QUEEN'S UNIVERSITY BELFAST

4 Year PhD – Projects Booklet

2024

Medicine, Dentistry and Biomedical Sciences

Pharmacy

Professor Margaret Topping
Pro-Vice Chancellor (Global Engagement)

WELCOME TO QUEEN'S

Thank you for considering Queen's University Belfast for your PhD experience.

At Queen's, we are proud to be a university that is internationally recognised and globally connected.

A member of the Russell Group of research-intensive universities, Queen's is at the forefront of developing new thinking right across the University, and in the QS World Rankings by subject 2024, 19 of Queen's subjects were ranked in the top 200.

With over 25,000 students, including over 4,400 international students from over 90 countries, Queen's is a dynamic and diverse institution, a magnet for inward investment, a patron of the arts and a global player in areas ranging from cancer studies to sustainability, and from pharmaceuticals to cyber security.

In recognition of its commitment to producing research that has an impact on society, Queen's is ranked in the top 200 in the world for impact and sustainability (THE Impact Rankings 2024/ QS World University Rankings 2024: Sustainability) and is ranked in the top 150 in the world for research quality (THE World University Rankings 2024). Queen's is ranked in the top 10 in the UK for graduate prospects (Complete University Guide 2025).

We are ranked 4th in the world for international outlook but are also a university that is proud to play a key role in its local community. Situated in the heart of one of the capital cities of Europe, Queen's is renowned for its teaching excellence and international research, while Belfast is known for its warm welcome, rich culture, innovation and entrepreneurship.

At Queen's our Strategy 2030 sets out our ambition over the next six years to shape a better world through life-changing education and research. Our vision is that of a global, research-intensive university, coupled with outstanding teaching and learning, focused on the needs of our society, locally and globally.

Our PhD student population is at the heart of those ambitions, and through a partnership between our academic Schools, research institutes, and award-winning Graduate School, we seek to develop future-ready individuals who push beyond conventional boundaries and who will return to their home countries equipped to take on the leadership roles which will respond to the national strategies and ambitions of our partner countries.

Professor Colin McCoy
Dean of The Thomas J Moran Graduate School

THE THOMAS J MORAN GRADUATE SCHOOL AT QUEEN'S

In addition to training our PhD students as experts in their fields, we also offer a wide range of opportunities for personal and professional development through our Graduate School. The Graduate School is a state-of-the art hub for tailored training, support and development of postgraduate students. Beyond academic subject expertise, we aim to develop thinkers, communicators, innovators and leaders who are future-ready.

The Graduate School is both an intellectual and social hub, connecting postgraduate students from all disciplines to each other and to mentors and employers within the University and beyond. It is grounded in intellectual challenge beyond disciplinary borders, personal effectiveness and the development of future-facing skills. We aim to build on the professional experiences which postgraduates arrive with at Queen's; our ethos is to nurture a culture of opportunity, innovation and enterprise and a rich, diverse, inclusive social community.

With emphasis on designing and delivering programmes which spark, encourage and support leadership, innovation and enterprise, the Graduate School is committed to providing a vibrant environment to develop economic and social participation and growth and to support wellbeing. Our aspiration is that you develop skills beyond your academic programme to facilitate your future success in today's global workplace.

We support global leaders to identify opportunities for innovation across a range of sectors and disciplines, and to develop the tools and mindset required to adapt to and ensure relevance in a changing world.

Being a postgraduate student at Queen's is about going beyond current conceptions and categories, redefining and rethinking assumptions and having a perspective that is flexible and adaptive. It's what we call 'What's Next' thinking.

This brochure provides you with a range of PhD projects for which you can apply, as well as information on the range of workshops and training opportunities available to you in our Graduate School. If you would like to discuss an individual project, please contact the supervisor whose details are provided. For general queries about doctoral study at Queen's or the wider University, please contact: Mrs Lynne Spence (l.spence@qub.ac.uk).

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FACULTY AND SCHOOL STRUCTURE

Queen's has three Faculties and a total of 15 Schools, each lead by a Head of School. Where projects are available, the order they appear within this booklet follows this structure.

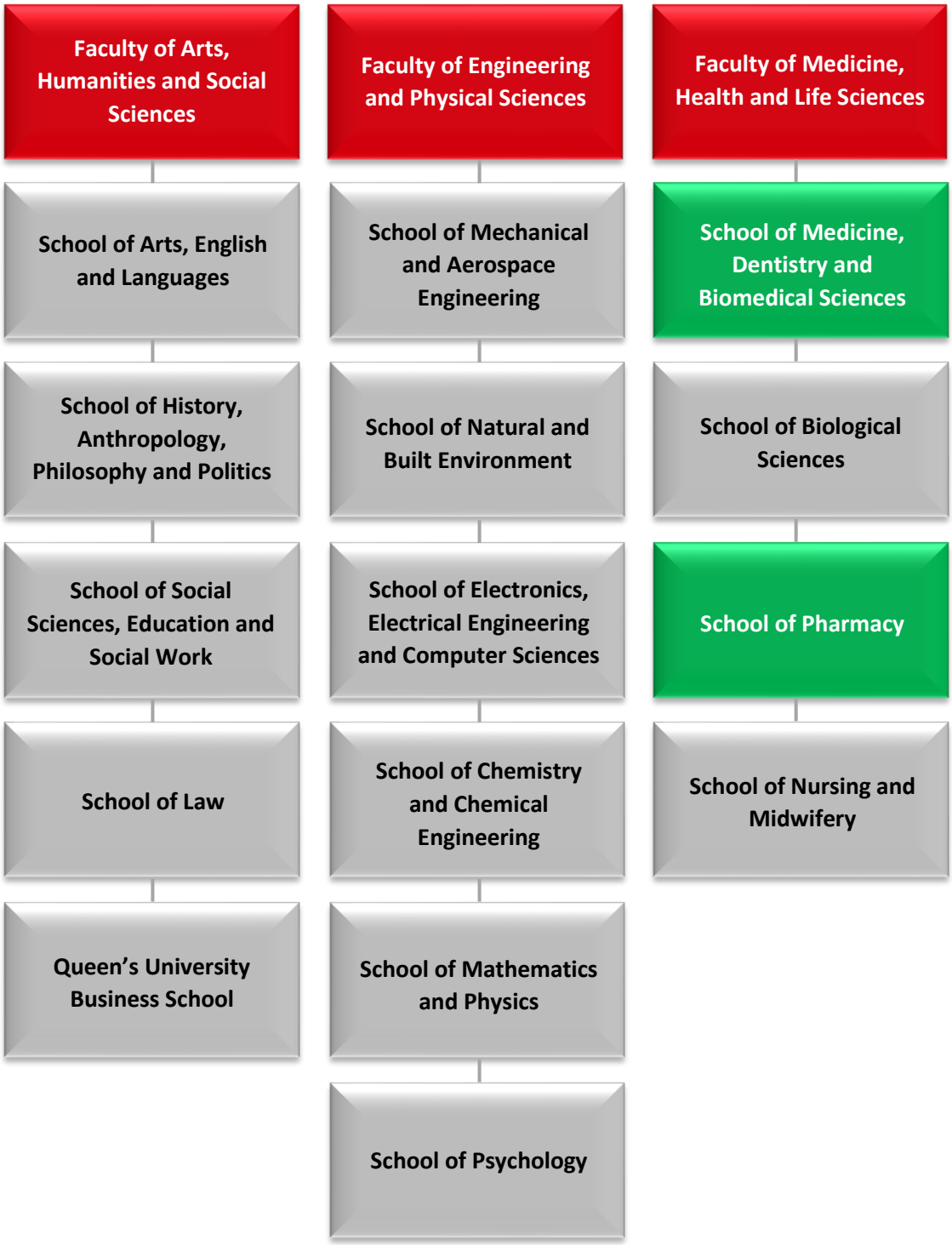


Figure 1: *Faculty and School Structure*

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

1. MEDICAL EDUCATION

1.1 "So What Happens After we Simulate?": A Qualitative Inquiry into the Experiences of Medical Students Following SBE Activities on their Professional Development

Supervisor	Dr Andrew Spence and Professor Gerry Gormley
Project Overview	Simulated-based education (SBE) is widely utilized in medical education as a form of experiential learning. Often employed to enhance High Acuity Low Opportunity (HALO) skills, such as managing cardiac arrest or mental health crises, much of the existing research has focused on refining the 'teaching tool 'of simulation. However, a broader perspective is necessary to understand the impact of SBE on learners and how it influences (or not) their competences and professional development. In this proposed PhD project, our aim is to explore medical students' experiences in SBE and its impact on their professional development as they integrate these experiences with other forms of clinical learning, especially work-based learning (WBL). The findings of this research hope to not only guide the optimal delivery of SBE learning opportunities but also highlight how it can be integrated with other forms of experiential learning, such as WBL.
Project Description: Detailed description of the project	This qualitative study will consist of three distinct phases: • The successful candidates will critically examine the concept outlined above and conduct an appropriate literature review. • Conduct a qualitative inquiry into the experiences that medical students gain from SBE activities and their impact on professional development. The methodologies (e.g. cGT) used will depend on the outcomes of Phase 1, with a longitudinal approach likely, such as using audio diaries. • Undertake a study that provides guidance on the practical implementation of the findings into educational practice and policy. Methodologies such as Interpretive Descriptive methodology or participatory research methodologies will be considered. Given the qualitative nature of this research, especially the critical thinking required, candidates must be highly motivated, possess a strong command of English, and ideally have a pre-established interest in simulation-based education.
Project Keywords	Simulation; Education; Work-based learning; Professional development; High Acuity Low Opportunity; Longitudinal

2. PUBLIC HEALTH

2.1 Digitalovigilance – Discovery and Management of Adverse Reactions in Digital Health Interventions

Supervisor	Dr Guillermo Lopez Campos
Project Overview	The aim of this project is to determine whether biomedical informatics solutions can be developed to identify, characterise, and predict adverse and unexpected events derived from the use of Digital Health interventions to ensure patient safety and a safe development of digital health.
Project Description: Detailed description of the project	Digital therapeutics (DTX) offer patients evidence-based therapeutic interventions that are delivered through high-quality software programs. Similar to drugs or other treatments they aim to cure, manage, or prevent a disease and they are tested on selected volunteers and patients prior to market launch to verify their efficacy and safety. DTX effectiveness of use must be proven through systematic clinical trials that assess the outcome in controlled settings to reduce bias. However, assessment of their potential safety has not been investigated so extensively. **This project aims to address the lack of research on harm and the adverse effects of digital therapeutics** and to develop "digitalovigilance" as a new research area for collecting, detecting, assessing, monitoring, and preventing adverse effects caused by digital health interventions. More specifically, the objectives are: 1. To identify potential unintended consequences of digital health interventions. 2. Aggregate information on unintended consequences of technology as digital health interventions that were assessed separately. 3. To develop a framework for assessing such consequences as part of clinical trials and reporting guidelines to ensure that these consequences are reported in a systematic, standardized manner To successfully address these objectives, we will combine and develop new health informatics solutions.
Project Keywords	Digital Health, Health Informatics, Artificial Intelligence, Adverse effects

2.2 Nutrigenomic Investigation of Cognitive Outcomes in the Northern Ireland Cohort of Longitudinal Ageing

Supervisor	Dr Gareth McKay
Project Overview	Please see Project Description below.
Project Description: Detailed description of the project	**Aims and Purpose:** Previous prospective and cross-sectional studies have identified associations between serum antioxidant levels and cognitive outcomes. Supplementation and dietary intervention have provided contrasting support for the beneficial effects antioxidants may provide in protecting against cognitive decline. Genetic variants in several metabolic pathway genes have been shown to attenuate antioxidant levels. We seek to investigate if underlying genetic and epigenetic variants influence antioxidant levels and subsequent decline in cognitive function. **Background:** Multiple neuropathological processes underlie cognitive decline with increased age, a process influenced by modifiable (e.g. lifestyle) and non-modifiable (e.g. genetic) risk factors. The brain is especially vulnerable to reactive oxygen species as neurons possess relatively low levels of endogenous antioxidants to offset their high metabolic activity. This antioxidant deficit leads to oxidative damage of major cell components and elevated inflammation leading to neuronal cell death. Nutritional factors may prove beneficial for retaining healthy cognitive function, but the influence of dietary carotenoids remains unclear. Despite numerous studies exploring whether lower antioxidant levels are associated with reduced cognitive function, findings have been inconsistent, in part due to insufficient consideration of potential confounder factors and insufficient understanding of the underlying molecular influences. Previous studies have shown vitamin E (VE) bioavailability is modulated, in part, by a combination of polymorphisms in at least 11 genes, accounting for up to 82% of genetic variation present. These genes are involved in the complex interactions that underlie antioxidant intake, absorption efficiency, blood clearance (e.g., liver secretion and tissue assimilation), utilisation and catabolism. As such, the therapeutic potential of antioxidant supplementation or dietary intervention is dependent on an individual's underlying genetic architecture. Therefore, improved understanding will enable a stratified approach to progress interventional study design and enhance the potential effects on the primary outcome. **Preliminary results:** Previously, we reported antagonistic interactions between VE isoforms that may alter functionality and bioavailability, highlighting concerns for clinical trials investigating VE supplementation.[1] Furthermore, APOE status has been shown to influence antioxidant status and we previously reported significantly lower alpha-tocopherol and higher gamma-tocopherol by APOE status, with APOE2 characterised as more neuroprotective. **Plan of investigation:** We will evaluate antioxidant levels, including retinol, α-tocopherol, γ-tocopherol, and six carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, lycopene, zeaxanthin), in 3,000 well characterised participants of the Northern Ireland Cohort of Longitudinal Ageing

	(NICOLA). We will use previously collected data from validated food frequency questionnaires, together with genome-wide and epigenome-wide association data to evaluate (epi)genetic variation associated with antioxidant status and measures of cognition. **We hypothesize that molecular variation in older populations may influence serum antioxidant levels which in turn may impact cognitive outcomes.** **Aim 1:** Evaluation of antioxidant profiles with cognitive function in NICOLA participants. Statistical approaches will include data comparisons using Pearson correlation coefficients and Bland-Altman plots in combination with cognitive measures (MMSE and MoCA) and regression analyses with adjustment for potential confounders. **Aim 2:** Identification of genetic and epigenetic variants associated with antioxidant status from NICOLA participants (Illumina Infinium CoreExome chip; ~550k variants and the Infinium MethylationEpic array [~850k methylation sites]) have been imputed and available for mixed model linear regression analyses with adjustment for confounders and population stratification. Major developments in methods for deriving causal inference through instrumental variable analysis such as Mendelian randomisation approaches will be adopted. With 3,000 study participants we can detect as statistically significant at the 5% level, a correlation coefficient of 0.2 or greater with over 90% power (PASS: Power Analysis and Sample Size. Kaysville, Utah). Independent replication and validation will be facilitated through ongoing collaborations.
Project Keywords	Nutrigenomics; healthy ageing; antioxidants; cognitive health; vitamins; genetics; methylation

2.3 Multiomic Signatures Associated with Healthy Ageing and Age-related Conditions

Supervisor	Professor Amy Jayne McKnight
Project Overview	Age-related diseases increase in prevalence as populations get older. They are expected to bankrupt the UK national health service if the current rates continue. There is an urgent need to identify biomarkers that predict health and disease across the lifecourse, with a focus on enabling identification of persons most a risk of developing disease, earlier detection of disease, and improved understanding of how diseases develop considering inherited features alongside the impact of where each person is born, lives, and works. We know that people who are poorer, less educated, and who experience more adverse life circumstances experience accelerated biological ageing that is associated with an earlier onset of age-related diseases such as diabetes, cardiovascular disease, and kidney disease.
Project Description: Detailed description of the project	This project leverages existing large-scale datasets to identify multiomic signatures associated with healthy ageing and diseases that are common in in older populations. There is scope for the successful student to generate new laboratory data, learning both wet-lab and complementary *in silico* analytical approaches, or to focus purely on an artificial intelligence training track that will enable them to be competitive employment in a range of fields.
Project Keywords	Ageing, public health, healthy ageing, artificial intelligence

2.4 Innovative Multiomic Approaches to Improve Early Detection and Diagnosis of Rare Kidney Conditions: A Transdisciplinary Approach

Supervisor	Professor Amy Jayne McKnight
Project Overview	**Background:** Rare kidney diseases are life changing, invisible and under-funded conditions. Around 50-75% of rare kidney diseases occur in children and they are the cause of almost all cases of kidney failure in children; in adults they contribute to about 10% of kidney failure. In children, kidney failure causes early cardiac death. Sadly, kidney transplant is not the ultimate cure, more life years are spent attached to a machine than with a functioning transplant and the quality of life of a child with kidney failure is worse than many other long term childhood conditions. NI has a strong track record of >50 years of kidney research. Prof McKnight has secured ~£30m in research funding with >130 publications and collaborates extensively with wet-lab experimental and computational technology companies. Identifying biomarkers for kidney disease has been a core focus of Prof McKnight's research for 20+ years, more recently focused on identifying multiomic signatures for rare conditions. She is driving using artificial intelligence tools to make best use of the sheer amount of data available for multiomic analysis. This project will be co-supervised by colleagues in Artificial Intelligence.
Project Description: Detailed description of the project	**Aim:** To interrogate large-scale multiomic datasets applying innovative analytical approaches to improve early detection and diagnosis of rare kidney conditions. **Objectives:** **1)** To access and clean data from existing and novel resources (including from Genomics England and Our Future Health) for >6 million individuals across the UK. Comprehensive biochemical and molecular (genetic, epigenetic, transcriptomic) biomarker data will be linked to hospital episode statistics, mental health services data, imaging data, rare disease registry data, rare kidney registry data, COVID-19 data, mortality data, electronic healthcare records, and (more limited) primary care data. GeL are delivering the Newborn genomes programme (commencing 2024) conducting whole genome sequencing to identify ~250 rare conditions at birth, which provides further opportunities, time permitting. **2)** To help characterise rare kidney conditions based on molecular and imaging data **3)** To apply multi-modal analytics to help detect and diagnose rare kidney conditions, exploring the potential clinical use for early detection, improved classification, and diagnostic testing. **4)** The successful student will benefit from multi-disciplinary and cross-sectoral expertise building a professional network and gaining transdisciplinary training in an area of skills shortage. They will be equipped to work at the academic/industry interface supporting their future career competitiveness and mobility.
Project Keywords	Rare disease, diagnosis, genetics, artificial intelligence

