Nature Communications, 2020 Sep 10;11(1):4534. ; 5. Poli J, Gasser SM, and Papamichos-Chronakis M. (2017). The INO80 remodeller in transcription, replication and repair. Philos Trans R Soc Lond B Biol Sci. 2017 Oct 5;372(1731).

Project Title:	**Dynamic contrast enhanced MRI to assess treatment response in brain tumours**
Project ID No:	16
Supervisor:	Prof Harish Poptani
Pathway:	Biotechnology;Animal Sciences;
Type of Project:	Laboratory

Project Description: MRI is the imaging modality of choice for the diagnosis of brain tumours and for monitoring treatment response. Despite being highly sensitive, the standard MRI methods are not highly specific and often fail to accurately differentiate primary from metastatic brain tumours or in differentiating treatment response from failure (pseudo-progression from recurrence). Our laboratory has previously developed several imaging and spectroscopic markers to address this challenge. In this project, we will evaluate the utility of dynamic contrast enhanced MRI for differentiation of different histological subtypes of brain tumours as well as for assessing treatment response. We have previously demonstrated the utility of these methods in predicting response to treatment as well prediction of overall survival in patients with head and neck cancer. In this project, we will use quantitative imaging processing and pharmacokinetic modelling to evaluate the utility of vascular imaging parameters for assessing treatment response.

Further Reading: 1. S Wang, M Martinez-Lage, Y Sakai, S Chawla, SG Kim, M Alonso-Basanta, RA Lustig, S Brem, S Mohan, RL Wolf, A Desai, H Poptani*. Differentiating tumor progression from pseudo-progression in patients with gliobalstomas using diffusion tensor imaging and dynamic contrast enhanced MRI. AJNR 37:28-36, 2016 2. S Chawla, LA Loevner, SG Kim, WT Hwang, S Wang, G Verma, S Mohan, V Lovolsi, H Quon, H Poptani*. Dynamic Contrast Enhanced MRI Derived Intracellular Water Lifetime (i): A Prognostic Marker for Patients with Head and Neck Squamous Cell Carcinomas. AJNR Am J Neuroradiol. 2018 Jan;39(1):138-144. doi: 10.3174/ajnr.A5440. Epub 2017 Nov 16 3. Alkanhal H, Das K, Poptani H*. Diffusion and Perfusion Weighted Magnetic Resonance Imaging Methods in Non-Enhancing Gliomas. World Neurosurg. 2020 Jun 7;S1878-8750(20)31257-2. doi: 10.1016/j.wneu.2020.05.278. 4. Chawla S, Kim SG, Loevner LA, Wang S, Mohan S, Lin A, Poptani H. Prediction of distant metastasis in patients with squamous cell carcinomas of the head and neck using DWI and DCE-MRI. Head Neck. 2020 Aug 1. doi: 10.1002/hed.26386

Project Title:	**Exploiting Deep Learning-based protein structure prediction for function annotation and structural biology**
Project ID No:	17
Supervisor:	Prof Dan Rigden
Pathway:	Bioinformatics;Biotechnology;Functional and Comparative Genomics;Host-Parasite Biology;Post Genomic Sciences;Structural Biology;Microbiology;
Type of Project:	Desk based

Project Description: Protein structural information is crucial for an understanding of protein function and evolution. Currently, only there is only experimental data for a tiny fraction of the protein universe. However, Deep Learning methods such as AlphaFold 2 (Jumper et al., 2021) allow structure predictions for the remainder to be made with unprecedented accuracy. These methods open up the dark proteome for structure-based function annotation and have profound implications for experimental structural biology. The project will entail application of new Deep Learning methods for cutting-edge protein structure prediction. Applied for function prediction, the project will focus on proteins of particular interest to the student. They might, for example, be derived from a pathogen, be involved in hereditary human diseases, be potential drug targets, be of relevance to green chemistry or biotechnology, or simply be mystery proteins of unknown function (Mesdaghi et al., 2020). To achieve the fullest possible picture, a battery of structure-based function prediction methods will be applied to models produced and those data complemented by sequence- and context-derived information (Rigden, 2017). The project may, alternatively or in addition, consider the application of the structure predictions in the contexts of X-ray crystallography or cryo-EM, exploiting long-standing collaborative links to CCP4 and CCP-EM. You will join a nurturing and productive group with a strong track record in structural bioinformatics, especially at the interface between bioinformatics and experimental structural biology. You will learn transferable and valuable bioinformatics skills working in an area of biology relevant to drug discovery and current health challenges.

Further Reading: Jumper J et al (2021) Highly accurate protein structure prediction with AlphaFold. Nature. 2021 596:583-589; Mesdaghi S, Murphy DL, Sánchez Rodríguez F, Burgos-Mármol JJ, Rigden DJ (2020). In silico prediction of structure and function for a large family of transmembrane proteins that includes human Tmem41b. F1000Res. 2020 9:1395; Rigden DJ, editor (2017) “From Structure to Function with Bioinformatics”, second edition Springer.

Project Title:	**Hypoxia and inflammation crosstalk**
Project ID No:	18
Supervisor:	Prof Sonia Rocha
Pathway:	Cell Signalling;Molecular Oncology;
Type of Project:	Laboratory

Project Description: Hypoxia and inflammation are intimately linked. It is known that nuclear factor κB (NF-κB) regulates the hypoxia-inducible factor (HIF) system, but little is known about how HIF regulates NF-κB. We have recently discovered that HIF-1α represses NF-κB-dependent gene expression. HIF-1α depletion results in increased NF-κB transcriptional activity both in mammalian cells and in the model organism Drosophila melanogaster. These results indicated that HIF-1α is required to restrain the NF-κB response, and thus prevent excessive and damaging pro-inflammatory responses. Despite these findings, there is no information on whether HIF-1a requires HIF-1b for this role (its obligatory binding partner) or even if HIF-2a is involved. This project will investigate the role of the HIF dimers in the control of NF-kB activity. Using RNA-seq and ChIP-seq data, novel HIF genes activated under inflammation will be investigated and validated. This analysis will determine the differences and commonalities between hypoxia and inflammation in mammalian cells, two important stimuli for human disease.

Further Reading: Bandarra, D., Biddlestone, J., Mudie, S., Muller, H. A., and Rocha, S. (2015). HIF-1alpha restricts NF-kappaB-dependent gene expression to control innate immunity signals. Dis. Models and Mech. 8, 169-181. D'Ignazio, L., Bandarra, D., and Rocha, S. (2016). NF-kappaB and HIF crosstalk in immune responses. FEBS J. 283, 413-424.

