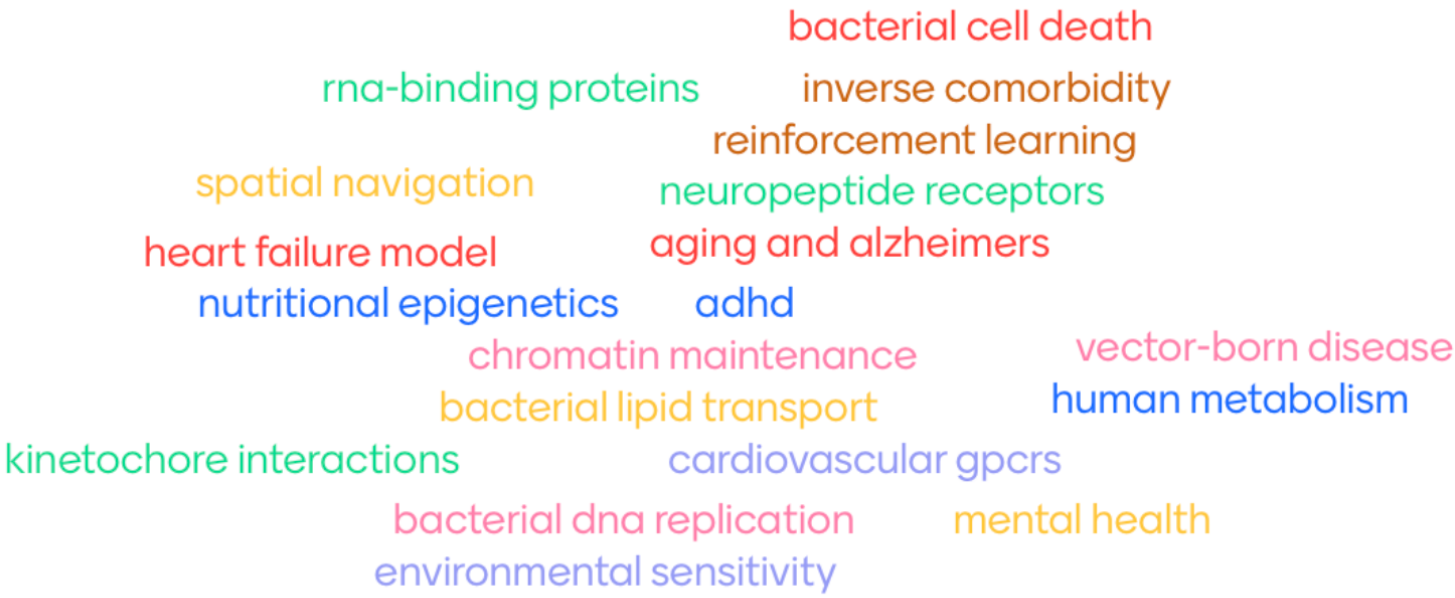
China Scholarship Council Projects at Queen Mary University of London

Application Year 2023



Selection of projects compiled for students on the Nanchang Joint Programme

R. Clyne, November 2022

Project Descriptions

Table of Contents

Project Title & Supervisor — Page

Project Title	**ADHD in girls & women over the life course**
Supervisor	Dr Jessica Agnew-Blais
Email	j.agnew-blais@qmul.ac.uk
Lab Website	
Co-supervisor(s)	Dr Georgina Hosang

Project Description

Until recently, attention deficit hyperactivity disorder (ADHD) was thought of as a childhood disorder predominantly affecting boys; thus the majority of research has neglected ADHD among girls and, to a greater extent, among adult women. Little is known about female-specific factors that may influence functioning among women with ADHD. This project will address this research question with several aims using a combination of qualitative and quantitative approaches.

The first aim will take a qualitative approach to generate new evidence on how hormonal changes affect women with ADHD. The student will run focus groups among girls and women with ADHD focusing on three key transitions over the life course: puberty, pregnancy and the perinatal period, and menopause. To-date no studies have investigated functioning among women with ADHD at these key life stages, thus this aim is a critical first step.

Second, the student will use existing longitudinal data from two British cohort studies, BSC70 and the Millennium Cohort Study (MCS) to investigate ADHD among women. In BCS70, they will examine the association between ADHD symptoms among women as reported at ages 11 and 16 with early onset of menopause later in life. In MCS the student will investigate associations between early pubertal onset and ADHD symptoms among girls. This studentship collaborates across different QMUL areas, including the SBBS Department of Psychology, and the Centre for Psychiatry at the Wolfson Institute of Preventative Medicine.

Project Title	The role of the chromatin modifier Kdm2aa in melanoma formation
Supervisor	Elisabeth Busch-Nentwich
Email	e.busch-nentwich@qmul.ac.uk
Lab Website	buschlab.org
Co-supervisor(s)	Paul Hurd

Project Description

This project will investigate the role of chromatin maintenance in cancer using cutting-edge functional genomics approaches and in vivo phenotyping techniques. We have previously demonstrated that loss-of-function (LoF) of the heterochromatin modifier Kdm2aa, a H3K36me2 demethylase and an interaction partner of Heterochromatin Protein 1 (HP1), causes melanoma and potentially other cancers in zebrafish. RNA-seq analysis in mutant larvae shows that already a few days after fertilisation DNA damage repair pathways are dysregulated. Likewise we find that DNA damage signalling seems to be reduced in Kdm2aa homozygous mutants. In addition, a group of genes, normally silenced and located in a large heterochromatic genomic region, is de-repressed suggesting defects in heterochromatin maintenance.

In this project we will take advantage of zebrafish genetics (our mutant library of 40,000 alleles and CRISPR/Cas9) and transgenesis in combination with cutting-edge molecular biology, functional assays and genomics techniques.

Aim 1: Which protein domains are responsible for the melanoma phenotype? Kdm2aa has several protein domains that facilitate its interaction with HP1 and its demethylase activity. We have shown previously, that only the HP1 interaction domain, but not the demethylase activity is required for an overexpression phenotype in zebrafish. We will use CRISPR/Cas9 and homology-driven repair to specifically generate Kdm2aa domain mutants to identify which domains are required to prevent melanoma formation.

Aim 2: Which DNA damage repair pathways are affected by Kdm2aa LoF? RNA-seq data suggests a downregulation of the double-strand break response. We will use antibodies and transgenic lines to investigate where in the DNA damage signalling and repair hierarchy Kdm2aa is required.

Aim3: How does chromatin change in Kdm2aa mutant derived cancers? We will use ATAC-seq and CUT&RUN sequencing to uncover the underlying chromatin changes in hyper-migratory melanocytes and melanoma.

References

1. Scahill CM, Digby Z, Sealy IM, Wojciechowska S, White RJ, Collins JE, Stemple DL, Bartke T, Mathers ME, Patton EE, Busch-Nentwich EM (2017) Loss of the chromatin modifier Kdm2aa causes BrafV600E-independent spontaneous melanoma in zebrafish. PLoS Genetics

2. Kettleborough RN, Busch-Nentwich EM, Harvey SA, Dooley CM, de Bruijn E, van Eeden F, Sealy I, White RJ, Herd C, Nijman IJ, Fényes F, Mehroke S, Scahill C, Gibbons R, Wali N, Carruthers S, Hall A, Yen J, Cuppen E, Stemple DL (2013) A systematic genome-wide analysis of zebrafish protein-coding gene function. Nature

Project Title	**Neural basis of cognitive reserve in ageing and Alzheimer's disease**
Supervisor	Guifen Chen
Email	Guifen.chen@qmul.ac.uk
Lab Website	https://www.qmul.ac.uk/sbbs/staff/guifen-chen.html
Co-supervisor(s)	Daniel Bor

Project Description

Spatial memory dysfunction and hippocampus atrophy has been associated with early AD. In mammals, the hippocampus and its adjacent areas in the medial temporal lobe have long been implicated in spatial navigation and learning. Several types of spatial neurons have been discovered in this area, including place cells and grid cells. The activity of these neurons represents an animal's current location.