2.5 Improving Diagnosis and Treatment for People Living with Rare Diseases

Supervisor	Professor Amy Jayne McKnight
Project Overview	More than 450 million people across the world live with rare diseases and significant unmet health and social care needs. On average, RD patients in the UK experience three misdiagnoses, attend multiple medical specialities, with many never obtaining a name for their condition. NHS costs for patients with undiagnosed RDs was >£3.4 billion in the 10 years prior to diagnosis. Many RDs are chronic, complex conditions; ~70% of RDs affect children; >60% of children who die <15 years have a RD. Many RD diagnoses are effectively invisible to national data systems.
Project Description: Detailed description of the project	There are opportunities for dedicated students to conduct research using rare disease registry data, including high-quality, UK-wide real-world population-based data, to help establish a virtual community of practice for rare disease, to develop patient reported outcomes for rare diseases, to support patients to participate in clinical trials for rare diseases, or to focus on research that enables access to orphan drugs. For example, Whole genome and exome sequencing are increasing diagnostic rates to ~40% for inherited diseases in NI, while newer approaches such as epigenetics and transcriptomics are helping drive up the diagnostic yield. We established a collaborative academic-clinical 'gene discovery' clinic for patients with undiagnosed rare diseases in NI, which uses multiomic approaches to maximise opportunities for diagnosis. However, even with a diagnosis, treatment options are limited. New gene therapies are emerging, which require correct molecular diagnosis before the patient can access the therapies, which is proving problematic for conditions where genetic testing is not routine or waiting on consultant appointments has long waiting times. Many novel drugs take >10 years to market so re-purposing of drugs already licensed for use in another disease is an attractive option for rare diseases. New approaches are also required to optimise trials to deal with the often paediatric onset, often severely life limiting rare conditions where there are a restricted number of participants and limited molecular diagnoses or natural history information. Emerging options such as adaptive and / or decentralised clinical trials and using real world data offer promising opportunities for rare disease researchers and patients. Rare-disease researchers pioneer a unique approach to clinical trials | Nature Medicine
Project Keywords	Rare disease, diagnosis, orphan drug, clinical trial, artificial intelligence

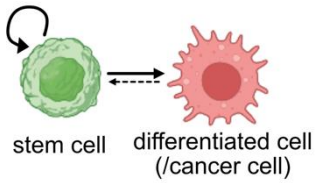
2.6 Psychiatric-onset Dementia with Lewy Bodies in a Mental Health Inpatient Cohort

Supervisor	Dr Joe Kane
Project Overview	The prodromal phase of dementia with Lewy bodies (DLB), which is the second most common form of neurodegenerative dementia, is hypothesised to comprise of three phenotypes(1). Only one of these phenotypes, mild cognitive impairment with Lewy bodies (MCI-LB), has diagnostic criteria and has been studied in biomarker-enriched longitudinal observational studies. Psychiatric-onset DLB (poDLB), in which late-onset psychiatric illness such as psychosis, depression and anxiety disorders represent another hypothesised prodromal DLB phenotype.
Project Description: Detailed description of the project	There is a comparative paucity of evidence on poDLB(2). A 2010 survey of people living with DLB in USA found that over 10% of respondents were initially treated for depression, psychosis or another functional psychiatric illness, before eventually being diagnosed with DLB; over 30% of respondents engaged with healthcare services for two or more years before being diagnosed(3). Accurate and timely diagnosis is no less crucial for poDLB than with MCI-LB, particularly as commonly prescribed psychiatric medications can be harmful, and even lethal, in DLB(4). As both DLB and MCI-LB are thought to be comparatively poorly detected in routine clinical care(5), this is also likely to be the case, perhaps to an even greater extent, for poDLB. **Aims** This project aims to determine the prevalence, clinical phenotype and disease progression of poDLB in a cohort of older people (>55 years) admitted to inpatient care for late-onset psychiatric illness. It will use a prospective cohort study design in which patients admitted to a mental health inpatient unit over one year, along with matched cognitively and psychiatrically healthy controls, are systematically screened at baseline and followed up over two years. **Method** All patients admitted to the Belfast Health & Social Care Trust Acute Mental Health Inpatient Centre (AMHIC) over a 12-month period for late-onset psychiatric illness will be approached for consent to participate. We estimate this to be 60-80 individuals. Patients diagnosed with neurodegenerative illness or those with established MCI will be excluded. Consent will also be sought to approach next of kin, or another healthy relative, to act as a control. As an inpatient, established measurements of cognition, parkinsonism (MDS-UPDRS), REM sleep behaviour disorder (MSI), fluctuations and other symptoms recognised as associated with DLB will be administered and clinical and neuroimaging data retrieved from patients' notes. The same scales will be repeated 12 and 24 months following recruitment. **Expected outcomes**

	We expect to demonstrate that few, if any patients are diagnosed with poDLB in the mental health inpatient environment, but that DLB-associated symptoms are more common than in matched controls. Cognitive and functional impairment, as well as progression in DLB-associated symptoms, will increase in 10-20% of cases when compared with controls. **References** 1. McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. Neurology. 2020;94(17):743–55. 2. Gunawardana CW, Matar E, Lewis SJG. The clinical phenotype of psychiatric-onset prodromal dementia with Lewy bodies: a scoping review. J Neurol. 2024 Jan 1;271(1):606–17. 3. Galvin JE, Duda JE, Kaufer DI, Lippa CF, Taylor A, Zarit SH. Lewy body dementia: The caregiver experience of clinical care. Parkinsonism and Related Disorders. 2010 Jul;16(6):388–92. 4. Aarsland D, Perry R, Larsen JP, McKeith IG, O'Brien JT, Perry EK, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. The Journal of clinical psychiatry. 2005 May;66(5):633–7. 5. Surendranathan A, Kane JPM, Bentley A, Barker SAH, Taylor JP, Thomas AJ, et al. Clinical diagnosis of Lewy body dementia. BJPsych Open. 2020;6(4).
Project Keywords	Neurodegenerative disease; mental health; dementia; movement disorders; psychiatry

3. CANCER RESEARCH

3.1 Investigating the Epigenetic Basis of Chemotherapy Resistance in Colorectal Cancer

Supervisor	Dr Yaser Atlasi
Project Overview	The Atlasi research group is dedicated to studying stem cell and cancer epigenetics. Specifically, we investigate the interplay between cell signalling and chromatin regulation in stem cells, as well as how these mechanisms are deregulated in cancer, including the development of chemotherapy resistance in tumours. We employ various stem cell models, such as embryonic stem cells and tissue-derived organoids, along with cutting-edge genomics, proteomics, and computational biology approaches. Our goal is to make fundamental discoveries that can ultimately address significant health challenges in society.  The Atlasi lab comprises 1 postdoctoral researcher, 4 PhD students, 1 MSc student, and 1 BSc student. The lab is funded by research grants from the Medical Research Council (MRC), the Royal Society, Breast Cancer Now, and Leukemia Lymphoma NI (LLNI).
Project Description: Detailed description of the project	Treatment with 5-fluorouracil (5FU)-based chemotherapy is the main option for most colorectal cancer (CRC) patients. However, chemotherapy resistance remains a major hurdle in CRC treatment. Recent discoveries highlight a remarkable similarity between chemo-resistant cancer cells and cells found in the early embryo, suggesting that cancer cells can hijack a range of stem, and embryonic programmes to enter a dormant state that enables them to survive treatment. This drug resistance-persistence state is associated with reversible epigenetic reprogramming allowing cells to reinitiate tumour growth upon drug release. In this project, we aim to identify the reversible epigenetic changes underpinning cell plasticity in response to 5FU treatment, with a particular focus on transcriptional enhancers s. Better understanding of these epigenetic mechanisms will provide new therapeutic approaches to prevent or overcome drug resistance in cancer. We have recently conducted multiple genomics approaches to understand the epigenetic basis of drug resistance in CRC. Through this research, we have identified several candidate epigenetic regulators that may play key roles in this process. In this project, the PhD student will utilize state-of-the-art CRISPR/Cas9 and genomics approaches to study the role of these candidate epigenetic regulators identified in our genomics screens. All proposed experiments are standard molecular biology approaches that have been used before by the lead PIs, mitigating the feasibility concerns. Furthermore, this project does not have a pre-defined outcome and both positive and negative results regarding identified epigenetic candidates will be important findings that shed light on the role of epigenetic regulation in drug resistance.

	The candidate PhD student will receive training in multi-disciplinary approaches combining genome-wide technologies, stem cell biology (including organoid culture) and various molecular biology techniques. The PhD candidate will also gain experience in computational biology for analysis of genome wide data.
Project Keywords	Epigenetics, colorectal cancer, therapy resistance

3.2 Investigating the Impact of Vascular Remodelling in Risk for Metastasis During Cancer Progression and Treatment

Supervisor	Dr Cristina Branco
Project Overview	The Branco Group is interested in metastatic disease, and how certain organs become hospitable to disseminated tumour cells to allow the growth of secondary tumours, in turn responsible for the large majority of cancer associated mortality. There is no treatment for metastatic cancer, and those used to treat primary tumours are not only ineffective in controlling metastases, but also carry adverse effects responsible for life changing morbidity; furthermore, recent reports suggest some treatments may indeed potentiate metastasis. Our research focuses primarily on triple negative breast cancer (TNBC) which is the most metastatic of all breast cancer subtypes. There are no targeted therapies for TNBC, due to their hormone receptor negative status, and treatment relies primarily in cytotoxic, systemic chemotherapy. Such treatment is delivered to the tumours through the blood stream, and have significant effects on vascular function, with consequences on the integrity microvascular networks (capillaries) and the building blocks of these unique vessels: endothelial cells (EC). EC behaviour regulates vascular permeability and vessel perfusion, impacting nutrient delivery and thus, organ homeostasis. We have shown that EC activation state is mediated by HIF transcription factors, and this is isoform-, time- and organ-specific (Branco-Price et al, 2012; Reiterer et al., 2019; Reiterer et al, 2022), with HIF-1a exerting a pro-metastatic effect, and HIF-2a anti-metastatic, in preserving vascular integrity.
Project Description: Detailed description of the project	**Preliminary data** recently obtained in our group shows that exposure to chemotherapy significantly alters EC status, including by dramatically decreasig the levels of the vasculoprotective HIF-2a isoform. This results also in a decrease in EC-EC adhesion and loss of barrier function. Additionally, the viability, angiogenic potential, secreted factors and intercellular communication is altered. More importantly, these responses are *organ-specific* and mirrored *in vivo*. **Aims:** The microenvironment of a metastatic organ is essential for disseminated tumour cells to survive and proliferate, and the organ-specific microvasculature has a critical role in the traffic of tumour cells from their site of origin to other tissues, as well as nutrients and signals exchanged within each organ. In the face of limited treatment options that succeed in eliminating the (metastatic) tumour cells, this project aims to elucidate how microvascular cell adaptations to tumour-derived signals and standard of care therapy affect the dissemination, frequency and outgrowth of metastatic lesions. Additionally, we aim to understand to what extent vascular parameters influence organotropism: where metastasis are more likely to form. To that end, this project will: (1) explore how ECsrespond, adapt and/or recover from tumour-derived signals and treatment cytotoxicity; (2) Compare the effects of tumours and treatments on microvascular remodelling in metastatic and non- metastatic organs, to reveal both vulnerabilities and resilience properties, which would

	potentially uncover (3) opportunities for intervention during TNBC treatment, that would protect tumour-free organs from metastatic disease. **Models and experimental approaches:** our group uses a combination of ex vivo (primary cells from murine and human origin, to confirm relevance of EC responses in human cells; this is complemented by using pre-clinical in vivo models or TNBC, which allow contextualising cells responses in complete, relevant and translational models of disease. This project will use a broad range of techniques, from standard tissue culture, western blotting, immunofluorescence, co-cultures and live cell assays, including migration, angiogenesis, permeability, metabolic assays. We will assess and validate cell signalling using secretome screens and ELISA assays, validated by flow cytometry and whole tissue multiplex immunofluorescence. Several core facilities in our centre , including Advanced Imaging, Histology, Flow Cytometry and Genomics, are in place to support and enable the delivery of these aims.
Project Keywords	Metastasis, triple negative breast cancer, metastatic niche, treatment resistance, treatment failure

3.3 Translational Regulation of Innate Immune Response in Cancers

Supervisor	Dr Seyed Mehdi Jafarnejad
Project Overview	The innate immune system plays a significant role in cancer. The mRNA translational control ensures that proteins involved in the immune response are synthesized only when necessary and in appropriate amounts. We aim to investigate if manipulation of the mRNA translation machinery could improve efficacy of anticancer immunotherapy treatments.
Project Description: Detailed description of the project	The innate immune response is the first line of defence against pathogens, providing a rapid and nonspecific reaction to infections. However, this response must be tightly regulated to avoid premature activation or overactivation, which can cause severe damage to the host's tissues and lead to chronic inflammation or autoimmune diseases. One of the key regulatory mechanisms is mRNA translational control. This process ensures that proteins involved in the immune response are synthesized only when necessary and in appropriate amounts, thus ensuring that the immune system can quickly respond to pathogens while minimizing the risk of excessive or inappropriate activation. The innate immune system also plays a significant role in cancer, influencing both tumour development and the body's defence against cancerous cells. It can recognize and destroy tumour cells through mechanisms such as the release of pro-inflammatory cytokines. The overarching objective of this project is to define the role of translational regulation in the dysregulated immunity in cancer cells. Subsequently, we aim to investigate if genetic or pharmaceutical manipulation of mRNA translation could affect tumorigenicity or improve efficacy of anticancer treatments. The outcome of this research could have profound impacts on the design and success of immunotherapy approaches to cancer therapy.
Project Keywords	Cancer, immune system, immunotherapy, mRNA translation anticancer treatments

3.4 Investigating the Impact of Commonly Occurring Blood Cancer Mutations on Innate Immune Signalling

Supervisor	Dr Katrina Lappin
Project Overview	Myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML) are clonal haematological malignancies that can disrupt normal haematopoiesis of multiple myeloid lineages. MDS/AML are frequently diagnosed in the older population (onset >60 years). They are characterised by molecular and/or cytogenetic abnormalities accompanied by peripheral blood cytopenias. Due to the age group affected, treatment can be difficult due to the frailty of the patient and the toxicity associated with therapies currently used. The successes of graft-vs-leukaemia observed following allogeneic hematopoietic stem cell transplant (HSCT) supports the value immunotherapy could have for MDS and AML patients. Biological pathways mediating immune activation or evasion in cancer are becoming apparent. This study will identify some of these pathways in a myeloid malignancy setting and explore the value of using targeted-drugs in combination with immunotherapies for the treatment of MDS/AML. The purpose of this research is to explore immune activation in myeloid malignancies, investigating the role of commonly occurring mutations in immune signalling in a blood cancer setting.
Project Description: Detailed description of the project	**Purpose:** The purpose of this research is to explore immune evasion mechanisms in myeloid malignancies. Aims: i) Deciphering the role of mutant FLT3, IDH2 and EZH2 in MDS/AML immune evasion. ii) Identify additional pathways playing a role in immune evasion. iii) Assess the efficacy of targeted therapies approved for use in AML on immune activation and in combination with immune checkpoint inhibitors. **Background:** Myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML) are clonal haematological malignancies that can disrupt normal haematopoiesis of multiple myeloid lineages. MDS/AML are frequently diagnosed in the older population with a median age of onset >60 years. They are characterised by molecular and/or cytogenetic abnormalities accompanied by peripheral blood cytopenias (PMID: 26614866). Due to the age group affected, treatment can be difficult due to the fitness of the patient and the toxicity associated with therapies currently used. ICIs as monotherapy or in combination with hypomethylating agents are being explored in clinical trial in the relapsed/refractory AML space, however the results have been underwhelming and this is due to a lack of combinations of ICIs with immune modulating drugs and/or a lack of biomarkers to guide the use of ICIs in MDS/AML. My team have identified commonly occurring gain-of-function (GoF) mutations which can upregulate immune signalling when treated with anthracyclines (also now accepted as agonists for cancer cell intrinsic immune signalling), paving the way for these specific mutations to be used as biomarkers to stratify patients into ICI treatment groups. To date, we have shown that when SF3B1 and SRSF2 are mutated (common in MDS/AML) can promote innate immune signalling (Fig.A). Additionally, we have identified some previously unexplored

mechanisms of immune evasion by the AML blast cells. We performed an esiRNA screen of the genes included in the CROP-seq experiment and used an immune cytokine ELISA readout of activation of innate immune signalling. This screen was performed with and without an anthracycline, to see which genes when lost can switch immune signalling off or on, respectively (Fig.B). This has highlighted a possible role for FLT3, IDH2 and EZH2 GoF mutations in immune evasion of MDS/AML cells. Additionally, midostaurin (FLT3), quizartinb (FLT3), enasidenib (IDH2) and tazometostat (EZH2) are now in clinical use for the targeted treatment of MDS/AML harbouring these mutations. When we used these agents to treat cell line models in combination with low dose anthracycline (used clinically as standard-of-care for high-risk MDS and AML), we observed significant up-regulation in the transcription of innate immune gene, CCL5 (Fig.C), and secretion of CCL5 (RANTES) (Fig.D) compared to single agents. These data highlight the possibility to generate novel therapeutic combinations to improve the functionality of ICIsin MDS/AML and improve the results seen in clinical trial.