Project Title:	**Impact of non-antibiotic drugs on the generation of bacteria persistant to antibiotics**
Project ID No:	19
Supervisor:	Dr J.Enrique Salcedo-Sora
Pathway:	Microbiology;
Type of Project:	Laboratory

Project Description: Antibiotic resistance is an ongoing threat to modern health care (Murray et al 2022,https://doi.org/10.1016/S0140-6736(21)02724-0). A relatively new source of risk for the development of bacterial resistant to antibiotics comes from unrelated medication of common practice (non-antibiotic drugs) N-ADs (Maier et al 2018, https://doi.org/10.1038/NATURE25979i). N-Ads seem to impose selective pressures that render bacteria also resistant to other stressors such as antibiotics. Examples of these interactions are the induction of bacterial antibiotic resistant upon exposure to antidepressants (Jin et al 2018, https://doi.org/10.1016/J.ENVINT.2018.07.046; Wang et al 2023, https://doi.org/10.1016/J.ENVINT.2018.07.046). In bacteria there are phenotypes such as slow growth that allow cells to tolerate high concentrations of antibiotics, a phenomenon known as persistance (Salcedo-Sora et al 2020, https://doi.org/10.3390/antibiotics9080508). Persistence facilitates the eventual generation of the genetic changes that underlie resistance to antibiotics (Salcedo-Sora et al 2020). Thus, this project is addressing the question do N-ADs influence in the first place the generation of persistence to antibiotics? In the present project six different N-ADs will be assessed in relation to their effect on the generation of persistence to antibiotics in two species that serve as models for gram-negative bacteria of clinical relevance Escherichia coli and Acinetobacter baumannii. Pharmacological in vitro work will be following by the study of the transcriptional profiles of bacteria exposed to N-ADs by RNAseq.

Further Reading:

Jin, M., Lu, J., Chen, Z., Nguyen, S. H., Mao, L., Li, J., Yuan, Z., & Guo, J. (2018). Antidepressant fluoxetine induces multiple antibiotics resistance in Escherichia coli via ROS-mediated mutagenesis. Environment International, 120, 421–430. https://doi.org/10.1016/J.ENVINT.2018.07.046 Maier, L., Pruteanu, M., Kuhn, M., Zeller, G., Telzerow, A., Anderson, E. E., Brochado, A. R., Fernandez, K. C., Dose, H., Mori, H., Patil, K. R., Bork, P., & Typas, A. (2018). Extensive impact of non-antibiotic drugs on human gut bacteria. Nature, 555(7698), 623–628. https://doi.org/10.1038/NATURE25979i Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S. C., Browne, A. J., Chipeta, M. G., Fell, F., Hackett, S., Haines-Woodhouse, G., Kashef Hamadani, B. H., Kumaran, E. A. P., McManigal, B., … Naghavi, M. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet, 399(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0 Salcedo-Sora, J.E.; Kell, D.B. A Quantitative Survey of Bacterial Persistence in the Presence of Antibiotics: Towards Antipersister Antimicrobial Discovery. Antibiotics 2020, 9, 508. https://doi.org/10.3390/antibiotics9080508 Wang, Y., Yu, Z., Ding, P., Lu, J., Mao, L., Ngiam, L., Yuan, Z., Engelstädter, J., Schembri, M. A., & Guo, J. (2023). Antidepressants can induce mutation and enhance persistence toward multiple antibiotics. Proceedings of the National Academy of Sciences, 120(5). https://doi.org/10.1073/PNAS.2208344120

Project Title:	**Elucidating the mito-pH physiology, using a new generation of Multiverse Genetically Encoded Fluorescent Probes.**
Project ID No:	20
Supervisor:	Dr Massimiliano Stagi
Pathway:	Cell Signalling;Chemical Biology;Biotechnology;
Type of Project:	Laboratory

Project Description:

Further Reading: Given its centrality to homeostatic signalling, lysosomes/mitochondrial contacts are regulated by a multiplicity of changes in systems (i.e membrane trafficking, protein recruitment, ion channel regulation) which are rarely examined in the same or comparable systems, leaving potentially major gaps in our understanding of how these systems may be manipulated. The primary supervisor's lab has developed a set of transfectable/transducable probes which allow the study of lysosomes in biochemical, proteomic and physiological applications, allowing the generation of directly matched data from the same preparations to be analysed by both 'omic and cell biological/live imaging techniques.

Project Title:	**Actomyosin mediated force feedback for healthy ageing.**
Project ID No:	21
Supervisor:	Dr Tobias Zech
Pathway:	Cell Signalling;
Type of Project:	Laboratory

Project Description: Background: We will identify how actomyosin mediated nuclear force coupling regulates the cellular response to mechanical forces and how dysregulation of this process leads to age-associated pathologies. This will add to our understanding of age specific changes of cells in the resilience to mechanical stress. Actomyosin-mediated tension applied on the nucleus regulate nuclear import/export, chromatin condensation/localisation and gene expression. Hutchinson-Gilford Progeria syndrome (HGPS; progeria) is a model system for laminopathy driven premature ageing. The cellular progeria phenotype, caused by accumulation of progerin in the nuclear lamina, manifests itself in DNA damage and deformation of the nuclear lamina. HGPS cells show increased cell death after mechanical strain. In patient-derived primary HGPS cells, we found drastically upregulated actomyosin tension that is driven by increased RhoA activity. Here, RhoA negative regulator, Rnd3, does not translocate from the nucleus to the cytosol; which is a mechano-dependent process. We hypothesize that cells use nuclear force coupling to tune actomyosin contractility for optimal robustness to external forces. Objective: Investigate the impact increased actomyosin tension in HGPS cells has on cellular pathologies including sensitivity to mechanical forces, DNA damage and nuclear import/export dynamics. Experimental Approach: Three pairs of age matched patient derived HGPS and control fibroblasts will be used in live cell confocal imaging of mechanical cell stretching established in the lab of applicant one to investigate: 1. Rnd3 protein import/export out of the nucleus 2. Actomyosin dynamics 3. Cell viability to establish the cellular mechanism behind actomyosin dysregulation in HGPS.

