RCSI StAR
INTERNATIONAL PhD PROGRAMME
RESEARCH PROJECTS

RCSI
Leading the world to better health

RCSI STAR INTERNATIONAL PHD PROGRAMME

RCSI's Strategic Academic Recruitment (StAR) Programme is now recruiting 5 prestigious fully funded PhD scholarships. This programme aims to attract high-achieving international students to an efficient four-year structured PhD training programme at RCSI.

The RCSI StAR PhD Programme aims to encourage scientists to develop innovative research projects in one of RCSI's areas of research strength, including but not limited to:

- Biomaterials and Regenerative Medicine
- Cancer
- Neurological and Psychiatric Disorders
- Population and Health Systems
- Surgical Science and Practice
- Vascular Biology
- Respiratory Medicine
- Gynaecology, Obstetrics & Perinatal Health
- Pharmacy, Pharmaceutical Sciences & Chemistry
- Infection, Immunity and Inflammation

RCSI

The Royal College of Surgeons in Ireland (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. As such it is the most internationally focused HEI in Ireland and is ranked 4th worldwide in terms of the percentage of international students enrolled in our core programmes. RCSI has been ranked among the top 2% of universities worldwide in the 2019 Times Higher Education (THE) World University Rankings and ranks second out of nine institutions in the Republic of Ireland. RCSI's performance in the rankings is linked in particular to the College's research strength reflected by a publication field-weighted citation impact that is the highest in Ireland and twice the world average. 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.

BENEFITS

- Opportunity for an international research training experience in a world class institution
- Four-year structured PhD training programme with the opportunity to gain an additional Professional Certificate in Research Practice
- Funded four-year PhD Scholarship, covering student fees (€6,950 p.a.) and student stipend (€18,000 p.a.).
- Relocation package: €5,000 per student
- Annual home travel allowance: ~€300-€800 p/a – depending on EU/Rest of World

PROGRAMME

The RCSI StAR International PhD Programme aims to encourage scientists to develop innovative research projects in the field of Health Sciences. Depending on the focus of the PhD research, students will choose their project based on 3 internal 10 week rotations or students will develop their proposal through the SPHeRE programme (Population Health and Health-services Research).

This structured training programme will include compulsory core modules in ethics, science communication, biostatistics and intellectual property. Core modules are complemented by many additional optional modules delivering skill sets including innovation and entrepreneurship, data management, coding. The structured training is designed to suit bench scientists, informatics based research, clinical researchers, and population heath researchers.

ELIGIBILITY

The PhD Programme is oriented towards high achieving overseas international students with a strong profile and a background in Biomedical Research, Clinical Research, Population Health Research, or Health Services Research coming from primary degree courses focusing on: Cell and Molecular Biology; Clinical and Translational Sciences; Medical Sciences (Biochemistry, Pharmacology, Physiology, Anatomy etc); Bioengineering; Pharmacy; Physiotherapy; Nursing and Midwifery; Medicinal Chemistry; Genetics and Neurosciences; Population Health; Social Sciences; Health Services Research; Education in Health Sciences.

- Students will have obtained or be about to obtain a 1st Class Honours degree or equivalent (i.e. top 10 % of primary degree - or equivalent) and should provide a grade point average (GPA) for each completed year of undergraduate degree.
- English requirements: IETLS ≥6.5 or must have completed primary degree through the medium of English.
- Preference will be given to applicants coming directly from their undergraduate degree into this PhD programme.
- Applicants have to use the GPA calculator we recommend.
- Applicants who do not submit all supporting documents will be deemed ineligible.

APPLICATION PROCESS

Details of available research projects and application portal will be available from 28th Sept 2018 at www.rcsi.ie/StARPhD.

Students must submit:

- a completed application form, detailing academic progress to date (with GPA)
- CV/Resume
- supporting tutor letter from degree awarding institution
- brief motivational statement describing your career plans.

Full details can be found at www.rcsi.ie/StARPhD.

Applications Open	12th October 2018
Applications Close	16th November 2018 (17:00 GMT)
Interviews	Week of 10th December 2018
4 year PhD Position begins	1 October 2019

INFORMAL ENQUIRIES

For informal enquiries or questions about the application process please contact starphd@rcsi.ie

Summary of available research projects

Research Theme: Biomaterials and Regenerative Medicine

Research project 1: Non-viral gene therapy to prevent cartilage degeneration in Osteoarthritis
Supervisors: Dr Caroline Curtain, Dr Oran Kennedy and Prof Fergal O'Brien, Anatomy, RCSI.
Research Project Description: Osteoarthritis (OA) is the most common form of joint disease, affecting one in five people in the EU and results in activity limitations for approximately one in ten. There is no treatment to reverse or prevent the progression of OA, with the two primary options being pain management, or ultimately total joint replacement. For pain management, intra-articular (IA) steroid injections are regularly used to postpone joint replacement. **Crucially steroid injections reduce inflammation, and thus pain, but do not actually target or alter the behaviour of cells or tissues within the joint and have recently been reported to actually increase cartilage loss.** Therefore, there is a major unmet clinical need for novel disease modifying therapeutics proposed in this application. This project will explore the potential for controlled delivery of novel genetic cargos using non-viral vectors to augment and improve the existing practice of IA steroid delivery. **This will allow us to target the cause, as well as the painful symptoms, of the OA disease process.** We have vast experience using non-viral gene delivery methods (with vectors such as polyethyleneimine (PEI) and chitosan) to modulate cell behaviour. More recently, we have optimised a novel GAG-binding enhanced transduction system (peptide (GET system; developed by our collaborator, Dr. James Dixon, University of Nottingham). In this system a multi-domain protein glycosaminoglycan (GAG)-binding capability will be tested in terms of its ability to deliver pDNA, miRNA and siRNA to modulate, and re-balance, anabolic/catabolic activities of chondrocyte cells in OA (using cell culture and explant models). In parallel, human mesenchymal stem cells (MSCs) will also be targeted for transfection with therapeutic pDNA, miRNA and siRNA. These will also be included in OA model systems to determine their ability to modulate OA progression. Therapeutic strategies based on miRNA/siRNA technology are extremely appealing as, unlike protein inhibitors or pDNA delivery (which only targets one protein at a time) - they can intercept entire gene cohorts. This multi-targeting effect on protein expression can modulate several cellular processes, thus makes miRNA/siRNA-based therapeutics particularly valuable and promising. The specific aims of this project are:

(1) To develop therapeutic gene delivery techniques to articular chondrocytes and MSCs using cell culture systems
(2) Functionalise and optimise gene delivery vectors to in situ chondrocytes using explants models of OA (using targeted antibodies and biomaterials)
(3) Test therapeutic efficacy in vivo, using a pre-clinical rodent model of OA

The impact of this research will be to establish optimal gene delivery techniques for modulating the disease process in OA. These will be developed in 2D cell culture systems (chondrocytes, MSCs), 3D explant models and finally tested in a pre-clinical model of OA. The technology proposed here would have the potential to alleviate suffering and enable sustained healthcare benefits for the aging worldwide population.
Keywords: Osteoarthritis, Tissue Engineering, Regenerative Medicine

Research project 2: Novel polypeptide bioinks for 3D printing of bioactive scaffolds for tissue engineering applications.
Supervisors: Prof Andreas Heise, Pharmaceutical & Medicinal Chemistry and Prof Fergal O'Brien, Anatomy, Prof. Sally Ann Cryan, Pharmacy.
Research Project Description: The development of defined three-dimensional (3D) architecture fabrication for tissue engineering has been a recent emergence within the field. In particular, 3D printing represents a promising rapid prototyping technology for the production of intricate bio-inspired scaffolds/constructs. Highly defined complex structures can be readily developed with computer-aided design (CAD) and deposited with stereolithography, extrusion, or ink-jet based printing. The primary feedstock materials used are natural hydrogels, which encompass the capability to augment native tissue due to their comparative 3D nano-architecture while holding the potential to act as a mimetic of the extracellular environment. Their disadvantage is varying source reproducibility and the limited possibility to modify the materials for example to improve cell compatibility. Hydrogels from synthetic polymers overcome these drawbacks and have been successfully applied in 3D printing but those often lack the biodegradability and biocompatibility.

