RCSI

RCSI StAR
SUMMER RESEARCH INTERNSHIPS

RCSI

RCSI has been at the forefront of educating healthcare professionals since 1784. Today we are Ireland's only focused health sciences institution, Ireland's largest medical school and one of the leading health sciences institutions in the world.

Based in Dublin, with students from over 80 countries and four overseas campuses, RCSI has a global reach through our network of Alumni in 97 countries.

RCSI is ranked among the top 2% of universities worldwide in the 2018 Times Higher Education (THE) World University Rankings and joint second out of the nine institutions in the Republic of Ireland.

RCSI's performance in the rankings is linked in particular to the College's research strength and it is ranked first in Ireland for publication citations.

RCSI's Strategic Academic Recruitment (StAR) Programme is an ambitious initiative to accelerate the delivery of innovative, impactful research to improve human health through innovative translational medical research.

PURPOSE

The purpose of the StAR Summer Research Internship Programme is to provide support for high calibre undergraduate students to conduct a research project at RCSI during the summer. The best performing students would be eligible to apply for the RCSI StAR PhD programme and other funded PhD programmes.

BENEFITS

- Opportunity for an international research placement as part of your undergraduate training in a world class institution.
- Potential to apply for the RCSI StAR PhD programme.
- Potential to apply for other funded PhD programmes (e.g. Government of Ireland Postgraduate Training Programme)

ELIGIBILITY

Eligible students must be entering the final year of their undergraduate degree programme in basic science/health sciences after completion of the internship and will have a clear plan to pursue a PhD. **Students can be from any country in the world, there are no restrictions on nationality and international applications are encouraged.**

EXTENT OF FUNDING

Students will receive a €2000 stipend and paid accommodation in Dublin city centre will be provided for 8 weeks commencing June 2020. Travel costs are not included and non-EU students will also require a Garda National Immigration Bureau (GNIB) card and appropriate visa. Assistance in obtaining both for successful applicants will be provided.

APPLICATION PROCESS

Students must submit completed application forms to StARintern@rcsi.ie. Applicants should detail academic progress to date, CV/Resume and a brief motivational statement. Applicants should also list their chosen research project in order of preference (1-10). Application forms and details of available research projects can be found at http://www.rcsi.ie/starugprogramme.

DEADLINE

Completed applications must be submitted by **Friday 6th March 2020.** Successful candidates will be notified by end of March 2020.

ENQUIRIES

For informal enquiries about the application process please contact StARintern@rcsi.ie

Project 1

‘Adolescent brain development and risk of psychosis’

Supervisor: Professor Mary Cannon, Department of Psychiatry.

Project summary:

Understanding adolescent brain development and how the mechanisms of structural neuroanatomical and functional brain development plays a central role in the formative phase of psychiatric disorders. The limbic system is a core component of emotion, memory, and executive control featuring key subcortical structures such as the amygdala, hippocampus, and thalamus in conjunction with known white matter fibre tracts supporting related functional and cognitive roles. Recent advances in MRI present researchers with additional novel tools to interrogate and quantify the limbic system on a much fine scale than before. Longitudinal data analysis will allow highly sensitive quantitative details of the developmental trajectories of the limbic system. Advanced neuroimaging quantitative and white matter diffusion based tractography techniques will be employed to measure and model developmental growth patterns of adolescents experiencing psychotic like systems compared to their neurotypical peers. Highly sensitive linear mixed modelling statistical approaches will be utilised to clarify the underlying patterns of limbic circuitry development and identify possible localized regions of developmental divergence in those experiencing subclinical psychotic symptoms.

This summer project will provide hands on experience of the neuroimaging techniques and how they can be applied to psychiatric research.

More specifically, the student will learn how to run quantitative MRI analysis of subcortical hippocampal, amygdala and thalamus including substructure delineation and volumetrics for subfield and sub nuclei measures. This will be done using the image analysis software suite called Freesurfer. In addition, the student will gain exposure to diffusion imaging tractography for the purpose of accurately delineating key white matter pathways of the limbic circuit.

Project 2

'The interaction between sub-epidermal moisture measurements and moisturising and protectant/barrier products in healthy adult volunteers'

Supervisor: Professor Zena Moore, School of Nursing & Midwifery.

Project summary:

Sub-epidermal moisture (SEM) is a biophysical marker and is a product of the leak of plasma after the inflammation process increases local vasculature permeability. When tissue damage progresses to a greater number of cells, the inflammation markers increase along with the plasma leakage through the blood vessels. Pressure ulcers, diabetic foot ulcers and lymphoedema are examples of conditions that trigger the inflammation process causing skin and soft tissue breakdown, increasing the patient's risk of infection and death. SEM measurement, using a handheld device, is able to detect electrical changes in soft tissues at the very early stages, leading to early diagnosis and prevention of skin and soft tissue ulceration. However, as part of the daily skincare routine, patients cared for in acute and community settings routinely have moisturising and protectant/barrier products applied on the skin surface. It is still unknown how these products applied to the skin affect the reliability of SEM measurement. Therefore, this study will explore how different moisturising and protectant/barrier products can interfere with the reliability of SEM measurements over time. A pre-post study design including healthy adult volunteers will measure the effect of moisturising and protectant/barrier products applied to heels and sacrum areas on SEM scores: before application of the products, immediately after products application, after 10 minutes, 20 minutes, 30 minutes, 1 hour and 2 hours. This study has the potential to significantly improve clinical protocols for the use of SEM measurement in both acute and community settings, meaning the potentially fatal skin damage can be detected before seen by the naked eye.

Project 3

‘Synthesis of novel heteroarotinoids based on SHetA2 for ovarian cancer’

Supervisor: Dr James Barlow, Department of Chemistry.

Project summary:

Ovarian cancer is the eighth most commonly occurring cancer in women, and is often difficult to detect until significantly advanced. Five-year survival rates remain between 30% and 50%. Therefore, there is a clear need for new and innovative strategies to improve prevention, detection and treatment. Treatments typically involve the use of surgery, drugs and sometimes radiation, in various combinations. Many existing drugs are toxic and their efficacy can become compromised. Novel strategies which seek to improve the efficacy and reduce the toxicity of established therapies have been shown to be a valid and worthwhile approach in the treatment of many diseases. In this project, we propose to design, synthesise and test a series of small molecules based on the anti-cancer ‘lead’ structure SHet-A2, a heteroarotinoid, designed via its relationship to vitamin A. This small molecule has a defined molecular target, namely the molecular chaperone mortalin, interaction with which leads to mitochondrial swelling and mitophagy. Such substances are known to regulate cell growth, and have demonstrated potential in both prevention and treatment of several cancers, including ovarian cancer. We propose the synthesis of novel heteroarotinoid scaffolds which offer a rational design approach towards potent and efficacious therapies for ovarian cancer.