Further Reading:

Project Title:	**Genome-empowered bioinformatic analyses of the adaptive evolution of electrostatic surface charge in respiratory proteins**
Project ID No:	22
Supervisor:	Dr Michael Berenbrink
Pathway:	Bioinformatics;Animal Sciences;Evolution and Behavioural Biology;Chemical Biology;Functional and Comparative Genomics;
Type of Project:	Desk based

Project Description: Uptake of environmental O2 and its transport to tissues is vital for vertebrates and aided by the respiratory proteins haemoglobin and myoglobin. Their proper functioning in animals adapted to different environments or life-styles frequently depends on the precise charge of amino acid residues that may allow advantageous interactions with allosteric effector molecules, between subunits or proteins, affect protein folding stability, and reduce deleterious protein aggregation at high concentration. The general importance of electrostatic interactions for function has led to the development and wide application of charge prediction tools that are utilised in this data analysis research project. The overall aim is to use of the increased availability of vertebrate globin sequences and protein structures in public databases and a suite of comparative bioinformatics analyses to trace the evolution of molecular mechanisms of haemoglobin and myoglobin function in vertebrates. Possible topics for study include mechanisms of (1) increased pH-sensitivity of haemoglobin O2 delivery supporting extremely high metabolic rates in small mammals and birds, (2) pH-dependent haemoglobin polymerisation and red blood cell sickling in fishes, and (3) convergent evolution of high myoglobin net surface charge enabling high muscle concentrations and extended breath-hold diving in aquatic birds and mammals. Depending on the topic, methods include comparative phylogenetic analyses, genome mining, molecular phylogenetics, ancestral trait and amino acid sequence reconstructions, structural homology modelling, and structure-based predictions of protein net charge and acid-base buffering properties. The project will be jointly supervised from the Departments of Evolution, Ecology & Behaviour and Biochemistry & Systems Biology.

Further Reading: He, K., Eastman, T.G., Czolacz, H., Li, S., Shinohara, A., Kawada, S.I., Springer, M.S., Berenbrink, M. and Campbell, K.L. (2021). Myoglobin primary structure reveals multiple convergent transitions to semi-aquatic life in the world's smallest mammalian divers. Elife, 10, p.e66797. DOI: 10.7554/eLife.66797 Berenbrink, M. (2020). Extinct proteins resurrected to reconstruct the evolution of vertebrate haemoglobin. Nature, 581, 388-389. DOI: https://doi.org/10.1038/d41586-020-01287-8 Mirceta, S., Signore, A. V., Burns, J. M., Cossins, A. R., Campbell, K. L., & Berenbrink, M. (2013). Evolution of mammalian diving capacity traced by myoglobin net surface charge. Science, 340, 1234192. DOI: 10.1126/science.1234192 Berenbrink, M. (2006). Evolution of vertebrate haemoglobins: histidine side chains, specific buffer value and Bohr effect. Respiratory Physiology & Neurobiology, 154, 165-184. https://doi.org/10.1016/j.resp.2006.01.002

Project Title:	**Examining the role of stable IL-10 dimers in countering bacterial and cytokine-induced inflammation and disruption of the intestinal epithelium**
Project ID No:	23
Supervisor:	Prof Barry Campbell
Pathway:	Cell Signalling;Microbiology;
Type of Project:	Laboratory

Project Description: Interleukin (IL)-10 has been well established to play an important role in maintaining gut homeostasis by imparting diverse effects on a variety of cell types. In the intestine, the source and the target of IL-10 include leukocytes and epithelial cells. Interleukin-10 (IL-10) is thought to exert its function partly through regulation of NFkappaB signalling. We recently revealed that intestinal epithelial cells in vitro do indeed regulate NFkappaB -driven transcriptional responses to pro-inflammatory cytokine tumour necrosis factor (TNF) via an autocrine mechanism dependent on IL-10 secretion. We also demonstrated the impact of IL-10 deficiency on the NFkappaB pathway and its downstream targets in the small intestinal mucosa in vivo. In patients with inflammatory bowel disease (IBD), NFkappaB activation is common, driven by bacteria interactions and increased levels of pro-inflammatory cytokines, resulting in disruption of the epithelial barrier. This project will examine both bacterial (adherent, invasive E. coli-, flagellin- and TNF-induced NFkappaB signal pathway activation patterns, downstream target effects and epithelial barrier disruption, utilising a human NFkappaB reporter cell-line and 3-D mini-gut organoid cultures. We will also examine the action of exogenous stable IL-10 dimers to block TNF-induced effects, and this approach may prove useful to support future therapeutic intervention for IL-10-regulated inflammatory conditions. Techniques will include mammalian and bacterial cell culture, recombinant protein production, luciferase reporter assays, infection bioassays, qPCR, IHC, immunoblotting and ELISA.

Further Reading: • Nguyen et al. Cell Mol Gastroenterol Hepatol. 2021; 12(4): 1343–1352 • Papoutsopoulou S et al. 2021. Front Immunol. 12: 690817 • Minshawi F et al. 2020. Front. Immunol. 11: 1794. • Papoutsopoulou S et al. Biology 2022;11(10):1377.

Project Title:	**Microbial evolution, mobile genetic elements, and horizontal gene transfer**
Project ID No:	24
Supervisor:	Dr James Hall
Pathway:	Microbiology;Host-Parasite Biology;Functional and Comparative Genomics;Evolution and Behavioural Biology;Bioinformatics;
Type of Project:	Laboratory

Project Description: We live in a microbial world. Bacteria have shown us time and again their capacity to rapidly adapt to the challenges of a new or changing environment, a process occurring dramatically before our eyes as bacteria evolve resistance to the antibiotics we develop to control infections. Interestingly, this process doesn't just involve bacteria. Mobile genetic elements (MGEs), including transposons, plasmids, and bacteriophage, are increasingly recognised for their role in bacterial evolution, because MGEs facilitate horizontal gene transfer (HGT) of traits associated with resistance, virulence, metabolism, and more. However, MGEs also impose a burden in the form of fitness costs. How do these costs come about? How can evolution resolve MGE fitness costs? What are the consequences for HGT and the spread of antimicrobial resistance? And how can we explain the distribution and spread of important MGEs in microbial communities? These are some of the questions that we could begin to explore. Various lab-based projects can be developed within this theme, according to the interests of the student, including: (i) isolating and sequencing new strains to explore the presence and distribution of MGEs in the wild, (ii) investigating interactions between MGEs and bacteria to understand how conflicts arise and how they might be resolved; and (iii) conducting laboratory evolution studies to understand how bacteria and MGEs co-adapt. Projects provide training in microbiology, evolutionary biology, molecular biology, and statistical analysis and can be supplemented with a bioinformatics component depending on the interests of the student. Please contact me to discuss (j.p.j.hall@liverpool.ac.uk)

Further Reading: 1. Hall JPJ, Harrison E, Baltrus DA. 2022 Introduction: the secret lives of microbial mobile genetic elements. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **377**, 20200460. (doi:10.1098/rstb.2020.0460) 2. Hall JPJ, Wright RCT, Harrison E, Muddiman KJ, Jamie Wood A, Paterson S, Brockhurst MA. 2021 Plasmid fitness costs are caused by specific genetic conflicts enabling resolution by compensatory mutation. *PLoS Biol.* **19**, e3001225. (doi:10.1371/journal.pbio.3001225) 3. Cazares A *et al.* 2020 A megaplasmid family driving dissemination of multidrug resistance in Pseudomonas. *Nat. Commun.* **11**, 1370. (doi:10.1038/s41467-020-15081-7)

Project Title:	**Symbiont-host interactions in insects**
Project ID No:	25
Supervisor:	Prof Greg Hurst
Pathway:	Microbiology;Evolution and Behavioural Biology;
Type of Project:	Laboratory

Project Description: Insects form intricate symbioses with microbes where the microbe is passed from female insect to her offspring (maternal inheritance). We work on a variety of insect-microbe symbioses, with a particular focus on protective symbiosis (where the microbe defends its host against attack) and male-killing symbiosis (where it kills male embryos). We develop projects with students on impacts of symbionts on individuals, field patterns of infection, and evolutionary consequences of symbiosis. We can host ecology, laboratory, molecular and bioinformatics based projects.