Our research is fused on bringing together the best of both worlds by using natural amino acids as building block and apply polymerization technology to convert them into suitable biomaterials. This approach is very successful as the materials are non-toxic, degradable and allow structural manipulation not possible with natural polymers. For example, we found that star polypeptides readily form strong self-supporting and sheer thinning hydrogels – ideal for 3D printing. Here we are seeking a chemist (desirably with polymer experience) for the development of a new class of bioinks based on star polypeptides. These materials could pave the way for the development of tailor-made cell-compatible hydrogel inks which can create bio-functional structures. Notably, the development of printer technology has significantly outpaced the development of new advanced inks and the limited number of suitable bioinks has been identified as the major barrier to progress for the development of tissue engineering applications. The proposed project is timely and fully aligned with national research interests and industry investments: Johnson&Johnson have recently agreed to fully fund a 3D printing laboratory in AMBER (all project (co)supervisors are AMBER PIs). Henkel Ireland also opened a new 3D printing laboratory. There will thus be a high demand for new bioinks which underpins the potential for RCSI to take a leading position in this area.
Keywords: Chemistry, Biomaterials, tissue engineering.

Research Theme: Cancer

Research project 3: The role of USP11 in ER+ Breast Cancer
Supervisors: Prof Darran O'Connor, Molecular & Cellular Therapeutics (MCT) and Prof Tracy Robson, Molecular & Cellular Therapeutics (MCT).
Research Project Description: Background: De-regulated estrogen receptor (ER) function is a key feature of approximately 70% of breast cancers. Given that the tumourigenic properties of ER primarily lie in its function as a growth-controlling transcription factor, we sought to discover novel modulators of ER transcriptional activity. Using an RNAi loss-of-function screen, we identified the deubiquitinating enzyme USP11 as a key regulator of ER transcriptional activity. Aims: We hypothesize that USP11 influences ER activation through removal of ubiquitin moieties that block acetylation and repress ER transcriptional activity. We propose to:
1) Determine the role of USP11 de-ubiquitinating activity in controlling ER function and the effect modulating USP11 has on the ubiquitination/acetylation balance of ER.
2) Determine the effect of USP11 on the response of ER+ breast cancer cells to anti-endocrine therapy and examine the effect of CRISPR knock-in ER mutations on the ability of USP11 to control ER function.
3) Further validate USP11 as a breast cancer biomarker and evaluate the in vivo effect of USP11 modulation on the growth of ER+ breast cancers and their response to anti-endocrine therapy.
Techniques and Methodology: A combination of immuno-precipitation, mass spectrometry and RNAi will be used to map target lysines and explore the functional relevance of their modification. Impact on response to anti-endocrine drugs will be evaluated using in vitro growth assays and xenografts in nude mice and the impact of ER mutations on these responses assessed. Tissue microarrays will be used to evaluate the clinical relevance of USP11.
Impact on breast cancer research ER remains a rational therapeutic target in both the primary and recurrent setting and the discovery of novel mechanisms controlling ER function offer attractive new therapeutic opportunities.
Host Laboratory: The Molecular Oncology Laboratory at the Dept. of Molecular & Cellular Therapeutics, led by Dr Darran O'Connor (http://www.rcsi.ie/index.jsp?p=256&n=726&a=6338), is a young, vibrant and well-funded research group focused on the identification and mechanistic anchoring of novel cancer biomarkers and therapeutic targets. As part of major national and international research consortia (e.g Breast-Predict Cancer Centre (www.breastpredict.com), RATHER (www.ratherproject.com) and Angiopredict (www.angiopredict.com)) the lab has a network of world-class collaborators in the cancer research field, with ample opportunity for national and international secondment.
Recent outputs:
1. Li B, Ni Chonghaile T, Fan Y, Madden S, Klinger R, O'Connor AE, O'Hurley G, Mallya G, Joseph J, Tarrant F, Conroy E, Gaber A, Chin SF, Bardwell HA, Provenzano E, Dubois T, Linn S, Jirstrom K, Caldas C, O'Connor DP* & Gallagher WM*. Therapeutic rationale to target highly expressed CDK7 conferring poor outcomes in triplenegative breast cancer. Cancer Res 2017 Jul 15;77(14):3834-3845 *Shared Senior Authorship.
2. Mulrane L, Madden SF, Brennan DJ, Gremel G, McGee SF, McNally S, Martin F, Crown JP, Jirström K, Higgins DG, Gallagher WM & O'Connor DP. miR-187 is an independent prognostic factor in breast cancer and confers increased invasive potential in vitro. Clin Cancer Res 2012 Dec 15;18(24):6702-13. 3. Brennan DJ*, O'Connor DP*, Rexhepaj E, Ponten F & Gallagher WM. Antibody-based proteomics: Fast-tracking molecular diagnostics in oncology. Nature Reviews Cancer, 2010 Sep;10(9):605-17. *Equal Contribution
Keywords: Cancer

Research project 4: Breast Cancer Associated Microcalcifications – Investigation of their Relationship with Tumour Molecular Subtype and Potential Consequences for Tumour Progression
Supervisors: Dr Maria Morgan, Molecular & Cellular Therapeutics (MCT) and Prof Leonie Young, Surgery.
Research Project Description: Radiographic mammary microcalcifications constitute one of the most important diagnostic markers of both benign and malignant lesions of the breast. Up to 50% of all nonpalpable breast cancers are detected solely through microcalcifications presenting during a mammogram scan and up to 93% of cases of ductal carcinoma in situ (DCIS) present with microcalcifications. During the past decade, cases of subclinical cancer, that is, breast cancers detected by mammography, have accounted for a progressively increasing percentage of breast cancers. Although the diagnostic value of these microcalcifications in breast cancer is well established, their genesis is not clear. In particular, the question as to whether they are a sign of degeneration or of an active cell process remains a matter of debate. It is generally accepted that the presence of oxalate-type microcalcification [CaC2CO4-2H2O, Type I] appears to be a reliable criterion in favour of the benign nature of the lesion or, at most, of a lobular carcinoma in situ, whereas calcium hydroxyapatite (HA) [Ca10(PO4)6(OH2), Type II] is generally associated with malignant breast tumours. With the exception of our recent publications, there have been no other reported investigations of the mechanism of calcium deposition or, the potential of differing mammary cell types to generate specific calcium mineral species. No study to date has examined the pro-inflammatory potential of the deposited hydroxyapatite found associated with breast cancer. Furthermore, the potential for mineralisation and the microenvironment regulating it representing a significant feature of selected tumours has not even been considered. This project will test the hypothesis that (i). Mammary cells can generate specific mineral deposits which reflect their molecular subtype and/or state of differentiation; and (ii). mineralisation induced local inflammation may promote an inflammatory niche which contributes to tumour progression. This PhD project will help elucidate the relationship between microcalcifications and the mammary tumour microenvironment, establishing the role for mineralization-associated pro-inflammatory molecules in influencing macrophage function and polarization. The project will further clarify the biological consequence of mineralization-induced epithelial to mesenchymal transition in promoting tumourigenesis through active tissue remodelling. This study will help resolve the unexplained prognostic association of these calcifications with benign and malignant disease of the breast and help to understand the full complexities of one of the most significant markers of pre-invasive breast cancer.
Keywords: Cancer

Research project 5: Modelling tumour – immune system interactions in 3D in vitro model of neuroblastoma using collagen-based scaffolds
Supervisors: Dr Olga Piskareva, Molecular & Cellular Therapeutics (MCT), Dr Caroline Curtin, Anatomy, Prof Fergal O'Brien, Anatomy and Prof. Donal O'Shea, Pharmaceutical & Medicinal Chemistry, RCSI.
Research Project Description: The main challenge in treating neuroblastoma, a paediatric cancer of the sympathetic nervous system, is to combat tumour metastasis and resistance to multiple chemotherapeutic drugs highlighting the unmet need in new more efficient pre-clinical models to study disease pathogenesis, drugs testing and development. Immune therapy holds great promise as a treatment modality for paediatric and adult cancers owing to the specificity of immune effector cells targeted to the tumour, potentially reducing the systemic side effects observed with other forms of treatment. In order to accurately study the interaction between immune and tumour cells, we need to develop an adequate 3D in vitro model system that mimics the native tumour microenvironment at the tissue level.
3D scaffold-based in vitro cell culturing is a recent advancement in cancer research bridging the gap between conventional 2D culture and in vivo tumours. A scaffold is a 3D matrix that provides the necessary support for cells to proliferate, differentiate, deposit extra-cellular matrix and respond to stimuli similar to in vivo biological systems.
To date, the collaborative efforts of Piskareva's and Prof. O'Brien research groups led to the development of a 3D tissue-engineered tumour cell model using collagen-based scaffolds for neuroblastoma). Neuroblastoma cells displayed > 100-fold increased resistance to cisplatin treatment when compared to 2D cultures exhibiting chemosensitivity similar to orthotopic xenograft models. This 3D in vitro model demonstrated a physiological similarity to in vivo models, making evident the potential of this model to serve as a tool to elucidate neuroblastoma pathogenesis and for the development of new drugs. Therefore, by growing cancer cells on the 3D scaffolds and allowing the formation of 'tumour mass', the shortcomings of using 2D cultured cells can be overcome as minimal communication networks and cellular gradients observed within in vivo tumours are re-established.