Project 4

‘Genomic analysis of clinical DNA sequence data to identify novel causes of rare neurological disease’

Supervisor: Professor Gianpiero Cavalleri, School of Pharmacy & Biomolecular Sciences

Project summary:

Genetic changes that are rare in the human population are increasingly recognised as a cause of a variety of diseases, including neurological disorders. Such knowledge is critical in the development of precision therapeutics, targeted at the specific underlying cause of an individual’s disease. Our ability to identify, characterise and interpret rare genetic variation has exploded in recent years, via the development of next-generation genomic sequencing technology and associated bioinformatic processes.

The SFI FutureNeuro Research Centre consists of over 60 researchers focused on delivering faster diagnosis, personalized treatments and patient-centred care for neurological disease. This internship provides a fantastic opportunity to work in the world class research environment provided by RCSI and FutureNeuro, studying novel genetic causes of neurological disease. Specifically, the student will work with genomic trio sequence data (affected child and unaffected parents) from people with rare forms of epilepsy, to identify de-novo mutations that are appearing in novel disease genes. The project would involve training in advanced bioinformatic processes, allowing the student to develop in-demand research skills in genomics data science.

Project 5

'Validation of microRNAs as novel diagnostic and therapeutic targets in ischaemic brain injury'

Supervisor: Dr Shona Pfeiffer, Department of Physiology.

Project summary:

Ischaemic stroke, caused by blockage of the blood supply bringing oxygen and nutrients to part of the brain by a blood clot, is one of the leading causes of death and disability worldwide. Without proper blood supply, parts of the brain are deprived of oxygen and start to die, causing parts of the body controlled by these nerve cells to stop working. The devastating effects of stroke often lead to poor recovery. Despite decades of research, treatment options remain limited and time-dependent and there is an urgent need for the development of new approaches to diagnose and predict patient outcome after suffering a stroke to achieve better functional recovery.

Identification of a molecule that can be detected by a simple blood test that would accurately diagnose and predict prognostic factors for each individual patient's recovery from stroke would enable clinicians to more effectively determine a rehabilitation strategy that maximizes individual patient's potential outcomes. Furthermore, identification of such markers represents a promising approach for the development of a protective agent that could be administered to help stop the progress of cell death and damage in the brain.

This study is focused on identifying such biomarkers in the blood that will accurately diagnose stroke and predict recovery. Any biomarkers found to significantly predict recovery from stroke can be used to develop personalised rehabilitation and treatment strategies potentially helping patients regain stroke- impaired function. Such markers also have potential to be developed into future neuroprotective agents to help prevent the devastating effects of stroke.

Project 6

'Delirium in critically ill children - development of a cross-sectional survey of European practices'

Supervisor: Dr John Hayden, School of Pharmacy & Biomolecular Sciences.

Project summary:

Delirium is the behavioural manifestation of acute brain dysfunction associated with serious underlying medical illness. It presents as an acute and fluctuating change in mental status, with disordered attention and understanding. (1) It is a well-known and highly prevalent problem in adult intensive care, linked to increased morbidity, mortality and healthcare costs. (1) The problem of delirium in critically ill children is gaining increased attention, although its detection is more challenging than in adults.

Six years ago an international survey found as a lack of routine delirium screening in PICUs worldwide and many differences in practice across paediatric intensive care units(PICUs).(2) However, most of those who responded to the survey were based in American PICUs and the results are now over eight years old. The last decade has seen significant efforts to recognise and manage delirium in the PICU with the introduction of nursing based detection tools and care plans in some PICUs.

Given recent progress in the area, the lack of studies in the European context and the potential to improve care through practice harmonisation, we wish to develop a survey to be conducted across European PICUs.

The intern will work with academic and clinical experts in Ireland's PICUs to develop and pilot a survey of delirium detection and management practices in Europe.

1. Silver G, et al. PCCM. 2015 May;16(4):303.
2. Kudchadkar SR, et al.. CCM. 2014 Jul;42(7):1592.

Project 7

‘Barriers and facilitators to discontinuing long-term benzodiazepine use: A theory-based questionnaire’

Supervisor: Dr Cathal Cadogan, School of Pharmacy & Biomolecular Sciences

Project summary:

Benzodiazepines have multiple clinical indications, including anxiety and insomnia. Guidelines recommend that benzodiazepine prescriptions should be limited to short-term use (i.e. ≤4 weeks) to minimise the risk of adverse outcomes such as dependence and withdrawal symptoms. However, these recommendations are often not adhered to as long-term use of these medications persists worldwide. Long-term benzodiazepine use is potentially inappropriate and can give rise to a range of adverse effects including cognitive and psychomotor impairment, particularly in older people.

This project will use a questionnaire to examine patient-reported barriers and facilitators to discontinuing long-term benzodiazepine use. The questionnaire will be developed using behaviour change theory in order to provide a detailed understating of patients’ current behaviour regarding long-term benzodiazepine use. The successful applicant will develop relevant knowledge and skills in the application of behaviour change theory in addressing clinical problems, as well as questionnaire development and analysis. The questionnaire findings will help to inform the development of an intervention to reduce long-term benzodiazepine use in primary care.

Project 8

'Novel approaches for the treatment of dry eye disease'

Supervisors: Professor Conor Murphy and Joan Ní Gabhann-Dromgoole, Department of Ophthalmology and School of Pharmacy & Biomolecular Sciences

Project summary:

Inflammation is a key unifying factor for a range of ocular surface inflammatory diseases including autoimmune-mediated dry eye disease (DED) and complications with corneal transplantation (CT). While each condition has a specific presentation there are elements of overlap among them, most strikingly (i) immune-mediated inflammation driving disease pathology (ii) use of immune suppression/corticosteroids as a primary treatment option (iii) lack of mechanisms to effectively deliver therapeutics to the ocular surface and (iv) no diagnostic tests that allow identification of patients who will go on to develop further complications. Recently non-coding microRNA species have been shown to regulate inflammation. Synthetic DNA sequences that mimic or antagonise miR function are a new class of drugs which exhibit enhanced stability, target specificity and bioactivity. An ability to effectively modulate miR function and thus ocular inflammation has wide ranging therapeutic and commercial implications. This proposal aims to address these needs by identifying bio-markers and targeting the molecular mechanisms that underpin DED disease pathology, with a strong emphasis on translational application of these findings to develop both diagnostics and novel therapeutics. We have generated promising preliminary data from epigenetic studies in Sjogrens Syndrome patients, who present with severe autoimmune mediated DED, where we have identified novel microRNAs (miRs) that contribute to ocular inflammation and the development of DED. We will build upon these findings and the strengths of our multidisciplinary team to progress personalised medicine in ocular surface diseases by developing and optimising an idealised medical device for effective and targeted delivery of anti-inflammatory agents.