The aim of this project is to study the neural basis of spatial cognitive reserve, comparing normal ageing and AD in mice. We will first design novel spatial navigation tasks in virtual reality environments where animals learn to associate their physical self-movement on a floating ball with the change of sensory inputs from virtual scenes and test whether the experience of learning the tasks helps to slow cognitive decline in ageing and AD. We will then monitor neural changes during the learning process using electrophysiology. Finally we will analyse the interaction of neural activity between subnetworks using cutting edge information theory tools, which divide the neural signal into different forms of information, and compare the information theory differences between normal ageing and AD.
The findings will shine a light on neural mechanisms implicated in age-associated cognitive decline, and potentially provide key insights into how to alleviate this decline in ageing and AD populations. This work aligns with health and wellbeing, AI&data modelling as well as fundamental discovery science themes.

References

1. Rowland, D. C., Roudi, Y., Moser, M.-B. & Moser, E. I. Ten Years of Grid Cells. Annu Rev Neurosci 39, 1–22 (2015).

2. Chen, G., Lu, Y., King, J. A., Cacucci, F. & Burgess, N. Differential influences of environment and self-motion on place and grid cell firing. Nat Commun 10, 630 (2019).

3. Chen, G., King, J. A., Lu, Y., Cacucci, F. & Burgess, N. Spatial cell firing during virtual navigation of open arenas by head-restrained mice. Elife 7, e34789 (2018).

4. Aronov, D., Nevers, R. & Tank, D. W. Mapping of a non-spatial dimension by the hippocampal–entorhinal circuit. Nature 543, 719–722 (2017).

5. Doeller, C. F., Barry, C. & Burgess, N. Evidence for grid cells in a human memory network. Nature 463, 657–661 (2010).

Project Title	**Designer MCE proteins: Unity and diversity of lipid transport function in double membranes**
Supervisor	Dr. Vidya Chandran Darbari
Email	v.darbari@qmul.ac.uk
Lab Website	https://www.qmul.ac.uk/sbbs/staff/vidyadarbari.html
Co-supervisor(s)	Dr Christoph Engl

Project Description

Membranes of diderm bacteria are the first line of defence, essential for survival in harsh environments and crucial for stress response. Mammalian Cell entry (MCE) proteins play a vital role in maintaining membrane integrity in unfavourable environments, probable role in membrane biogenesis, for assimilating lipids as nutrient sources in mycobacteria and probable host immune modulatory roles in intracellular pathogenic bacteria. They assemble into ABC lipid transporter in various double membranes of distinct lipid compositions. Structure function relationship will aid small molecule designs for antimicrobials and lipid transport modulators for biotechnology applications such as biofuels and sterol assimilation. Although proteobacterial MCE protein structures are characterised (MlaD, PqiB and YebT/LetB (LetB: Lipophilic envelope spanning tunnel B), the mechanism for lipid substrate specificity and the unified role of MCE proteins in stress response is still not understood. This project aims to understand the specific role of MCE domains for substrate specificity and its link to membrane integrity and membrane functions using structural biology and microbial cell biology. To understand if substrate specificity is gated by MCE domains which typically assemble as hexamers and how lipid binding specific to MCE domain affects membrane functions, we will create various MCE domain chimeras using MCE domains from mycobacteria or cyanobacteria that transport varied lipids on PqiB template or LetB template. Alphafold multimer will be used to aid the design for the chimeric constructs and in silico substrate docking and binding studies carried out to investigate lipid specificity. Functional mutations in lipid binding loops of the various MCE constructs will also be generated. Complementation studies in Δpqi/Δmla/Δyeb E. coli strains will be carried out to do detailed microbial phenotypic analysis to understand the specific role of MCE domains. Interesting MCE constructs will be taken forward for both lipid binding studies and structural studies using CryoEM.

References

1. Fenn K, Wong CT, Darbari VC. Mycobacterium tuberculosis Uses Mce Proteins to Interfere With Host Cell Signaling. Front Mol Biosci. 2020 Jan 8;6:149. doi: 10.3389/fmolb.2019.00149. PMID: 31998747; PMCID: PMC6961568.
2. Isom GL, Coudray N, MacRae MR, McManus CT, Ekiert DC, Bhabha G. LetB Structure Reveals a Tunnel for Lipid Transport across the Bacterial Envelope. Cell. 2020 Apr 30;181(3):653-664.e19. doi: 10.1016/j.cell.2020.03.030. PMID: 32359438; PMCID: PMC7335425.
3. Nakayama, T., & Zhang-Akiyama, Q. M. (2016). pqiABC and yebST, Putative mce Operons of Escherichia coli, Encode Transport Pathways and Contribute to Membrane Integrity. Journal of bacteriology, 199(1), e00606-16. https://doi.org/10.1128/JB.00606-16
4. Ekiert DC, Bhabha G, Isom GL, Greenan G, Ovchinnikov S, Henderson IR, Cox JS, Vale RD. Architectures of Lipid Transport Systems for the Bacterial Outer Membrane. Cell. 2017 Apr 6;169(2):273-285.e17. doi: 10.1016/j.cell.2017.03.019. PMID: 28388411; PMCID: PMC5467742

Project Title	*Using computational and experimental methods to predict and test novel neuropeptide-receptor partnerships*
Supervisor	Prof Maurice Elphick
Email	m.r.elphick@qmul.ac.uk
Lab Website	https://www.qmul.ac.uk/sbbs/staff/mauriceelphick.html https://www.qmul.ac.uk/spcs/staff/academics/profiles/ariannafornili.html
Co-supervisor(s)	Dr Arianna Fornili

Project Description

Neuropeptides have fundamental roles in regulating physiological and behavioural processes in humans and other animals. Furthermore, neuropeptide receptors are known and potential novel targets for therapeutic drugs. For example, morphine exerts its powerful pain-relieving effects by mimicking the action of endogenous neuropeptides and binding to specific G-protein coupled receptors (GPCRs). There are several hundred genes encoding GPCRs in humans and many of these are activated by neuropeptides that regulate physiologically/clinically important processes. Neuropeptide receptors have long been recognised as attractive targets for therapeutics in humans and for pesticides in pest species. However, progress has been hindered by the lack of information on neuropeptide receptor structures. Recent advances in cryo-EM methods are providing the first insights into neuropeptide-receptor binding sites at the atomic level. Furthermore, with the development of novel AI-based protein structure prediction tools (Alphafold), there are exciting opportunities to investigate neuropeptide receptor structure in all animals.