Here, we suggest advance the current model to study tumour – immune system interactions by characterization of the microenvironment in 3D using a panel of neuroblastoma cell lines with distinct genomic and biological characteristics and incorporating cellular and molecular components of the immune system. Neuroblastoma cell death will be examined by real-time using a patented RCSI Amphiphilic NIR-Fluorescent Probe developed in Prof. O'Shea's lab and optimized to label neuroblastoma cells. This fluorophore permits real-time imaging of cellular uptake, trafficking and efflux without perturbing function. The combination of new generation of fluorophore and 3D in vitro culturing will allow to mimic the tumour immune interactions and to test the response of the platform to anti-GD2 immunotherapy, which entered clinical trials for children with high-risk neuroblastoma.
The major ambitions and aspiration for this project are:

- the development of a new 3D tumour tissue engineered model to study tumour - immune system interactions;
- the reduction and/or replacement of live animals and provide a new platform for pre-clinical testing;
- the acceleration of the paediatric cancer drug development process leading to more effective and tailored therapies.

Keywords: Cancer, Immunology, Tissue-engineering

Research project 6: A key role for FKBPL in the regulation of cancer stem cell signalling and the microenvironment; therapeutic implications for tumour growth and metastasis
Supervisors: Prof Tracy Robson, Molecular & Cellular Therapeutics (MCT) and Dr Darran O'Connor, Molecular & Cellular Therapeutics (MCT).
Research Project Description: 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 worrying, 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 FDA. 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 easily killed by chemotherapy. This project will assess the impact of FKBPL on 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.

- Valentine A, O'Rourke M, Yakkundi A, Worthington J, Hookham M, Bicknell R, McCarthy H, McClelland K, McCallum L, Dyer H, McKeen H, Waugh D, Roberts J, McGregor J, Cotton G, James I, Harrison T, Hirst D, Robson T FKBPL and peptide derivatives: novel biological agents that inhibit angiogenesis by a CD44-dependent mechanism. Clin Cancer Res. 2011 Mar 1;17(5):1044-56.
- 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.
- Annett S, Robson T. Targeting cancer stem cells in the clinic: Current status and perspectives. Pharmacol Ther. 2018 Jul;187:13-30.

Keywords: Cancer, metastasis, stem cell signalling

Research project 7: Theranostic Combination of Targeted Fluorescence Imaging and Photodynamic Therapy
Supervisors: Prof Donal F O'Shea, Pharmaceutical & Medicinal Chemistry and Dr Brona Murphy, Physiology & Medical Physics.
Research Project Description: Research Project Description: Photodynamic therapy (PDT) is a modern treatment that uses light to locally photosensitize tissues, resulting in the selective killing of targeted cells. Following administration of a photosensitizer, the cancerous lesion is irradiated with low energy light, promoting a set of photochemical reactions to damage the irradiated cell population, resulting in tumor ablation. Although PDT is an effective means of killing cancer cells, photosensitizers generally have little intrinsic selectivity for tumors. Increasing tumor selective accumulation could improve the efficacy of PDT and reduce any risk of side effects caused by photosensitizer accumulation in non-target tissue.

The various types of cells that comprise a tumor mass express many molecular receptors on their surface that distinguish them from normal cells. Nanobodies (smallest active targeting component of an antibody) can selectively recognize and target such surface receptors leading to delivery of a therapeutic payload exclusively at the desired site of disease. This research project will focus on exploring a less harmful approach to cancer therapy through nanobody derivatization to facilitate a controlled and definable conjugation to the highly efficient photosensitizing agents dibromo-BF2-chelatedazadipyrromethenes (ADPMs). The ADPM photosensitizer class has been developed within the O'Shea research team and their covalent combination with nanobody targeting agents would yield a drug-light combination that lends itself to two layers of selectivity. The inherent fluorescence of the ADPM class allows them to be readily visualized in vitro and in vivo thereby allowing for a theranostic approach as imaging of the diseased tissue during treatment. Such an approach will increase treatment efficiency while reducing the undesirable side effects associated with traditional chemotherapies. This truly multidisciplinary project will advance knowledge in the fields of bio-conjugation chemistry, chemical biology and efficacy assessment of targeted PDT.
Keywords: Cancer, chemical biology, synthetic chemistry, live cell fluorescence imaging, in vitro/in vivo testing.

Research project 8: Predicting variability in glioblastoma proliferation and spread using stochastic mathematical models and 3-D-cultures of patient-derived neurospheres.
Supervisors: Dr Brona Murphy, Physiology & Medical Physics and Dr Mark Sturrock, Physiology & Medical Physics.
Research Project Description: Brain tumours are the biggest cancer killer of adults under 40. Brain tumours reduce life expectancy by an average of 20 years, the highest of any cancer. Survival rates have improved little in over 40 years. The most common and aggressive primary brain tumour is glioblastoma (GBM). Despite intense effort to combat GBM with surgery, radiation and temozolomide (TMZ) chemotherapy, 90-95% of patients succumb to the disease within 5 years of diagnosis and nearly all patients experience disease recurrence, usually within 6-8 months of treatment onset (Stupp et al. 2009). New, better, more-personalised treatments are urgently required.
The extensive molecular heterogeneity found between GBM tumours contributes significantly to the limited effectiveness of current therapies and the difficulty in developing new efficacious treatment regimes. The theory that a ‘one-size-fits-all’ approach to treating this disease is not valid. Instead, as our laboratories and others have published, a more personalized approach is necessary to select the most appropriate drugs for a given patient (Paul et al. 2010; Murphy et al. 2013; Weyhenmeyer et al. 2016). Diagnostic tools that can predict case-specifically if and which treatment (Murphy et al. 2013; Weyhenmeyer et al. 2016) is likely to be beneficial for a specific subset of GBM patients are therefore of high interest, both for innovative clinical trials design (enrolment of patients which are likely to respond) and to optimise/personalise treatment. As we and others have highlighted, for this to work, reliable in silico models of the disease that can accurately predict treatment responsiveness need to be developed (Weyhenmeyer et al. 2016).
Such novel approaches are pursued in the field of mathematical modelling (Sturrock et al. 2015; Neal et al. 2013; Jackson et al. 2015). However, one major weakness of existing studies is that they do not capture variability in rates of glioma growth and spread. Hence, the primary objective of this project is to develop stochastic mathematical models of glioma growth that capture and quantify the variability in glioma growth and spread in vivo. Furthermore, model predictions of tumour growth under current and novel treatment conditions will be validated using spatio-temporal imaging data of 3-D-cultures of patient-derived neurospheres grown under these same treatment conditions. Our project holds tremendous potential to develop clinically relevant tools that can identify patients that will likely benefit from currently approved and novel treatment options. This would be an excellent step-forward for patients as it will spare them toxic treatments that hold no overall benefit to them, as well as helping to preselect patients for clinical trials. The aims of this research address one of the most significant problems in the field of brain cancer, and we are confident that our research can make a significant contribution towards improving GBM treatment and patient survival in the future.
Keywords: Cancer, computational biology