Project 9

‘A 3D melanoma model to study tumour biology and screen novel therapeutics’

Supervisor: Dr Olga Piskareva, Department of Anatomy & Regenerative Medicine

Project summary:

Skin tissue equivalents are gaining interest and investment for research and drug development as an alternative to traditional animal-free experimental models of human skin. 3D scaffold-based models are a recent advancement in cancer research because they bridge the gap between conventional 2D culture and tumours seen in patients. Oncology drugs tested in 3D models have increased likelihood of FDA approval and the global market for 3D models is expected to reach $1.7 billion by 2022.

This proposal focuses on the development of a bioengineered 3D in vitro platform MelanoColl for basic and translational research, clinical development of drugs and precision medicines. We propose to use well-characterised melanoma cell lines and grow them using collagen-based scaffolds in 3D (MelanoColl) to replicate the native tumour environment. We hypothesise that this 3D tumour model can predict patient response to therapy, shifting the paradigm for the evaluation of current and future therapeutic strategies in skin cancers. The ability of this model to predict drug response will be confirmed retrospectively using the clinical drug toxicity data. This platform will allow for an increase in drug screening options and combinations and a reduction of expensive animal models in pre-clinical research, accelerating the progression of promising drugs from development stage to patient treatment. This 3D platform can be used to model other skin-related conditions, e.g. inflammation by replacing melanoma cells with keratinocytes and macrophages for toxicological and cosmetic studies complying with the recent European legislation banning animal testing.

Project 10

‘Super-resolution microscopy of actin nodules in platelets’

Supervisor: Dr Ingmar Schoen, School of Pharmacy and Biomolecular Sciences

Project summary:

Platelets are small blood cells. Upon blood vessel injury, they adhere and aggregate at the wound site to stop bleeding. Whether they actively participate in the later remodelling of the blood clot is elusive. A recent report showed that platelets migrate at wound sites (Gaertner et al. 2017 Cell). How platelets were able to squeeze through the dense clot is not clear. Immune cells use specialized adhesion structures called podosomes for this purpose. The discovery of actin-rich ‘nodules’ in platelets that resemble podosomes (Poulter et al. 2015 Nature Communications) thus points towards a potentially similar, yet poorly understood, mechanism.

The aim of this project is to characterize the nanoscale architecture of actin nodules in platelets. To this end, the student will use techniques related to blood separation, immunostaining, state-of-the-art super-resolution microscopy, image analysis, and statistics. The formation of actin nodules in platelets will be induced. Fixed samples will be fluorescently stained for typical components of podosomes and imaged by STORM which yields an about 5x higher resolution compared to previous reports. By using one stained component as a reference, the relative localization of other proteins will be determined and the 3D architecture of the actin nodule will be reconstructed.

The Schoen Lab is very interdisciplinary. We adapt tools from physics to study cell mechanics and cell biology. Our research is driven by the need to develop better diagnostics and treatments for cardiovascular diseases.

Students with a physics or engineering background are specifically encouraged to apply.

Project 11

‘Engineering the virtual heart: reconstructing patient imaging to examine cardiac valvular disease’

Supervisor: Dr Claire Conway, Department of Anatomy & Regenerative Medicine

Project summary:

An estimated 5 million people have valvular heart disease in the United States alone. Valvular heart disease is now being described as the ‘next cardiac epidemic’. Given this clinical landscape, it is imperative that new treatments and devices are developed. Key to innovation in the valvular disease space, is bettering our understanding of the heart anatomy in both healthy and dysfunctional states.

In the clinic, different imaging types enable us to look into the patient’s heart, at both its structure and function. This anonymised imaging data can be reconstructed to create a 3D virtual heart. Within this project, a virtual reconstruction of the cardiac anatomy of an individual patient will form the basis for a library or databank of virtual patients. These reconstructions will also enable detailed examinations of cardiac structure that will be linked with Dr Conway’s group’s work in computational simulation of the mechanics of valvular disease and cardiac device simulation.

Within this project, the successful applicant will develop a protocol for cardiac image segmentation and reconstruction, perform a detailed literature review on cardiac imaging, and create a library of virtual patient hearts from cardiac imaging linked with clinical metrics of cardiac function.

Project 12

'Targeting Tamoxifen Pre-Resistance to prevent disease progression in breast cancer'

Supervisor: Jean McBryan, Department of Surgery.

Project summary:

Tamoxifen is an effective breast cancer drug. It stops estrogen from making cancer cells grow. However, sometimes cancer cells adapt and find another way to grow. This happens for 3 out of every 10 patients. It may be years or even decades before it happens. The adapted cells grow to form a secondary tumour. Once this happens, treatment success is limited.

Existing strategies to treat breast cancer are based on the biology of the initial tumour or the biology of the secondary tumour. Our fresh approach is to look at how the initial tumour cells change in response to therapy. We grow breast cancer cells in the lab and treat them with Tamoxifen until they adapt and become resistant. Rather than studying the resistant cells, we look at the genes and proteins that help to keep cells alive before they adapt to become resistant. By monitoring these molecular changes, we hypothesise that we will find novel opportunities to treat breast cancer. Indeed, we may already have the necessary drugs in our armoury; we just don't know it because no-one has ever studied this survival phase in detail.

Working in a vibrant lab with basic and clinical scientists, this research project will involve a range of lab techniques including cell culture, growth assays, PCR and western blot analysis. The student will work with the research team with the aim of defining a rational drug combination to prevent the formation of secondary, Tamoxifen-resistant breast cancers.

Project 13

‘ChemoGel - a novel thermoresponsive hydrogel for direct intratumoral delivery in solid tumours’

Supervisor: Dr Helena Kelly, Department of Pharmacy & Biomolecular Sciences

Project summary:

Systemic intravenous chemotherapy has long been a central pillar of cancer treatment, however the inherent physiological complexity of solid tumours present a significant barrier to effective drug delivery and treatment. This results in a need for higher systemic doses of drug, leading to increased toxicity and patient morbidity, often with limited efficacy. Thermoresponsive hydrogels loaded with chemotherapeutic drugs, for direct intratumoural administration in solid tumours have been proposed as a safer and more effective method of treatment for patients in certain scenarios.

ChemoGel is a novel chemoablative thermoresponsive hydrogel for delivery in solid tumours, specifically formulated to address past challenges with intratumoural delivery, in particular poor retention at the required site of action. ChemoGel’s thermoresponsive nature means it is a liquid at room temperature but a semi-solid gel at physiological temperatures. This enables direct delivery to a solid tumour via minimally invasive procedures where it will transition to a gel and be retained for a sustained period allowing for prolonged duration of action at the tumour site.