Further Reading: Hurst, G.D.D. 2017. Extended genomes: symbiosis and evolution. Interface Focus 7: 20170001 https://doi.org/10.1098/rsfs.2017.0001

Project Title:	**Climate drivers of Infectious Disease Outbreaks in the Horn of Africa**
Project ID No:	26
Supervisor:	Dr Louise Kelly-Hope
Pathway:	Host-Parasite Biology;
Type of Project:	Desk based

Project Description: This desk-based project will examine the spatial and temporal relationship between climate factors, and extreme weather events such as rainfall, temperature, floods, drought, and outbreaks of vector-borne (e.g., malaria, dengue, rift valley fever) and/or water-borne (e.g., cholera) disease outbreaks in the Horn of Africa region over the past decade You will obtain data from publicly available climate and disease databases, learn to use open-source GIS mapping software, and high-resolution satellite imagery. You will create a series of risk stratification maps to highlight the multiple intersecting climate risk factors, including the occurrence of natural disasters in outbreak areas. This will help to identify the high-risk priority areas that national programmes may use to support intervention strategies.

Further Reading: https://www.who.int/health-topics/climate-change#tab=tab_1 www.ipcc.ch https://public.wmo.int/en/our-mandate/climate/wmo-statement-state-of-global-climate/Africa https://www.emdat.be/

Project Title:	**Can a beneficial bacteria that protects plants from aphids also protect against an aphid-transmitted virus?**
Project ID No:	27
Supervisor:	Dr Daniel Leybourne
Pathway:	Evolution and Behavioural Biology;Food Sercurity;Microbiology;Plant Sciences;
Type of Project:	Laboratory

Project Description: Cereal aphids are agricultural pests on many crops, including wheat and barley. Aphids cause significant damage to crops through direct feeding and/or the transmission of plant viruses, including barley yellow dwarf virus (BYDV). Intra-species variation within aphids (e.g., genotype and endosymbiont infection) is a key driver of aphid phenotype, influencing aphid population dynamics, aphid-predator interactions, aphid-plant interactions, and aphid-environment interactions. Developing more sustainable, and non-chemical, methods for aphid and virus control in cereal crops is essential in order to grow food more sustainably and achieve net zero. Plant-associated bacteria have been described that can provide protection against aphids. However, the potential defensive role these bacteria play in providing protection against aphid-transmitted viruses, such as BYDV, remains unclear. In this project, the student will determine whether the plant-associated bacteria that provide aphid protection confer additional services, such as protection against BYDV. The student will also explore the potential top-down influence aphid diversity (genotype and endosymbiont infection) has on the level of protection provided against the virus; this will be achieved by comparing aphid populations that vary in their BYDV transmission ability. The student will receive training in experimental design and statistical analysis, alongside a range of experimental techniques, including: Aphid reproduction and development assays, virus transmission assays, molecular quantification of virus titre (e.g., qPCR, ELISA), and molecular characterisation of aphid populations (e.g., PCR). The student will also have the opportunity to conduct novel electrophysiological experiments to monitor aphid feeding behaviour.

Further Reading: Kern et al., 2022. Infection of susceptible/tolerant barley genotypes with Barley yellow dwarf virus alters the host plant preference of Rhopalosiphum padi clones depending upon their ability to transmit BYDV. Journal of Pest Science, 95, 215-229 Sanchez-Mahecha et al., 2022. Impaired microbial N-acyl homoserine lactone signalling increases plant resistance to aphids across variable abiotic and biotic environments. Plant, Cell & Environment, 45, 3052-3069 Leybourne et al., 2020. A fitness cost resulting from Hamiltonella defensa infection is associated with altered probing and feeding behaviour in Rhopalosiphum padi. Journal of Experimental Biology, 223, jeb207936

Project Title:	**Identifying successful crop mixtures for the sustainable management of cereal aphids and associated viruses**
Project ID No:	28
Supervisor:	Dr Daniel Leybourne
Pathway:	Food Sercurity;Plant Sciences;Evolution and Behavioural Biology;
Type of Project:	Laboratory

Project Description: Cereal aphids cause significant damage to crops through direct feeding and/or the transmission of plant viruses, including barley yellow dwarf virus (BYDV). Developing more sustainable, and non-chemical, methods for aphid and virus control in cereal crops is essential in order to grow food more sustainably and achieve net zero. Cereal crops can be intercropped with legumes (e.g., pea and bean) to provide a range of agronomic benefits, including Nitrogen fixation. The introduction of a non-host plant into the cropping system also has the potential to disrupt herbivorous insects when moving between individual host plants. In this project, the student will identify the benefits of intercropping with regards to the suppression of aphid and virus infestation in cereals. The student will identify multiple cereal-legume combinations that could be used in an intercropping system. The student will then design, manage, and run a series of pot/mesocosm-trials in the glasshouse and identify which mixtures provide the greatest suppression of cereal aphids and associated viruses. The student will also determine how intercropping affects natural enemy success (parasitoid wasps and ladybirds). The student will have the opportunity to incorporate their study into field trials currently being planned within the wider research team, although this is dependent on the outcome of external funding applications. The student will receive training in experimental design and statistical analysis, alongside a range of experimental techniques, including: Aphid reproduction assays, virus transmission assays, molecular quantification of virus titre (e.g., qPCR, ELISA), and parasitoid and predator assays.