Research project 9: Evaluation of Junctional Adhesion Molecule-A (JAM-A) as a novel potential biomarker and therapeutic target in thyroid
Supervisors: Dr Ann Hopkins, Surgery and Prof Christopher Thompson, Medicine, ERC.
Research Project Description: Thyroid cancer is a growing problem in Ireland and across Western nations in general. Although many cases are surgically treatable, the lack of a national screening programme in Ireland means that some thyroid tumours are diagnosed late and thus patient survival prospects are extremely poor. In conjunction with the fact that genetic mutations are relatively rare in thyroid tumours (compared to, for example, breast or lung cancer); this highlights the importance of seeking or validating new proteins that might contribute to disease progression or open up alternative therapeutic approaches. We propose that the protein Junctional Adhesion Molecule-A (JAM-A) represents a potential biomarker and therapeutic target worthy of investigation in thyroid cancer. The overexpression of JAM-A has already been demonstrated to correlate with disease progression and poor patient prognosis in many solid tumours, but nothing is known about its potential contribution to thyroid cancer. However, the expression of a structurally-similar protein belonging to the same protein superfamily as JAM-A has recently been linked with thyroid cancer severity. This project proposes a joint scientist-/clinician-led approach towards interrogating the role of JAM-A in thyroid cancer. It will span a continuum of translational research: using molecular and cell biology data from patients to inform functional assays and ultimately test the druggability of JAM-A in thyroid cancer settings. Collectively, this will ensure broad-spectrum training for the student and the exciting possibility of defining a novel biomarker and therapeutic target for a cancer which is both intellectually stimulating and socio-economically challenging.
Keywords: Cancer

Research project 10: RET a novel therapeutic target to treat breast cancer brain metastasis
Supervisors: Prof Leonie Young, Surgery and Prof Arnold Hill, School of Medicine.
Research Project Description: Metastatic disease recurrence occurs in up to 30% of breast cancer patients with approximately 20% of these tumours metastasising to the brain. With the advent of better systemic therapies, brain metastases are increasing in incidence and confer poor prognosis, which is compounded by limited treatment options. Breast cancer brain metastases are defined by complex adaptations to both adjuvant treatment regimens and the brain microenvironment. Consequences of these alterations remain poorly understood, as does their potential for clinical targeting. Previous research using experimental models and primary tumour datasets has proposed some mechanisms of disease progression relating to brain metastasis. Mutational analysis on longitudinal breast and metastatic samples by our group and others illustrated acquired mutations affecting HER2 and the PI3k/AKT/mTOR pathway. Although current emphasis for longitudinal profiling of tumours is on mutation-level alterations, these approaches have failed to uncover genomic alterations for site-specific metastasis or the molecular determinants that drive adaptation to treatment. Conversely, transcriptional and epigenetic re-programming develops with higher frequency and has been observed to functionally affect oncogenes and related signalling pathways. In preliminary studies, we have characterized the brain metastatic-altered transcriptome across 21 patient-matched primary breast tumours and their associated brain metastases to identify new therapeutic targets. Considerable shifts in breast cancer cell-specific gene expression profiles were observed upon brain colonization, which had a large degree of metastatic selectivity.
Bioinformatic analysis for readily druggable targets revealed recurrent gains in expression of the tyrosine kinase receptors RET and HER2. In preliminary studies, ex vivo patient explants and PDX brain metastatic studies demonstrated significant anti-tumour activity for therapies directed against both RET and HER2.
This project as part of the StAR International Training Programme will address clinically relevant questions arising from these observations.

- What is the molecular profile of the primary tumour of patients at risk of developing brain metastasis?
- How does enhanced tyrosine kinase signalling and in particular RET contribute to brain metastasis?
- What is the efficacy of cabozantinib to inhibit progression to brain metastatic disease?
- Can we use next generation sequencing in multiple models of brain metastasis to define a gene signature to predict response to RET treatment?

A multidisciplinary approach, with input from molecular biologists, bioinformaticians, clinicians and industrial partners, will be taken to address these questions. Retrospective and on-going prospective clinical trials will be used to profile at risk patients. In vitro, ex vivo and in vivo models will be used for mechanistic and functional studies, bioinformatics and biostatistics will be employed for advanced data analysis and computational modelling.

The output of this research will be:
Full evaluation of RET as a new therapeutic target to treat breast cancer patients at risk of and with overt brain metastatic disease ready for commercial partnership.
Publications in high-impact journals
In combination with structured StAR PhD training modules, this research will provide a breath of experience in clinically relevant advanced technologies providing the candidate with a competitive advantage for international post-doctoral and/or industrial placements.
Keywords: Cancer, Breast, Brain

Research Theme: Infection, Immunity and Inflammation

Research project 11: Investigating novel metabolites on the regulation of microRNAs for the treatment of Multiple Sclerosis
Supervisors: Dr Clare McCoy, Molecular & Cellular Therapeutics (MCT) and Prof Luke O'Neill, Biochemistry & Immunology Dept, Trinity Biomedical Sciences Institute, TCD.
Research Project Description: The study of metabolites has yielded new insights into the mechanisms that mediate immune cell function. Recent advances have highlighted that in addition to regulating energy states in a cell, metabolites can have a major impact on immune cells such as macrophages. For example, succinate, an intermediate metabolite of the Krebs' cycle, has been shown to accumulate and act as a potent signal inducing the inflammatory state of macrophages (1). On the other hand, another metabolite called itaconate can act as an anti-inflammatory molecule, counteracting the actions of succinate, through the inhibition of pro-inflammatory signals and reactive oxygen species (2). Interestingly, succinate has been shown to drive an inflammatory state within the central nervous system of a Multiple Sclerosis (MS) disease model (3), whereas the administration of itaconate can reverse this effect (2). This suggests that the repurposing of metabolites holds huge potential as anti-inflammatory agents in many diseases including MS.
The discovery of microRNAs has led to a very exciting and rapidly growing area of research. microRNAs are extremely small RNA molecules that play a critical role in normal immune cell function. However, for reasons that we don't fully understand, microRNAs are also dysregulated in multiple inflammatory diseases. MicroRNA (miR)-155, a pro-inflammatory microRNA, has been particularly implicated in MS (4). Elevated levels of miR-155 are found in the serum and brain lesions of MS patients (5), while data from Dr McCoy's laboratory has identified that miR-155 is particularly elevated in macrophages that infiltrate and cross the blood brain barrier in a MS disease model. miR-155 activation results in the release of pro-inflammatory cytokines and toxic mediators and contribute to the damage observed in MS brain pathology (4). Significantly, we have shown for the first time that inhibition of miR-155 in macrophages can change their phenotype to an anti-inflammatory state that could potentially promote tissue repair (6, 7). Thus, inhibition of miR-155 in macrophages could offer a novel therapeutic approach for the treatment of MS. This PhD project will focus on examining a range of metabolites and assessing their impact on miR-155 expression, macrophage metabolism and plasticity, with the aim that a metabolite will be selected for its efficacy in the MS disease model. The PhD candidate will be based in Dr Claire McCoy's laboratory at RCSI who leads a research team investigating the impact of miR-155 on MS disease pathology. She was the recent recipient of a prestigious President of Ireland Future Research Leader Award. Prof Luke O'Neill will act as a co-supervisor, he is a world leader and expert in Immunometabolism, publishing frequently in Nature, Cell and Science. The successful candidate will have opportunities to engage with Prof O'Neill's lab at Trinity College Dublin, as well as undertake industry secondments associated with his research programme.
References:
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2. Mills EL, & O'Neill LA. Nature. 2018
3. Paraboschi EM. Int J Mol Sci, 2011
4. McCoy CE. Adv Exp Med Biol. 2017
5. McCoy CE, et al., J Biol Chem. 2010
6. Quinn SR & McCoy CE.J Biol Chem. 2014
Keywords: Multiple Sclerosis, Immunology