ChemoGel offers a platform technology for use in chemical ablation of solid tumours using existing chemotherapeutic drugs, in conjunction with other treatment approaches. However, ChemoGel also shows intrinsic anti-tumour activity. The aim of this project is to evaluate the efficacy and toxicity of ChemoGel and its excipients. The intern will gain experience in hydrogel formulation and material characterisation. They will also receive training in cell-culture and in vitro studies on relevant cell-lines, including evaluation of cell viability (e.g. Live/Dead staining and microscopy) and metabolic assays (e.g. CCK-8).

Project 14

‘Nanomedicines for mucosal drug delivery’

Supervisor: Professor Andreas Heise, Department of Chemistry.

Project summary:

Mucus is a hydrated viscoelastic gel that lines epithelial cells in the respiratory, digestive, and urogenital systems, as well as the eyes. The delivery of therapeutics through mucosal surfaces, such as lung airways, GI tract, female reproductive tract, nose and eye, is particularly attractive as a localized, non-invasive form of drug delivery to target tissue and also to the systemic circulation. However, the development of biomaterials that efficiently penetrate mucus and tissues remains challenging due to the fact that the biological role of the mucus layer is to protect the body by rapidly trapping and removing foreign particles. We have recently developed new mucus penetrating nanomaterials based on star-shaped polypeptides which efficiently permeated isolated rat mucus and intestinal jejunal tissue mounted in Franz diffusion cells. These materials offer significant advantages such as full biodegradability and straightforward synthesis over other reported mucus penetrating systems.

The aim of this project is the systematic testing of polypeptide nanocarriers for drug delivery across the mucosal layer. It will involve the formulation of nanoparticle drug conjugates and the monitoring of their permeation through artificial mucus layers of various thickness. Permeation, particle degradation and drug release will be accessed using analytical tools such as Gel Permeation Chromatography (GPC), High- Performance Liquid Chromatography (HPLC) and Infrared Spectroscopy (IR). Promising nanoparticle/drug combination will be tested ex vivo on rat mucus and intestinal jejunal tissue.

Project 15

'Why does α-synuclein in Multiple System Atrophy not form Lewy bodies like the other alpha-synucleinopathies?'

Supervisors: Dr Melanie Focking, Dr Conor Fearon, Professor Michael Farrell and Professor David Cotter, Departments of Psychiatry and Clinical Neurological Service.

Project summary:

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder which can affect movement, balance and the autonomic nervous system (the part of the nervous system that controls involuntary action such as blood pressure or digestion). The signs and symptoms reflect the progressive loss of function and death of specific types of nerve cells in the brain due to aggregation of the protein α-synuclein in the cytoplasm of oligodendrocytes. α-synuclein is also the protein responsible for Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB), however in these cases, the protein accumulates in the neurons.

Based on the current literature, our research question is:
Why does α-synuclein form neuronal (Lewy body) inclusions in PD and DLB, but forms cytoplasmic inclusions (GCIs) in oligodendroglial cells in MSA creating two very different forms of neurodegeneration?

We are planning to initially use mass spectrometry to test different brain regions of both diseases: substantia nigra (where Lewy bodies should be in greatest concentration in PD), pons/putamen (where GCIs should be in greatest concentration in MSA) and normal grey/white matter. This will allow us to detect differential expression of α-synuclein and other proteins between diseases and compared to healthy controls. We will also use pathway analysis tools to determine which sets of proteins are most relevant to α-synuclein. Different methods will then be used to validate the most promising findings (e.g. ELISA, Western Blotting).

Project 16

'BET inhibition as a rational therapeutic strategy for Invasive Lobular Breast Cancer (ILBC)'

Supervisor: Dr Elspeth Ward, School of Pharmacy and Biomolecular Sciences.

Project summary:

What's the project about?
Invasive lobular breast cancer (ILBC) is a form of hormone receptor-positive (ER+) breast cancer that accounts for about 10-15% of all new breast cancer cases diagnosed. Since it is ER+, it is treated the same way as all other ER+ breast cancer, with surgery, radiotherapy, anti-hormone therapy (and in many cases, chemotherapy). However, patients with ILBC do not have the same clinical course as other ER+ patients. Their cancer is more likely to (i) spread to the ovaries and the digestive system, (ii) occur in both breasts, (iii) come back in the other breast (iv) be unresponsive to additional chemotherapy (as well as having the same problems with hormone therapy-resistance as other forms of ER+ breast cancer). In addition to a different clinical course, the tests used to determine treatment options for ER+ patients (such as OncotypeDx), give very different results for ILBC patients, making it difficult to determine the most appropriate treatment plan. As such, the lack of tailored options for ILBC patients represents an unmet clinical need and it is time we start to consider ILBC as a distinct type of ER+ breast cancer and devise new treatment and diagnosis options specifically for these patients. Our research suggests that some ILBC patients who do not respond to anti- hormone therapy would benefit from using a BET inhibitor, and the remaining patients from a combination with an anti-FGFR drug. This project will confirm whether BET inhibitors are a useful treatment option for ILBC patients and which drugs we need to combine them with to reach the best outcome for ILBC patients.

What will I learn during this project?
The specific aims of this project will be to test the use of BET inhibitors in a pre-clinical model of ILBC, as well as the combination with anti-FGFR drugs, using BET sensitive and resistant ILBC cell lines. The student will receive training in cell culture, in vitro growth assays, apoptosis assays, RNAi technology, Western blotting, qRT-PCR, and determination of drug synergy using Compusyn software.

The Molecular Oncology Laboratory at the School of Pharmacy & Biomolecular Science (https://www.rcsi.com/people/profile/darranoconnor), is a young, vibrant and well-funded research group focused on the identification and mechanistic anchoring of novel cancer biomarkers and therapeutic targets.

Examples of recent work by the group:

1. Walsh L, Haley K, Moran B, Mooney B, Tarrant F, Madden S, di Grande A, Fan Y, Das S, Rueda O, Dowling C, Vareslija D, Chin SF, Linn S, Young LS, Jirström K, Crown JP, Bernards R, Caldas C, Gallagher WM*, O'Connor DP*§ & Ní Chonghaile T*. BET inhibition as a rational therapeutic strategy for invasive lobular breast cancer. Clin Cancer Res 2019 Dec 25 (23), 7139-7150 (impact factor 10.199) Journal Quartile Rank: Oncology Q1 *Equal Contribution, §Corresponding author

2. Smeets D*, Miller IS*, O'Connor DP*, Das S, Moran B, Depreeuw J, Gaiser T, Betge J, Barat A, Klinger R, van Grieken NCT, Cremolini C, Prenen H, Boeckx B, Bacon O, Fender B, Brady J, Hennessy BT, McNamara D, Kay EW, Verheul HM, Maarten N, Gallagher WM, Murphy V, Prehn JHM, Loupakis F, Ebert MP, Ylstra B, Lambrechts D & Byrne AT. Copy number load predicts outcome of metastatic colorectal cancer patients receiving bevacizumab combination therapy. Nature Commun 2018 Oct 5;9(1):4112. (impact factor 12.353) Journal Quartile Rank: Biochemistry, Genetics and Molecular Biology Q1 *Equal Contribution