Further Reading: Grauby et al., 2022. Can Mixed Intercropping Protect Cereals from Aphid-Borne Viruses? An Experimental Approach. Insects, 13, 521. Mc Namara et al., 2020. Management of yellow dwarf disease in Europe in a post-neonicotinoid agriculture. Pest Management Science, 76, 2276-2285. Lopes et al., 2016. Wheat (Triticum aestivum L.)-based intercropping systems for biological pest control. Pest Management Science, 72, 2193-2202

Project Title:	**Population genetics and molecular taxonomy of rats in South-East Asia**
Project ID No:	29
Supervisor:	Prof Ben Makepeace
Pathway:	Animal Sciences;Bioinformatics;Evolution and Behavioural Biology;Functional and Comparative Genomics;
Type of Project:	Laboratory

Project Description: Rodents are reservoirs or vehicles for numerous zoonotic diseases, such as plague, scrub typhus, murine typhus, leptospirosis, and hantavirus pulmonary syndrome. However, the species of rodents involved and intraspecific population dynamics are poorly understood in many parts of the world, including South-East Asia. In this project, the population genetics and cryptic diversity of rodents acting as reservoirs of scrub typhus and other zoonoses will be investigated using amplicon-based next-generation sequencing on the portable Oxford Nanopore system. We will focus predominantly on the Asian house rat, Rattus tanezumi, and closely related species. Sequencing of a range of markers from the nuclear genome will be used to infer whether populations from various parts of South-East Asia are the same species or morphologically indistinguishable cryptic species that could exhibit different habitat preferences, behaviour and disease transmission risk for zoonoses. The project will involve PCR, sequencing and bioinformatics to resolve rat population structures.

Further Reading: https://pubmed.ncbi.nlm.nih.gov/23278980/ and https://pubmed.ncbi.nlm.nih.gov/33437884/

Project Title:	**Comparative genomics of Rickettsiella symbionts of parasitic mites of veterinary and agricultural importance**
Project ID No:	30
Supervisor:	Prof Ben Makepeace
Pathway:	Animal Sciences;Bioinformatics;Food Sercurity;Host-Parasite Biology;Post Genomic Sciences;
Type of Project:	Laboratory

Project Description: Many arthropods, especially those with simple diets, rely on bacterial symbionts to provide a source of amino-acids or vitamins. The poultry red mite, Dermanyssus gallinae, is one of the most important pests of domestic poultry worldwide. Recently, D. gallinae has been shown to harbour a bacterial symbiont in the genus Rickettsiella that is capable of synthesizing B-vitamins that are deficient in blood diets. Rickettsiella symbionts are also present in parasitic mites of bees, Tropilaelaps mercedesae and Varroa destructor, which are vectors of deformed wing virus. However, the function of these bee symbionts is not known. In this project, you will screen bee mites for Rickettsiella symbionts by PCR and perform comparative genomics of existing Rickettsiella genome assemblies to infer functional parallels or differences between them. Targeting of these symbionts may open up new avenues for mite control that are less environmentally damaging than current methods.

Further Reading: https://pubmed.ncbi.nlm.nih.gov/34539600/ and https://pubmed.ncbi.nlm.nih.gov/28327890/

Project Title:	**Role of mammalian interferon-gamma in the innate immune response of tick cells to tick-borne pathogens**
Project ID No:	31
Supervisor:	Prof Ben Makepeace
Pathway:	Cell Signalling;Host-Parasite Biology;Microbiology;
Type of Project:	Laboratory

Project Description: Ticks are vectors of numerous diseases of medical and/or veterinary importance, including Lyme disease, anaplasmosis, tick-borne encephalitis and spotted fevers. The Tick Cell Biobank at Liverpool has the world's largest collection of tick cell lines obtained from numerous species worldwide. Recently, it has been demonstrated that ticks respond to mammalian interferon-gamma ingested in the bloodmeal by accelerating blood imbibement and physiological development, and upregulating antimicrobial immune pathways. This is mediated by activation of the JAK–STAT signalling cascade via specific binding of interferon-gamma to the tick receptor Dome-1. Despite the increased antimicrobial response, the Lyme disease agent, Borrelia burgdorferi, established more effectively in ticks exposed to interferon-gamma from the host. In this project, you will determine the effect of interferon-gamma on tick cell lines infected with a panel of different tick-borne intracellular pathogens. This will involve cell culture, microscopy and quantitative PCR to monitor pathogen levels, and analysis of pathogen density using basic statistics.

Further Reading: https://pubmed.ncbi.nlm.nih.gov/36634189/ and https://pubmed.ncbi.nlm.nih.gov/29886187/

Project Title:	**Impacts of land-use and climate change on tick-borne disease risk in the UK**
Project ID No:	32
Supervisor:	Dr Caroline Millins
Pathway:	Conservation Biology;Food Sercurity;Host-Parasite Biology;Microbiology;
Type of Project:	Laboratory

Project Description: My research groups focus is understanding how land-use and climate change impacts the risk from tick-borne diseases in the UK by combining empirical and modelling approaches. An MRes project will be developed together with the student within the broad context of understanding how policy driven woodland expansion is affecting the risk of Lyme disease to humans and the risk of Anaplasmosis and Babesiosis to livestock in the UK. Research in my lab involves fieldwork, laboratory and data analysis, and MRes projects can be designed to focus on one or more of these aspects for example by linking to research and samples collected as part of a wider research projects, eg Ticksolve https://ticksolve.ceh.ac.uk/ or working alongside PhD students. Some examples of research questions we can develop projects on are; How does farmland habitat and management practices impact tick-borne disease risk ? How does landscape structure impact wildlife host communities and tick-borne disease risk? How does woodland proximity to farms impact livestock tick-borne disease risk?

Further Reading: Current research: https://ticksolve.ceh.ac.uk/1. Mitchell S. Surveillance for disease in extensively managed livestock. Vet Rec. 2019;185(22):686–7. 2. Johnson N, Phipps P, McFadzean H, Barlow A. An outbreak of bovine babesiosis in February, 2019, triggered by above average winter temperatures in southern England and co-infection with Babesia divergens and Anaplasma phagocytophilum. Parasites and Vectors. 2020;13(1):1–5. 3. Folly AJ, Dorey-Robinson D, Hernández-Triana LM, Phipps LP, Johnson N. Emerging Threats to Animals in the United Kingdom by Arthropod-Borne Diseases. Front Vet Sci. 2020;7(February):1–19. 4. Millins C, Gilbert L, Medlock J, Hansford K, Thompson DB, Biek R. Effects of conservation management of landscapes and vertebrate communities on Lyme borreliosis risk in the United Kingdom. Philos Trans R Soc B Biol Sci. 2017 Jun 5;372(1722):20160123.

Project Title:	**Comparative analysis of different photogrammetric approaches for 3D modelling of animal organs**
Project ID No:	33
Supervisor:	Prof Lorenzo Ressel
Pathway:	Animal Sciences;
Type of Project:	Laboratory

Project Description: The DiMo (Digital Morphology) lab has been recently established within VAPP. This facility hosts state of the art Image analysis computing equipment and is supporting PhD and collaborative projects using Artificial Intelligence (AI) and digital image analysis applied to tissues and organs. One of the missions of the DiMo lab is the creation of anatomy and pathology 3D models. Examples of the models are available here (Heart: https://sketchfab.com/3d-models/dog-heart-open-plastinated-natural-02f810b43de64108bb9d19d4dcbe5357: Bone: https://sketchfab.com/3d-models/dog-t12-vertebra-9acc7e243fa94736b050e21c8ba09bfc). The project will involve training of the student in photogrammetry techniques and application of photogrammetry in creating 3D models of anatomical and pathological specimens of animal tissues. The student will approach different protocols of data acquisition (photogrammetry), meshing, texturing and post processing, and will compare the different approaches in order to establish the most appropriate workflow for different organs and preservation condition for visualisation and 3D printing purposes.