The primary aim of our research is to discover missing links in neuropeptide evolution and function (Elphick et al., 2018; https://doi.org/10.1242/jeb.151092). To accomplish this, we use echinoderms (e.g. starfish, sea urchins) as experimental systems and there are several reasons for doing this. Firstly, as deuterostomes, echinoderms are more closely related to vertebrates than the majority of invertebrates and accordingly our research has provided important new insights into neuropeptide relationships. For example, research done by a former CSC-funded PhD student in our group and published in *PNAS* has revealed that neuropeptides (somatostatin and allatostatin-C) that hitherto were thought to be orthlogs are in fact paralogs (Zhang et al., 2022; https://doi.org/10.1073/pnas.2113589119). Secondly, starfish have many remarkable morphological and physiological characteristics – they are typically five-sided and have a unique ability to rapidly autotomise (under neural control) and then regenerate arms, which makes them of great interest from a medical perspective. Thirdly, echinoderms are of economic importance as foodstuffs (sea urchins, sea cucumbers). In the proposed PhD project the expertise of **Prof. Elphick (School of Biological & Behavioural Sciences, QMUL)** on the evolution and comparative physiology of neuropeptide signalling systems and **Dr. Fornili (School of Physical & Chemical Sciences, QMUL)** on the computational analysis of protein structure and dynamics will be combined to co-supervise an **interdisciplinary PhD project.** The first aim will be to use computational methods to analyse the structure of "orphan" receptors (receptors for which neuropeptide ligands have yet to be discovered) and then use docking methods to test candidate ligands computationally. Informed by the findings, *in vitro* cell-based assays will be employed to test predicted neuropeptide-receptor partners. The main focus of the project will be to deorphanise receptors in the starfish *Asterias rubens* because of its importance as a model system in reconstucting neuropeptide evolution, as recogised in a recent ~ £1.2 M **BBSRC grant** award to M. Elphick (QMUL), A. Fornili (QMUL) and P. Oliveri (UCL). Furthermore, extending findings of the project to other species, including humans and insects, will provide a basis for potential applications and impact in development of novel drugs or pesticides. The project is a unique and cutting-edge interdisciplinary training opportunity for a student with BSc/MSc training in biochemistry, biology or pharmaceutical chemistry and we welcome applications from students interested in this field of research. Training in a wide-range of research techniques will be provided, including bioinformatics, genomics, computational analysis of protein structure and peptide-protein interactions, cell-based methods for deorphanisation of GPCRs, molecular histology and *in vitro/in vivo* pharmacology. Personalised training in writing and communication skills will be provided, complemented with generic transferable skills training from the QMUL Learning Institute. The **Elphick group** currently has three CSC-funded PhD students: Yuling Feng (year 4; yuling.feng@qmul.ac.uk) Weiling Feng (year 3; weiling.huang@qmul.ac.uk) and Wenbin Kang (year 2; w.kang@qmul.ac.uk). If you would like to find out more about working in the Elphick group, Yuling, Weiling or Wenbin would be happy to talk to you.

References

For further details of the recent publications from the Elphick group, including publications by CSC-funded students, see: http://www.researchpublications.qmul.ac.uk/publications/staff/21463.html.
For further details of the recent publications from the Fornili group, including publications by CSC-funded students, see: https://researchpublications.qmul.ac.uk/publications/staff/34522.html

Project Title	**Molecular Modelling of an orphan G-protein coupled receptor with cardiovascular function**
Supervisor	Arianna Fornili
Email	a.fornili@qmul.ac.uk
Lab Website	https://afornililab.wordpress.com
Co-supervisor(s)	Peter McCormick (https://www.qmul.ac.uk/whri/people/academic-staff/items/mccormickpeter.html), Andrew Tinker (https://www.qmul.ac.uk/whri/people/academic-staff/items/tinkerandrew.html)

Project Description

Project Details: G-protein coupled receptors (GPCRs) are transmembrane proteins involved in a wide range of cell signalling processes. Their regulation through small molecule modulators is used for the treatment of different types of diseases and GPCRs currently account for more than 30% of drug targets.

This project is part of a research collaboration led by the William Harvey Research Institute and focusing on an orphan receptor that has been recently shown to have a role in cardiovascular function. However, the development of small-molecule drugs that can regulate its activity is hindered by the absence of direct information on endogenous or exogenous ligands of the receptor.

The aim of this project is to use computational techniques to a) provide high quality models of the structure and dynamics of the receptor, b) gain new insight into its mechanism of regulation and c) identify candidate ligands that can be subsequently tested with wet lab assays at WHRI. Available experimental information on this and other closely related receptors will be used to guide the modelling, the identification of druggable binding sites and the generation of libraries for the screening.

Research environment: Dr Fornili's research group focuses on the computational study of biomolecular dynamics and in particular of proteins involved in muscle contraction. Recent contributions from the lab include the study of the effects of a heart failure drug on cardiac myosin dynamics (J. Mol. Inf. Model., 2020; PLOS Comp. Biol., 2017), the first theoretical observation of a binding pocket induced by mechanical stress (JCTC, 2019) and the development of methods for the prediction of rescue binding pockets in proteins (Bioinformatics, 2018). The lab has regular access to national supercomputing facilities and is equipped with dedicated servers for biomolecular simulation and data storage. More information can be found at https://afornililab.wordpress.com.

The project is part of a wider collaboration led by Prof. Andrew Tinker at the William Harvey Research Institute and involving different research teams (Andrew Tinker, Peter McCormick and Patricia Munroe's labs) with an outstanding track record of research on cardiovascular function and disease.

Techniques and Training: the successful candidate will be trained in different modelling techniques, including molecular docking, homology modelling, virtual screening, pharmacophore modelling and molecular dynamics simulations. The student will also use machine learning techniques for data analysis and learn how to implement structural analysis tools using scientific programming languages (R/Python).

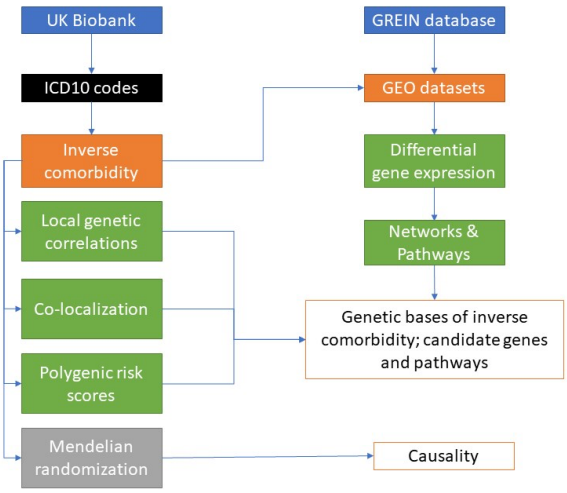
Project Title	Genetic bases of inverse comorbidity
Supervisor	Maxim Freydin
Email	m.freydin@qmul.ac.uk
Lab Website	https://www.qmul.ac.uk/sbbs/staff/maxim-freydin.html
Co-supervisor(s)	N/A

Project Description

Multimorbidity describes a phenomenon of a non-random co-existence of several diseases in a single patient. Multimorbidity significantly complicates diagnosis and treatment, is associated with increased disability and mortality, and leads to polypharmacy. Recognition of a non-random fashion of multimorbidity through the analysis of genetic component of diseases, led to the concept of diseasome, or the human disease network. The analysis of diseasome revealed shared genes underlying multimorbidity and their disease-specific functional modules. Thus, it is understood that the phenomenon of multimorbidity, at least in part, is founded on common genetic background.