3. van Dijk E, Biesma HD, Cordes M, Smeets D, Neerincx M, Das S, Eijk PP, Murphy V, Barat A, Bacon O, Prehn JHM, Betge J, Gaiser T, Fender B, Meijer GA, McNamara DA, Klinger R, Koopman M, Ebert MPA, Kay EW, Hennesey BT, Verheul HMW, Gallagher WM, O'Connor DP, Punt CJA, Loupakis F, Lambrechts D, Byrne AT, van Grieken NCT & Ylstra B. Chromosome 18q11.2-18q21.1 loss predicts response to bevacizumab for patients with metastatic colorectal cancer. J Clin Oncol 2018 Jul 10;36(20):2052-2060 (impact factor 26.303) Journal Quartile Rank: Oncology Q1.

Project 17

'In-silico characterisation of immune checkpoint alterations and evaluation of their significance in predicting clinical outcome in patients with HER2+ breast cancer from the TCHL trial?'

Supervisor: Prof Darran O'Connor, School of Pharmacy & Biomolecular Sciences.

Project summary:

Immune checkpoints play a crucial role in tumour progression as these checkpoints regulate T cells. Deregulation of these molecules allow tumour cells to avoid destruction by the immune system [1], [2]. Drugs like ipilimumab, pembrolizumab and nivolumab target these immune checkpoints and have dramatically improved cancer therapy [3]–[5]

Currently none of these novel immunotherapy drugs are approved for treatment in breast cancer, but it has been shown that the alteration of immune checkpoints are involved in breast cancer progression and are prognostic markers for recurrence [6].

As part of an ongoing project we are analysing multi-omics (DNA, RNA, DNA Methylation) data of matched HER2+ breast cancer tissue acquired pre- and post-treatment of docetaxel, carboplatin and trastuzumab (TCH), and randomised with addition of lapatinib (TCHL). The aim of this project is a profound characterisation of HER2+ breast cancer, leading to better understanding of the disease, and identification of clinically prognostic and predictive characteristics. This information will eventually be used to develop a prototype decision support tool for the treatment of patients with HER2+ breast cancer.

The student's project will be to analyse the pre-processed, cleaned multi-omics data with regards to alteration of immune checkpoints. Part of the project will be a literature review on genes involved or related to immune checkpoints. The student will further extract the information for the identified genes from the multi-omics data. In this dataset the student will investigate the predictive and prognostic roles of immune checkpoint activation in pre-treatment samples, and the changes in post-treatment samples and how these relate to treatment and response.

Experience in basic usage of R is beneficial but not required.

[1]D. R. Leach, M. F. Krummel, and J. P. Allison, 'Enhancement of Antitumor Immunity by CTLA-4 Blockade', Science, vol. 271, no. 5256, pp. 1734–1736, Mar. 1996, doi: 10.1126/science.271.5256.1734.
[2]G. J. Freeman et al., 'Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation', J. Exp. Med., vol. 192, no. 7, pp. 1027–1034, Oct. 2000, doi: 10.1084/jem.192.7.1027.
[3]M. Reck et al., 'Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer', N. Engl. J. Med., vol. 375, no. 19, pp. 1823–1833, 10 2016, doi: 10.1056/NEJMoa1606774.
[4]C. Robert et al., 'Nivolumab in previously untreated melanoma without BRAF mutation', N. Engl. J. Med., vol. 372, no. 4, pp. 320–330, Jan. 2015, doi: 10.1056/NEJMoa1412082.
[5]F. S. Hodi et al., 'Improved survival with ipilimumab in patients with metastatic melanoma', N. Engl. J. Med., vol. 363, no. 8, pp. 711–723, Aug. 2010, doi: 10.1056/NEJMoa1003466.
[6]D.-W. Lee et al., 'Immune recurrence score using 7 immunoregulatory protein expressions can predict recurrence in stage I-III breast cancer patients', Br. J. Cancer, vol. 121, no. 3, pp. 230–236, Jul. 2019, doi: 10.1038/s41416-019-0511-9.

Project 18

‘Synthesis and functionalisation of gold nanoparticles with attenuated protein corona’

Supervisor: Dr Marco Monopoli, Department of Chemistry

Project summary:

Nanotechnology is one of the primary drivers of technology innovation, where nanoparticles (NP) of 100nm or less, have the potential to treat chronic diseases as they are capable of targeting diseased area and carry drugs. Their enhanced therapeutic effect is caused by their small size as they are actively processed by cellular machineries and they are capable of crossing the biological barriers and penetrate diseased tissue for a selective and targeted therapeutic effect. Despite these high expectations, their clinical translation has been obstructed by many factors affected the NPs efficacy. These factors include, but not limited to, the NP stability in complex fluid, such as blood or cell culture media, which contain thousands of biomolecules including proteins, lipids and sugars that can adsorb on the surface of NPs forming what is called protein corona. The resulting corona constitutes the actual NPs' surface of interaction with biological cell membranes and strictly dictates the NPs’ biological fate including cellular uptake, toxicity, biodistribution, etc. Therefore, engineering the NPs’ surface has been used as a successful strategy to control the biomolecular adsorption on the NP surface can increase their colloidal stability and control the formation of proteins corona, which can increase/ improve the NPs efficiency. In this context, the object of this study is to modify the NP surface in order to Increase the NP colloidal stability and biocompatibility and to prevent the biomolecular adsorption and maintains corona-free behavior of the NPs in the physiological environment.

Project 19

'Old drugs new tricks'

Supervisor: Dr Marian Brennan, School of Pharmacy & Biomolecular Sciences.

Project summary:

The development of a new drug is estimated to cost approximately $2.6 billion. While the costs have gone up year on year, the approval rates have gone down, with only 12% of candidates entering clinical trials being approved. Many approved drugs have off-target effects. Some of these can be significant, allowing some drugs to be approved as a treatment for more than one disease. This is one way to identify a new drug at a lower cost, allowing it to be fast tracked into the clinic. An alternative is to also investigate drugs that have failed in clinical trials. Many drugs fail in development due to lack of effect for the disease they are being tested. This project involves using bioinformatic tools to identify new uses for drugs that are already approved. This project will also investigate new uses of drugs that have already completed phase II clinical studies and therefore have been shown to be safe in humans. We will use 3D structural analysis of disease targets and high-throughput screening of approved drugs and post phase II compounds in silico. Applying this methodology can progress drugs to the clinic faster providing benefits to patients. We will look at novel targets for orphan diseases with no current treatment. It would be beneficial for students who choose this project to have an interest in bioinformatics, chemoinformatics or programming. Programming skills are not necessary, but enthusiasm for manipulating large data sets, and running computational experiments is required.