Brief outline plan of investigation:

WP1 – Deciphering the role of mutant FLT3, IDH2 and EZH2 in MDS/AML immune evasion.

WP2 – Identifying further AML pathways involved in immune regulation/evasion.

WP3 – Immune competent in vivo validation of targets from WP1 and WP2 using the chicken egg chorioallantoic model.

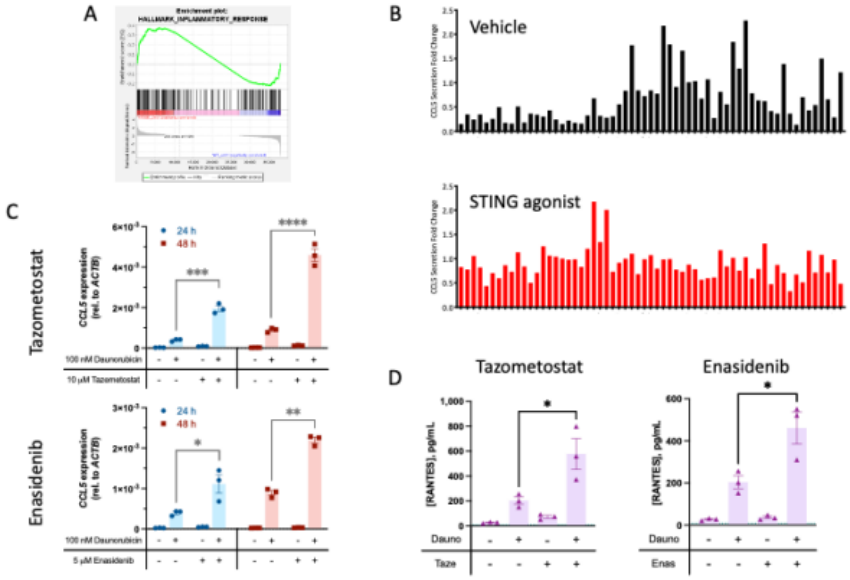


Figure 1 – Immune biology in myeloid malignancies. (A) GSEA showing enrichment of inflammatory pathways associated with the frequently occurring in MDS/AML SF3B1-K700E mutations. (B) esiRNA screen of the most commonly mutated MDS/AML genes with (red) and without (black) an anthracycline. (C-D) Validation of targets from (B) using targeted therapies to reduce activity of mutant protein to recapitulate the

	knockdown from (B) investigating CCL5 transcription (C) and secretion (D). N=3 biological replicates, paired T-tests performed.
Project Keywords	Blood cancers (myelodysplastic syndromes and acute myeloid leukaemia); Immune activation; Immune evasion; Immune checkpoint inhibitors; Genetic screening

3.5 Identifying Cancer Vaccine Targets in Azacitidine-Treated AML

Supervisor	Dr Sarah Maguire
Project Overview	Acute Myeloid Leukaemia (AML) is an aggressive cancer of the bone marrow which disrupts healthy blood production by generating immature and non-functional white blood cells. More than 3,000 people are diagnosed in the UK annually, and 42% of these patients are over 75-years old. While intensive chemotherapy offers a conventional treatment option, its harshness and limited efficacy in specific patient groups, like older adults, necessitates alternative approaches. Azacitidine, a drug that alters DNA methylation patterns, provides a more well-tolerated approach for these patients and is standard of care in combination with venetoclax in this patient group. However, its effectiveness, particularly in TP53-mutant cases, remains limited (Median survival in azacytidine/venetoclax treated AML is 12-18 months), motivating the search for further new well-tolerated treatments which improve outcomes for these patients. Cancer cells have unique proteins (antigens) that can be targeted by the immune system. While vaccines are a promising approach to fight cancer, none exist yet for AML. This project aims to identify new antigens on AML cells treated with a specific drug (azacitidine) to develop a potential AML vaccine. This builds on prior research by AilseVax Ltd, a spin-out company from Queen's University Belfast, that currently has over 40 lead antigens under investigation in colorectal cancer. This project proposal will build on this work to investigate whether the leukaemic cells in AML patients treated with azacitidine display new antigens on their surface and whether these targets would be suitable for vaccine development.
Project Description: Detailed description of the project	To achieve this, the proposed studentship will use cutting edge technologies (including short- and long- read RNA sequencing) to explore how AML cells change on exposure to azacitidine using lab models and samples from azacitidine-treated AML patients available from the NIBiobank. The student will then use the AilseVax AltRNA8V™ computational cancer antigen platform to identify antigens which have the potential to act as new vaccine targets. Finally, the student will test how effective these new antigens are at priming the immune response using pre-clinical *in vivo* models, paving the way for future development of a vaccine that can be administered along with azacitidine to patients.
Project Keywords	Acute Myeloid Leukaemia

3.6 Why Does a Cancer Susceptibility Locus Differentially Influence Risk of Male Versus Female Breast Cancer

Supervisor	Dr Nick Orr and Dr Colin Adrain
Project Overview	**Background** Breast cancer is the most commonly occurring and frequently devastating cancer in the UK, yet its aetiology remains poorly understood. Besides age, genetic susceptibility and reproductive factors are the best-established risk factors for the disease. Although mutations in genes such as *BRCA1*, *BRCA2* and *PALB2* are strongly associated with breast cancer predisposition, they account for only a small proportion of cases overall. In fact, most cases occur sporadically under the influence of multiple genetic, environmental and lifestyle factors. However, how these factors impinge on cancer susceptibility at the molecular level, and how they interact with biological gender, remains largely unknown. We, and others, have recently identified a germline single nucleotide polymorphism (SNP), rs13066793, that is associated with risk of breast cancer. Intriguingly, the minor allele of rs13066793 is associated with a decreased risk of breast cancer in females, but an increased risk of the disease in men. The SNP localises to the first intron of a gene called *VGLL3*, which encodes a transcriptional coactivator implicated in development, differentiation and organogenesis. VGLL3 controls the expression of target genes (e.g. cytokines) that are involved in cell proliferation, apoptosis, and tissue homeostasis. Several studies have shown that dysregulation of *VGLL3* expression can contribute to the development and progression of various types of cancer, including breast cancer, lung cancer, liver cancer. Intriguingly, VGLL3 has recently been implicated in influencing sexual maturation in a sex-biased manner, perhaps explaining the opposite breast cancer risk effects attributed to rs13066793 in males and females. We hypothesise that VGLL3 expression governs critical yet undefined gender-specific cancer risk mechanisms.
Project Description: Detailed description of the project	**Preliminary data** Our preliminary data indicates that rs13066793 localises to a genomic regulatory element (GRE). We have demonstrated, using reporter assays that the genomic sequence demarcated by rs1306793 has sex-biased functional enhancer activity in breast epithelial cells. The enhancer activity is lost following the introduction of the minor allele of rs13066793. We have also shown, using expression quantitative trait locus (eQTL) analysis, that the minor allele of rs13066793 is associated with reduced *VGLL3* expression. This, along with our observations from our epidemiology studies, suggests that increased expression of *VGLL3* is associated with risk of female breast cancer while decreased expression is associated with risk of male breast cancer. **Aims and objectives** In this project we will characterise the genomic mechanisms that influence *VGLL3* expression. We will also define the role of VGLL3 in mammary development, using state of the art organoid models, while its role in

	crosstalk between mammary cells and the cancer microenvironment will be defined using cell culture and organoid models. We will use CRISPR-based genetic perturbation approaches to directly link the GRE to *VGLL3*. We will then identify the VGLL3-associated transcriptional coregulators that bind to rs13066793 using SNP-specific DNA competition pulldown-mass spectrometry approaches, then use allele-imbalanced DNA pulldown assays to detect allele-specific protein binding in different breast-relevant cell lineages. CRISPR knockout models and state-of-the-art genomics approaches will be used to illuminate the VGLL3-directed transcriptome of breast cells thereby nominating key processes and pathways for downstream study. Overall, this PhD studentship will reveal substantial insights into the molecular mechanisms that underpin gender-specific cancer risk factors.
Project Keywords	Breast cancer organoids; Cancer microenvironment; Gender specific cancer risk; CRISPR-based genetic perturbation; Cellular crosstalk in breast cancer

4. RESPIRATORY MEDICINE

4.1 Exploration of Therapeutic Potential of the Engineered Mesenchymal Stem Cells Exosomes in Pre-Clinical Models of Acute Respiratory Distress Syndrome (ARDS)

Supervisor	Dr Anna Krasnodembskaya
Project Overview	In this project we wish to develop the novel unique next-generation stem cell therapy product based on MSC exosomes and iPSC technology which will have superior scaling capabilities for GMP manufacturing. Overexpression of specific factor (previously identified by our group) will enable enhanced therapeutic efficacy of MSC EVs through their capacity to more effectively restore mitochondrial function in recipient cells. Given that mitochondrial dysfunction underpins pathophysiology of multiple diseases as well as the process of aging, translational potential of such product is very high. Collectively, this work will enable further translational development of iPSC MSC cell therapy product, new foreground IP and open opportunities for new collaborations with academic, clinical and industrial partners. This project offers exciting training opportunities for early career researcher in the fast developing field of stem cell based therapies.
Project Description: Detailed description of the project	Acute Respiratory Distress Syndrome (ARDS) is a major cause of acute respiratory failure in critically ill patients requiring mechanical ventilation and is associated with high mortality and morbidity. ARDS has no specific pharmacological therapy and advanced therapeutics based on mesenchymal stromal cells extracellular vesicles are rapidly moving towards clinical translation. Previously we demonstrated that mitochondrial dysfunction in the lung tissue significantly contributes to development of severe lung injury in ARDS while Mesenchymal Stromal Cells (MSC) exosomes are able to improve survival and reduce severity of lung injury at least partially through restoration of mitochondrial fitness in the recipient host cells. Interestingly, we have identified that MSC EVs carry mitochondrial transcriptional co-factor which is capable of enhancing mitochondrial biogenesis. In this project we aim to develop 'engineered' MSC extracellular vesicles overexpressing this co-factor with the enhanced capacity to modulate mitochondrial function in recipient cells and enhanced therapeutic efficacy in ARDS.
Project Keywords	Mesenchymal stem/stromal cells, exosomes, ARDS, iPSCs, mitochondrial dysfunction

5. IMMUNOLOGY AND MICROBES

5.1 Investigating the Role of Gut-Derived Short-Chain Fatty Acids in Macrophage Response to *Non-Typeable Haemophilus Influenzae* and Therapeutic Manipulation by Novel Drug Delivery Systems

Supervisor	Dr Aoife Rodgers and Professor Cliff Taggart
Project Overview	This project will investigate the effects of microbial-derived short-chain fatty acids on macrophage response to *non-typeable haemophilus influenzae* (NTHi), the most common cause of bacterial infection in the lungs of COPD patients.
Project Description: Detailed description of the project	Gut microbial-derived SCFA regulate both local and systemic immune responses and more recently, have been demonstrated to affect the growth of pathogens such as *Pseudomonas aeruginosa.*[2] The levels of SCFA are altered in several diseases including chronic obstructive pulmonary disease (COPD),[3] however, the impact this has with respect to outcome to infection, is currently unknown. Specifically, while it is acknowledged that gut-derived SCFA reach the systemic circulation and bone marrow (BM),[4] the precise mechanistic effects of SCFA on innate immune cells during infection has not been defined. This project will investigate the effects of SCFA on macrophage response to infection caused by the bacterium *non-typeable haemophilus influenzae* (NTHi). NTHi is the most common cause of bacterial infection in the lungs of COPD patients and contributes to episodes of acute exacerbations which are associated with hospitalisation and increased mortality.[5] Primary murine BM-derived macrophages will be utilised for functional and mechanistic *in vitro* studies in the presence and absence of individual and combinations of SCFA to precisely define the signalling mechanisms induced/modulated by SCFA. Such studies will be supported by *in vivo* models of bacterial lung infection induced by NTHi. With knowledge gained from such studies, novel drug delivery systems will be utilised for therapeutic manipulation. **References:** 1. Morrison, D. J. & Preston, T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* **7**, 189 (2016). 2. Ghorbani, P. *et al.* Short-chain fatty acids affect cystic fibrosis airway inflammation and bacterial growth. *Eur Respir J* **46**, 1033–1045 (2015). 3. Bowerman, K. L. *et al.* Disease-associated gut microbiome and metabolome changes in patients with chronic obstructive pulmonary disease. *Nat Commun* **11**, (2020). 4. Boets, E. *et al.* Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. *J Physiol* **595**, 541 (2017). 5. Millares, L. & Monso, E. The Microbiome in COPD: Emerging Potential for Microbiome-Targeted Interventions. *Int J Chron Obstruct Pulmon Dis* **17**, 1835–1845 (2022).
Project Keywords	Short-chain fatty acids; gut-lung axis; microbiome; drug delivery

5.2 Defining the Role of Host Proteins in Rhinovirus Replication

Supervisor	Dr Aurelie Mousnier
Project Overview	This project will determine, though virology, molecular biology and cell biology techniques, the molecular mechanisms by which specific host proteins, which we identified as pro-viral, facilitate rhinovirus replication in cells. In the long term, this knowledge will enable the design of antivirals against rhinoviruses.
Project Description: Detailed description of the project	Rhinovirus infections are the main cause of common colds and a major cause of exacerbation of chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD), leading to an acute worsening of symptoms. However, there is currently no vaccine or antiviral treatment against rhinoviruses. This project will be part of a programme of research in Dr Mousnier's lab, aiming to precisely understand the molecular mechanisms by which rhinoviruses use host cells to replicate, to design new antiviral strategies. It will build on a current MRC-funded project, in which we found that specific host proteins interact with rhinovirus replication proteins and are important for the replication of the virus. The project will analyse, for the most promising host protein hits, the precise molecular mechanisms involved. This will include the identification of the step of the viral replication cycle where the host proteins play a role and the analysis of the molecular interactions involved and their role in viral replication. Through a range of virology, molecular biology and cell biology techniques, this work will uncover new mechanisms by which rhinoviruses subvert host cells to facilitate their replication. In the long term, this knowledge will be used to design novel antivirals.
Project Keywords	Rhinoviruses, host-pathogen interactions, viral replication, molecular mechanisms

5.3 Probing the Signal Transduction Mechanisms Involved in Neuroinflammation Induced by Astrocytes in Response to Substance P

Supervisor	Dr Bianca Plouffe
Project Overview	Neuroinflammation, a condition associated to excessive cytokine production, promotes neuronal death. Astrocytes play a major role in neuroinflammation. Substance P stimulates neurokinin-1 receptor (NK1R) abundantly expressed by astrocytes leading to cytokine secretion. This project aim to identify the transduction mechanisms involved in NK1R-mediated cytokine secretion in the context of astrocytes.
Project Description: Detailed description of the project	Infection to pathogens, neurodegenerative diseases (multiple sclerosis, Alzheimer's and Parkinson's diseases), and brain injuries can cause neuroinflammation, a condition associated to excessive production of cytokines promoting neuronal death. Astrocytes, a type of glial cells in the central nervous system, play a major role in neuroinflammation. These cells express neurokinin-1 receptor (NK1R) and stimulation of NK1R by the neuropeptide substance P secreted by injured neurons induces cytokine secretion by astrocytes. Although the role of NK1R in cytokine secretion by astrocytes is well established, the molecular mechanisms translating NK1R activation into this cellular response remains obscure as it mainly occurs at endosomes rather than at the plasma membrane. The objective of this project is to understand how endosomal NK1R activates nuclear ERK1/2 and NFκB, two major drivers of transcription involved in cytokine production, by investigating: 1. The production of the canonical second messenger diacylglycerol at the membrane of endosomes following stimulation with substance P. 2. The role of phosphatidylinositol-3-phosphate (PI3P), the most abundant phosphoinositide at the membrane of endosomes, as a potential substrate for phospholipase Cβ.
Project Keywords	Neuroinflammation, astrocytes, substance P, signal transduction, neurokinin 1 receptor

5.4 Parasite-Derived Peptides as Regulators of Inflammation and Infection

Supervisor	Professor Cliff Taggart and Dr Aoife Rodgers
Project Overview	Helminth Defence Molecules (HDMs) play an important role in allowing parasites to regulate the human immune response. In this study, we will evaluate the effect of one of these HDM's as a potential treatment for infection and inflammation associated with lung diseases such as Chronic Obstructive Pulmonary Disease (COPD) or Cystic Fibrosis (CF) lung disease.
Project Description: Detailed description of the project	Helminth defence molecules (HDMs) are a family of proteins first discovered within the excretory secretory (ES) products of trematode parasites that can modulate the inflammatory response. We have demonstrated that some of these peptides also exhibit novel immunomodulatory activity in *in vivo* and in *in vitro* co-infection models (*Tanaka A et al, J Allergy Clin Immunol. 2018 Jun;141(6):2316-2319*). The successful student will map the immunomodulatory activity of one of these peptides and evaluate this activity in *in vivo* models of lung infection and inflammation. The student will also determine the mechanism of action of this peptide using co-incubation models of macrophage and bacteria. In addition, the student will spend time with a medical device company (Aerogen) to determine the ability to nebulise this peptide directly to the human lung (*Creane S et al, Eur J Pharm Sci. 2023 Apr 1;183:106398*). There will also be the opportunity to spend time in the laboratory of Professor John Dalton (Science Foundation Ireland Professor) in the National University of Ireland, Galway learning novel assays applicable to the project. The successful student will have the opportunity to learn a range of skills including *in vivo* lung infection and inflammation studies, qPCR, ELISA assays, confocal microscopy and cell-based functional assays. The project outlined above is feasible within the timeframe of the studentship and support will be available from another researcher in the Taggart laboratory working in parallel with the student in a related project.
Project Keywords	Helminth; nebulise; lung infection; inflammation