One of the most intriguing discoveries in framework of multimorbidity studies, is the presence of diseases that very rarely or never co-occur, called inverse comorbidity (IC). Examples include allergic diseases and tuberculosis, neuropsychiatric/CNS disorders and cancer, multiple sclerosis and lung diseases. Unlike co-morbidity, little is known about the genetic basis of IC, and little attention is given to the phenomenon as such in scientific literature. The importance of genetic studies of IC relies on the idea that finding the mechanisms by which the presence of one disease prevents the development of another, may pave the way for discovery of novel drug targets and improved diagnostic approaches.

This project will explore a hypothesis **that genetic predisposition to one complex disease may be protective against another disease**, thus leading to the phenomenon of IC. To test the hypothesis, genetic epidemiology (genetic correlations, co-localization, polygenic risk scores, Mendelian randomization) and bioinformatics (genome-wide differential gene expression analysis, pathway and network analyses) will be applied to large datasets (UK Biobank, in particular) and using publicly available transcriptomic datasets (Figure). This is an *in silico* project for a student with a strong interest in human and medical genetics and genetic epidemiology.



References

1. Goh, K.I., et al., *The human disease network.* Proc Natl Acad Sci U S A, 2007. **104**(21): p. 8685-90.
2. Dong, G., et al., *A global overview of genetically interpretable multimorbidities among common diseases in the UK Biobank.* Genome Med, 2021. **13**(1): p. 110.
3. Ibanez, K., et al., *Molecular evidence for the inverse comorbidity between central nervous system disorders and cancers detected by transcriptomic meta-analyses.* PLoS Genet, 2014. **10**(2): p. e1004173.
4. Tabares-Seisdedos, R. and J.L. Rubenstein, *Inverse cancer comorbidity: a serendipitous opportunity to gain insight into CNS disorders.* Nat Rev Neurosci, 2013. **14**(4): p. 293-304.

Project Title	**The influence of diet on evolution of human metabolism revealed by artificial intelligence and verified by cell biology**
Supervisor	Matteo Fumagalli
Email	m.fumagalli@qmul.ac.uk
Lab Website	mfumagalli.github.io
Co-supervisor(s)	Stephen Rossiter

Project Description

Glucose metabolism is critical for brain and muscle function, while excess glucose is toxic, so the glucose metabolism pathway is highly regulated and its evolution in animals is linked with diet. Human diets changed with farming and cooking and more recently with modern food production technology. We previously demonstrated a shit to Western diet may be linked to Type-2 diabetes in Inuit (Science, 2015) and that one gene belonging to the clathrin family has evolved in response to changes in human diet (eLife, 2019). We hypothesise that other genes in the GLUT4 glucose metabolism pathway will also have undergone variation in response to dietary selection. New methods in artificial intelligence developed by Dr Fumagalli will be used to analyse databases of genomic sequences from two different human populations whose diet has changed at different times in human evolution. We will select genes implicated in regulation of the insulin-responsive GLUT4 pathway using interactome data, and analyse their genetic variation in ancient and modern human samples from Arabic and South American populations. The former underwent historical dietary change, while the diet of the latter has changed within the past 500 years. Deep learning algorithms developed by Fumagalli (BMC Bioinformatics, 2019) will be deployed to identify signals of natural selection, and therefore pinpoint putative functional variants. Once genetic variants are identified their function relative to each other will be studied in cellular models of human glucose metabolism developed in the Brodsky laboratory at UCL, external collaborator. Co-supervisor Rossiter is interested in molecular adaptations underpinning high sugar diets across mammals more widely. Variants from humans will also be compared to orthologues across species with naturally sugar-rich diets to test for parallelism. This project combines cutting edge machine learning and bioinformatic tools with techniques for studying cell function for functional validation.

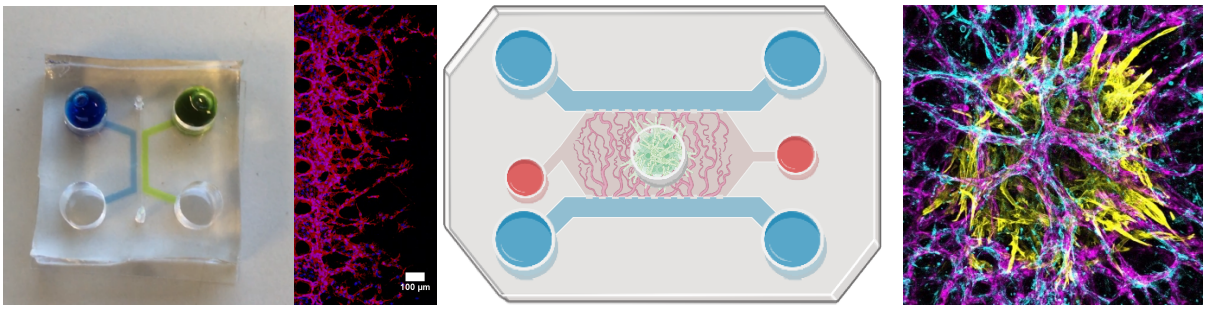
References

1. Fumagalli et al. Science 2015 10.1126/science.aab2319
2. Fumagalli et al. eLife 2019 10.7554/eLife.41517.001
3. Torada et al. BMC Bioinformatics 2019 10.1186/s12859-019-2927-x

Project Title	**Advanced vascularised organ-on-chip models of glioblastoma for the testing of oligonucleotide delivery systems**
Supervisor	Prof Julien Gautrot
Email	j.gautrot@qmul.ac.uk
Lab Website	http://biointerfaces.qmul.ac.uk/
Co-supervisor(s)	Prof. Silvia Marino

Project Description

A studentship in the design of organ-on-chip technologies is available in the group of Prof Julien Gautrot. The research will focus on the formation of microvascularised organ-on-chip systems mimicking vascularised tumours (in the context of glioblastoma). These models will make use of microfluidic systems that incorporate synthetic extra cellular matrix hydrogels with controlled physical (mechanical properties, porosity) and biochemical (cell-matrix adhesion, cell-mediated degradation, matrix remodelling) properties.



Example of microfluidic systems used for organ-on-chip applications in the Gautrot Lab and vascularised networks formed within hydrogels embedded in these microchips, for the embedding of spheroids.

Drug efficacy and toxicity testing requires the development of novel *in vitro* tissue models. Organ-on-chips have recently been developed and have highlighted exciting opportunities for the development of improved models for drug efficacy and toxicity testing, and the study of cell and tissue biology. Advantages of tissue-on-a-chip models include: 1, formation of complex architectures; 2, capture of tissue functions; 3, ease of imaging (live) as tissues are already "mounted" on a thin glass coverslip; 4, the study of tissue homeostasis and pathology in a human context (ideal compromise between classic in vitro models and animal models); 5, simple recovery of liquids from the microfluidic channels in real time (e.g. for the monitoring of metabolites). This project will apply the glioblastoma-on-a-chip models developed to the testing of safety and efficacy of oligonucleotide nanotherapeutics. Evaluation of these systems will be investigated using immunostaining, confocal microscopy, western blotting and qPCR.

Our research group has a strong track-record in the field of bioengineering, advanced in vitro models and stem cell biology: their design and synthesis, application as smart materials and biomaterials, microfabrication and study of cell interactions, but also the development of nanotherapeutics for gene delivery (http://biointerfaces.qmul.ac.uk/; see Biomaterials 2022, 2021, Nat. Communications 2021, Nature Materials 2012, Nature Cell Biology 2010, Nano Letters 2014 and 2018 and ACS Nano 2018). The successful candidate will join our multidisciplinary team and build a strong expertise in the fields of organ-on-chip technologies and their application for the testing of nanotherapeutics.