Research project 12: Multi-antibiotic resistant Enterobacteriaceae and near-patient environmental decontamination: are current methods adequate in the face of changing epidemiology and enhanced transmission
Supervisors: Prof Deirdre Fitzgerald-Hughes, Clinical Microbiology and Prof Fidelma Fitzpatrick, Clinical Microbiology.
Research Project Description: Patients with infections caused by antibiotic-resistant bacteria are at increased risk of worse clinical outcomes and death. Klebsiella pneumoniae – a common intestinal bacteria that can cause life-threatening infections, is increasingly resistant to a last resort antibiotic, carbapenem, making it a multidrug resistant (MDR) pathogen and an almost untreatable 'superbug'. Carbapenemase-producing (CP) Enterobacteriaceae (CPE) which include mainly K. pneumoniae and Escherichia coli have spread to all regions of the world. CPE are a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients. In some countries, because of resistance, carbapenem antibiotics do not work in more than half of people treated for K. pneumoniae infections and hence morbidity rates as high as 50% are reported. Infections rates involving CPE are rising and outbreaks are increasingly reported globally. To protect patients and prevent transmission in the USA, agencies such as the Centre for Disease Control and Prevention (CDC), Health Protection England and the Irish Health Protection Surveillance Centres provide recommendations for prevention and control of CPE that include contact precautions, patient/staff cohorting, hand-washing, surveillance and antibiotic stewardship. However, guidelines lack emphasis on the environments role in the transmission of CPE. Aggressive decontamination of the environment close to patients colonised with CPE has been pursued in some hospitals but mainly in response to the identification of environmental reservoirs and the finding of ineffective disinfection. Appropriate and effective decontamination of the healthcare environment in relation to CPE requires a more evidence-based understanding of the epidemiology and transmission of CPE in healthcare settings, a goal that this proposal will address.
We showed that CP Klebsiella survive longer than other CPE on surfaces commonly found in patient bed-spaces and are more resistant to disinfectants at twice the recommended concentrations. In this project, we will further investigate the survival of antibiotic-resistant and -susceptible K. pneumoniae and E. coli on surfaces, correlated with the adherence traits of these organisms and bacterial fitness. Bacterial survival on surfaces, decontaminated using current disinfection guidelines, will be investigated under laboratory conditions and the development of disinfectant tolerance will be investigated. In a hospital-based study, we will determine the burden of K. pneumoniae and E. coli in the environment of colonised/infected patients. We will determine the effectiveness of routine surface cleaning in relation to target organisms and simultaneously we will evaluate the cleaning standard achieved on surfaces, based on removal of a fluorescent dye applied to multiple surfaces. The relatedness of environmental isolates and isolates recovered from patients will be investigated by whole genome sequencing to identify routes and reservoirs of transmission. These studies will provide evidence of potential clinical sources of patient acquisition and will determine the relationship between cleaning thoroughness and cleaning effectiveness for recovery of these pathogens. As such, it will inform future infection prevention and control policy with regard to CPE.
Keywords: Public Health, Infection Prevention and Control, antibiotic resistance.

Research project 13: Could cold atmospheric air plasma be a potential novel therapy for treating infected diabetic foot ulcers?
Supervisors: Dr Niall Stevens, Clinical Microbiology and Prof Hilary Humphreys, Clinical Microbiology.
Research Project Description: In Ireland, diabetes mellitus is reported to affect 207,490 people, or 6.5% of the population in the 20-79-year-old age group (www.diabetes.ie). By 2030, this number will rise to 278,850 people; representing an increase of 34.39% in fifteen years. Foot ulcers are common in patients with diabetes and they are the most frequent diabetes-related cause of hospitalisation. The HSE in Ireland estimates that one-in-twenty sufferers will get a foot ulcer in their lifetime and approximately half of these will be infected at presentation. Diabetic foot infections (DFIs) can be associated with significant morbidity and at least one-in-five result in lower extremity amputations. The ultimate treatment goal for a diabetic foot ulcer (DFU) is to achieve wound closure but management is dictated by the severity of the ulcer, presence of neuropathy, vascularity, and importantly, whether there is an infection. The impact of infection and the subsequent amputation of a limb can severely impact the quality of life of patients with diabetes mellitus. Finding new therapies to treat infected ulcers would help improve patient care and prevent the patient losing their leg or foot. Plasma is the "fourth state of matter" and there are different types depending on the gas used. We generate plasma be applying high voltage electricity to a gas. We know that plasma can kill bacteria but we don't know if it will work on the bacteria that infect the ulcers of patients with diabetes and we also do not know if this treatment is safe to use in patients.

This research proposal aims to investigate the potential of plasma to be a novel and non-invasive therapeutic that could quickly treat infected ulcers, promote healing and prevent the loss of limbs. We believe this would advance care and improve the quality of life of patients with diabetes mellitus.
Keywords: Infection, diabetic foot ulcers, microbiology

Research project 14: Development of small molecule inhibitors of FcεRI
Supervisors: Prof Dermot Cox, Molecular & Cellular Therapeutics (MCT) and Prof Mauro Adamo, Pharmaceutical & Medicinal Chemistry.
Research Project Description: Allergic diseases are one of the most common diseases in the Western world. A report from the American academy of allergy, asthma and immunology indicated that between 40-50% of children are sensitized to at least one allergen. Its most severe presentation is anaphylaxis with an incidence of approximately 20 per 100,000 person-years.
Allergies occur when patients form IgE antibodies to a foreign protein. When subsequently exposed to the protein the IgE-antibody complex binds to the Fc receptor on basophils and mast cells. Binding to FcεRI triggers degranulation of the target cell which specifically releases histamine and other inflammatory cytokines. These agents cause bronchoconstriction and vasodilation leading to difficulties breathing and life-threatening hypotension.
Current treatment of allergic reactions is mainly symptomatic including anti-histamines, steroids, adrenaline and bronchodilators. However, none of these alter the underlying disease, thus, there is a need for more effective agents to treat allergic reactions. One possibility is to target the IgE-FcεRI interaction. This could be achieved by blocking FcεRI with a small molecule. We will use the expertise that we have developed in discovering small molecule inhibitors of FcγRIIa-IgG to develop small molecule inhibitors of the IgE-FcεRI interaction.
There are a number of potential benefits to an orally active small molecule inhibitor of Fcε. Firstly, it will be a lot cheaper than a monoclonal antibody. Secondly, it can be used prophylactically where patients could take a daily tablet during hay fever season to prevent symptoms. Finally, it could also be used in an emergency situation where a tablet could be taken when symptoms develop to prevent further deterioration in the patient.
Keywords: Immunology, pharmacology, drug discovery

Research project 15: Innovative technologies for the development of lead candidates in the treatment of sepsis
Supervisors: Prof Steve Kerrigan, School of Pharmacy and Prof Ger Curley, General Practice.
Research Project Description: Sepsis is the most common condition, and the single biggest cause of mortality, in critically ill patient. Outside of Critical Care Units, sepsis contributes to one-half of all hospital deaths. In addition, sepsis confers a major long-term economic burden on survivors and on society due to functional and cognitive disability. Improved treatment of sepsis could offer meaningful improvements in population health, quality of life and survival. In the developed world, sepsis is dramatically increasing by an annual rate of between 8-13 % over the last decade, and now claims more lives than heart attack, stroke or colon cancer and breast cancer combined. Sepsis involving multiple organ dysfunction is associated with especially high morbidity and mortality (up to 50%) and consumes a vast amount of healthcare resources. In Ireland, the cost of treating hospitalized sepsis patients was in the region of €250 million in 2013 alone (National Sepsis Steering Committee report, 2015). These figures do not take into account the costs associated with the lifelong follow up that is required post hospital discharge (most survivors experience lifelong complications due to sepsis). This makes sepsis the most expensive condition treated in Irish hospitals. **At present there is no specific anti-sepsis treatment available**, therefore management of sepsis patients relies on therapeutic measures to be initiated as soon as possible after sepsis diagnosis to include administration of appropriate antibiotics, source control measures when necessary and resuscitation with intravenous fluids and vasoactive drugs when needed. Although antibiotics play a key role in fighting the infection treatment success is often poor as downstream events as a result of endothelial dysregulation is not controlled. A January 2018 search of the www.clinicaltrials.gov revealed almost 550 trials of drugs and devices for the treatment of sepsis in various stages of completion, however no therapeutic options have made it to the market yet. It can be conservatively estimated that of upwards of $30billion has already been spent on the objective of developing a higher order therapy for the treatment of sepsis, indicating the market need. Previous approaches have focused on treating or controlling late stage pathophysiological effects (such as inflammation, thrombus formation & coagulation etc), an approach which has resulted in the failure of many compounds in clinical trials as a result of later intervention in the disease progression pathway.