5.5 Elucidating the Mechanisms of GREM1-Mediating Cancer Cell Signalling in Colorectal Cancer

Supervisor	Dr Derek P Brazil
Project Overview	Gremlin1 (GREM1) is a key protein involved in the development and progression of colorectal cancer. GREM1 is upregulated in many human cancers, including colon cancer, but the mechanisms of how GREM1 drives cancer progression are unknown. This project will decipher the mechanisms of GREM1 signalling and develop new small molecule inhibitors of GREM1 as potential novel anti-cancer drugs.
Project Description: Detailed description of the project	**Background** Gremlin1 (Grem1) is a secreted protein that binds to and antagonizes the action of bone morphogenetic proteins (BMPs). Grem1 binding to BMPs is essential for the normal development of limbs, kidneys and other tissues. Apart from its developmental role, Grem1 is an important protein in a range of human diseases including diabetic kidney disease, lung fibrosis and cancer. High levels of Grem1 expression has been shown to act as a biomarker for a range of cancers (including colon, brain and liver). Indeed, high levels of Grem1 expression match with poor patient survival in triple negative breast cancer and other forms of cancer, suggesting that increased Grem1 expression contributes to more aggressive tumour development. Patients with many forms of colon cancer have high levels of Grem1 in their tumours. The focus of this project is the to define the cellular function of Grem1 in colon cancer and intestinal cells. **Aims and Objectives** 1. To identify novel GREM1 signalling pathways that contribute to tumour growth and cancer formation using colorectal cancer cell culture and mouse models 2. To identify novel GREM1 binding proteins using a proximity biotinylation/mass spectrometry approach 3. To characterise novel GREM1 small molecule inhibitors as potential novel anti-cancer drugs **Techniques** Cell culture, transfection, Western blotting, confocal microscopy, Q-PCR, mouse models of colorectal cancer, immunohistochemistry, smFISH, luciferase assays. **Expected Outputs** This 4-year project is designed for an ambitious, hard-working student, who can expect 2-3 high impact publications and review articles from their PhD. Students will also have the opportunity to present their work at national and international conferences.
Project Keywords	Gremlin1, bone morphogenetic proteins, SMAD signalling, intestine colorectal cancer, epithelial cells, tumour

5.6 Dissecting the Regulation of Antibacterial Responses of Immune Cells Role by Protein Glycosylation

Supervisor	Dr Gunnar Schroeder
Project Overview	Bacterial infections, driven by rising human populations with health conditions, such as diabetes, cause suffering and mortality worldwide. How these conditions modulate antibacterial immunity remains poorly understood. This project will determine how protein glycosylation, a post-translational modification linking protein function and metabolic state, regulates the antibacterial capacity of immune cells.
Project Description: Detailed description of the project	Bacterial infections, a leading cause of suffering and mortality worldwide, are exacerbated by increasing antibiotic resistance and growing populations with health conditions. Macrophages and neutrophils are the first line of defence. Recent research highlights the link between immune cell metabolism and antibacterial responses, making it a potential target for host-directed therapy. However, we still lack a deep understanding of how changes in metabolites translate into protein activity and antimicrobial capacity. Post-translational modifications, e.g. O-GlcNAcylation, are implicated (Chang, 2020); however, which proteins are regulated, their role in the host response and if and how bacteria counteract this to evade immune responses is unknown. The project aims to dissect these mechanisms using interdisciplinary approaches, including infection microbiology, immunobiology, microscopy, gene-editing, and proteomics. We will 1. Engineer cells in which we can control protein glycosylation 2. Perform infections with different pathogens, with and without modulation of glycosylation, and determine the antibacterial response (pathogen survival, phagocytosis…) 3. Determine the glycoproteomes during infection with wild-type bacteria and strains lacking virulence factors 4. Analyse the effect of glycosylation on the function of selected proteins in cell signalling and immune response. You will gain hands-on experience and training in experimental design, data analysis, and communication skills.
Project Keywords	Microbiology, Immunobiology, Bacterial infection, Host-pathogen interaction, Cell biology, Glycobiology, Innate Immune Signalling

5.7 Dissecting the Antimicrobial and Anti-Eukaryotic Weapons of the Human Pathogen *Klebsiella Pneumoniae*

Supervisor	Professor Jose Bengoechea
Project Overview	*Klebsiella pneumoniae* is recognized as a global threat to human health. This project will unveil how *Klebsiella* antagonizes other microbes exploiting the type VI secretion (T6SS) nanoweapon, and identify the conserved toxins required for. The project will also characterize which T6SS toxins are used to blunt the activation of host defenses.
Project Description: Detailed description of the project	*Klebsiella pneumoniae* is one of the pathogens sweeping the World in the AMR pandemic. Despite the clinical importance, we lack a complete understanding of how *Klebsiella* counteracts the activation of our defences and about how *Klebsiella* is able to compete in polymicrobial niches such as the human gut. The Bengoechea laboratory has described and started to characterize the type VI secretion system (T6SS) nanoweapon. This is a system used by bacteria to antagonize competitors by injecting effectors toxins into target species. We did demonstrate its role in antimicrobial and anti-fungal competition, and its role in gut colonization. Only recently, we have unveiled its role targeting the mitochondria to blunt inflammation. Initial bioinformatics approach using artificial intelligence uncovered the diversity of T6SS toxins in *Klebsiel*la and most of them of unknown function/activity, offering the unparallel opportunity to discover new antimicrobial toxins as well as new toxins targeting cell signalling pathways. By probing a collection of 100 strains representing the diversity of *Klebsiella* in terms of AMR and virulence, and 1000 strains from sub–Saharan Africa and leveraging a high-throughput assay challenging eukaryotic cells, and prey *E. coli* we will characterize the diverse portfolio of T6SS toxins. Subsequent work will dissect the function of the most common T6SS toxins found in most strains. This work represents a step-change in our understanding on the tools deployed by a human pathogen to flourish in polymicrobial human tissues.
Project Keywords	*Klebsiella pneumoniae*, type VI secretion system, bacteria and anti-eukaryotic toxins

5.8 To Investigate the Role of Histamine in the Regulation of Neutrophil Phagocytosis

Supervisor	Dr Karim Dib
Project Overview	Histamine regulates human neutrophil phagocytosis by engaging two histamine receptors, the H2R and the H4R. We proposed that histamine produced during periods of infection may boost neutrophil phagocytosis by engaging the H4R and production of histamine by respiratory pathogens may impair neutrophil phagocytosis by hijacking the H2R.
Project Description: Detailed description of the project	**Background**: A hallmark of chronic airways diseases is persistent presence of respiratory pathogens causing an uncontrolled and overwhelming recruitment of neutrophils to the airways. Normally, recruitment of neutrophils to the airways leads to bacterial clearance, but in these diseases, neutrophils fail to eradicate the pathogens and adversely cause airways damage. What disables the bacterial-killing capacity of neutrophils is only partly known. These respiratory diseases are associated with Gram-negative bacteria synthesizing histamine. Thus, production of histamine may be a strategy used by bacteria colonizing the airways to impair neutrophil phagocytosis. **Aim 1: To decipher the molecular mechanisms by which the H_4R and H_2R regulate neutrophil phagocytosis.** 1.1. Investigating the role of the H_4R in intracellular killing of bacteria and phagosome maturation; 1.2. Studying the regulation by histamine of the phagocytic receptors Mac-1; 1.3 Examining the dynamic regulation of the H_2R and H_4R during inflammation; 1.4. Performing quantitative phosphoproteomic analysis of histamine signalling. **Aim 2: To test the role of histamine in mouse neutrophil phagocytosis *in vivo.*** 2.1. Investigating the role of histamine in neutrophil phagocytosis in a mouse model of *P. aeruginosa* airways infection; 2.2. Evaluating the effect of the H_2R antagonist famotidine in a murine model of *P. aeruginosa* airways infection.
Project Keywords	Neutrophils, phagocytosis, histamine, histamine receptors, cell signalling

5.9 Love/Hate Relationship of Achromobacter Species and Human Macrophages: Unravelling a New Model Opportunistic Pathogen

Supervisor	Professor Miguel Valvano, Dr Rebecca Coll and Professor Andriana Margariti
Project Overview	Successful pathogens must overcome innate immune barriers including cells (e.g., macrophages) that engulf and kill bacteria. The biology of pathogen-macrophage interactions in infection-permissive hosts is not well understood. This project will explore the hypothesis that *intracellular pathogens engulfed by macrophages, combined with host underlying defects (e.g., Cystic fibrosis), induce a basal proinflammatory state that becomes deleterious to the hos*t.
Project Description: Detailed description of the project	This interdisciplinary project will use the emerging opportunistic bacterium *Achromobacter* as a new model system to investigate its infection biology in macrophages and develop tools to compare bacterial survival mechanisms and immune evasion in normal and CFTR-defective human macrophages, as non-susceptible and susceptible host-cell infection models, respectively. *Achromobacter* species are increasingly becoming the dominant bacteria recovered from people with CF (PwCF) including those with end-stage lung disease and from infections in people with other immunocompromised conditions. The Valvano group has discovered recently that: **(i)** *Achromobacter* isolates from PwCF and non-CF sources display high-level resistance to last-resort antimicrobial peptides and survive intracellularly in human macrophages, and **(ii)** intracellular survival leads to proinflammatory cell death by pyroptosis, which depends on a functional bacterial Type-3 secretion system (T3SS) engaging the intracellular NLRC4 and NLRP3 inflammasomes. **AIMS–**To address the specific *hypothesis that Achromobacter Type 3 Secretion system components interact with cellular targets and pathways in human macrophages that result in pro-inflammatory responses and intracellular survival* this project will: 1) define the bacterial properties enabling intracellular survival, 2) elucidate the macrophage cellular responses upon infection, especially concerning the activation of the NLRP3 pathway, and 3) establish the role of *Achromobacter*-induced proinflammatory responses in bacterial clearance *vs.* bacterial persistence in CFTR-defective macrophages, which will be used as a susceptible host model. This research lies at the interface of molecular/cellular microbiology and inflammation cell biology. Key methods/strategies include: **(i)** identifying the gene set required for bacterial intracellular survival by high-throughput screen (TnSeq); **(ii)** elucidating the components of *Achromobacter'*s T3SS and the T3SS secretome (identifying effectors by proteomics); **(iii)** characterisation of the *Achromobacter*-containing vacuole (ACV) inside macrophages using state-of-the-art confocal microscopy; **(iv)** elucidating how the NLRP3 inflammasome becomes activated in human macrophages

	in response to intracellular *Achromobacte*r; **(v)** establishing a human *in cellulo* infection model that can be exploited (in future work) for screening of molecules to treat cellular inflammation. Pyroptosis will be confirmed by detecting processed (active) IL-1β in cell supernatants, and caspase-1 and Gasdermin D (GSDMD) cleavage; **(vi)** Examining the proinflammatory potential of *Achromobacter* infection in CF-defective macrophages developed by gene editing technologies on human immature progenitor stem cells (iPSCs).
Project Keywords	Cystic fibrosis, macrophages, bacteria-host interactions, innate immunity, human immature progenitor stem cells

5.10 Exploiting the Protein O'Glycosylation Pathway in Opportunistic Bacteria as a Novel Antimicrobial Target

Supervisor	Professor Miguel Valvano
Project Overview	**The problem.** Antibiotic resistance has become a global health problem of epidemic proportions, especially for infections caused by Gram-negative bacteria. One critical need is to identify novel microbial targets that can be exploited to develop new classes of antimicrobial molecules, which could work alone, or preferably in combination, with existing antibiotics. The most effective antibiotics target central functions of bacterial cells (e.g., protein and cell wall synthesis, DNA replication and transcription). However, post-translational protein modifications have not been explored as antimicrobial targets. Protein glycosylation is a post-translational modification widespread among microorganisms. Recent work by our group has revealed that loss of protein glycosylation in our Gram-negative model bacterium, the opportunistic cystic fibrosis pathogen *Burkholderia cenocepacia*, dramatically reduces bacterial fitness and virulence (Mohamed *et al*; 2019; *J. Biol. Chem.* 294, 13248-13268. These findings suggest protein glycosylation can provide a novel target to reduce the burden of antibiotic resistance. The general protein glycosylation systems in bacteria target multiple membrane secreted proteins, and glycosylation defective mutants display pleiotropic phenotypes that cannot be readily correlated with the loss of glycosylation of any specific protein. For example, loss of general O-glycosylation in *B. cenocepacia* is essential for virulence and swimming motility, but these are complex phenotypes that denote major physiological disturbances in the glycosylation-defective mutants. However, the mechanistic bases underpinning these phenotypes are unknown. We hypothesize that loss of protein glycosylation affects the stability of unglycosylated proteins in the bacterial cell envelope resulting in an unfolded protein response leading to stress, which in turn causes dramatic reduction in cell fitness.
Project Description: Detailed description of the project	This PhD proposal, underpinning fundamental studies at the forefront of microbial glycobiology, molecular biology and glycochemistry research, will address this hypothesis by: 1. Elucidating the mechanism behind the physiological alterations due to loss of protein glycosylation in bacteria. 2. Developing proof of principle that molecules inhibiting protein glycosylation can provide antimicrobial activity. ***Aim 1:*** **Global transcriptomics and proteomics analyses.** The global gene expression of parental *B. cenocepacia* K56-2 strain and its isogenic Δ*ogc* and Δ*pglL* mutants will be compared by RNA-SEQ. RNA samples will be prepared and processed in the Core Unit of the University of Würzburg under the advice of Dr. Franziska Faber, a collaborator. After quality control read preparations (e.g. by FastQC & Trimmomatic), sequence reads will be mapped against the reference *B. cenocepacia* genome (STAR/Bowtie/Subread). The expression values will be calculated as counts

	(HTSeq/Featurecounts) prior to the statistical analysis to determine the differentially expressed genes (voom-limma/EdgeR). To determine the differentially expressed genes, we will apply general lineal models combined with the use of a fold-based cut-off selection. This pipeline will help us to identify up- and down-regulated genes in the mutants vs. the parental strain. These data will be further analysed at a systems level (pathway and co-expression networks) linking pathways and networks with the different phenotypic traits already known for the *O*-glycosylation mutants (e.g. oxidative stress) and those derived from the Biolog phenotypic microarrays (e.g. differential growth in specific carbon sources) and the global proteomic analysis by Dr. Scott. These experiments will employ robust bioinformatic methods, custom software and scripts, assisted by the second supervisor, Dr. Guillermo Lopez Campos. ***Aim 2:*** **Are the non-glycosylated proteins degraded?** Preliminary analyses of null glycosylation strains suggest processing of glycoproteins in the absence of glycosylation raising the hypothesis that loss of *O*-linked glycosylation leads to protease sensitivity of the unglycosylated proteins. We will use MS-based degradomics approaches to probe protein stability and half-life on a proteome scale. This work will be conducted by the PhD student under the guidance of our Australian collaborator, Dr. Nichollas Scott, and will involve a short stay of the PhD student at the University of Melbourne. To measure protein degradation, the endogenous peptides in the bacterial cells, which result from the turnover of proteins, will be enriched and subjected to LC-MS/MS analysis. Further, the selective enrichment of protein cleavage events will be monitored using the N-terminal amine isotopic labelling of substrates (N-TAILS) previously used by Dr. Scott to probe protein cleavage changes in response to apoptosis. To assess protein turnover, pulse chase experiments will utilise SILAC labelling. We will also generate diaminopimelate decarboxylase (LysA) and argininosuccinate lyase (ArgH,) mutants in *B. cenocepacia* K56-2 to allow for the incorporation of isotopically labelled amino acids. This approach, also established in the lab of Dr. Scott, facilitates assessing the incorporation rate and subsequent protein turnover rates at the proteome level. These experiments will be complemented by targeted studies in the Valvano lab undertaken with endogenous tagging experiments (e.g. with NanoLuc luciferase) to assess the role of glycosylation on specific proteins observed to change at proteomic and degradomics levels. Endogenously tagged proteins will be monitored by immunoblot, followed by purification and protein characterization by MS or alternative by fluorometry. To investigate the role of individual glycosylation sites in proteolysis, site-directed mutagenesis will be undertaken replacing the serine glycan acceptor residue by alanine. Disruption of glycoproteins of interest will be undertaken and comparative proteomics used to assess if these proteins are driving the changes associated with the loss of glycosylation. PhD candidates will join a **vibrant, world-class** team engaged in **interdisciplinary studies** on microbial pathogenesis using molecular biology, structural, biochemistry, and cell biology approaches, and are strongly advised to consult the following links

	(http://publish.uwo.ca/~mvalvano/Advice-to-grads.html) and (http://publish.uwo.ca/~mvalvano/index.html) for additional information on what to expect in the Valvano lab.
Project Keywords	Protein glycosylation, proteomics, transcriptomics, cystic fibrosis, Burkholderia, antimicrobial resistance

5.11 Bacterial Lipocalins: Novel Role in Bacterial Protection Against Antibiotic-Induced Membrane Lipid Peroxidation

Supervisor	Professor Miguel Valvano
Project Overview	We recently discovered that bacteria can resist antibiotics by mechanisms operating extracellularly in response to near-lethal antibiotic concentrations. This means microbes fight antibiotics even before they reach bacterial cells. Key molecules involved in this mechanism are the polyamine putrescine and lipocalins (LP), a highly conserved group of barrel-shaped proteins of unknown function produced by >6,500 bacterial species. We demonstrated LPs scavenge different classes of antibiotics from the extracellular milieu. Also, LPs bind isoprenoids (e.g. octaprenyl-phosphate) into the interior of the barrel, while low-affinity antibiotic binding occurs at the rim of the molecule. The physiological role of LPs remains unknown. Bacteria exposed to near-lethal antibiotic concentrations (e.g. during treatment of chronic and biofilm infections), also mount an oxidative response, which in turn stimulates transcription of LP encoding genes. We have now discovered that bacterial mutants defective in LP production display enhanced membrane lipid peroxidation and fail to survive under conditions that stimulate peroxidative stress. This means that LPs may have a novel role in protecting bacteria against toxic byproducts of lipid peroxidation. How bacterial cells overcome lipid peroxidation, especially the double membraned Gram-negatives, is virtually unknown. Our experimental results bridge this knowledge gap and uncover LPs as components of a novel mechanism to protect bacterial cell membranes from lipid peroxidative damage.
Project Description: Detailed description of the project	This programme will address two questions: (i) What are the structure-function properties of diverse LPs involved in antibiotic binding and protection against lipid peroxidation? and (ii) What other bacterial components are needed for protection against lipid peroxidation? The model bacteria employed are the Gram-negative members of the ESKAPE group, namely *Klebsiella, Acinetobacter, Pseudomonas and Enterobacter* species. This research project combines molecular microbiology, biochemistry, metabolomics, bioinformatics, and infection models to elucidate the role of LPs in antibiotic binding and in maintaining the homeostasis of the bacterial membranes under oxidative stress, commonly found upon exposure to near-lethal doses of antibiotics. The PhD student will investigate the function of LPs in the bacterial defences against lipid peroxidation by tackling 3 aims: 1. To determine the structure-function of LP and its secretion state in protection against lipid peroxidation 2. To identify and characterise additional components to LP required to protect bacteria from lipid peroxidation upon exposure to antibiotic stress and *in vivo* infection 3. To assess the global effects of LP and related proteins in bacterial physiology by comparative transcriptomics on mutants *vs.* the parental strain pairs both exposed to sublethal concentrations of antibiotics.