References

1. Raynold, A.A.M.; Li, D.; Chang, L.; Gautrot, J.E. "Competitive Binding and Molecular Crowding Regulate the Cytoplasmic Interactome of Non-Viral Polymeric Gene Delivery Vectors" ***Nat. Commun.*** 2021, 12, 6445.
2. Jones, C.; di Cio, S.; Connelly, J.; Gautrot, J.E. "Design of an Integrated Microvascularised Human Skin-on-a-Chip Tissue Equivalent Model" ***Front. Bioeng. Biotechnol.*** 2022, 10, 915702.
3. Dibble, M.; di Cio, S.; Luo, P.; Balkwill, F.; Gautrot, J.E. "Stabilisation of Microvascular Networks in Microfluidic Systems and the Role of Pericytes on their use in Nanotoxicity Testing " ***BioRxiv*** 2022, DOI:doi.org/10.1101/2022.05.03.490457.

Project Title	**Engineering symbionts for control of vector born diseases**
Supervisor	Dr. Lee Henry
Email	l.henry@qmul.ac.uk
Lab Website	https://www.henry-lab.co.uk/
Co-supervisor(s)	Dr. Chema Duran-Martin

Project Description

Insects vector globally important disease in agriculture and humans that pose significant health and economic burdens (e.g. dengue, malaria, mosaic viruses). Current insecticide-based control methods are becoming ineffective and undesirable due to environmental pollution, and insecticide resistant insect populations. Endosymbionts provide a promising new approach for controlling disease by making insects less susceptible to carrying pathogens by up regulating host immune systems, while also rapidly spreading through insect population via maternal transmission. For example, introducing *Wolbachia* to mosquitos has reduced dengue virus by 77% in Indonesian field trails[1]. However, our current understanding of how symbionts interact with hosts is limited by a lack of genome editing tools in symbionts, most of which cannot be cultured outside of hosts. New models are urgently needed to understand how symbionts interact with host immunity, cause virulence, and transmit through host populations to improve their efficacy and applicability in vector-borne disease control. In this PhD, we will take advantage of a newly discovered culturable endosymbiont, *Serratia symbiotica* CWBI-2.3, which can be genetically engineered and tracked using fluorescent protein expression (GFP, Fig 1)[2]. We aim to identify symbiont genes responsible for up regulate host immunity, causing virulence, and improving symbiont transmission to gain a mechanistic understanding of traits important for designing symbionts to effectively combating vector borne diseases.

The PhD will build off our pilot data that revealed candidate symbiont genes interacting with host immunity and causing virulence in aphids. The student will silence candidate genes in CWBI-2.3, quantify impacts on hosts, and track the symbiosis using GFP. These techniques will then be applied to symbionts found in other insect vectors using a novel culturing method developed by our US collaborator (K.Oliver)[3,4]. Our goal is to develop symbiont-based control strategies for diverse insect vectors of global importance in agriculture and human health (e.g. aphids, sandflies, ticks).

Figure 1. Colonization dynamics of CWBI-2.3 in pea aphids using green fluorescent protein expression (GFP) in *A. pisum*.

References

1. Simmons CP et al. (2012) Dengue. *N Engl J Med* 366:1423-1432

2. Perreau J et al (2021) Engineering a Culturable *Serratia symbiotica* Strain for Aphid Paratransgenesis. *Appl. Environ. Microbiol*. 87:e02245-20.

3. Brandt JW et al. (2017) Culture of an aphid heritable symbiont demonstrates its direct role in defence against parasitoids. *Proc Biol Sci* 284:20171925Patel et al (2019) Cultivation-Assisted

4. Genome of *Candidatus* Fukatsuia symbiotica; the Enigmatic "X-Type" Symbiont of Aphids. *Genome Biol. Evol.* 11:3510

Project Title	Epigenetic basis of nutrition-mediated development in the honeybee
Supervisor	Paul Hurd
Email	p.j.hurd@qmul.ac.uk
Lab Website	http://qmulepigenetics.com/hurd
Co-supervisor(s)	Chema Martin-Duran

Project Description

The honey bee is an important emerging model organism for understanding epigenetic mechanisms. The honey bee genome encodes three phenotypically distinct but genetically indistinguishable organisms (queens, workers and drones) that are determined during early post-embryonic development by differential nutrition. The molecular mechanisms responsible for this differential development are unknown but through previous and current funding, we were the first to demonstrate that queen and worker honey bees have caste-specific chromatin epigenetic states that establish and orchestrate the distinct patterns of gene expression that determine developmental trajectory (1, 2, 3).

Building on this work, the PhD project will examine the role of specific nutritional components as epigenetic modulators of phenotypic plasticity during development using our well-established in vitro honey bee rearing techniques. The student will be trained in state-of-the-art molecular techniques for epigenomics (ATAC-seq, ChIP-seq, CUT&RUN, CUT&TAG, RNA-seq), proteomics (mass spectrometry), metabolomics (gas chromatography-mass spectrometry), biochemistry (chromatin biology, recombinant protein techniques) and apiculture (general beekeeping, queen rearing, in vitro bee rearing). You will not only gain extensive experience in hands on experimental approaches but also develop proficiency in computational and statistical analyses of large genomic datasets.

The aim of this truly multidisciplinary PhD project is to exploit the unique opportunities of the honey bee system to understand how an environmental cue (nutrition) shapes phenotype through epigenetic mechanisms in an economically and ecologically important organism.

References

1. Lowe, R., Wojciechowski, M., Ellis, N. & Hurd, P. J. (2022) Chromatin accessibility-based characterisation of brain gene regulatory networks in three distinct honey bee polyphenisms. *Nucleic Acids Res.* https://doi.org/10.1093/nar/gkac992

2. Wojciechowski, M., Lowe, R., Maleszka, J., Conn, D., Maleszka, R. & Hurd, P. J. (2018) Phenotypically distinct female castes in honey bees are defined by alternative chromatin states during larval development. *Genome Res*. 28, 1532-1542.

3. Dickman, M. J., Kucharski, R., Maleszka, R. & Hurd, P. J. (2013) Extensive histone post-translational modification in the honey bee. *Insect Biochem. Mol. Biol*. 43, 125-137.

Project Title	Molecular Basis for helicase loading onto a bacterial replication origin.
Supervisor	Aravindan Ilangovan
Email	a.ilangovan@qmul.ac.uk
Lab Website	https://www.ilangovan-lab.com/
Co-supervisor(s)	Benjamin Stieglitz

Project Description

Antibiotic resistance is a global health crisis, new molecular targets and novel methods are required to tackle this issue. To be able to address this, we intend to study the replication of chromosomal DNA in bacteria, a fundamental cellular process that enables the transfer of genetic information from one generation to another in all cells.

Our work will particularly focus on the initiation of replication in bacteria, which is unique compared to all other organisms, and we intend to understand this process at the molecular level. By using state-of-the-art techniques such as cryo electron microscopy, we aim to elucidate the structural and mechanistic details of this process at the molecular level. This knowledge can be directly used for the design of novel antibiotics targeting these systems.