Further Reading: https://pubmed.ncbi.nlm.nih.gov/30919299/

Project Title:	**Molecular evolution of taste perception and feeding ecology in mammals**
Project ID No:	34
Supervisor:	Prof Soraya Shirazi-Beechey
Pathway:	Animal Sciences;Chemical Biology;Evolution and Behavioural Biology;Functional and Comparative Genomics;
Type of Project:	Laboratory

Project Description: Taste perception plays an important role in food selectivity. The feeding ecology of vertebrates has shaped taste perception over evolutionary time scales and is associated with specific amino acid substitutions at key positions in the taste receptor binding sites. In other cases, such as the land-to-water transition in the ancestors of cetaceans, certain taste receptors have become pseudogenes, indicating dynamic interactions between taste receptor evolution and feeding ecology in mammals. This project focusses on the molecular evolution of taste perception and feeding ecology in the mammalian order Cetartiodactyla. They include omnivorous pigs, crustacean- and fish-feeding cetaceans, but also the hippopotamus and other, non-ruminant and ruminant herbivores, such as camels, mouse deer, deer, and domestic cattle. We hypothesise that differences in key amino acid residues in Cetartiodactyla taste receptor binding sites are the results of past shifts in their feeding ecology, which have led to distinct variations in their response to dietary amino acids and sugars. You will mine whole genome sequences of Cetartiodactyla species to obtain the predicted protein sequences of their sweet and umami (amino acid) taste receptors. You will then build molecular phylogenetic trees and use ancestral sequence reconstruction to identify at which point in the past major changes in key amino acid residues of receptor binding sites have occurred. These results will be used to construct such amino acid changes in taste receptor sequences and test their functional implication by expressing taste receptor genes in cell lines2 and determining responses to different amino acids and sugars.

Further Reading: 1- Daly, K., Al-Rammahi, M., Moran, A., Marcello, M., Ninomiya, Y., & Shirazi-Beechey, S. P. (2013). Sensing of amino acids by the gut-expressed taste receptor T1R1-T1R3 stimulates CCK secretion. American Journal of Physiology-Gastrointestinal and Liver Physiology, 304(3), G271-G282. 2- Daly, K., Moran, A. W., Al-Rammahi, M., Weatherburn, D., & Shirazi-Beechey, S. P. (2021). Non-nutritive sweetener activation of the pig sweet taste receptor T1R2-T1R3 in vitro mirrors sweetener stimulation of the gut-expressed receptor in vivo. Biochemical and Biophysical Research Communications, 542, 54-58. 3- Berenbrink, M. (2020). Extinct proteins resurrected to reconstruct the evolution of vertebrate haemoglobin. Nature, 581, 388-389. 4- Toda, Y., Hayakawa, T., Itoigawa, A., Kurihara, Y., Nakagita, T., Hayashi, M., ... & Misaka, T. (2021). Evolution of the primate glutamate taste sensor from a nucleotide sensor. Current Biology, 31(20), 4641-4649.

Project Title:	**Fitness cost of co-infection by different pathogens in Drosophila melanogaster**
Project ID No:	35
Supervisor:	Venera Tyukmaeva
Pathway:	Host-Parasite Biology;
Type of Project:	Laboratory

Project Description: Co-infection of individual hosts by multiple parasite species is common in natural populations. Unveiling the interactions which underlie the patterns of co-infection is an important key enabling us to understand the genetics of parasite susceptibility and host–parasite ecology and evolution. In this project, we propose to investigate the co-infection with two Drosophila pathogens, Jaenimonas drosophilae, a natural monoxeous trypanosomatid parasite [1], and Drosophila C Virus, a natural Drosophila pathogen commonly used in antiviral host defense studies in flies [2]. During the project, a set of susceptible and resistant lines from the Drosophila Genetic Reference Panel [3], chosen for their susceptibility to one of these pathogens, will be co-infected with another and several fly fitness traits will be evaluated. Using the molecular methods, the dynamics of the pathogens in the host will be traced. The results of the project will shed a light on the evolution of co-infections and parasite infection dynamics.

Further Reading: [1] Hamilton et al, mBio 6(5), 1-11 (2015) [2] Chtarbanova et al Journal of Virology, 88(24), 14057-14069 (2014) [3] MacKay et al, Nature, 482(7384) 173-178 (2012)

Project Title:	**Impacts of climate change on plant-soil co-adaptation and ecosystem functioning**
Project ID No:	36
Supervisor:	Dr Raj Whitlock
Pathway:	Conservation Biology;Evolution and Behavioural Biology;Food Sercurity;Plant Sciences;Microbiology;
Type of Project:	Laboratory

Project Description: Interactions between plants and their root microbiome (root-colonising bacteria, fungi and other microbes) play a key role in adapting plants to environmental stress and also influence ecosystem functioning. As a result, these plant-soil interactions are expected to be critical in defining the responses of plants and the ecosystems they form to climate change. This project will investigate the impacts of climate change on the plant root microbiome, and the role of plant-microbial co-adaptation in shaping the responses of plants, root-dwelling microbes and dependent ecosystem processes to drought. The project will make use of plant clones and microbial isolates previously collected from the UK's longest-running climate manipulation experiment: the Buxton Climate Change Impacts Lab, where grassland plots have been subjected to 29 years of simulated climate change (summer drought, warming, watering). Work will involve inoculating plant populations that have evolved under drought selection or under ambient climatic conditions with field-collected microbial isolates, and testing the impacts of these on plant growth and performance. Parallel molecular and genomic work may also be undertaken to assess the responses of soil microbial community structure and plant gene expression patterns to drought under different inoculation treatments. Additional work may also be done to characterise the phenotypes and properties of existing microbial isolates collected from Buxton.