	PhD candidates will join a **vibrant, world-class** team engaged in **interdisciplinary studies** on microbial pathogenesis using molecular biology, structural, biochemistry, and cell biology approaches, and are strongly advised to consult the following links (http://publish.uwo.ca/~mvalvano/Advice-to-grads.html) and (http://publish.uwo.ca/~mvalvano/index.html) for additional information on what to expect in the Valvano lab.
Project Keywords	Antibiotic resistance, lipid peroxidation, RNAseq, metabolomics, protein structure-function, lipocalin, outer membrane, Gram-negative bacteria, stress responses, mass spectrometry, bioinformatics

5.12 Macrophage-Bacteria Interactions in Cysctic Fibrosis: The Cellular Microbiology of the Novel Opportunistic Bacterium Achromobacter Species

Supervisor	Professor Miguel Valvano
Project Overview	Chronic infection and persistent inflammation in people with cystic fibrosis (PWCF) lead to progressive lung damage. Despite novel therapies to correct the CFTR disfunction chronic antibiotic treatments, compounded with extended life expectancy of PWCF, challenge the ecology of the lung microbiome and gives rise to the emergence of potential new pathogens displaying multidrug antibiotic resistance. Of these, *Achromobacter* sp. are particularly concerning since they are often the dominant bacteria recovered from sputum samples in an increasing number of PWCF including those with end-stage lung disease and they are also commonly found in the airways' microbiome. We understand little about the association of *Achromobacter* with lung disease and lack information on pathogenic traits of *Achromobacter* sp. and their ability to interact with innate immune cells (e.g. macrophages, neutrophils), as well as an overall lack of information on the biology of these bacteria. The overarching objective of this project is to understand the cellular microbiology of *Achromobacter* infections.
Project Description: Detailed description of the project	Our group has recently demonstrated that *Achromobacter* CF isolates can survive and replicate in human monocytic macrophages by surviving in a modified phagolysosome, and also that the intracellular infection results in macrophage pro-inflammatory cell by pyroptosis. The mechanistic details of how this occurs are unknow, and also unknown are the bacterial factors involved in promoting inflammation. This project has 2 objectives: 1) identifying the bacterial properties associated with intracellular survival 2) elucidating the macrophage cellular responses upon *Achromobacter* infection, especially in terms of proinflammatory responses and in particular, in human CF-defective cells. To address objective (i) the PhD student will identify the bacterial properties involved in survival by a two-pronged approach. First, a candidate gene-based strategy to mutagenize genes suspected to be involved in intracellular survival (Primary targets include genes of putative Type III, IV and VI systems, O antigen and capsule biosynthesis clusters and several haemolysin-like genes. Second, in parallel, the PhD student will use an unbiased approach based on high-throughput transposon mutagenesis employing various systems (e.g. plasposons, TnSeg, Tradis). Mutants will be tested for intracellular survival using macrophages seeded in microtiter plates and the phenotypes further validated by genetic complementation. These experiments will identify genes involved in cell entry and intracellular survival using fluorescent microscopy and biochemical analyses, as appropriate. To address objective (ii), the student will characterize the inflammatory response in macrophages upon *Achromobacter* infection in normal and

	CFTR-defective human cells. These studies will employ a variety of approaches including but not limited to cytokine profiling, pathway inhibitors, and a new developed microscopic assay to image, detect, and quantify inflammasome complexes in cells, as well as a various cell biology approaches to precisely identify the properties of the *Achromobacter*-containing vacuoles in macrophages. These studies will be complemented with setting up a mouse model of *Achromobacter* infection in lungs. PhD candidates will join a **vibrant, world-class** team engaged in **interdisciplinary studies** on microbial pathogenesis using molecular biology, structural, biochemistry, and cell biology approaches, and are strongly advised to consult the following links (http://publish.uwo.ca/~mvalvano/Advice-to-grads.html) and (http://publish.uwo.ca/~mvalvano/index.html) for additional information on what to expect in the Valvano lab.
Project Keywords	Macrophage, cystic fibrosis, intracellular survival, inflammation, pyroptosis, virulence factors, CFTR, opportunistic bacteria, lung infection, microbial pathogenesis

5.13 Elucidation of Innate Immune Responses to Respiratory Virus Infection in Airway Epithelium as a Function of Age

Supervisor	Professor Ultan Power
Project Overview	Respiratory viruses cause substantial morbidity and mortality worldwide, particularly in the very young and old. Most viruses target the airway epithelium. Innate immune responses of the epithelium following infection likely triggers the immune-mediated pathogenesis responsible for disease symptoms. This project aims to understand how these responses vary as a function of age, which may provide insights into susceptibility to severe disease.
Project Description: Detailed description of the project	Respiratory viruses, such as RSV or SARS-CoV-2, are responsible for enormous morbidity and mortality worldwide and place a huge burden on health care systems. The largest burden of disease for most respiratory viruses occurs in the extremes of age (young infants and the elderly). The airway epithelium is the primary target of infection for most respiratory viruses and innate immune responses in these cells likely play an important role in controlling disease severity. Using our well-differentiated primary airway epithelial cell (WD-PAEC) culture models of RSV infection, we previously demonstrated that innate immune responses to infection of airway epithelium are more robust with chronological age in young infants. However, we do not know whether a similar situation applies to airway epithelium from healthy adults or the elderly. Therefore, in this project we will generate WD-PAECs from the elderly, young infants, and healthy adults and determine whether the type and robustness of innate immune responses to respiratory virus infection differ as a function of age. We will employ well validated techniques, such as OMICs (NGS, proteomics), multi-analyte BioPlex assays, RT-qPCR, immunofluorescence/confocal microscopy, and virus titrations, to study whether extremes in age influence cytopathogenesis and differential gene and protein expression to infection, with particular emphasis on innate immune response pathways. Ultimately, this project will shed light on increased susceptibility to severe respiratory virus infections at the extremes of life.
Project Keywords	Airway epithelium; respiratory viruses; RSV; innate immunity

5.14 Using the Immune System to Repair Tissue Damage in the Brain

Supervisor	Dr Yvonne Dombrowski
Project Overview	To develop novel regenerative therapies, understanding the crosstalk between immune and regenerative mechanisms is crucial. This project at the interface of neuroscience, immunology and tissue regeneration, will use immune mechanism to direct the regeneration of damaged brain tissue. This will benefit patients with neurodegenerative diseases such as multiple sclerosis, dementia, and patients with brain injury.
Project Description: Detailed description of the project	In multiple sclerosis (MS), the myelin sheath covering neuronal axons is destroyed resulting in neurodegeneration and permanent disability. There is no cure for MS to date and patients will live with this debilitating disease for the rest of their life. Current treatments can alleviate symptoms but cannot fully stop disease progression nor repair the damage in the brain and spinal cord of MS patients. Novel therapeutic strategies are urgently needed that promote myelin regeneration. These therapies have huge potential to prevent disability and restore function in patients. We have shown that the immune system plays a critical role in myelin regeneration (Dombrowski et al 2017 NatureNeuro, Guzman de la Fuente et al, 2024 NatureComms). Yet, we still barely understand how these complex immune mechanisms direct and promote myelin regeneration on a molecular and cellular level. Understanding these underlying immune mechanisms in myelin repair and how to use them to support repair holds great potential for future MS therapies. This project will investigate how immune mechanisms regulate the regenerative response after myelin damage and stimulate the brain cells that can regenerate myelin. The aim of this project is to identify potential novel molecular and immune targets that can boost myelin regeneration for potential future therapies. To achieve this, preclinical MS models, brain in-a-dish and in vitro models of brain cells will be used to manipulate immune mechanisms to investigate the impact on myelin repair on molecular and cellular level. With our clinical collaborators, we will also use human MS samples to determine if pro-regenerative immune mechanisms are altered in patients with MS. The focus of this project will be on inflammasomes that have recently been linked to regulate immune mechanisms in animal models of MS (Chou et al Nature 2021, Ma et al 2021, JExpMed). **Objectives:** 1. Determine how AIM2 inflammasome regulates brain cells 2. Identify the AIM2-mediated molecular mechanisms in myelin repair 3. Modulate AIM2 inflammasome pathways in human oligodendrocytes to promote myelin generation

Project Keywords	Neuroimmunology, tissue repair, multiple sclerosis, neuroscience, neurodegeneration, immunology, inflammation, tissue regeneration, regenerative immunology, brain repair, stem cells, MS, dementia, brain damage, experimental medicine,

5.15 Generating and Validating a Novel Human 3D-Brain Cell Culture System as a tool for Neuro-Immune Research

Supervisor	Dr Yvonne Dombrowski
Project Overview	There is a gap in readily available human brain culture systems that can replace animal models and do not require specialist resources. This project will develop a novel tool to study human brain cells using a commercially available stem cell line. The model could serve as a link between early pre-clinical and clinical studies and as a (semi-)high throughput screening tool for potential targets for neurological research such as for MS, neurodegeneration, dementia and Alzheimer's.
Project Description: Detailed description of the project	This project aims to generate a novel human brain glial culture model from a human neural stem cell line as a replacement for commonly used animal-derived glial cultures. This could vastly reduce animal use in neuroscience and act as a tool linking preclinical to clinical studies. **Objectives:** **1. Establish and characterise a 3D glial culture from human neural stem cells (hNSC)** Individual brain cell types present in murine mixed glial cultures (e.g. neurons, oligodendrocyte progenitor cells, oligodendrocytes, astrocytes) will be generated from hNSC in their specific differentiation condition. Differentiated cells will be detached and combined in a step-wise process combining those with similar maintenance conditions first. Once viability and stability is confirmed the next brain cell type will be added and so on. A variation of culture conditions and kinetics will be tested at each level to ensure viability of the increasingly complex 3D glial culture. **2. Establish brain cultures with modified gene expression** Animal-derived glial cultures are often generated from genetically altered mice to investigate the function of a specific gene. As a proof- of-principle, we will knock out gene expression in hNSC by CRISPR/cas9 before differentiating cells and then combining them. Stability of k.o. and cell type will be tested along the way. **3. Application of the new tool: Do human regulatory T cells (Treg) promote oligodendrocyte differentiation?** To show its applicability in neuro-immune research, we will use the model to test our findings from our previous study in the mouse showing that Treg promote oligodendrocyte differentiation (Dombrowski 2017, NatNeuro).
	Neuroscience, neuroimmunology, stem cells, CRISPR/cas9, MS, glia, brain cells, dementia, neurodegeneration, Alzheimer's

5.16 Deciphering the Role of the E3 Ubiquitin Ligase Pellino-2 in COPD

Supervisor	Professor Paul Moynagh and Dr Aoife Rodgers
Project Overview	This project will investigate the molecular mechanisms through which the E3 ubiquitin ligase, Pellino-2, plays a role in COPD pathogenesis.
Project Description: Detailed description of the project	Pellino1, Pellino2 and Pellino3 form a family of E3 ubiquitin ligases that have been implicated in the regulation of innate immune signalling pathways including that employed by IL-1. IL-1 signalling is an important component in the development of emphysema and COPD, for which there is no known cure. This project will investigate the role of Pellino-2 in the development of COPD. Our preliminary data suggested that Pellino-2 plays a key role in the development of emphysema, the effects of which are mediated through neutrophil-induced inflammation. We will determine the molecular mechanisms through which Pellino-2 is mediating its affects. Primary murine bone-marrow derived neutrophils will be utilised for molecular and functional studies, in combination with an *in vivo* elastase-induced emphysema model to decipher the precise signalling mechanisms involved. The successful applicant will be integrated into QUB research groups of experienced researchers with access to world-leading facilities. The PhD student will be encouraged to engage in a variety of impact activities, including participation at local, national, and international conferences, and publication of scientific papers in peer reviewed journals.
Project Keywords	ubiquitin ligase; Pellino 2; COPD; infection; neutrophils

6. ORAL HEALTH

6.1 ExPloring the oRal health care needs of older pEople Living with neUrodegenerative Disease at homE (PRELUDE)

Supervisor	Dr Gary Mitchell and Professor Gerry McKenna
Project Overview	There is a paucity of investigation around the oral health needs of older people living with neurodegenerative disease at home. The PRELUDE study will provide the candidate with the opportunity to undertake novel research through a scoping review, a cross-sectional survey, semi-structured interviews and a modified Delphi technique.
Project Description: Detailed description of the project	**Background:** Despite clinical evidence of poor oral health and hygiene in older people living with neurodegenerative disease (e.g., dementia and Parkinson's disease) at home, there is presently a paucity of research that has sought to explore the oral health needs of this population. **Aim:** The aim of this study is to explore the oral health care needs and experiences of older people living with neurodegenerative disease at home. **Objectives:** There are four research objectives (RO). RO1: Scoping review of the international literature on the oral health care needs of older people living with neurodegenerative disease at home. RO2: Using existing supervisory networks, carry out a five-country (UK & Ireland) cross-sectional survey using the validated OHIP-14 to determine oral health related quality of life in approximately 150 people living with neurodegenerative disease at home. RO3: Using findings from RO2, carry out a five-country-wide patient-public consultation, with approximately 12-15 dyads, to explore the experiences of older people (and their carers) living with neurodegenerative disease about oral health. RO4: A five-country wide extended stakeholder consultation with patient/family representatives and professional experts to determine priority areas for people living with neurological disease at home in relation to oral health using a modified Delphi survey.
Project Keywords	Oral Health, Neurological Disease, Quality of Life, Community Care, Mixed Methods Research

6.2 Addressing Oral Health for Older Adults in Care Homes

Supervisor	Professor Gerry McKenna
Project Overview	This project will develop and pilot test nutritional interventions for older adults which better consider their oral health. The intervention will be co-designed with care homes residents, care home staff and managers.
Project Description: Detailed description of the project	Prevention and management of malnutrition in care homes is a significant clinical challenge meaning that residents are often provided with diets rich in complex carbohydrates, including sugars, plus additional sugared medications and oral nutritional supplements to increase caloric intake. However, this creates a significant problem for oral health as the causal link between sugar intake and dental caries is well established. Epidemiological changes have meant that the majority of older adults within care homes now retain their natural teeth, giving rise to a partially dentate care home population who are very susceptible to dental disease as their ability to manually clean their teeth declines. Currently the oral health of care home residents is significantly worse than their community living peers, with a very high prevalence of dental caries and periodontal disease. This results in pain, discomfort and negative impacts on oral function and quality of life. Poor oral health may also exacerbate a range of medical conditions including aspiration pneumonia and delirium, increasing healthcare costs and leading to poorer overall outcomes. This project will develop and pilot test nutritional interventions for older adults which better consider their oral health. The intervention will be co-designed with care homes residents, care home staff and managers.
Project Keywords	Older adults, oral health, nutrition