Project 20

'Barriers and Enablers in Providing Laparoscopic Cholecystectomy Procedures as Day Cases'

Supervisors: Professor Jan Sorensen (Health Outcome Research Centre), Professor Deborah McNamara (National Clinical Programme for Surgery) and Dr Dara Kavanagh (Department of Surgery).

Project summary:

The national HSE has formulated key performance indicators for Laparoscopic Cholecystectomy (Lap Chole) which suggest that 60% should be done as day cases. This is a modest target. Recent data from the National Quality Assurance Information System (NQAIS) shows that there is huge variation ranging from 0.7% to 95% despite the national DRG-tariff incentivise day case surgery (same tariff for day case and inpatient). The system factors that impact the observed variation are poorly understood.

The purpose of this project is to develop clarity to system factors that may differentiate hospitals with high day case rate from hospitals with low day case rate.

This project will apply a mixed-method approach and use quantitative methods to analyse hospital episode data from NQAIS and qualitative methods to explore barriers and enablers of Lap Chole day case provision.

Based on the quantitative analysis we will identify the three top and three bottom ranging hospitals in terms of Lap Chole day case rates. For these hospitals we will conduct face-to-face audio recorded interviews with staff representing surgeons, anaesthetists, nurse managers and general managers from each hospital.

Interview guides will be developed informed by the quantitative analysis and will include open-ended questions relating to perceived enablers and barriers to the provision of Lap Chole day case procedures.

Before the interview, consent will be obtained and participants will be informed about the purpose of the study and that their answers will remain confidential and anonymous. Interviews will be audio recorded and transcribed verbatim and anonymized.

The transcribed data will be analysed with a grounded theory approach by using standardised coding system developed during the readings. These codes will be grouped to identify themes from the texts. Themes will be analysed by background and site of the interviewees.

The analysis will be documented in a scientific manuscript aimed at publication in a academic surgical journal.

Project 21

‘Development of a prototype intestinal patch to improve intestinal permeation of poorly absorbed drugs’

Supervisor: Dr Sam Maher, School of Pharmacy & Biomolecular Sciences.

Project summary:

The oral route of administration is the cornerstone for the successful use of medicines in healthcare. A growing number of promising bioactive chemical entities are poorly absorbed via the oral route. Hydrophilic macromolecules such as peptides, proteins and carbohydrates are often shown to have improves safety, efficacy and tolerability compared to small molecules, but the size and molecular complexity that imparts these desirable properties also imparts sub-optimal permeation across the GI tract into the systemic circulation. These actives must be either formulated as injectable dosage forms or excluded from pharmaceutical development. There is growing demand for delivery technologies that address low and variable oral absorption of hydrophilic macromolecules. Technologies that facilitate absorption of poorly permeable molecules would permit reformulation of several marketed injectable drugs, diversify discovery screening and enrich the pharmaceutical pipeline. The objective of this research is to design a prototype bioadhesive intestinal patch loaded with a poorly permeable active and an absorption modifying excipient. Adhesion of the patch to the gut wall will create a microclimate where the active can be co-presented with an excipient that transiently alters intestinal permeability, which may facilitate transport of the active across the intestinal wall. The successful candidate will prepare a panel of prototype patches and determine if permeation from the patch is more effective than aqueous solution in intestinal cell culture monolayers.

Project 22

'A key role for FKBPL in the regulation of cancer stem cell signalling and the microenvironment; therapeutic implications for tumour growth and metastasis'

Supervisor: Professor Tracy Robson, School of Pharmacy & Biomolecular Sciences.

Project summary:

Cancer stem cells (CSCs) are a special type of cell found within tumours that are able to undergo unlimited self-renewal and are highly resistant to therapy. Indeed, these cells are left behind and go on to divide rapidly, leading to tumour regrowth. Even more worryingly, this population of cells have special features allowing them to move through the body, invading vital organs; a process known as metastasis. We have identified a novel protein, called FKBPL, that occurs naturally in the body and which inhibits tumour blood vessel development, thereby stopping tumour growth. A therapeutic drug derived from the protein and designed to harness its therapeutic effects, has successfully completed phase I cancer clinical trials and was recently granted Orphan Drug status in ovarian cancer by the Food and Drug Administration (FDA), to facilitate development. However, we have acquired data which suggests that this protein also targets breast and ovarian CSCs by transforming them into a more 'normal' cancer cell, which can be more easily killed by chemotherapy. This project will assess the impact of FKBPL on CSCs and other cells within the ovarian tumour microenvironment that are known to support the growth and survival of CSCs cells in the primary tumour and at distant sites. We will evaluate exactly how FKBPL controls these cells and the implications on the ability of CSCs to become metastatic. Understanding how this protein works will allow us to design future clinical trials that are more likely to demonstrate better response rates in cancer patients.

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McClements L, Yakkundi A, Papaspyropoulos A, Harrison H, Ablett MP, Jithesh PV, McKeen HD, Bennett R, Donley C, Kissenpfennig A, McIntosh S, McCarthy HO, O'Neill E, Clarke RB, Robson T. Targeting treatment resistant breast cancer stem cells with FKBPL and its peptide derivative, AD-01, via the CD44 pathway. Clin Cancer Res. 2013 Jul 15;19(14):3881-93. PMID: 2374106.

Annett S., Moore G., Short A., Marshall, A., McCrudden, C., Yakkundi, A., Das, S., McCluggage, W.G., Nelson, L., Harley, I., Moustafa, N., Kennedy, C. J., DeFazio, A., Brand, A., Sharma, R., Brennan, D., O'Toole, S., O'Leary, J., Bates, M., O'Riain, C., O'Connor, D., Furlong, F., McCarthy, H., Kissenpfennig, A., McClements, L., Robson, T. (2019) FKBPL based peptide, ALM201, targets angiogenesis and cancer stem cells in ovarian cancer. British Journal of Cancer. doi:10.1038/s41416-019-0649-5

Project 23

‘Does substrate stiffness contribute to the inflammatory response of spinal cord glial cells?’

Supervisor: Dr Adrian Dervan, Department of Anatomy & Regenerative Medicine.

Project summary:

Spinal cord injury (SCI) is one of the severest traumatic events suffered by the human body. Because of the poor outcomes seen after injury, extensive research has identified many of the pathophysiological processes that occur following cord damage; one such structure is the complex inhibitory glial scar tissue that develops at the site of injury and is a potent barrier to axon regrowth. Astrocytes, the major non-neuronal cells of the CNS are a major component of the glial scar and change to a reactive scar-forming phenotype.