References

1. Positive and negative control of helicase recruitment at a bacterial chromosome origin. Winterhalter C, Stevens D, Fenyk S, Pelliciari S, Marchand E, Cronin NB, Soultanas P, Costa TRD, Ilangovan A, Murray H (2021). BioRxiv

Project Title	A novel in vitro model for heart failure
Supervisor	Thomas Iskratsch
Email	t.iskratsch@qmul.ac.uk
Lab Website	https://www.sems.qmul.ac.uk/staff/t.iskratsch; http://iskratschlab.com;
Co-supervisor(s)	Hossein Heidari

Project Description

Heart failure (HF) is a major cause of death in the UK. New therapies are urgently needed but their development has been hindered by the still limited understanding of the biological basis. Apart from genetic and humoral factors, the mechanical/physical signals are critically involved in the process.

Better understanding of the mechanobiology can open new perspectives for treating heart failure. Especially, the cardiac extracellular matrix (ECM) stiffens in heart disease, which drives disease progression. However, not only the stiffness, but also changes in ECM composition will alter the downstream mechanosignalling. Therefore, novel tools are needed to help understand the complexity of both stiffness and receptor ligand architecture in heart disease.

To overcome the limitations of prior in vitro cardiovascular models, we plan to develop a 3D printed ECM-based hydrogel that has biophysical properties similar to those of the native tissue of interest. We have adapted stereolithography (SLA) techniques to enable the creation of 3D tissue geometries and functional intravascular topologies in biocompatible hydrogels. To further improve the physiological relevance, the effect of stiffness and oxygen concentration in the surrounding microenvironment will also be included via patterned optical stimulation and varying degrees of matrix photopolymerization. This will allow us to study the specific roles of hypoxia and matrix stiffening in our ischemic heart failure model.

Aim: This project will develop a novel in vitro model for ischemic heart failure

Objectives:

1. develop a 3D matrix for embedding cardiomyocytes and fibroblasts
2. develop patterned optical stimulation to induce hypoxia to mimic ischemia and analyse effect on cardiomyocyte and fibroblast populations
3. develop patterned optical stimulation induce matrix photopolymerisation for stiffness modulation to mimic heart failure and analyse effect on cardiomyocyte and fibroblast populations

References

1. B. E. Kelly *et al.*, *Science* (2019).

2. T. Iskratsch, H. Wolfenson, M. P. Sheetz, *Nat Rev Mol Cell Biol* (2014).

3. P. Pandey *et al.*, *Dev Cell* (2018).

Project Title	How place and grid cells encode uncertainty during spatial navigation
Supervisor	Dr. Yul Kang
Email	yul.kang@qmul.ac.uk
Lab Website	https://yulkang.net
Co-supervisor(s)	Dr. Guifen Chen

Project Description

Spatial navigation requires combining multiple sources of information considering their uncertainty. For example, if we turn at a tenth crossroad to visit a particular supermarket only to discover an unexpected signboard, we should think we are at a wrong crossroad if we are unsure how many crossroads we have passed (uncertainty in path integration). However, if we are unsure about the supermarket's name, we should think we remembered the name incorrectly (uncertainty in landmark recognition). To perform such arbitration, the brain must track uncertainty about different sources of information on the animal's current location. However, while it is well known that neurons in the hippocampus and neighbouring areas (place and grid cells) respond to the location of human and nonhuman animals in an environment, it is largely unknown how they respond to uncertainty in the location, and how it relates to the animal's behavioural performance in navigation.

Finding out how the biological brain handles uncertainty has implications for both medicine and artificial intelligence. For medicine, it can help early diagnosis and inform finding the therapeutic target of Alzheimer's disease, because the hippocampus and neighbouring areas are the first brain areas to show pathology in Alzheimer's disease. For artificial intelligence, it can inform the design of artificial neural networks that need to handle uncertainty in a complex real-life task such as spatial navigation.

In this project, we aim to study how different sources of uncertainty differentially affect the location coding in brain areas. (1) We will extend the primary supervisor (YK)'s computational model that provided a unifying explanation of distortion of neural activity and behavioural response pattern in spatial navigation, to account for moment-by-moment dependence of neural activity on evolving spatial uncertainty (e.g., after seeing an unexpected signboard). (2) We will compare the model's prediction with the existing data from the secondary supervisor (GC)'s electrophysiological recordings from place and grid cells from rodents navigating in a virtual reality where the path-integration and landmark uncertainty has been manipulated. (3) We will build a human version of the virtual reality task and assess the impact of different sources of uncertainty on navigation performance.

References

1. Kang YHR, Wolpert DM, Lengyel M, Spatial uncertainty provides a unifying account of navigation behavior and grid field deformations, Contributed Talk, Bernstein Conference (2021). https://vimeo.com/showcase/8949778/video/612895009
2. Chen, G., Lu, Y., King, J. A., Cacucci, F. & Burgess, N. Differential influences of environment and self-motion on place and grid cell firing. Nat Commun 10, 630 (2019). https://www.nature.com/articles/s41467-019-08550-1

Project Title	**Bridging the gap: dissecting the role of RNA binding proteins during spiral cleavage**
Supervisor	Chema Martin
Email	Chema.martin@qmul.ac.uk
Lab Website	https://martinduranlab.com
Co-supervisor(s)	Paul Hurd and Viji Draviam

Project Description

Animal development is classified as conditional or autonomous based on whether cell fates are specified through inductive signals or maternal determinants, respectively. In spiral cleavage –a stereotypic early embryonic programme ancestral to nearly half of the animal phyla– embryos can specify homologous cell fates either conditionally (through cell-cell interactions) or autonomously (via segregation of maternal inputs). This variation occurs naturally in annelids and molluscs, even between closely related species, which makes spiral cleavage the ideal system to dissect the mechanisms that underpin shifts between conditional and autonomous development. Yet our understanding of this embryonic mode is still very limited.

RNA binding proteins (RBPs) are crucial in connecting maternally provided mRNAs to the cytoskeleton, hence ensuring their proper segregation during cell division. In molluscs with autonomous spiral cleavage, the association of mRNAs to the mitotic spindle is essential for their proper asymmetric segregation, yet the exact protein machinery involved in this process is unknown. Recently, my lab discovered that a set of RBPs involved in segregating RNAs asymmetrically in the oocyte of vertebrates and flies are also loaded in annelid eggs. This project will dissect the evolution and function of RBPs during conditional and autonomous spiral cleavage by combining molecular evolutionary approaches with experimental embryology and super resolution microscopy in annelid worms. Specifically, this project will:

1. Characterise the repertoire of RBPs and their bound RNAs in conditional and autonomous annelid embryos at the oocyte/zygote stage combining pull downs, mass spec and high throughput sequencing.

2. Characterise the patterns of expression and localisation of maternally loaded RBPs in the annelids *Owenia fusiformis* (conditional development) and *Capitella teleta* (autonomous development) with super resolution microscopy.

3. Functionally investigate the role of RBPs during spiral cleavage.

Together, this project will investigate a fundamental biological phenomenon – how embryos distribute maternal determinants asymmetrically to guide early development – at multiple levels of biological complexity, from patterns of molecular evolution to gene expression and function, which will eventually lead to a better understanding of how new embryonic modes emerge.