6.3 Exploring the Potential Oral Health Benefits of Indigenous Medicinal Plants as Alternatives to Antimicrobials

Supervisor	Dr Chen Situ & Professor Gerry McKenna
Project Overview	Antimicrobial resistance (AMR) has been declared by WHO as one of the top global public health threats facing humanity. Misuse and overuse of antimicrobials are the main drivers in the development of drug-resistant pathogens. This project aims to evaluate phytochemicals in the oral environment as safe, effective, and sustainable antibiotic alternatives to combat AMR.
Project Description: Detailed description of the project	The widespread use and heavy reliance on antimicrobials across human and veterinary medicine as well as agricultural food production have inevitably resulted in the emergence of AMR which is now one of the biggest threats to healthcare systems worldwide including dental health. AMR is a significant issue in dentistry due to over prescription of antibiotics for dental infections. There are also other bacterial infections which can occur in the mouth including periodontitis and caries which are bacterial driven chronic inflammatory conditions leading to natural tooth loss. Reducing unnecessary use of antibiotics to preserve effectiveness of existing antimicrobials, and utilising antibiotic alternatives are among the current global actions to combat AMR. The continual use of herbal medicines to date in many parts of the world supports the anecdotal effectiveness of phytochemicals against human and animal infections. Recent scientific evidence suggests that medicinal plants and their phytochemicals possess potent antibacterial properties again many pathogenic bacteria including their resistant strains. This project seeks to provide scientific evidence of the efficacy of plant substances (phytochemicals) against dental bacteria and to elucidate their underlying antibacterial mechanisms using contemporary scientific tools and advanced technological platforms interlinking different disciplines of dentistry, microbiology, biochemistry, molecular biology and biotechnology.
Project Keywords	Oral health, periodontal disease, caries, AMR, phytochemical, medicinal plant

7. EYE HEALTH

7.1 Optimising Delivery of Ophthalmology Services

Supervisor	Dr David Wright
Project Overview	Demand for Ophthalmology services is growing, driven by aging populations and the development of new treatments for chronic eye diseases. The most prevalent sight-threatening conditions, glaucoma, diabetic retinopathy and age-related macular degeneration all require regular monitoring to ensure that treatments are given in a timely manner. One of the main classes of medication, anti-VEGF drugs, may be needed for many years on a monthly basis, administered by injection into the eye. In the UK, Ophthalmology is the busiest specialty for outpatient activity and clinics are overloaded with little prospect of increasing capacity. Excessive demand can lead to an overstressed workforce and poor staff retention and there is evidence that patients are losing vision due to delayed treatment. In future, home-monitoring of chronic conditions may be part of the solution, with manufacturers building small imaging devices that patients can use at home, with AI-driven analysis software to automatically flag problems. At present, these solutions are not suitable for wide-scale deployment.
Project Description: Detailed description of the project	This project is focused on using technology to optimise Ophthalmology services, **improving outcomes within the available resources**. Each year, approximately 10% of patient appointments in Ophthalmology are missed due to non-attendance and patients with persistent non-attendance are far more likely to suffer serious complications and lose vision, increasing clinic demands still further. Several socio-economic factors are associated with risk of non-attendance but one area that has received little attention is competing time demands; patients may not attend because the appointments they receive clash with work or other commitments. In this project the student will investigate whether giving patients greater choice in booking their appointments can increase attendance and improve health and economic outcomes. This will be achieved through parallel work packages. • A scoping review of the influence of time constraints on attendance at ophthalmic appointments. • Retrospective analysis of records from ophthalmic clinics (e.g. glaucoma service, macular service, diabetic eye screening service) to estimate the attendance rate and explore factors associated with non-attendance. • Simulation modelling to determine the clinical and economic costs of missed appointments annually and the likely benefits of increasing attendance. • A trial comparing performance of a prototype online booking system with the current standard booking system in terms of attendance rate. This project would suit a student with an interest in digital healthcare and learning advanced programming and analytical techniques.
Project Keywords	Health services research; statistical analysis; digital health; simulation

7.2 Identifying Novel Biomarkers and Risk Factors for Age-Related Eye Disease

Supervisor	Dr Ruth Hogg
Project Overview	Age-related eye disease is a significant contributor to disability and reduced quality of life in older age. We wish to identify novel biomarkers of age-related eye disease and determine the burden of disease within the population attributable to these diseases within the Northern Ireland Cohort for the Longitudinal Study of Aging (NICOLA).
Project Description: Detailed description of the project	**Background:** Multi-disciplinary longitudinal epidemiological studies provide the opportunity to explore risk factors for development or progression of disease and the development of novel biomarkers to aid diagnosis and prognosis. NICOLA is an ongoing population-based epidemiological study that has recruited 8,500 participants from across Northern Ireland, followed for nearly a decade. At baseline and wave 3 they underwent multi-modal retinal imaging as well as other health assessments. This data combined with the medical history, lifestyle, demographic, genetic and blood-based biochemistry provides a very rich dataset to explore the development and progression of diseases such as age-related macular degeneration or diabetic retinopathy. Strong links with EEECS Computer Vision group enable students to develop novel imaging biomarkers or Artificial Intelligence/Machine Learning approaches. This provides the opportunity to craft a project to a student's interest potentially including a comparative component from the student's own country. **Aim:** to identify novel biomarkers of age-related eye disease and determine the burden of disease within the population attributable to these diseases within NICOLA. **Objectives:** • Use the NICOLA longitudinal dataset to design a study focused on novel risk factors or biomarkers for age-related eye disease. • Adopt innovative methodologies including machine learning to identify novel relationships within the high-dimensional data. A project can be developed to suit the interests, skills and career goals of the student with full training provided in new methods.
Project Keywords	Age-related macular degeneration, ophthalmology, Diabetic Retinopathy, machine learning, epidemiology, artificial intelligence

8. DRUG DELIVERY AND BIOMATERIALS

8.1 3D-printed Implantable Long-acting Drug Delivery Systems for the Treatment of Chronic Conditions

Supervisor	Dr Eneko Larrañeta
Project Overview	This project targets the problem of treatment non-adherence seriously affecting patients with chronic conditions like schizophrenia, Parkinson's, HIV, and Alzheimer's. Moreover, this issue costs the NHS £500M/year. The project aims to develop implantable long-acting drug delivery systems through 3D-printing technology to adapt the system to patient's needs.
Project Description: Detailed description of the project	Non-adherence to treatment can cost up to £500M/year, impacting patients with chronic conditions such as schizophrenia, Parkinson's, HIV, and Alzheimer's. Also, non-compliance reduces patients' quality of life and can lead to premature death. Accordingly, there is an urgent need for systems capable of prolonged, unattended drug administration. **Aim:** This PhD project aims to develop implantable long-acting drug delivery systems using 3D-printing, enabling personalized dosage forms tailored to patient needs and precise release profiles for effective therapy delivery. The project will focus on delivering two representative compounds: risperidone and tizanidine, used to treat schizophrenia and spasticity in multiple sclerosis, respectively. **Objectives:** • Develop/validate HPLC methods for quantifying tizanidine and risperidone. • Develop implants containing risperidone and tizanidine using various 3D-printing methods. • Characterize the implants through techniques like thermal analysis, FTIR, X-ray diffraction, SEM, Raman microscopy, and acoustic microscopy. • Assess in vitro drug release from the implants. • Evaluate *in vivo* drug release using a rat animal model. The student will have a unique opportunity to work on a novel and challenging project at the interface of formulation science and pharmaceutical engineering, providing them with a distinctive set of complementary skills and enhancing their career prospects augmenting their CV and informing their career choices.
Project Keywords	3D-printing, implantable devices, sustained drug delivery, chronic conditions, adherence to treatment

8.2 Development of 3D-printed Intra-Oral Devices for the Treatment of Dry-Mouth

Supervisor	Dr Eneko Larrañeta
Project Overview	This project seeks to develop 3D-printed intra-oral devices capable of providing lubrification and release of active compounds such as fluorine ions and antimicrobial agents into the oral cavity. This is a highly multidisciplinary project combining different areas of expertise such as dentistry, biomaterials and pharmaceutical-sciences
Project Description: Detailed description of the project	Dry-mouth, or xerostomia, is a condition in which the salivary glands of the patient do not produce enough saliva to keep the oral cavity wet and hydrated. This condition can be due to Sjögren's syndrome, a side effect of certain medications or radiation exposure during cancer treatment. Due to the protective effect of saliva, the quality of life in patients suffering from dry mouth is poor and they are severely affected by dental disease particularly dental caries. In this project we propose to develop 3D-printed intra-oral devices to treat this condition. These devices will be designed to fit the mouth of the patient specifically. For this purpose, two different types of 3D-printing will be used: fused deposition modelling and digital light processing. FDA approved materials such as poly(lactic acid) and dental resins will be used to prepare these devices. The resulting devices will provide lubrification. Moreover, the formulation will contain different cargos such as fluorine ions and antibacterial agents to prevent tooth decay. The resulting systems will be characterised, and its antimicrobial properties and biocompatibility will be evaluated. In addition to 3D-printing this project will cover techniques such as spectroscopy, microscopy (optical and electronic), microbiological evaluation and cytocompatibility assays.
Project Keywords	Dry-mouth; 3D-printing; Intra-oral devices

8.3 Innovative Long-acting Drug Delivery Systems for Treating Ocular Diseases

Supervisor	Professor Raj Thakur
Project Overview	Globally, 285 million people suffer from visual impairment, with prevalent eye diseases like age-related macular degeneration, diabetic retinopathy, glaucoma, and cataract. Our project aims to develop innovate long-acting drug delivery systems targeting the eye diseases, enhancing treatment effectiveness.
Project Description: Detailed description of the project	This project aims to develop innovative, long-acting drug delivery systems for treating eye diseases, utilizing gel-based formulations loaded with drug-containing nano/microparticles. Our focus encompasses the design, fabrication, physicochemical characterization, and in vitro evaluation of these novel delivery systems. Key objectives include: 1. **Material Selection and Characterization:** Comprehensive assessment of candidate materials for production of effective delivery systems. 2. **Mechanical Performance Evaluation:** Using novel ex vivo models to assess the mechanical properties and performance of the formulations. 3. **Drug Release Modelling:** Conducting mathematical modelling to predict and optimize drug release profiles from the developed formulations. 4. **Long-Term Stability Assessment:** Investigating the stability of drugs within the implants over an extended period. 5. **Biodegradation and Biocompatibility Studies:** Evaluating the implants' biodegradation process and ensuring compatibility with ocular tissues. By achieving these objectives, our goal is to advance the development of efficient and safe drug delivery systems tailored for treating eye diseases. This research holds promise in enhancing therapeutic outcomes and patient compliance through sustained drug release mechanisms.
Project Keywords	Biologics, Controlled drug delivery, Sustained release, Long-acting, Implants

8.4 3D Printed Based Drug Delivery Systems for Local Treatment of the Oral Cavity

Supervisor	Professor Dimitrios Lamprou
Project Overview	The project involves the development of an advanced drug delivery system by 3D printing for the delivery of drug(s) through the surface of the patients' oral mucosa. In this project, different 3D printed systems, such as microneedles & patches will be investigated.
Project Description: Detailed description of the project	The conventional methods of drug delivery require repeated dosing in the oral cavity due to the presence of saliva. Therefore, "implantable" devices that could provide sustained release of the drug in the oral cavity is needed. Microneedle (MN)-mediated drug delivery systems (DDS) and patch systems have been developed to enable patients to painlessly administer therapeutic micro- and macromolecule drugs. A wide range of designs including solid metal or polymeric or hallow microneedles, and reservoir or matrix patches. 3D printing process was patented in 1986; however, only in the last decade has been used for medical application, and has been utilized in the fields of prosthetics, bio-fabrication, and pharmaceutical printing. The aim of this project is to develop 3D printed systems of various designs using advanced additive manufacturing technologies. The printing capabilities of suitable polymer grades will assess in terms of flexibility, mechanical strength and drug efficiency. Furthermore, printed patches will be evaluated both *in vitro* and *in vivo* to investigate release patterns, drug loading, stability and clinical effectiveness.
Project Keywords	Microfabrication, microneedles, patches, oral applications, drug delivery

8.5 Regulation of CaaX Protein Processing

Supervisor	Dr James Burrows
Project Overview	USP17 is required for proper localisation of multiple CaaX proteins (H/N-Ras, Rho, Rac1, Cdc42). We have shown that USP17 regulates Ras converting enzyme (RCE) 1 isoform 2, a protease which processes CaaX proteins. This project will further explore the role of RCE1 isoform 2, and USP17, in CaaX protein regulation.
Project Description: Detailed description of the project	USP17 is over-expressed in a range of primary tumours including NSCLC, breast, colorectal, cervical, ovarian and osteosarcoma and its depletion has been shown to block the growth of cells from all these cancer types, as well as the migration of a range of cancer cells. We have been working to further elucidate the function of USP17 to help understand how targeting it would impact cancer cells. We have shown that depleting USP17 blocks proper localisation of CaaX proteins such as H/N-Ras, Rho, Rac1, and Cdc42, all of which have been strongly implicated in cancer progression. In addition, we have demonstrated this is mediated via USP17 regulating a novel isoform of Ras converting enzyme (RCE) 1, which is involved in processing CaaX proteins. USP17 facilitates the trafficking of RCE1 isoform 2 out of endoplasmic reticulum (ER) indicating it is involved in trafficking RCE1 isoform 2, and possibly CaaX proteins. Therefore, this project will further investigate the role of USP17 in RCE1 isoform 2 regulation, and how this contributes to its role in cancer cells. The student involved will be part of a cross-disciplinary team and will have the opportunity to learn a broad range of molecular and cell biology techniques.
Project Keywords	RCE1, USP17, protease, cancer

8.6 Does One Size Fit All for Antimicrobial Delivery Via Nanoparticles?

Supervisor	Dr James Burrows & Professor Brendan Gilmore
Project Overview	Bacteria can avoid antibiotics by hiding in our cells. Nanoparticles can deliver antibiotics to intracellular infections, but our studies indicate some bacteria are in cellular compartments nanoparticles don't reach. This project will further investigate where within the cell different bacteria reside, and whether altering nanoparticles can help target these locations.
Project Description: Detailed description of the project	Antimicrobial resistant bacteria are a growing problem and new ways are needed to target bacterial infections more efficiently. One way in which bacteria can avoid therapeutics is via intracellular infection, where they hide within our own cells. Multiple bacteria can establish intracellular infections and much work has focussed on delivering antimicrobials into cells via various mechanisms. We have carried out preliminary work using nanoparticles to deliver antibiotics to combat intracellular infections. However, we have had mixed success, due to the finding that some bacteria reside in compartments within the cell these nanoparticles don't reach. We have also observed that altering some parameters of nanoparticles can alter their cellular uptake, and possible their destination within the cell. Therefore, this project will further investigate where within the cell different bacteria reside, and whether nanoparticles can be used to target these locations. The student will be part of a cross-disciplinary team based in the School of Pharmacy, and will have the opportunity to learn a broad range of molecular biology, tissue culture, bacterial culture, and cell biology related techniques.
Project Keywords	Antimicrobial, nanoparticles, bacteria, intracellular

8.7 Relationship Between Antibiotic Therapy and Development of Antimicrobial Resistance in Patients with Bronchiectasis and COPD

Supervisor	Professor Michael Tunney and Dr Deirdre Gilpin
Project Overview	This project will determine if there is a relationship between use of antibiotics and other drug therapies and the development of antimicrobial resistance in patients with bronchiectasis and COPD.
Project Description: Detailed description of the project	To decrease the risk of acute infective exacerbations or flare-ups of their condition, individuals with bronchiectasis and COPD are frequently prescribed long-term oral and inhaled antibiotics. However, it is not clear what effect such antibiotic treatment has on microbial community composition and the development of antibiotic resistance and how this relates to patient outcomes. As part of an ongoing collaboration between Queens University Belfast and the University of Dundee, we have access to a large number of clinical samples and extensive clinical and biomarker data from patients enrolled in clinical studies and the European Bronchiectasis Registry (EMBARC). In this project, we will determine whether microbiota composition and presence of resistance genes in these samples correlates with previous antibiotic treatment. Metagenomic analysis will be performed to determine the abundance of genes encoding antimicrobial resistance, the 'resistome', within the community of bacteria, and how it changes in response to treatment. The relationship between development of resistance and an extensive range of clinical outcomes (lung function, quality of life, time to next exacerbation) and measures of inflammation will also be determined. This project will provide extensive training in, clinical pharmacy, clinical trial methodology, molecular microbiology, inflammatory biomarker measurement and statistical analysis as part of an inter-disciplinary and internationally renowned research team. Moreover, this project will use rich clinical metadata and molecular resistance markers to explore prognostic markers that have potential to drive improvements in clinical care of people with bronchiectasis and COPD.
Project Keywords	Infection, antimicrobial resistance, PCR, next-generation sequencing, metagenomics, clinical pharmacy

8.8 4D Printing Technologies in Cancer Therapeutics

Supervisor	Professor Dimitrios Lamprou
Project Overview	Despite the advances achieved in cancer management, improvements in the quality of life of cancer survivors are urgent. Moreover, considering the heterogeneity that characterizes tumours and patients, focusing on individuality is fundamental. In this context, 3D printing (3DP) and 4D printing (4DP) techniques allow for a patient-centred approach.
Project Description: Detailed description of the project	According to WHO, cancer is the second leading cause of death worldwide, with nearly 1 in 6 deaths been due to cancer. The principal modes of cancer management are surgery, radiotherapy, chemotherapy and pharmaceutical agents. However, there are many side effects from extant treatments e.g., invasiveness of surgery, and with other treatments being systemic in nature; therefore, only a small fraction of the drugs reaches the tumour site. Due to the short period of actions, repeated doses are often required, which can lead to exacerbation of side effects and inconvenience. Due to these obstacles, targeted or localized release technology coupled with long-acting treatment functionality is a key research theme to replace systemic administration therapies and show potential for advancing cancer treatment including capability of personalizing the treatment. One especially promising therapeutic option gaining prominence is the use of multifunctional implants combining tumour-killing ability while promoting bone resorption/growth. Therefore, the main goal of this project is to investigate new approaches for targeted long-acting drug release for effective cancer therapies based on 3D & 4D printed / bioprinted drug-loaded implants.
Project Keywords	Bioprinting, Scaffolds, cancer, long-acting implants