We are developing an axon guidance scaffold (AGS) system based on successes in peripheral nerve regeneration (e.g. Roche et al. (2017) Stem Cells Trans Med, 6:1894–1904), for therapeutic insertion into the injured spinal cord to encourage axon growth and restore function. The scaffold will consist of a complex 3D printed scaffold built from the biodegradable polymer Polycaprolactone (PCL) that will integrate and bridge the injured cord tissue. The AGS structure should not exacerbate cellular responses in the lesion site and scaffold stiffness is known to have a strong effect on cellular physiology (e.g. Moshayedi et al. (2014) Biomaterials 35: 3919-3925). Understanding the interaction between polymer stiffness and astrocytes is essential for proper AGS design and functionality. This project will assess the effects of PCL polymer stiffness on astrocyte physiology and will consist of culturing glial cells on polymers with three different levels of stiffness and determining changes using histological staining combined with immunohistochemistry.

Project 24

‘Developing new tools to understand how blood clotting enzymes talk to cells’

Supervisor: Dr Roger Preston, School of Pharmacy & Biomolecular Sciences.

Project summary:

Protease-activated receptor 1 (PAR1) is a cell surface receptor expressed on the surface of blood vessels that has an important role in transmitting cell signalling by blood coagulation enzymes. Dysregulated PAR1 activity has been shown to contribute to thrombosis, inflammatory disease and tumour cell metastasis. The blood protease activated protein C (APC) activates PAR1 to protect cells from inflammatory or toxic stimuli. Despite this, we do not fully understand how APC signalling via PAR1 occurs. An enhanced understanding of the molecular parameters that control PAR1 signalling by APC is particularly important, given the early promise of recombinant APC variants for the treatment of inflammatory disease.

The objective of this study is to identify how APC activation of PAR1 causes an APC-specific cell signalling response. This will be achieved using a combination of state-of-the-art molecular biology and cell signalling techniques that are well-established in the Preston lab.

The project will be performed under the supervision of Dr Roger Preston. The Preston lab (www.prestonlab.com) is a multi-disciplinary research group with well-established expertise and an international reputation in the study of the mechanistic basis of coagulation enzyme signalling.

Willis Fox O, Preston RJS. Molecular basis of protease-activated receptor 1 signaling diversity. *J Thromb Haemost.* 2020 Jan;18(1):6-16.

Project 25

‘Epigenomic regulation of breast cancer brain metastasis’

Supervisors: Dr Damir Varešlija and Professor Leonie Young, Department of Surgery.

Project summary:

Our group is focused on the molecular mechanisms underlying metastatic spread in breast cancer. With a particular focus on breast-cancer-brain-metastasis, we aim to identify new vulnerabilities that can be exploited as novel therapeutic opportunities.

Although treatment therapies for primary breast cancer have improved, aggressive breast cancer which spreads to the brain, known as brain metastasis, has inadequate treatment options and poor survival outcomes. Brain metastases occur in 10-30% of patients with metastatic breast cancer. Even where treatment is successfully controlling cancer elsewhere in the body, brain metastases often grow rapidly. More than half of the patients diagnosed with brain metastases will die within a few months

The objective of our work is to identify the key features which enable a breast tumour to spread from the breast to brain. We use a variety of molecular profiling and next-generation sequencing approaches to identify brain metastasis epi-genetic switches (various chemicals turning genes on/off) that will enable the development of new therapeutic strategies. Our previous studies of breast cancer patients’ biopsies revealed how cancer cells can transform to survive in the brain. Using state-of-the-art models of brain metastasis, we test whether controlling these chemical switches can regulate faulty genes to 1) stop cancer cells from spreading to the brain; 2) kill growing brain metastasis.

Considering more than half of the patients diagnosed with brain metastases succumb to disease within months, our proposed research aims to benefit those with very limited treatment options. Our study will use both genetic and drug based approach to test the therapeutic benefit of targeting potential vulnerabilities identified in our epi-genomic profiling of breast cancer brain metastasis.

Project 26

‘Students’ views, experiences and expectations of public and patient involvement and engagement in healthcare professionals’ education - a qualitative exploration’.

Supervisors: Professor Judith Strawbridge, School of Pharmacy & Biomolecular Sciences.

Project summary:

There is increasing recognition that patients and the public have an integral role in the teaching of healthcare professionals. Many studies have demonstrated that, not only is it feasible to have patient and public involvement and engagement (PPI/E) in education, this involvement has the capacity for motivating students by fostering empathy, demonstrating the relevance of learning and encouraging the development of key professional skills such as communication.[1] Despite the well-documented benefits of PPI/E, patient involvement in education is currently at a low level. Attempts are being made by academic institutions to expand patient involvement so that patients act as central participants in the design of curricula and in the delivery of education. The primary research question of this project is to investigate the views, experiences and expectations regarding PPI/E from the students’ perspective. We aim to find out how students would like the public and patients to be involved in their education, what they have gained from it and/or what they expect to gain from this involvement. This question will be answered primarily based on information acquired during focus group sessions, and the data generated will help form recommendations for the development of a strategic framework for PPI/E.

1 Regan De Bere S, Nunn S. Towards a pedagogy for patient and public involvement in medical education. Med Educ. 2016;50(1):79-92.

Project 27

'The development of bioengineered scaffolds with pathological mechanical properties to recapitulate and understand idiopathic pulmonary fibrosis pathophysiology'

Supervisor: Dr Cian O'Leary, School of Pharmacy & Biomolecular Sciences.

Project summary:

Despite the encouraging clinical impact from recently-approved anti-fibrotic drugs, idiopathic pulmonary fibrosis (IPF) persists as a devastating disease that requires new therapies to reduce its significant morbidity and mortality within 3-5 years of diagnosis. Although IPF pathogenesis is incompletely understood, a central component is dysregulated communication between epithelial cells and the surrounding stroma within the lung microenvironment, resulting in excessive extracellular matrix (ECM) deposition by myofibroblasts that aberrantly remodel alveoli with excessive, fibrotic matrix, and loss of respiratory function. Accordingly, pathophysiologically-relevant human disease models of IPF are warranted that accurately integrate the prominent features of stroma in disease progression. However, current preclinical cell models fail to recapitulate the contribution of ECM that influences a range of cell and tissue characteristics; for IPF, changes in the composition and physical properties of the lung tissue can influence pro-fibrotic signalling to exacerbate disease progression, with possible modulation on pharmacological action of a novel therapeutic. Thus, it is paramount to not only develop new medicines for the treatment or improved management of IPF, but also to utilise organotypic cell models that exhibit the key features of the human pathophysiology for more relevant and robust preclinical data prior to animal testing and human trials.