This project will use cutting edge technology to identify lead candidate drugs that target very early in sepsis progression by targeting the human vascular endothelium.
Keywords: Therapeutics, sepsis

Research Theme: Neurological and Psychiatric Disorders

Research project 16: The microbiome as a mediator of focal epilepsy
Supervisors: Prof Gianpiero Cavalleri, Molecular & Cellular Therapeutics (MCT) and Prof Norman Delanty, Molecular & Cellular Therapeutics (MCT).
Research Project Description: Epilepsy is a group of common brain disorders characterized clinically by the occurrence of recurrent unprovoked seizures. There are many different types of epilepsy, both common and rare. Non-lesional focal epilepsy (NLFE) is a common type, whereby the patient has a focal onset of seizures in the brain, without a demonstrable cause visible on good quality MRI brain imaging. Most cases are unexplained and poorly understood. In addition, many patients with NLFE are do not respond to drug therapies, underpinning the pressing clinical need to further explore and understand this type of epilepsy.
The gut micobiome is defined as the collection of genes of all the microbes present within the gastrointestinal (GI) tract, and studies of the microbiome examine the interaction of all GI flora within the host. There is increasing interest in the gut microbiome as an important determinant of human health and disease, and emerging results from studies of brain disorders such as multiple sclerosis and neuromyelitis optica, supports the hypothesis that perturbations of the microbiome may be of aetiological significance in neurological conditions. Recent work in a mouse model of epilepsy has illustrated how the ketogenic diet (an effective way to control seizures) appears to act through changes in the gut microbiota. Despite this emerging interest in the microbiome and disease, there has been little if any work in humans on its possible role in the development and treatment of epilepsy.
The project will address three principal questions – 1) are changes in gut microbiota correlated with a diagnosis of epilepsy? We will answer this question by comparing the gut microbiota of people with nonlesional focal epilepsy to that of a healthy control population 2) are distinct gut microbioate profiles associated with response to epilepsy treatment? We will answer this question by comparing the gut microbiota of people with treatment-resistant epilepsy to those who respond to treatment. 3) Does the ketogenic diet impact on gut microbiota in people with epilepsy? We will answer this question by comparing the microbiome of people on the ketogenic diet too those who are not on the diet.
This project will be conducted through the SFI FuturNeuro Centre of Excellence and the Epilepsy Program at Beaumont Hospital,the main tertiary referral centre for complex epilepsy in Ireland, and is the national centre for epilepsy surgery. It will facilitate the PhD student to develop cutting edge skills in the generation and analysis of next-generation sequence data, bioinformatics, statistics as well as exposing them to the clinical neurology at Beaumont Hospital.
Keywords: Epilepsy, microbiome

Research project 17: Molecular mechanisms of blood-brain barrier dysfunction and repair in epilepsy
Supervisors: Dr Cristina Ruedell Reschke, Physiology & Medical Physics and Prof David Henshall, Physiology & Medical Physics.
Research Project Description: Epilepsy is a common, chronic neurological disorder characterized by recurrent, unprovoked seizures. Current treatments fail at least one third of patients and we have no disease-modifying therapies. Thus, there is a critical need for new ideas about patho-mechanisms of epilepsy. The blood-brain barrier (BBB) is a critical structure comprising specialized endothelial cells with tight junctions that physically and chemically separates brain tissue from circulating factors in the blood. Acute injuries to the brain and certain chronic neurological diseases are associated with BBB impairment which allows passage of molecules and cells normally excluded into brain tissue. This is thought to cause inflammation and promote neuronal dysfunction. There is growing evidence that epilepsy is associated with BBB dysfunction. Moreover, when seizures occur they may directly open the BBB and further promote molecular changes that contribute to an enduring state of hyper-excitability.
Several key questions remain unanswered which form the basis for the hypothesis to be tested in this PhD project. What are the molecular changes within the BBB that contribute to barrier breakdown? What is the mechanism initiating and maintaining these changes? What size of molecular pore is required to provoke or maintain epilepsy? How long must barrier breakdown persist in order to be epileptogenic? Can epilepsy be resolved by repairing the BBB? If so, how and is there a time limit on when this is possible?

This PhD research project will involve a multi-disciplinary approach comprising neuroscience, genetics, RNA and protein chemistry, microscopy and neuropharmacology to explore the molecular mechanisms of BBB dysfunction and its repair in epilepsy. The project will feature a strong imaging component, including use of pre-clinical models of epilepsy and two-photon microscopy and magnetic resonance imaging (MRI) to study blood brain barrier function in the living brain. A translational research element will involve opportunities to analyze human brain samples from patients with epilepsy and feature the design and delivery of gene therapy and oligonucleotide-based experimental treatments to restore BBB integrity. The researcher will work with a highly dynamic team of neuroscientists based at the recently launched FutureNeuro Research Centre at RCSI as well as molecular biologists, clinicians and bioinformaticists and our broader network of scientific and clinical collaborators.
In summary, this project will provide a neuroscience-focused researcher with a comprehensive, diverse and cutting-edge training experience that will uncover novel molecular mechanisms and treatments for BBB dysfunction in epilepsy.
Keywords: Neuroscience, epilepsy

Research project 18: Mechanisms of fever-induced epilepsy and related cognitive impairment
Supervisors: Dr Gary Brennan, Physiology & Medical Physics and Prof David Henshall, Physiology & Medical Physics.
Research Project Description: Temporal-lobe epilepsy is a common chronic neurological disorder characterized by spontaneous recurrent seizures. Fever-induced seizures (febrile seizures) are the most common type of seizure in young children and are generally harmless. However prolonged febrile seizures and complex febrile seizures are associated with developmental delay, cognitive impairment and an increased risk of developing epilepsy in later life. Additionally up to one third of patients who develop epilepsy are resistant to current medical treatments and will experience uncontrolled seizures. The disorder is also associated with a higher risk of developing anxiety disorders and depression as well as sudden unexpected death from epilepsy. There are currently no treatments for the prevention of adverse outcomes following a prolonged febrile insult during childhood and a real clinical need remains for the development of novel therapeutics which treat the underlying causes of the disease. The mechanisms by which prolonged febrile seizures cause cognitive impairment and epilepsy however remain poorly understood. The current project will explore the role of a novel class of non-coding RNAs called microRNAs as a potential regulator of febrile seizure-induced cognitive impairment and subsequent epilepsy development. MicroRNAs are a class of small non-coding RNAs which negatively regulate gene expression by binding to target RNAs and blocking their translation. Previous work from our group and others has found that these molecules play an important role in temporal lobe epilepsy. Their role in febrile seizures however is as yet unexplored.
The project will employ a variety of innovative methodologies to explore the role of a novel class of RNAs in specific cellular populations to decipher the role of microRNAs in febrile seizure related epilepsy and cognitive impairment. Specifically we will develop a novel in vivo model of febrile seizures and combine with cutting edge cell specific RNA-sequencing and ChIP-sequencing approaches as well as subsequent intervention strategies.
The inter-disciplinary nature of this project (molecular biology, in vivo pharmacology and bioinformatics approaches) will provide the student with broad training and a unique skillset. The project will be incorporated into the SFI-funded FutureNeuro Research Centre where students will have access to world class research facilities and the chance to work within an integrated team consisting of scientists with diverse backgrounds as well as clinicians and e-health researchers.
Keywords: Febrile seizures, Molecular biology, Neuroscience, microRNAs

Research project 19: KETOGENIC DIET: An in vitro single-cell imaging and molecular analysis approach to determine and therapeutically target the control principles of neuronal bioenergetics for the treatment of epilepsy with ketogenic diet
Supervisors: Prof Jochen Prehn, Physiology & Medical Physics and Dr Susan Byrne, Physiology & Medical Physics.
Research Project Description: Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS)CNS. Glutamate receptor activation imposes a significant work load and energy demand on neurons which requires neurons to increase ATP production. However, excessive activation of glutamate receptors induces neuronal dysfunction and nerve cell death, a process termed ‘excitotoxicity’. Interestingly, neuronal excitation and excitotoxic injury is substantially modulated by alterations in energy substrates.