References

1. Seudre O#, Carrillo-Baltodano AM#, Liang Y, Martín-Durán JM. 2021. ERK1/2 is an ancestral organizing signal in spiral cleavage. ***Nature Communications***, 13, 2286.
2. Martín-Durán JM, Marlétaz F. 2019. Unravelling spiral cleavage. ***Development*** 147, dev181081

Project Title	**Psychosocial factors promoting positive outcomes in neurodivergent young people: the role of environmental sensitivity**
Supervisor	Dr Giorgia Michelini
Email	g.michelini@qmul.ac.uk
Lab Website	https://www.qmul.ac.uk/sbbs/staff/giorgia-michelini-.html
Co-supervisor(s)	Professor Michael Pluess

Project Description

This project will examine the role of psychosocial factors and environmental sensitivity in promoting positive mental health outcomes in neurodivergent young people. The notion of neurodiversity represents an emerging framework to conceptualise neurodevelopmental conditions (e.g. autism and ADHD), which are diagnosed in 15% of children and young people worldwide. A pillar of this framework is that the mental health difficulties and everyday challenges experienced by neurodivergent individuals are a product of the social environment in which they live, rather than of neurodevelopmental symptoms. However, there is little research on which factors promote positive outcomes in this population. Moreover, research has not considered whether an individual's environmental sensitivity (the extent to which an individual is sensitive to positive and negative stimuli/events in their environment) plays a role in the association between neurodiversity and mental health outcomes. This PhD project will address this research gap by investigating environmental sensitivity, neurodiversity, and mental health and associated outcomes in large existing longitudinal cohorts. Specifically, we will examine the role of environmental sensitivity in the longitudinal association between neurodivergent traits and long-term outcomes, to identify factors that may be promoting positive outcomes in neurodivergent young people. Genetic information in these longitudinal cohorts will be leveraged to investigate and account for shared genetic factors, allowing us to identify potential causal relationships between neurodiversity, environmental sensitivity and long-term outcomes. This research will provide novel insights into the ways in which the environment and an individual's sensitivity to it impact mental health and related outcomes in neurodivergent young people across development, with the potential to influence future policy and interventions.

References

1) Michelini, G., Gair, K., Tian, Y., Miao, J., Dougherty, L. R., Goldstein, B. L., MacNeill, L. A., Barch, D. M., Luby, J. L., Wakschlag, L. S., Klein, D. N., Kotov, R. (2022). Do general and specific factors of preschool psychopathology predict preadolescent outcomes? A transdiagnostic hierarchical approach. Psychological medicine. https://doi.org/10.1017/S003329172200246X

2) Michelini, G., Barch, D. M., Tian, Y., Watson, D., Klein, D. N., & Kotov, R. (2019). Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. Translational psychiatry. https://doi.org/10.1038/s41398-019-0593-4

3) Michelini, G., Eley, T. C., Gregory, A. M., & McAdams, T. A. (2015). Aetiological overlap between anxiety and attention deficit hyperactivity symptom dimensions in adolescence. Journal of child psychology and psychiatry. https://doi.org/10.1111/jcpp.12318

4) Lionetti, F., Klein, D. N., Pastore, M., Aron, E. N., Aron, A., & Pluess, M. (2021). The role of environmental sensitivity in the development of rumination and depressive symptoms in childhood: a longitudinal study. European child & adolescent psychiatry. https://doi.org/10.1007/s00787-021-01830-6

5) Assary, E., Zavos, H., Krapohl, E., Keers, R., & Pluess, M. (2021). Genetic architecture of Environmental Sensitivity reflects multiple heritable components: a twin study with adolescents. Molecular psychiatry. https://doi.org/10.1038/s41380-020-0783-8

Project Title	**Learning to avoid misinformation**
Supervisor	Rani Moran
Email	r.oran@qmul.ac.uk
Lab Website	https://www.qmul.ac.uk/sbbs/staff/rani-moran.html
Co-supervisor(s)	Lucie Charles

Project Description

Reinforcement Learning (RL) is a multidisciplinary filed with implications for a broad range of disciplines including Psychology, Neuroscience, Medicine, Computer Sciences, Machine Learning and Artificial Intelligence. RL studies how animals and humans adapt to their environment by learning from experience which actions maximize reward acquisition [1]. Extant research has focused on the case learners receive veridical reward-feedback (e.g., true monetary earnings). However, as social creatures, much of the real-life feedback we receive is provided by others. Critically, such feedback may be misleading since others might manipulate us based on their own, even if well-intended, interests. For example, a friend might spare your feelings, expressing enthusiasm regarding you PhD proposal when in truth they find it superficial. Indeed, the prevalence of misinformation in our culture poses a pressing question: How do we adopt to environments where false and misleading feedback is provided?

The goal of this project is to unravel the learning processes governing such adaptation. Aim 1 is to develop novel RL behavioural tasks, in which participants receive reward-feedback (following choices) from various feedback-sources varying in reliability, i.e., the extent of misinformation they provide. Participants will also rate their beliefs regarding the reliability of feedback they receive. We will develop computational models for testing whether and how people learn which information sources are more or less reliable, and to what extent participants base subsequent choices on reliable feedback, while filtering out misinformation. Aim 2 is to test a hypothesis that deficits in aforementioned learning processes might relate to detrimental outcomes for social-communication and mental health such as political radicalisation, belief in conspiracy-theories, social anxiety and paranoia. Aim 3 is to develop training protocols, based on our tasks, for increasing people's sensitivity to feedback reliability, fostering an ability to ignore false feedback.

This project promises a better understanding of the mechanisms governing adaptation in the presence of misinformation, how these affect social interaction and mental health, and interventions for keeping these detrimental influences at bay.

This project will foster diverse skills including: Experimental task design, complex statistical analysis, computational modelling, working in a team, programming of online experiments, MATLAB, and academic writing.

References

1. Sutton, R. S., & Barto, A. G. (2018). *Reinforcement learning: An introduction*. MIT press.

Project Title	Biophysics of bacterial cell death
Supervisor	Nikola Ojkic
Email	n.ojkic@qmul.ac.uk
Lab Website	https://www.qmul.ac.uk/sbbs/staff/nikola-ojkic.html
Co-supervisor(s)	

Project Description

The School of Biological and Behavioural Sciences at Queen Mary is one of the UK's elite research centres, according to the 2021 Research Excellence Framework (REF). We offer a multi-disciplinary research environment and have approximately 180 PhD students working on projects in the biological and psychological sciences. Our students have access to a variety of research facilities supported by experienced staff, as well as a range of student support services.

A PhD project titled "Biophysics of bacterial cell death" will be conducted in the group of Dr Nikola Ojkic. Members of Ojkic's group use experimental, theoretical and computational approaches to investigate biophysical principles of bacterial cell shape and size control. Ojkic's group is particularly interested in the biophysics of bacterial adaptation to environmental stress and how bacteria develop resistance to antibiotics.

Our PhD students become part of Queen Mary's Doctoral College which provides training and development opportunities, advice on funding, and financial support for research. Our students also have access to a Researcher Development Programme designed to help recognise and develop key skills and attributes needed to effectively manage research, and to prepare and plan for the next stages of their career.

The prospective student will develop theoretical and computational skills in the field of cell biophysics and will also have a unique opportunity to develop experimental microbiology and imaging skills. The student will also have a chance to interact with other national and international experimental groups through different collaborative projects.

The work will be carried out in the research group of Dr Nikola Ojkic, based in the Mile End campus of Queen Mary University of London. The PhD student will use mathematical and biophysical modelling, image analysis and simulations to investigate how bacteria transform their shape and size under harsh environmental conditions. Using theoretical approaches in close collaboration with experimentalists the project will be aimed to investigate fundamental physical principles of how bacterial cells lose cell integrity under high antibiotic concentrations.