Tissue-engineering strategies are capable of improving physiologically-relevant in vitro disease models by supporting long-term cellular growth and differentiation, in addition to co-culture with multiple cell types. Previous work by our group has successfully manufactured collagen-based scaffolds as 3D respiratory co-culture models of the normal tracheobronchial airway region. Accordingly, the objective of this project is to use our current model as a platform to develop to develop a bioengineered model of co-cultured IPF cells in a biomaterial ECM analogue as an organotypic in vitro disease model.

Specifically, the student will utilise scaffold manufacture techniques together with cell culture and in vitro analysis to create a dynamic model with the capacity to exhibit the stiffness of fibrotic tissue, and to examine how this stiffness mediates cell behaviour in disease. In this way, this model will serve as a novel platform to identify new "druggable" disease mechanisms that can potentially pave the way towards the development of life-saving therapies in IPF.

Project 28

‘HealthEIR: Developing innovative design-based care models for community-based health promotion’

Supervisor: Dr Michelle Flood, School of Pharmacy & Biomolecular Sciences.

Project summary:

The challenges of keeping people healthy through promoting health behaviours are well established, and existing national and international campaigns have demonstrated limited success. The HealthEIR project is an interdisciplinary project, nationally funded by Slaîntecare that aims to develop, implement, and evaluate new models of health promotion in community health settings (pharmacy and general practitioner/family doctors).

Drawing together the skills of health workers, patients/public, designers, and researchers, this project aims to develop radically new ways of delivering health promotion in the community through combining innovative technology with human-centred design. The project includes collaborators from the School of Pharmacy and Biomolecular Sciences (RCSI), Department of General Practice (RCSI), Department of Psychology (RCSI), the National College of Art and Design (NCAD), and Technological University Dublin (TUD) and an industry partner.

Working as part of the interdisciplinary team, the student will receive day-to-day support to conduct research and develop skills in both traditional research (e.g. systematic reviews, quantitative methods, and qualitative methods) and design research (e.g. fieldwork, observations, task analysis, usability testing, and service blueprint development). The student will develop a unique skillset to build on in the future, through dedicated support. The student will have day-to-day support from both a postdoctoral researcher and interaction designer, as well as meetings with wider study team several times a week, and be encouraged to actively contribute ideas as an important member of the team. No specific previous experience or training is required.

Project 29

'The effect of serum deprivation on breast cancer cells in a 3D collagen-based scaffold model'

Supervisor: Dr Caroline Curtin, School of Anatomy & Regenerative Medicine.

Project summary:

Breast cancer, a complex, multifactorial disease that usually presents as solid 3D tumours, is the most common cancer in women worldwide. Culturing of cancer cells in 2D has traditionally been used to study complex tumorigenic mechanisms but lacks the structural microenvironment required for cell-cell and cell-extracellular matrix interactions. The alternative involves animal xenograft models but also has various limitations. Recently, 3D cancer cell culturing has been proposed to bridge the gap between conventional 2D culture and in vivo tumours by enabling cells to acquire phenotypes and respond to stimuli similar to in vivo biological systems. Collagen-based scaffolds capable of supporting cell culture have been widely used as 3D cancer models within our laboratory [1, 2]. Recent studies have demonstrated the involvement of collagen 1 in breast cancer cell survival even in the presence of serum-depleted conditions in 2D culture [3]. Thus, we are interested to assess this phenomenon in our 3D collagen-based scaffolds. Briefly, cell-seeded scaffolds will be deprived of serum following 24hrs of normal cell culture and cultured for a further 48 hours or 7 days before analysis. Gene expression, histology and DNA assays will be performed. Apoptosis and Bax expression, which have been shown to decrease in serum-deprived conditions, will be compared to breast cancer cells grown on plastic and serum-treated cell-scaffolds.

1. Fitzgerald, K.A. et al. Biomaterials, 2015. 66: p. 53-66.

2. Curtin, C. et al, Acta Biomater, 2018. 70: p. 84-97

3. Badaoui M et al. Oncotarget. 2017. 9(37):24653-24671.

Project 30

'Targeting mRNA polyadenylation as novel treatment strategy in epilepsy'

Supervisor: Dr Tobias Engel, Department of Physiology.

Project summary:

Epileptogenesis, the process leading to a reduced threshold for seizures after transient brain insults, is associated with large-scale changes in gene expression which ultimately lead to the formation of seizure-generating neuronal networks. Targeting single genes has repeatedly failed to alter the development of epilepsy or reduce the percentage of drug-refractory patients, suggesting approaches which target larger signaling networks may be required. First, however, we must precisely understand which pathological changes contribute to the development of epilepsy and to the maintenance of the epileptic state.

Cytoplasmic polyadenylation is a process by which dormant, translationally inactive mRNA become activated by the elongation of their poly(A) tails. Cytoplasmic polyadenylation element binding proteins (CPEBs1-4) are central factors controlling polyadenylation-induced translation. In the brain, CPEBs mediate numerous cellular processes including long-term potentiation, synaptic plasticity and neurotransmitter receptor expression, processes altered during epileptogenesis. Our data shows, for the first time, that CPEB expression is changed in experimental models of epilepsy and in drug-refractory epilepsy patient brains and by using mRNA arrays, we have demonstrated mRNA polyadenylation changes affecting up to 20% of the transcriptome during epilepsy. To date, however, neither changes in polyadenylation, nor the contribution of cytoplasmic polyadenylation to disease progression have been studied in the setting of epilepsy. By using experimental models of epilepsy and patient tissue, this project will characterize and decipher an untested layer of gene control contributing to epileptogenesis and provide a new set of therapeutic target genes with a different mechanism of action to better treat patients with epilepsy.

Project 31

‘Development of a drug delivery system containing Allopurinol for loco-regional delivery to the heart post myocardial infarction’

Supervisor: Dr Aamir Hameed, Department of Anatomy & Regenerative Medicine.

Project summary:

Heart failure is defined as inability of the heart to supply adequate blood to the body. It can occur due to the injury to the heart muscle. The most common cause is blockage of the blood vessels in the heart, commonly referred to as a ‘heart attack’. As the demographics suggest, with increasing ageing population, prevalence of heart failure is also increasing. Depending upon the severity of the disease, the ability of the affected heart muscle to beat and pump blood around the body can be reduced. Therefore the heart has to do extra work to try and pump the blood to the whole body. This can cause the heart to become enlarged. One of the causes of this process is thought to be the inflammatory process following a heart attack. Current medical care and surgical/device based therapies help in relieving the symptoms but they do not address the underlying cause. There is a need to reduce the inflammation to reduce the development of heart failure. In this research project, we will develop a loco-regional drug delivery platform to deliver the medicines that can effectively reduce the inflammatory process, thus reducing the damage to the heart. And lowering the likelihood of developing heart failure.