Protective effects of ketone bodies and fatty acids on neuronal excitotoxic injury and in the setting of epilepsy treatment in patients have been described. Their mechanism of action however is poorly understood.
The main aim of this PhD project is to analyse the effects of the metabolic switch imposed by a ketogenic diet on mitochondrial function and neuronal bioenergetics, by using a combined single cell imaging and molecular deep phenotyping approach. First, the candidate will analyse the influence of acetoacetate, beta-hydroxybutyrate and decanoic acid (core components of a ketogenic diet) on basal bioenergetics and neuronal excitability at the single cell level by employing time-lapse confocal microscopy studies. He/she will avail of key a set of established, fluorescent reporters (FRET probes) that were previously characterized by the host laboratory (Connolly et al., J Neurosci, 2014; D'Orsi et al., J Neurosci, 2015). Studies will be done in primary hippocampal neurons under baseline conditions, under conditions of hyperexcitation, and after a prolonged glutamate challenge which is normally toxic to neurons. Next the candidate will perform a systems approach to fully understand and optimise the effects of ketogenic diet on neuronal bioenergetics and excitability. The candidate will perform RNA sequencing studies to analyse the transciptome of neurons exposed to ketogenic diet and to provide insights into the mechanism of action of this novel treatment. Alterations in gene expression in response to ketogenic diet will be validated by PCR and Western blotting, and further interrogated using genetic manipulation of differentially expressed genes that are of relevance for neuronal energy metabolism, excitation and excitotoxic cell death.
Unravelling the mechanisms by which ketogenic diet modulates neuronal bioenergetics, excitability and survival is pivotal for the use and optimization of dietary approaches for the treatment of epilepsy.
Keywords: Neuroscience, epilepsy

Research project 20: Validation of microRNAs as novel diagnostic and therapeutic targets in ischaemic brain injury
Supervisors: Dr Shona Pfeiffer, Physiology & Medical Physics and Prof David Williams, Geriatric and Stroke Medicine.
Research Project Description: Ischaemic stroke is a leading cause of death and most common cause of acquired major disability resulting from death of brain tissue and focal neurological deficits; however, despite decades of research, treatment options remain limited and the lack of therapeutic treatment strategies is a critical clinical problem. To this end, there is a need for biomarkers as clinically useful diagnostic and prognostic indicators for outcome in patients, improving functional recovery through individualised therapeutic strategies. Furthermore, such biomarkers have potential to be developed into neuroprotective agents aimed at rescuing ischaemic neurons from irreversible injury, widening the therapeutic window, improving neurological outcome and facilitating brain recovery.
Endogenous microRNAs (miRNA) are potent regulators of gene function elevated in a wide range of diseases, with crucial roles as regulators of signaling pathways involved in ischaemia-reperfusion injury. The complex nature of the ischaemic cascade has made identification of clinically useful biochemical markers of ischaemia challenging despite statistical associations with stroke and therefore targeting a single pathway may be ineffective. The roles played by miRNAs and their dysregulation in disease, particularly their ability to regulate multiple genes in similar pathways given the heterogeneity of stroke pathophysiology, combined with remarkable stability in biofluids and easy detection leave them uniquely poised as ideal biomarkers and therapeutic targets in many future clinical trials. Identification of a stable, endogenously expressed biomarker will be of significant clinical value in the development of a rapid blood test based on simple, cost-effective, near-patient technology, thereby contributing valuable and timely information necessary for prompt patient management decisions in the acute setting. Such information would aid in the choice of appropriate therapeutic intervention, treatment and secondary prevention and help with identifying timing of onset. Furthermore, identification of multi-targeting endogenously expressed biomarkers has significant potential for the development of neuroprotective agents, reducing stroke mortality rates. The outcomes of this research will have significant potential for application and translation as effective and feasible interventions, substantially improving patient care and outcome.
Keywords: Neuroscience

Research Theme: Pharmacy, Pharmaceutical Sciences & Chemistry

Research project 21: Bioorthogonal Chemistry and Fluorescent Post-Labeling for Real-Time Tracking of a Platinum-based Anticancer Drug.
Supervisors: Dr Darren Griffith, Pharmaceutical & Medicinal Chemistry and Prof Donal F O'Shea, Pharmaceutical & Medicinal Chemistry.
Research Project Description: Metal-based drugs have a wide range of medicinal applications and are routinely used clinically as therapeutic and diagnostic agents. In particular platinum (Pt) drugs such as cisplatin, carboplatin and oxaliplatin, have played a very important and well documented role in treating cancer and are employed in nearly 50% of anti-cancer regimens.
The cytotoxicity of Pt drugs, which hydrolyse (loss of chlorido or carboxylato ligands) inside cells, has traditionally been primarily attributed to their ability to covalently bind DNA, forming DNA adducts, leading to DNA damage responses and ultimately programmed cell death, apoptosis.
Significantly, it is becoming increasingly clear that the exact biomolecular mechanisms of action of Pt drugs have not been fully elucidated. It has been demonstrated recently for example that oxaliplatin, in contrast to cisplatin and carboplatin, does not kill cells via the DNA-damage response but by inducing ribosome biogenesis stress.
Trackable metal-based drugs which incorporate an organic fluorophore for example offer the prospect of real-time imaging of important biological processes in vitro and providing vital information concerning the biodistribution, cellular transport, subcellular localization, and mechanisms of action and resistance to metallotherapeutics.
The near-infrared (NIR) spectral region (700–900 nm) provides ideal imaging spectral wavelengths, reduced light toxicity and does not interfere with competing endogenous chromophore absorbance. Significantly NIR probes have been successfully employed to image tumours in vitro and in vivo and as sensors for ROS, RNS, thiols, ions, pH and enzyme activities.
Bioorthogonal chemistry describes chemical reactions that can occur in living systems without interfering with native biochemical processes. Bioorthogonal chemical ligation strategies include for example 1,3-dipolar cycloaddition between azides and cyclooctynes, between nitrones and cyclooctynes, oxime/hydrazone formation from aldehydes and ketones, tetrazine ligation and the quadricyclane ligation for example.
This multidisciplinary project, which will incorporate medicinal chemistry, cell biology and imaging, will employ bioorthogonal chemistry to develop Pt anticancer compound surrogates that feature reactive biocompatible handles that can be tagged with a reporter NIR fluorophore in cellulo. Such conjugates will play an important role in the ongoing investigation into the non DNA-binding effects of Pt-based drugs.
Keywords: Cancer, Medicinal Inorganic Chemistry, Imaging

Research project 22: Novel antibiotic candidates against drug-resistant bacteria causing the highest threat to human health
Supervisors: Prof Marc Devocelle, Pharmaceutical & Medicinal Chemistry and Dr Deirdre Fitzgerald-Hughes, Clinical Microbiology.
Research Project Description: 'A post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century ', reported the World Health Organisation (WHO) in 2015. The pipeline for the development of new antibiotics is now virtually empty, it will take at least 10 years to develop new antibacterial agents and the useful lifespan of an antibiotic (avoiding resistance) can typically be as short as 2 years.
The number of strategies currently identified to potentially delay the emergence of antibiotic resistance is particularly limited. Among them is the therapeutic use of natural molecules which have enabled, for millions of years, the first line of defence against infections in living organisms, the antimicrobial peptides. They have a number of unique features, particularly attractive against antibiotic resistance. Their clinical exploitation is however limited by a number of shortcomings, in particular their potential toxicity.
The host laboratory has developed a unique approach for the generation of PEG-based peptidomimetics of AMPs. Peptidomimetic is a generic term describing a molecule which displays the biological activity of a parent peptide, but which is structurally different. Peptidomimetic conversion is usually apply to address the clinical shortcomings of a parent peptide. Different peptidomimetic candidates of AMPs have been developed worldwide, in particular polymer-based mimetics, where a synthetic polymer backbone replace the peptide's poly-amide backbone. These metabolically stable analogues can be administered at lower doses, increasing thereby the therapeutic window. Some of these candidates have progressed to clinical trials where they have shown significant advantages over classical (approved) antibiotics. However, while polyethylene glycol (PEG) is described as 'the gold standard biocompatible polymer for pharmaceutical and medical applications', it has not been for the generation of polymer-based peptidomimetics to date.