Applications are invited from outstanding candidates with or expecting to receive a first or upper-second class honours degree or a masters degree in an area relevant to the project – mathematics, physics, biophysics, and/or computer science. A masters degree is desirable, but not essential.

A strong mathematical, physical, and computational background and interest in biological systems are required.

Informal enquiries about the project can be sent to Dr Nikola Ojkic at n.ojkic@qmul.ac.uk. Formal applications must be submitted through our online form by 31st January 2023 for consideration, including a CV, personal statement, and qualifications.

References

1. Ojkic, Serbanescu, Banerjee: "Antibiotic resistance via bacterial cell shape-shifting", mBio, 13 (3) e00659-22 (2022).

2. Ojkic, Banerjee, "Bacterial cell shape control by nutrient-dependent synthesis of cell division inhibitors", Biophysical Journal, 120, 2079-2084 (2021)

3. Ojkic, Serbanescu, Banerjee, "Surface-to-volume scaling and aspect ratio preservation in rod-shaped bacteria", eLife, 8:e47033, (2019)

Project Title	**Positive balance: building wellbeing and resilience skills for youth via digital technologies**
Supervisor	Dr Elisabetta Versace
Email	e.versace@qmul.ac.uk
Lab Website	preparedmindslab.org/ - http://sid.eecs.qmul.ac.uk
Co-supervisor(s)	Prof Nick Bryan-Kinns, Dr Sevasti Foka, Dr Giorgia Michelini, Dr Manuela Angioi

Project Description

Digital apps to support mental health interventions are becoming popular, so rigorous experimental studies are needed to validate these approaches. The efficacy of positive psychology interventions delivered via digital apps has just started to be investigated. We have showed that short positive psychology interventions delivered during adolescence can counteract the negative effects of stressful events, enhancing character strengths, positive emotions, hope and meaning in life. However, few adolescents have access to positive psychology interventions. An app to deliver positive psychology interventions for adolescents and young adults could address this need. The aim of this project is to develop and test a smartphone app to support positive psychology interventions during adolescence and compare its efficacy to in-person delivery. We will focus on a general population of vocational dance students, since this is a non-clinical population exposed to potentially stressful events and life transitions, that can benefit from a positive psychology intervention. In this interdisciplinary project, the student will develop the smartphone app, become familiar with positive psychology interventions, learn how to deliver the positive psychology intervention in person and using the app, test its efficacy on a general population of adolescents/young adults using advanced statistical methods. This project will provide much needed evidence to evaluate, validate and improve positive psychology and mental health digital interventions.

Applications are invited from outstanding candidates with or expecting to receive a first or upper-second class honours degree in an area relevant to the project such as clinical and positive psychology, mental health, interactive technologies, interaction, human-computer interaction, digital interfaces. A masters degree is desirable, but not essential. We don't expect candidates to have experience in all the areas of this interdisciplinary project, but at least in some, and to have interest in both digital technologies and mental health/psychology.

Self-motivation, commitment, Interest in mental health and digital technologies, computational skills, excellent communication and interpersonal skills are required.

The successful applicant will be part of the vibrant Department of Psychology, in the Resilience, Health and Well-being thematic group and in the Prepared minds lab (Dr Versace, https://www.preparedmindslab.org/), and will also be part of the Bryan-Kinns lab, contributing to the Interaction Design theme of the Sonic Interaction Design Lab (http://sid.eecs.qmul.ac.uk). More broadly, the student will join the Social Interaction Health and Wellbeing (SIHW) group, a research group joint between Psychology, Engineering and Psychiatry at Queen Mary University of London. This will be an opportunity to expand skills in different research areas.

References

1) Foka, S, K Hadfield, M Pluess, and I Mareschal. 'Promoting Well-Being in Refugee Children: An Exploratory Controlled Trial of a Positive Psychology Intervention Delivered in Greek Refugee Camps'. Development and Psychopathology 33, no. 1 (February 2021): 87–95.
2) Patton, GC et al. 'Our Future: A Lancet Commission on Adolescent Health and Wellbeing'. The Lancet 387, no. 10036 (June 2016): 2423–78.
3) Torous, J et al. (2019), Towards a consensus around standards for smartphone apps and digital mental health. World Psychiatry, 18: 97-98.
4) Gallo, V et al. 'MotionPerfection: An Agile Tool for the Visualisation, Analysis, Annotation, and Record of Motor Practice', 2022, 5.
5) Twitchett, E et al. 'The Demands of a Working Day Among Female Professional Ballet Dancers' Journal of dance medicine & science 127–132.

Project Title	***In vitro* reconstitution of cooperative interactions at the kinetochore-microtubule interface**
Supervisor	Dr. Vladimir Volkov
Email	v.volkov@qmul.ac.uk
Lab Website	https://www.qmul.ac.uk/sbbs/staff/vladimir-volkov.html

Project Description

We are seeking a PhD student eligible for the China Scholarship Council Scholarships to join the Volkov group at Queen Mary University of London and work on an exciting research project involving protein design, force sensing, and advanced methods of light and electron microscopy.

Duiring cell division, eukaryotic cells must ensure proper attachments between chromosomes and the mitotic spindle to avoid the loss of genetic material, which can lead to aneuploidy, cancer, or cell death. These attachments are mediated by multiple copies of identical microtubule-binding protein complexes at the kinetochore interacting with microtubule ends. It is poorly understood how cooperative binding of these complexes to microtubules is regulated at molecular level. The project will make use of budding yeast as a simplified model system with only one microtubule per kinetochore, and well defined stoichiometry of the microtubule-binding proteins, such as the Ndc80 complex and the Dam1 complex. *In vitro* reconstitution of an interaction between a microtubule end and recombinantly expressed Ndc80 and Dam1 complexes will allow to dissect the self-assembly of microtubule end-bound oligomers, and the molecular interactions that hold them together, in a systematic manner.

You will build on the unique methodologies established in the lab, including single-molecule fluorescence microscopy to assess the stoichiometry of microtubule-bound oligomers (1,4), a DNA origami force sensor to study force coupling by these oligomers (2), and electron cryo-tomography to study the molecular interfaces involved in oligomerisation of microtubule end-bound protein complexes (3).

References

1. Polley S, Müschenborn H, Terbeck M, De Antoni A, Vetter IR, Dogterom M, Musacchio A#, Volkov VA#, Huis in ‘t Veld PJ#. Stable kinetochore-microtubule attachment requires loop-dependent Ndc80-Ndc80 binding. *bioRxiv* (2022). doi: 10.1101/2022.08.25.505310

2. Nick Maleki A , Huis in 't Veld PJ, Akhmanova A, Dogterom M, Volkov VA#. Estimation of microtubule-generated forces using a DNA origami nanospring. *J Cell Sci* (2022) 136 (5), jcs260154. doi: 10.1242/jcs.260154

3. Maan R*, Reese L*, Volkov VA*, King MR, van der Sluis E, Andrea N, Evers W, Jakobi AJ, Dogterom M. Multivalent interactions facilitate motor-dependent protein accumulation at growing microtubule plus ends. *Nature Cell Biology* (2022), in press. doi: 10.1101/2021.09.14.460284

4. Volkov VA*, Huis in 't Veld PJ*, Dogterom M, Musacchio A. Multivalency of NDC80 in the outer kinetochore is essential to track shortening microtubules and generate forces. *eLife* (2018) 7, e36764. doi: 10.7554/eLife.36764