Further Reading: Grime et al., 2008 https://doi.org/10.1073/pnas.0711567105; Fridley et al., 2011 https://doi.org/10.1111/j.1365-2486.2010.02347.x; Sayer et al., 2017 https://doi.org/10.1002/ece3.2700; Sayer et al., 2021 https://www.nature.com/articles/s42003-021-02037-w; Trinder et al. 2020 https://doi.org/10.1111/1365-2745.13304

Project Title:	**Evolutionary resistance to climate change in plant populations exposed to chronic climate treatments**
Project ID No:	37
Supervisor:	Dr Raj Whitlock
Pathway:	Conservation Biology;Evolution and Behavioural Biology;Plant Sciences;
Type of Project:	Laboratory

Project Description: How organisms adapt to and cope with anthropogenic climate change is a fundamental part of understanding and predicting how biodiversity will respond to environmental change. This project will investigate how an organisms' genotype and phenotype (traits) contribute to its ability to resist simulated climate change (drought and warming). The project will make use of the UK's longest running climate manipulation experiment, the Buxton Climate Change Impacts Lab where grassland plots have been subjected to 29 years of simulated climate change (summer drought, warming, watering). The work will focus on populations of 16 plant species previously collected from the climate treatments at Buxton, whose phenotypes have evolved in response to the climate treatments. The project will involve molecular and experimental approaches (including climate change treatments), to dissect climate-driven evolution, informing on its adaptive significance and molecular basis.

Further Reading: Trinder et al. 2020 https://doi.org/10.1111/1365-2745.13304; Ravenscroft et al. 2015 https://doi.org/10.1111/gcb.12966; Ravenscroft et al. 2014 https://doi.org/10.1111/1365-2745.12168; Grime et al., 2008 https://doi.org/10.1073/pnas.0711567105; Fridley et al., 2011 https://doi.org/10.1111/j.1365-2486.2010.02347.x

Project Title:	**Ecological responses to climate change in response to 30 years of drought, warming and watering treatments**
Project ID No:	38
Supervisor:	Dr Raj Whitlock
Pathway:	Conservation Biology;Evolution and Behavioural Biology;Plant Sciences;
Type of Project:	Laboratory

Project Description: Anthropogenic climate change is expected to have profound impacts on plant communities, and the wide range of ecosystem services they provide us with. However, little is known about the long-term responses of plant communities to climate change, in particular, whether plant traits can be used to reliably to predict these responses. The project will make use of the UK's longest running climate manipulation experiment, the Buxton Climate Change Impacts Lab where grassland plots have been subjected to almost 30 years of simulated climate change (summer drought, warming, watering). The goal of the project is to characterise plant community responses to multi-decadal environmental change, and the role of traits in shaping these responses. Project work will take place in the field in the Derbyshire Dales and Peak District National Park and using experimental approaches at Ness Gardens and in controlled growth chambers. Plant community responses to environmental change will be assessed using field survey and through collection of data on plant phenotypes and reproductive effort in the field. The role of traits in mediating these responses will be approached using standardised trait measurements in the common garden, and controlled climate response experiments in the field and lab.

Further Reading: Grime et al., 2008 https://doi.org/10.1073/pnas.0711567105; Fridley et al., 2011 https://doi.org/10.1111/j.1365-2486.2010.02347.x; Fridley et al., 2016 https://www.nature.com/articles/nclimate3032

Project Title:	**Genomic responses to climate change in an ecological model plant species**
Project ID No:	39
Supervisor:	Dr Raj Whitlock
Pathway:	Evolution and Behavioural Biology;Plant Sciences;Conservation Biology;Food Sercurity;
Type of Project:	Laboratory

Project Description: Climate-driven evolutionary change has now been shown to occur in a number of plant species, and could buffer populations from the detrimental effects of anthropogenic climate change. However, the molecular basis of such evolutionary change, and links between plant genotypes, phenotypes and fitness have rarely been studied. This project will investigate the genomic basis for adaptation to long-term simulated drought (moisture availability) within Festuca ovina, a native plant species. Work will take place on collections of plants from two study systems (i) the UK's longest-running climate manipulation experiment, the Buxton Climate Change Impacts Lab, where grassland plots have been subjected to 29 years of simulated climate change (summer drought, warming, watering) and (ii) A naturally occurring system of soil moisture microhabitats that occur in alvar grassland on the Baltic island of Öland, Sweden. Genome-wide SNP genotyping will be used to investigate the distribution of variation at gene loci in F. ovina that are candidates for mediating tolerance of drought conditions in natural grassland ecosystems. Experimental work (including lab-or field-based drought treatments) to test for linkages between plant genotypes, traits and fitness, and exposing the nature of local adaptation.

Further Reading: Trinder et al. 2020 https://doi.org/10.1111/1365-2745.13304; Ravenscroft et al. 2015 https://doi.org/10.1111/gcb.12966 ; Ravenscroft et al. 2014 https://doi.org/10.1111/1365-2745.12168; Grime et al., 2008 https://doi.org/10.1073/pnas.0711567105; Fridley et al., 2011 https://doi.org/10.1111/j.1365-2486.2010.02347.x

Project Title:	**Nutritional toxicity in Drosophila melanogaster**
Project ID No:	40
Supervisor:	Dr Stuart Wigby
Pathway:	Evolution and Behavioural Biology;
Type of Project:	Laboratory

Project Description: Lifespan and fecundity are highly plastic in response to diet in Drosophila melanogaster, and principally mediated by the dietary protein axis. In females, the continuous relationship (reaction norm) between lifespan and diet is maximised at low protein - at the expense of fecundity - whereas high protein intake optimises immediate fitness at a cost to lifespan. Some evidence suggests a protein intake threshold exists, beyond which both lifespan and fecundity will decline. You will investigate the physiological trade-off between lifespan and reproduction, modulating dietary yeast content and performing lifespan and reproductive assays, to determine if any observable cost to fitness in nutrient-rich conditions is mitigated by an improvement in egg viability, larval developmental time, or population growth rate. Additionally, you will test whether such unbalanced macronutrient intakes are likely to be observed in naturalistic settings, or if physiological constraints on nutritional targets would likely prevent this. These questions are key to understanding the life-history trade-offs involved in dietary restriction (DR) - a phenomenon whereby nutrient restriction, counterintuitively, elongates lifespan. DR itself is a highly valuable perturbation to aid in the study of the ageing process. You will aim to reconcile your results with classical evolutionary theories of DR and ageing, while gaining valuable insight into the field.

Further Reading: Shanley DP, Kirkwood TB. Calorie restriction and aging: a life-history analysis. Evolution. 2000 Jun;54(3):740-50. Fanson BG, Fanson KV, Taylor PW. Cost of reproduction in the Queensland fruit fly: Y-model versus lethal protein hypothesis. Proc Biol Sci. 2012 Dec 22;279(1749):4893-900. Metaxakis A, Partridge L. Dietary restriction extends lifespan in wild-derived populations of Drosophila melanogaster. PLoS One. 2013 Sep 10;8(9):e74681. McCracken AW, Buckle E, Simons MJP. The relationship between longevity and diet is genotype dependent and sensitive to desiccation in Drosophila melanogaster. J Exp Biol. 2020 Dec 2;223(Pt 23):jeb230185. McCracken AW, Adams G, Hartshorne L, Tatar M, Simons MJP. The hidden costs of dietary restriction: Implications for its evolutionary and mechanistic origins. Sci Adv. 2020 Feb 21;6(8):eaay3047.