8.9 Design and Evaluation of a Bone-on a-Chip Microfluidic Device

Supervisor	Professor Dimitrios Lamprou
Project Overview	Bone-on-a-chip models are mimicking the key features of bone and can potentially shift the paradigm of future therapeutic, research development, and be used for drug screening and testing new implants.
Project Description: Detailed description of the project	Cancer is a leading cause of death worldwide and characterized by an aggressive growth of cells, which divide without normal limitations, invade, and destroy adjacent tissues, and spread to distant anatomic sites through a process called metastasis. Bone is the most common site for metastatic spread from the breast, prostate or lung, and is associated with damage to the bone tissue, pain, and a high degree of patient mortality. This underscores the need for effective treatment options including safe and efficacious drugs. The development of new medicines is resource-intensive, and the high costs of development and attrition rates in anticancer drug development represent significant challenges for the pharmaceutical industry, healthcare providers and patients. Enhanced screening tools could help address the problem of late-stage failures and reduce the attrition rate of drugs in the clinical development pipeline by providing more informative, critical information at an earlier stage. Most in-vitro cancer studies are conducted using common 2D cell culture methods that fail to recapitulate the biological cues inherent in native tissue. This project will manufacture a microfluidic (lab-on-a-chip) device to mimic the 3D microenvironment in vitro more closely giving rise to the more physiologically relevant bone-on-a-chip.
Project Keywords	Bioprinting, lab-on-a-chip, microfluidics, cancer

8.10 Design of Novel Mucoadhesive Lubricants for the Treatment of Xerostomia and Xerostomia-induced Infection

Supervisor	Professor David Jones and Professor Gavin Andrews
Project Overview	This project will design, characterise and evaluate novel mucoadhesive lubricants for topical application to the oral cavity for the treatment of xerostomia (dry mouth). Additionally, such systems will be further designed to incorporate antimicrobial/anti-fungal agents for the treatment of xerostomia-related infection.
Project Description: Detailed description of the project	Xerostomia is defined as the subjective complaint of oral dryness and is associated with either permanent or transient salivary hypofunction. Current treatment options for xerostomia aim to relieve oral discomfort by keeping the mouth moist. Gustatory or pharmacological sialogogues such as chewing gum and pilocarpine stimulate saliva secretion and are effective in some patients with residual salivary gland function. However, many patients have insufficient functional tissue to respond to sialogogues and these patients rely on saliva substitutes. There are a variety of aqueous-based substitutes available, but their efficacy is limited by a short duration of action/insufficient lubricity. Building on previous work this PhD will design thermoresponsive gels that can be applied to the oral cavity as a spray but will undergo a viscosity change and interact with the oral mucosa/hard tissues. Uniquely these systems will simultaneously co-deliver both moisture to the applied site and will provide a lipid coating at the site which offers enhanced and prolonged lubricity. If required antimicrobial agents will be included. Initially, characterisation of current products will be performed to understand their current limitations (including information from current users). The project will then develop a series of formulation platforms and characterise their in vitro properties relative to the proposed clinical condition. Additionally, an in vitro model will be developed to understand lubricity before potentially examining their in vivo efficacy.
Project Keywords	Xerostomia, gel, lubricant, infection

8.11 Development of Novel Mucoadhesive Drug Delivery Platforms Containing Antimicrobial and Anti-Inflammatory Agents Designed for the Improved Treatment of Periodontal Disease

Supervisor	Professor David Jones and Professor Gerry McKenna
Project Overview	This project will design, characterise and evaluate novel gels systems that offer enhanced retention within the periodontal pocket and, whilst in situ, will provide controlled (>1 week) release of a unique combination of antimicrobial and anti-inflammatory agents.
Project Description: Detailed description of the project	Periodontitis is an inflammatory condition affecting the supporting structures of teeth (the periodontium) that is characterised by the formation of a space between the gingiva and tooth, termed the periodontal pocket. The primary aim in the treatment of periodontitis is to promote periodontal healing through eradication of sub-gingival pathogens. Due to the limited clinical efficacy/patient acceptability of oral (systemic) antibiotics and antimicrobial mouthwashes/instillation solutions, an interest has developed in the clinical use of implantable antimicrobial drug delivery systems that are designed for direct implantation into the periodontal pocket and offer controlled drug release whilst in this environment. Building on previous work this PhD will design polymeric platforms that will be retained in the periodontal pocket through an adhesive interaction between the formulation and the lining of the pocket (mucoadhesion). Previously we have provided strong clinical evidence of this approach. This study will progress this work to enable the co-delivery of an anti-microbial agent and a non-steroidal anti-inflammatory agent, thereby enabling simultaneous resolution of the infection and the resulting inflammation. The project will develop a series of formulation platforms using our unique Eutectic technology and characterise the in vitro properties relative to the proposed clinical condition. Additionally, it is hoped that the clinical efficacy of these systems may be examined.
Project Keywords	Periodontal disease; Infection; Inflammation; Rheology; Eutectic

8.12 Development of Novel Topical Strategies for the Treatment of Xerostomia

Supervisor	Professor David Jones and Professor Gerry McKenna
Project Overview	This project will design, characterise and evaluate novel mucoadhesive lubricants for topical application to the oral cavity. Additionally, such systems will be designed to incorporate antimicrobial/anti-fungal agents for the treatment of xerostomia-related infection.
Project Description: Detailed description of the project	Xerostomia is defined as the subjective complaint of oral dryness and is associated with either permanent or transient salivary hypofunction. Current treatment options for xerostomia aim to relieve oral discomfort by keeping the mouth moist. Gustatory or pharmacological sialogogues such as chewing gum and pilocarpine stimulate saliva secretion and are effective in some patients with residual salivary gland function. However, many patients have insufficient functional tissue to respond to sialogogues and these patients rely on saliva substitutes. There are a variety of aqueous-based substitutes available but their efficacy is limited by a short duration of action/insufficient lubricity. Building on previous work this PhD will design thermoresponse gels that can be applied to the oral cavity as a spray but will undergo a viscosity change and interact with the oral mucosa/hard tissues. Uniquely these systems will simultaneously co-deliver both moisture to the applied site and will provide a lipid coating at the site which offers enhanced and prolonged lubricity. If required antimicrobial agents will be included. The project will develop a series of formulation platforms and characterise their in vitro properties relative to the proposed clinical condition. Additionally, an in vitro model will be developed to understand lubricity before potentially examining their in vivo efficacy.
Project Keywords	Xerostomia; Thermoresponsive gels/emulsions; Rheology; Lubricity

8.13 Dip-coating Using Silicone Elastomer Dispersions as a Strategy for Preparing Reservoir-type silicone Elastomer Vaginal Rings for HIV prevention

Supervisor	Professor Karl Malcolm and Dr Peter Boyd
Project Overview	Matrix-type devices generally release drugs according to root-time kinetics. However, dip-coating is a simple method for converting the matrix devices into reservoir devices. In this project, we will evaluate the utility of dip-coating silicone elastomer matrix-type devices containing the antiretroviral drug dapivirine to produce reservoir devices suitable for HIV prevention.
Project Description: Detailed description of the project	**Background** A matrix-type silicone elastomer vaginal ring releasing the antiretroviral drug dapivirine—developed here at QUB—is now being used by women across eleven African countries to prevent sexual acquisition of HIV infection. This matrix ring is relatively easy to manufacture via a simple one-step injection molding process. However, an inherent disadvantage with this matrix ring is that it does not provide constant daily release of dapivirine; instead, a burst of dapivirine is first released followed by steadily declining amounts on subsequent days. Although reservoir-type silicone elastomer vaginal rings providing zero order release kinetics can be manufactured via injection molding, the multi-step process is relatively complex and expensive. **Aims/objectives** In this project, you will investigate the potential to manufacture reservoir-type dapivirine-loaded rings by dip-coating silicone elastomer matrix-type rings using custom silicone elastomer dispersion materials. Activities will include developing a dip-coating method, developing an HPLC method for quantification of dapivirine, performing in vitro release studies, and characterising the devices using thermal analysis methods (such as DSC and TGA). The homogeneity of coating will be assessed using microscopy techniques, and the influence of applying multiple dip-coated layers evaluated on the dapivirine release rate.
Project Keywords	HIV prevention; silicone elastomer; dip-coating; matrix and reservoir devices; in vitro release

8.14 Novel Statin Formulations for Treatment of Bacterial Vaginosis

Supervisor	Professor Karl Malcolm and Dr Deirdre Gilpin
Project Overview	Use of statins is associated with reduced *G. vaginalis* and increased beneficial lactobacilli in the human vaginal microbiome. In this project, we will develop vaginal ring formulations that provide sustained/controlled release of statins—in combination with conventional antibacterial drugs—as potential new treatments for bacterial vaginosis.
Project Description: Detailed description of the project	**Background** Bacterial vaginosis (BV) is most prevalent vaginal condition, affecting 30% of women globally. It is associated with depletion of healthy lactobacillus and overgrowth of certain anaerobic bacteria, such as *Gardnerella vaginalis*. Current treatment options include use of antibiotic drugs, such as metronidazole and clindamycin, administered orally or vaginally. However, many women experience an endless cycle of BV episodes; treatment efficacy is poor and recurrence rates are high. Abdelmaksoud et al., (2017) reported that oral statin use was associated with reduced proportions of *G. vaginalis* and greater proportions of beneficial lactobacilli in the vaginal microbiome. These data suggest that statins may be useful in the treatment of BV, either alone or in combination with more conventional treatments. **Aims/objectives** The aim is to develop and characterise long-acting vaginal ring formulations—containing combinations of statins and conventional antimicrobial drugs—suitable for novel treatment of BV. Initial studies will evaluate the potential for incorporation and release of selected statin drugs and antimicrobial drugs, both singly and in combination, from silicone elastomer vaginal rings. Various analytical methods (including DSC, TGA, HPLC, etc.) will be developed to characterise/quantify the drugs. Microbiological studies will be conducted to explore the effects of statins and antibacterial drugs, singly and in combination, on growth of lactobacillus and *Gardnerella vaginalis.*
Project Keywords	Bacterial vaginosis; *G. vaginalis*; vaginal microbiome; lactobacillus; statins; 5-nitroimidazole drugs; vaginal rings; vaginal gels

9. NANOMEDICINE AND BIOTHERAPEUTICS

9.1 Peptide-based Nanoparticles for Brain-targeted Gene Delivery

Supervisor	Dr Emma McErlean
Project Overview	Development of novel peptide-based gene delivery systems designed to overcome the blood-brain barrier and target brain tissue for gene therapy; for the treatment of neurodegenerative disease and cancer.
Project Description: Detailed description of the project	Gene therapy has the potential to provide therapeutic benefit in treatment of neurodegenerative diseases, such as Parkinson's Disease, and cancer. Delivery into the brain is hampered by the blood-brain barrier (BBB), which limits the efficacy of both conventional and novel therapies at the target site. Therefore, innovative delivery strategies are required, and nanoparticles (NPs) are at the forefront of future solutions. The aim of this project is to develop novel peptide-based NPs to efficiently deliver therapeutic agents to the brain, overcoming the restrictive properties of the BBB. The objectives are: to formulate and systematically characterise the physicochemical characteristics of novel peptide-based NPs; analyse the *in vitro* and *in vivo* functionality of peptide-based NPs for gene delivery to the brain and; assess the therapeutic outcomes following delivery of gene therapy to the brain via peptide-based nanoparticles.
Project Keywords	Cell Penetrating Peptides, Gene Delivery, Gene Therapy, Nanomedicine, Targeted Treatments, Blood Brain Barrier.

9.2 Infection-Responsive Coatings for the Prevention of Medical Device-Associated infections

Supervisor	Dr Matthew Wylie and Professor Colin McCoy
Project Overview	Using our research groups expertise in designing stimuli-responsive polymers, this project will develop novel polymeric device coatings responsive to device-associated markers to allow detection and/or prevention of device-associated infections. This interdisciplinary project will provide the student with experience in organic synthesis, materials science, and microbiology, using cutting edge microscopy equipment.
Project Description: Detailed description of the project	Medical devices play a significant role in modern healthcare. However, they are prone to bacterial contamination which can facilitate biofilm formation and subsequent medical device-associated infections. Prevention of biofilm development on medical devices is most commonly achieved through use of antimicrobial-eluting coatings but this is often short-lived, uncontrolled, and may give rise to antibiotic resistance. Our research group has focused on the use of 'smart' stimuli-responsive coatings that exploit chemical changes, such as pH, to modify the device surface or control drug release to provide long term protection from biofilm development. This project will continue this strand of exciting research by developing materials capable of responding to specific bacterial biomarkers to produce an infection-responsive coatings for the prevention of medical device-associated infection. Specifically, the project aims to: • Identify suitable biomarker targets of clinically relevant bacteria/device-associated infections • Synthesise and characterise bacterial-responsive monomeric (and their polymers) candidates suitable for responsive drug delivery systems • Assessment of the coatings to prevent bacterial biofilm development using *in vitro* dynamic flow models. Through the development of novel polymeric coatings and assessment using sophisticated infection models e.g. ex vivo urethral/bladder models, the project will develop new strategies to address the rising incidence of device-associated infection.
Project Keywords	Device-associated infections, Biomaterials, Coatings, Materials Science

9.3 Designing Next-generation Urinary Catheter Materials for Clean Intermittent Self-catheterisation Through Control of the Urinary Microbiome

Supervisor	Dr Matthew Wylie and Dr Laura Sherrard
Project Overview	This project aims to characterise the urinary microbiome of intermittent catheter users to determine potential links with catheter-related complications, such as infection. Furthermore, the effect of different catheter materials and coatings will be assessed in conjunction with microbiomics to design next-generation urinary catheter materials for clean intermittent self-catheterisation.
Project Description: Detailed description of the project	Intermittent urinary catheterisation is used to address chronic urinary retention in conditions such as spinal cord injury. Intermittent catheters (ICs) are designed as single-use lubricated devices and as such can be associated with a high cumulative cost – the UK's National Health Service (NHS) spends >£88 million annually on ICs. However, in countries such as USA, as many as 83% of patients reuse a single IC up to 20 times before disposal, mainly due to the lack of affordable healthcare, social aspects, or environmental reasons. Reuse increases the risk of IC complications such as discomfort, urethral trauma, and scarring with chronic use. Repeated IC use may also increase risk of developing a catheter-associated urinary tract infection (CAUTI). Novel IC coatings are required to reduce complications and facilitate safe reuse of ICs to reduce costs and environmental impact associated with single-use ICs. This project will investigate the relationship between intermittent urinary catheterisation and the urinary microbiome and how changes in the microbiome can impact IC complication risk. The project will use these findings to aid development of next-generation catheter coatings with improved surface properties and resistance to CAUTI. This project will provide experience in microbiology, organic chemistry and materials science.
Project Keywords	Medical device infection, Microbiome, Biomaterial coatings, Materials Science

9.4 Enzyme-triggered Injectable Peptide Hydrogels for the Prevention of Latent Tuberculosis

Supervisor	Dr Garry Laverty
Project Overview	This project is aimed at developing a long-acting injectable technology that will provide prophylaxis against latent tuberculosis in at-risk populations. It will focus on developing a new drug delivery system administered subcutaneously as a single soluble injection. This platform will be developed using our innovative peptide drug delivery system. Upon administration, this solution will transform into a drug-releasing hydrogel depot in response to the action of enzymes present in the skin.
Project Description: Detailed description of the project	Low to middle-income countries (LMIC) account for 95% of tuberculosis infections and deaths. Tuberculosis is currently the second highest infectious killer worldwide, after Covid-19, and is responsible for more deaths than HIV/AIDS. There is an urgent need for new convenient drug delivery systems to combat global health challenges in infectious disease, including tuberculosis. In this project, the aim to develop a long-acting preventative strategy to deliver single or multiple tuberculosis drugs within one injectable hydrogel depot. This strategy should eliminate pill fatigue encountered with existing oral therapies, enable better access to multiple drugs for a longer duration and be simple to administer in LMIC environments. To achieve this we will use a promising peptide-like, peptoid-peptide system. This platform has proven to form a drug-releasing hydrogel implant *in situ* in response to enzymes present in the subcutaneous skin space. The objective is to select the most promising peptoid-peptide formulation and demonstrate *in vivo* practicality for at least 84-day drug delivery. This selection will be made by characterising the mechanical (rheology), structural (microscopy, spectroscopy, neutron scattering at large scale facilities), biocompatibility (toxicity, immune response) and stability profiles for each formulation and establishing their relationship to drug release *in vitro*.
Project Keywords	Hydrogel; drug delivery; formulation; long-acting injectable; peptides; tuberculosis

9.5 Peptide-like Hydrogels as a Long-acting Multipurpose Drug Delivery Platform for Combined Contraception and HIV prevention

Supervisor	Dr Garry Laverty
Project Overview	This project will advance the development of our promising long-acting injectable peptoid-peptide drug delivery technology for use in combined HIV prevention and contraception. It has the potential to provide extended combined protection within one discrete product, empowering women to take control of their sexual health and reducing the incidence of new HIV infection in the most at-risk demographic.
Project Description: Detailed description of the project	HIV in women, girls and mother-to-child transmission in pregnancy remain a significant source of new infections and the needs of females are inadequately addressed. Our advanced drug delivery system is composed of a versatile peptide-like, peptoid-peptide hydrogel depot, which has several important advantages as a long-acting injectable platform for sustained drug delivery. Unlike existing long-acting formulations used in medicine, e.g. suspensions, this technology exists as a fully soluble water-based (aqueous) formulation. This means multiple drugs can be incorporated within one injectable platform without encountering stability issues e.g. aggregation due to drug insolubility. The aim of this project is to progress the freeze-dried formulation and to consider factors important to medicine regulators (e.g. MHRA, EMA). This will involve developing our platform as a freeze-dried powder that is readily reconstituted in a water-based solvent prior to administration by injection. Pharmaceutical stability to ICH standards, without cold chain storage/transport across several climatic zones, is a key consideration for effective clinical adoption. We will then progress to testing pharmacokinetics and preliminary safety using established *in vivo* models.
Project Keywords	Hydrogel; drug delivery; formulation; long-acting injectable; peptides; HIV

9.6 Smart Enzyme-triggered Injectable Peptide Hydrogels for the Prevention of Malaria

Supervisor	Dr Garry Laverty
Project Overview	This project is aimed at developing a long-acting injectable technology that will provide malaria prophylaxis to at-risk populations. We will focus on engineering a new drug delivery system administered subcutaneously as a single soluble injection. This platform will be developed using our innovative peptide drug delivery system. Upon administration, this solution will transform into a drug-releasing hydrogel depot in response to the action of enzymes present in the skin.
Project Description: Detailed description of the project	There is an urgent need for new convenient drug delivery platforms to combat global health challenges in infectious disease, including malaria, and especially within low to middle-income countries (LMIC). In 2021, there were 247 million cases of malaria and almost half of the global population was at risk of infection. In this project, the aim to develop a long-acting preventative strategy to deliver single or multiple malaria drugs within one injectable hydrogel depot. This strategy should eliminate pill fatigue encountered with existing oral therapies, enable better access to multiple drugs for a longer duration and be simple to administer in LMIC environments. To achieve this we will use a promising peptide-like peptoid-peptide system. This platform has proven to form a drug-releasing hydrogel implant *in situ* in response to enzymes present in the subcutaneous skin space. The objective is to select the most promising peptoid-peptide formulation and demonstrate *in vivo* practicality for at least 84-day drug delivery. This selection will be made by characterising the mechanical (rheology), structural (microscopy, spectroscopy, neutron scattering at large scale facilities), biocompatibility (toxicity, immune response) and stability profiles for each formulation and establishing their relationship to drug release *in vitro*.
Project Keywords	Hydrogel; drug delivery; formulation; long-acting injectable; peptides; malaria

9.7 Investigating Relationships Between the Gut Microbiome and the Metabolism of Commonly Prescribed Drug Compounds

Supervisor	Dr Stephen Kelly
Project Overview	This project will investigate the effect of commonly prescribed prescription medicines on the gut microbiome. It will also examine the effect of different microbiome profiles on drug metabolism, such as those seen in different disease states, informing future personalised medicine prescribing.
Project Description: Detailed description of the project	The human gut is home to trillions of microorganisms and their genes, known as the gut microbiome. This microbiome has a profound effect on human health, as well as on the metabolism of pharmaceuticals. Prescription medicines, in particular antibiotics, have been shown to disrupt the gut microbiome, creating a state of dysbiosis. However, a considerable amount remains unknown about the effect of non-antibiotic medicines on the gut microbiome, and why people respond differently to certain medicines. This project aims to investigate the effect of non-antibiotic prescription medicines on the gut microbiome. It also aims to investigate the effect of different microbiome profiles on the metabolism of various drugs compounds. Project aims will be achieved through the use of an established *in vitro* gut screening model, and downstream microbiome and metabolite analysis. The successful candidate will join a dynamic research group focused on the analysis and functional characterisation of microbiomes from various niches, to help investigate the link between the microbiome and metabolism of drugs. This project will involve wet lab experiments, as well as considerable bioinformatics analysis. Full technical training will be provided, providing skills which will help prepare the student for a career in a variety of sectors.
Project Keywords	Microbiome, drug metabolism, personalised medicine, human health

9.8 Nanoparticle Delivery of Antibiotics for Treatment of Pulmonary Infection

Supervisor	Dr Vicky Kett and Professor Michael Tunney
Project Overview	The aim of the project is to develop novel nanoparticles encapsulating antibiotic that can be used to deliver payload in a targeted manner to the lung for treatment of chronic respiratory infection.
Project Description: Detailed description of the project	Antimicrobial resistance (AMR) poses a major global risk to human health by causing death, disability, longer hospitalisations, and increased healthcare costs. In respiratory diseases such as bronchiectasis Cystic Fibrosis (CF) and COPD, the lungs are colonized by diverse polymicrobial bacterial communities. Inhaled antibiotics are currently only used in the treatment of chronic P. aeruginosa infection in CF and a major challenge with such treatment is antibiotic penetration into sputum. We have developed formulations with excellent powder properties for pulmonary delivery. We have extensive data to show that several antibiotics used in the treatment of chronic lung infection can be encapsulated in these formulations. The aim of this project will be to determine the activity of nanoparticle encapsulated antibiotics against a wide range of pathogens detected in the lung microbiome. In vitro activity will be determined using planktonic and biofilm models of infection under aerobic and anaerobic conditions, similar to those found in sputum in the people with longterm respiratory conditions. Depending on results, further formulation studies may be undertaken to optimize antimicrobial activity. Extensive training will be provided throughout the project as part of internationally renowned research teams. Extensive training will be provided in all aspects of the fundamentals of nanoparticle manufacture together with physicochemical methods required to optimise the manufacturing process, and to characterise inhaled antibiotic products such as thermal stability and microbiological activity.
Project Keywords	Nanoparticles, Respiratory infection, antibiotic

9.9 Characterisation of Novel Therapeutic Targets for the Treatment of Tumour Metastasis

Supervisor	Dr Roberta Burden
Project Overview	Elevated expression of cathepsin proteases has been associated with poor clinical outcomes across many different cancer types. This project will examine the mechanistic role of cathepsins in tumour biology, enhancing our understanding of how they promote tumour cell metastasis and aiding the development of new targeted therapies.
Project Description: Detailed description of the project	There is a major unmet clinical need to develop improved treatment strategies for patients with recurrent and metastatic cancer, which can only be facilitated by better understanding of the biology driving disease progression, enabling the development of new targeted therapies. Elevated cathepsin expression is associated with several hallmarks of cancer including increased tumour cell proliferation, angiogenesis, invasion and metastasis. The main hypothesis of this project is: ***Cathepsins promote an aggressive tumour cell phenotype, contributing to poor clinical outcomes. Targeting cathepsins can offer therapeutic benefit to patients who exhibit disease recurrence and metastasis.*** We plan to examine this by three main objectives: 1. Investigate the contribution of cathepsin activity on the metastatic phenotype of tumour cells. 2. Examine the impact of cathepsin targeting on the tumour microenvironment. 3. Determine the significance of cathepsin targeting on the anti-tumour immune response by enhancing immune cell cytotoxicity. Collectively, this research could lead to a new paradigm in precision medicine treatment tumours by targeting aberrant cathepsin activity associated with many different malignancies. This could have significant impact in the context of reducing metastatic spread of tumours, as metastatic cancers have significantly poor outcome, with no targeted treatment strategies.
Project Keywords	Cancer, invasion, metastasis, therapeutic, protease, immunotherapy

9.10 Bacteriophage Control of Oral Microbiota for the Prevention and Treatment of Oral Disease

Supervisor	Dr Timofey Skvortsov and Professor Gerry McKenna
Project Overview	Bacteriophages are bacterial viruses that demonstrate high specificity and are able to quickly and efficiently kill pathogenic bacteria without affecting healthy microbiome. This project will investigate the use of bacteriophages for the prevention and treatment of bacterial infections of the oral cavity.
Project Description: Detailed description of the project	The oral microbiome is a complex ecosystem consisting of multiple species of bacteria, fungi, and viruses. The microbiome composition changes depending on various factors. Some of the reorganisations of the microbiome might lead to the development of bacterial infections, including dental caries and periodontitis, which constitute a global public health problem. Although antibiotic treatments are available, they are not always effective in elimination of bacterial biofilms and their frequent use can lead to the emergence of antibiotic-resistant strains. An attractive alternative approach that has been gaining popularity recently is bacteriophage therapy – the use of bacterial viruses (bacteriophages) for prophylaxis and treatment of infectious diseases. The aim of this study is to investigate the potential of bacteriophages in prevention and treatment of bacterial infections of the oral cavity. The following objectives will be pursued: 1. Bioinformatics analysis of newly generated and/or publicly available metagenomes for the identification of key bacteria implicated in oral infections. 2. Isolation and characterisation of bacteriophages and their lytic enzymes against the key pathogens identified at Stage 1. 3. Investigation of antibacterial activity of bacteriophages against the selected bacteria *in vitro* and in the available model systems. 4. Formulation of prophylactic antibacterial gels based on bacteriophage cocktails.
Project Keywords	Bacteriophage, microbiome, caries, periodontitis, prevention

10. CARDIOVASCULAR MEDICINE

10.1 Engineering the Future: Vascularized Cardiac Organoids as a Platform for Studying Diabetic Cardiovascular Complications

Supervisor	Professor Andriana Margariti
Project Overview	Under Professor Margariti's supervison at Queen's University Belfast, this PhD program in regenerative medicine focuses on developing next-generation of vascularized cardiac organoids using patient-specific induced pluripotent stem cells. The research aims to unravel diabetic cardiac complications and create personalized therapies, offering unparalleled growth in cardiovascular research, and a unique training opportunity for the PhD student.
Project Description: Detailed description of the project	The burgeoning field of regenerative medicine and cardiology has led to the development of next generation vascularized cardiac organoids, offering unprecedented opportunities to study diabetic cardiac complications. Under the visionary leadership of Professor Margariti at the Wellcome-Wolfson Institute for Experimental Medicine (WWIEM) at QUB, this groundbreaking research utilizes advanced cell reprogramming techniques with patientspecific iPSCs. This innovative approach aims to uncover the pathophysiological mechanisms underlying diabetic cardiac complications and paves the way for developing personalized therapeutic strategies. Through this pioneering work, the team is setting new standards in using patient-derived iPSCs for cardiac disease modelling, offering hope for targeted and effective treatments for diabetes-related cardiac disorders. The PhD program provides a unique opportunity for growth and development in regenerative medicine and cardiovascular research. The PhD student will engage in cutting-edge research at the forefront of regenerative medicine and cardiovascular disease, developing expertise in iPSC technology and cardiovascular lineage differentiation. They will collaborate with leading experts, benefit from close-mentorship, and access advanced research facilities and resources at QUB. The program provides opportunities to publish and present research findings in highimpact journals and international conferences, participate in professional development activities such as workshops and seminars, and interact with a diverse community of scholars to foster interdisciplinary learning. This comprehensive training and experience prepare students for successful careers in academia, industry, or clinical research.
Project Keywords	Regenerative Medicine; Cardiovascular Disease, Diabetes, Vascular Complications; Patient Specific iPSCs; Next Generation of Vascularised Cardiac Organoids

10.2 Overwriting Blood Vessel Identity to Prevent Coronary Graft Failure

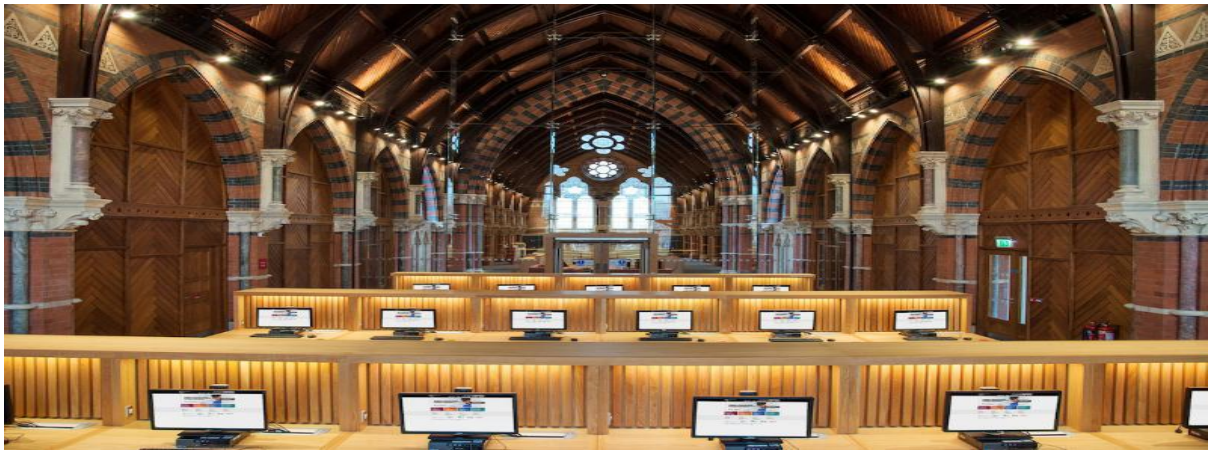
Supervisor	Dr Denise McDonald
Project Overview	**Cardiovascular disease (CVD)** is the leading cause of death worldwide. Coronary heart disease (CHD) is the most common type of CVD and is responsible for 10 million deaths globally every year. CHD is caused by thrombotic occlusion of the blood vessels that supply the heart, which leads to local tissue ischaemia and irreversible damage to the underlying cardiomyocytes. Currently, treatment relies on stenting or **coronary artery bypass graft (CABG) surgery** whereby a blood vessel is removed from the patient's leg (saphenous vein), chest (internal mammary artery) or arm (radial artery), and used to bypass the obstructed vessel, allowing re-vascularisation of the damaged heart. While very successful, this procedure is limited by the development of accelerated atherosclerosis, a condition called **vein graft disease** which leads to 75% of grafts being occluded within 10 years. The reasons for this accelerated disease progression are not well understood. Recently, we have identified several novel targets that we hypothesise could be used therapeutically to enhance blood vessel stability to prevent graft failure or significantly extend its efficiency. Ethical approval and a well-rehearsed SOP for collecting and processing human samples will facilitate the speed of this project.
Project Description: Detailed description of the project	***OBJECTIVE:*** *Using our unique expertise in vascular and molecular/ cell biology, this study will investigate the underlying mechanisms that disturb healthy endothelial cell (EC) function in patients with cardiovascular disease.* **Overall outcomes of research project:** This study will elucidate novel ways to promote the long-term survival of EC and prevent the deleterious consequences of graft failure. **AIMS AND EXPERIMENTAL DESIGN** **Aim 1:** Investigate the function of novel proteins important for promoting arterial properties in EC. **Aim 2:** Investigate the impact of these novel targets on EC biology using genome engineering. **Aim 3:** Investigate how these targets are altered in disease using in vitro models of vascular disease. **The student will gain state-of-the-art expertise in cell and molecular biology techniques which will be transferable to a wide range of disciplines and research areas.** **<u>Training will be provided:</u>** 1. Primary cell culture of EC. 2. Molecular biology techniques such as RNA isolation, PCR, protein extraction and western blot, immunocytochemistry and sub-cellular tracking using GFP/ RFP constructs. 3. Gene transfer techniques and reporter assays to investigate the role of key signalling pathways implicated in disease models.

	4. Key skills: Data mining and Gene expression profiling and analysis; Data analysis; Critical analysis of the literature; Presentation skills; scientific writing. Overall, the proposed project will provide training in a wide range of laboratory skills essential for a future career in science.
Project Keywords	cells (EC), nitric oxide, oxidative stress, vein graft disease, coronary artery bypass surgery (CABG)

10.3 Neuronal vs Vascular Clock Disruption in Early Diabetic Retinopathy

Supervisor	Dr Eleni Beli and Professor Tim Curtis
Project Overview	Diabetic retinopathy (DR) is a major diabetes complication causing blindness. The disease involves retinal vessel dysfunction and ischemia. Dysregulation of the circadian clock, especially Bmal1 protein, may impact DR. This project investigates the roles of neuronal versus vascular clock disruption in DR using mice models, aiming to identify targeted therapies.
Project Description: Detailed description of the project	Diabetic retinopathy (DR), a leading cause of blindness, is the most common complication of diabetes, manifesting as a microvascular disease with retinal vessel damage, ischemia, and uncontrolled vessel growth. The pathogenesis of DR is complex and not fully understood. However, the circadian clock, which regulates cellular functions by aligning gene expression with the daily light/dark cycle, is known to be dysregulated before retinal vascular complications arise. The role of Bmal1, a circadian clock protein, in DR is unclear, with studies suggesting that its deletion in different cells could variably affect the disease. It is proposed that the neuronal, rather than the vascular, clock influences pathological neovascularization, yet the specific roles of Bmal1 in retinal vessels versus neuronal cells in early DR stages remain uncertain. This research project aims to elucidate these roles by creating murine models with Bmal1 selectively deleted from retinal neurons (Ret-Bmal1 KO) or vessels (Endo-Bmal1 KO) and comparing DR progression. Structural and functional criteria will be assessed at 2, 4, and 6 months of diabetes duration using histological methods, optical coherence tomography (OCT-A), fluorescence angiography, and electroretinography. Subsequent in vitro co-cultures will validate the results. Understanding the impact of clock dysregulation on DR progression could reveal novel therapeutic targets and aid in designing targeted therapies for DR prevention.
Project Keywords	Diabetic retinopathy, circadian rhythms, Bmal1, vascular clock, neuronal clock

CONTACT INFORMATION



Postgraduate Research Solutions Centre (PGRSC)

The Postgraduate Research Solutions Centre is responsible for supporting the 4 Year International PhD and any questions you have may be directed to Mrs Lynne Spence at the Centre.

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