Project Title:	**Anti-ageing drugs and male fertility: trade-offs or delayed reproductive ageing?**
Project ID No:	41
Supervisor:	Dr Stuart Wigby
Pathway:	Evolution and Behavioural Biology;
Type of Project:	Laboratory

Project Description: Declining fertility with age is a well-established phenomenon, but it is better understood in females than males. In humans, as with many species, sperm production and semen quality decline with male age, and this contributes to reduced couple fertility. We know that some drugs, known as "geroprotectors", can extend lifespan in model organisms, and ultimately the hope is that these will be useful as medical treatments. Could these geroprotectors help delay reproductive ageing? Or is there an inevitable trade-off between lifespan and reproduction? We don't currently know. Using Drosophila, this project will explore whether anti-ageing drugs known as "geroprotectors", which are known to extend lifespan and aspects of late life health, can be used to delay male reproductive declines, or alternatively whether they mediate trade-off between reproduction and lifespan. Drosophila are short lived, making this work feasible, and there is good knowledge of which drugs extend lifespan, and methods to assay male fertility. The project will help reconcile competing evolutionary theories of ageing, and may ultimately lead to medical treatments for improved healthy reproductive ageing. Skills and training: the project will develop skills and knowledge in insect culture and behavioural and physiological assays, experimental design, drug delivery, statistical analysis and scientific writing.

Further Reading:

- Sepil, I., Hopkins, B. R., Dean, R., Bath, E., Friedman, S., Swanson, B., Ostridge, H. J., Harper, L., Buehner, N. A., Wolfner, M. F., Konietzny, R., Thézénas, M.-L., Sandham, E., Charles, P. D., Fischer, R., Steinhauer, J., Kessler, B. M., & Wigby, S. (2020). Male reproductive aging arises via multifaceted mating-dependent sperm and seminal proteome declines, but is postponable in Drosophila. Proceedings of the National Academy of Sciences, 117(29), 17094–17103. https://doi.org/10.1073/pnas.2009053117
- Perry, J. C., Sirot, L., & Wigby, S. (2013). The seminal symphony: how to compose an ejaculate. Trends in Ecology & Evolution, 28(7), 414–422. https://doi.org/10.1016/j.tree.2013.03.005
- Sepil, I., Carazo, P., Perry, J. C., & Wigby, S. (2016). Insulin signalling mediates the response to male-induced harm in female Drosophila melanogaster. Scientific Reports, 6(1), 30205. https://doi.org/10.1038/srep30205

Project Title:	Mechanisms of post mating sexual selection
Project ID No:	42
Supervisor:	Dr Stuart Wigby
Pathway:	Evolution and Behavioural Biology;
Type of Project:	Laboratory

Project Description: The females of most species mate with multiple males. This creates the opportunity for sexual selection to continue after mating, via sperm competition and cryptic female choice. Research to date has shown that male success in post-copulatory sexual selection is influenced by sperm and seminal fluid traits, and female behaviour and physiology. We also know that males are capable of adjusting their reproductive effort in response to social cues of competition (strategic ejaculate allocation), and that females are capable of biasing sperm usage after mating (cryptic female choice). This project will use Drosophila fruit flies to investigate the factors that underly male and female control of fertilization outcomes, to better understand the mechanisms of sperm competition and cryptic female choice. The project could take several directions, including focussing on male and female condition and physiology, the social environment, or specific reproductive cells, genes and molecules. Skills and training: the project will develop skills and knowledge in insect culture and behavioural and physiological assays, experimental design, precision nutrition, statistical analysis and scientific writing; optionally, genetics, cell biology and transcriptomics/proteomics.

Further Reading:

- Wigby, S., Brown, N. C., Allen, S. E., Misra, S., Sitnik, J. L., Sepil, I., Clark, A. G., & Wolfner, M. F. (2020). The Drosophila seminal proteome and its role in postcopulatory sexual selection. Philosophical Transactions of the Royal Society B: Biological Sciences, 375(1813), 20200072. https://doi.org/10.1098/rstb.2020.0072
- Hopkins, B. R., Sepil, I., Thézénas, M.-L., Craig, J. F., Miller, T., Charles, P. D., Fischer, R., Kessler, B. M., Bretman, A., Pizzari, T., & Wigby, S. (2019). Divergent allocation of sperm and the seminal proteome along a competition gradient in Drosophila melanogaster. Proceedings of the National Academy of Sciences, 116(36), 17925–17933. https://doi.org/10.1073/pnas.1906149116
- Hopkins, B. R., Sepil, I., & Wigby, S. (2020). Structural variation in Drosophila melanogaster spermathecal ducts and its association with sperm competition dynamics. Royal Society Open Science, 7(3), 200130. https://doi.org/10.1098/rsos.200130

Project Title:	**Impact of microbial bioprotectants on grain malting quality of barley**
Project ID No:	43
Supervisor:	Dr Sharon Zytynska
Pathway:	Food Sercurity;Plant Sciences;
Type of Project:	Laboratory

Project Description: An aim of regenerative agriculture is to improve soil quality, which can include manipulating the soil microbiome to increase soil health. Harnessing the soil microbiome for crop protection is a quickly growing area of research, as an optimal soil microbiome can promote plant growth and resistance to pests and disease. Our research uses a set of plant beneficial bacteria that induce plant defences against aphids – small insects that feed on plant sap and can transmit devastating plant viruses. Our crop of interest is barley, for which the malted grain can be used for making beer and whisky. Malting quality of barley grains is affected by the plant variety, as well as the environment the plant was grown in. This project will examine the effect of microbial inoculation of beneficial microbes on the malting quality of heritage varieties of barley that are used by small scale whisky producers. The student will receive training in experimental design and statistical analysis, alongside a range of experimental techniques, including: grain analysis, aphid rearing, bacteria growing, and plant maintenance. Additionally, we will measure the expression of plant defence-related genes induced by bacterial inoculation across plant growth stages, including at grain production.

Further Reading: Zytynska, S.E., Eicher, M., Rothballer, M. & Weisser, W.W. (2020) Microbial-mediated plant growth promotion and pest suppression varies under climate change. Frontiers in plant science, 11, 1385. Trivedi, P., Mattupalli, C., Eversole, K. & Leach, J.E. (2021) Enabling sustainable agriculture through understanding and enhancement of microbiomes. New Phytol, 230, 2129-2147. Halstead, M., Morrissy, C., Fisk, S., Fox, G., Hayes, P., & Carrijo, D. (2022). Barley grain protein is influenced by genotype, environment, and nitrogen management and is the major driver of malting quality. Crop Science, 00, 1– 13. https://doi.org/10.1002/csc2.20842