The first PEG-based peptidomimetics were produced by the host lab; they mimicked a Cell Penetrating Peptide, a peptide sequence able to translocate across cell membrane and to act as a delivery agent for a large number of therapeutic molecules. The CPP peptidomimetic was shown to be more efficient than the parent peptide in the delivery of nucleic acids, while being non-toxic. The first peptidomimetics of ultrashort AMPs (tripeptides) were also successfully generated. Despite their small size, they displayed interesting antibacterial and antibiofilm activities, at least equivalent to those of the parent peptides. The approach used to generate these candidates can be adapted to produce larger candidates, approaching the size of the best AMPs know to date.
The aim of this project is to produce this second generation of AMP PEG-based peptidomimetics and to test and optimize their antimicrobial and antibiofilm activities against most bacteria in the WHO list of pathogens causing the most significant threat to human health (Nature, 2017, Vol. 543, p. 15).
Keywords: Pharmaceutical Sciences, Novel antibiotics, Drug-resistant bacteria

Research project 23: Development of an inhalable anti-tubercular therapies to include pre-clinical screening and 3D printing/additive manufacturing.
Supervisors: Prof Sally Ann Cryan, School of Pharmacy and Prof Joseph Keane, School of medicine, Trinity College Dublin, Prof. Andreas Heise, Pharmaceutical & Medicinal Chemistry, RCSI, Ronan MacLoughlin, Science Manager, Aerogen and Honorary Senior Lecturer, RCSI.
Research Project Description: Mycobacterium tuberculosis (TB) is the primary infectious disease killer in the world. In 2016 alone 1.7million people died from TB and 10 million people fell ill [1]. It is the main cause of death related to antimicrobial resistance and the leading killer of patients with HIV. TB is primarily a pulmonary pathogen but current treatment regimens are based on oral and parenteral drug therapy requiring a minimum of 6-9 months for successful treatment. These treatments are lengthy, associated with a high risk of adverse drug reactions and poor patient adherence that is leading to multi-drug resistance (MDR-TB) strains emerging. Therefore, new therapies and treatment modalities are urgently required. By localising new and existing TB therapies to the lungs via aerosol, to target the site of TB infection in the alveolar macrophage (AM), the occurrence of these adverse events can be diminished/eliminated, patient dosing requirements reduced and clinical efficacy enhanced. Recent pharmacokinetic studies have shown that inhaled anti-tubercular drug formulations can achieve not only greater levels of concentration in the lungs than oral formulations but also have longer residence times. The student will bas based in RCSI'S St Stephens' Green campus but will have an opportunity to spend time in the clinical (St James Hospital) and industrial laboratories (Aerogen, Galway) of their co-supervisors. This project seeks to encapsulate innovative emerging TB therapies into inhalable delivery platforms designed for cell-specific targeting through additive manufacturing. Previous work by our group has investigated the key parameters required for targeting the macrophage using inhalable particle technology [2.3]. Working alongside a clinical research group in St James Hospital Dublin a range of novel host-directed [4] and peptide-based therapeutics that have emerged from research within our teams over the last number of years will first be assessed for their efficacy using a well-established in vitro TB infection model [5]. In the second stage of the project these lead therapeutics will be encapsulated into inhalable polymeric particles using additive manufacturing (3D PRINT) technology being developed within the Drug Delivery and Advanced Materials team in RCSI. These drug-loaded particles will be characterized pharmaceutically and their cellular targeting and efficacy assessed using well established advanced cellular imaging and infection models respectively [2, 4]. Key to the clinical use of inhalable therapies is integration with an appropriate inhaler device. Working with our industrial collaborators the inhalable therapies will be loaded into devices for aerosol testing including simulation modelling.
For truly advanced treatment modalities to be efficiently translated into the clinical environment a convergence of biomedical sciences and delivery platforms early in a research programme is becoming critical. Overall, this PhD project will integrate screening of novel TB therapies using state-of-the art cellular and biological models combined with pharmaceutical design, advanced additive manufacturing processes and medical device integration to support their clinical translation offering hope to the thousands of patients worldwide who die and fall ill daily due to TB.
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Keywords: Respiratory Medicine, pharmaceutical sciences and bioengineering

Research project 24: Optimisation and Preclinical Evaluation of Targeted Nanoformulations of Anti-TNF-α Therapeutics for the Treatment of Inflammatory Bowel Disease (IBD)
Supervisors: Dr Zeibun Ramtoola, School of Pharmacy and Dr Brian Kirby, Pharmacy.
Research Project Description: Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition that affects the gastrointestinal tract (GIT) of the patient and comprises of Crohn's disease (CD) and ulcerative colitis (UC). In CD inflammation can occur in any part of the GIT, whereas in UC, ulceration is usually limited to the lower part of the GIT, namely small intestine, colon and rectum[1]. IBD patients suffer a wide variety of symptoms including abdominal pain, diarrheoa, rectal bleeding, and anaemia, thus negatively impacting their quality of life[2]. Current treatment comprises the administration of small molecule therapeutics such as 5---aminosalicylic acid, corticosteroids and immunosuppressants and more recently, the anti-TNFα monoclonal antibodies (mAbs) including infliximab, adalimumab and certolizumab pegol. While conventional small molecules provide relief from IBD symptoms and maintain symptomatic remission, disease progression ultimately leads to surgical resection of diseased tissues.
It is now recognised that anti-TNFα mAbs in addition to causing induction and maintenance of remission also promote GI mucosal healing, now recognized as a key goal of IBD treatment, as this reduces the need for surgery[3]. A major disadvantage of the mAb therapy, however, is the resulting severe adverse effects such as leucopenia, serious infection and increased risk of malignancy due to their systemic administration at high doses. In addition, intravenous administration requires skilled personnel and mAb short shelf life after reconstitution, adds to the overall cost of IBD therapy. The development of novel drug delivery strategies of anti-TNFα therapeutics that can enhance their efficacy and reduce their side effects is a priority for treatment of IBD. Biodegradable PLGA nanoparticles of budesonide administered orally in a colitis mouse model, were shown to be preferentially taken up by the inflamed gastrointestinal cells, resulting in enhanced efficacy and reduced side effects[4]. Nanoparticles of biological therapeutics have not been formulated and studied due to their known sensitivity to environmental and processing stressors. We recently studied the effect of various processing stressors and environmental factors on the stability of the anti-TNFα mAb, Infliximab, and designed novel nanoformulations of Infliximab, in non-digestible polymeric envelopes, to provide stability of the mAb[5]. We demonstrated retention of biological activity of Infliximab from these nanoformulations and showed enhanced cell uptake and transport of the nanoformulations in an in-vitro intestinal inflamed epithelial cell model. Treatment with these Infliximab nanoformulations resulted in reduced inflammation and recovery of the epithelial barrier function. The aim of this project is to examine the potential of these novel Infliximab nanoformulations, administered orally, in targeting the inflamed intestinal mucosa of IBD, in a colitis mouse model. As part of this project the nanoformulations will be formulated and optimised for drug loading, drug release and stability. Optimised nanoformulations will be investigated in an in vivo colitis mouse model for their ability to target and interact with the inflamed intestinal tissues, to reduce inflammation and promote healing. Such a targeted strategy may provide increased efficacy and dose reduction, resulting in lower systemic side effects and improve the benefit to risk ratio of anti-TNFα mAbs).
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Keywords: Pharmaceutical Sciences, Anti-inflammatory therapeutics, Inflammatory Bowel Disease

Research Theme: Population and Health Systems

Research project 25: Developing, piloting and evaluating a theoretical-based intervention to support endocrine therapy medication taking behaviour in women with stage I-III breast cancer
Supervisors: Dr Kathleen Bennett, Division of Population Health Science and Dr Caitriona Cahir, Division of Population Health Science.
Research Project Description: Almost 3,000 women are diagnosed with breast cancer annually in Ireland. In women with hormone-responsive early breast cancer, 5-10 years of endocrine therapy is recommended to prevent breast cancer recurrence and mortality, with a reduction in cancer recurrence of up to 50%. However, despite the proven clinical efficacy of endocrine therapy, many women (30-70%) do not take their treatment as recommended. To date only a minority of published medication taking behaviour (MTB) interventions have improved MTB or enhanced patient outcomes.
Aims: To develop, pilot and evaluate a theoretical-based behavioural intervention to improve endocrine therapy MTB and health outcomes in women with stage I-III breast cancer.

Methods: The Medical Research Council's framework for the development of complex interventions will be used with the Theoretical Domains Framework (TDF) and taxonomy of Behaviour Change Techniques (BCTs) as the theoretical framework. Three inter-related work-packages are proposed. Work-package 1, building on previous research, will identify and model the demographic, clinical, treatment-related, psychological and health behavioural determinants of endocrine therapy MTB and associated health outcomes (quality of life, side-effects) in women with stage I-III breast cancer using data from the National Cancer Registry Ireland (NCRI) linked to national breast cancer patient questionnaire data (N=1,606, response rate=66%). Work-package 2 will identify the content and implementation options for the intervention by establishing a definitive list of MTB BCTs and their form of delivery to be tested, through Steering Group consensus. The BCTs will be pre-tested in a feasibility study and piloted in a randomized control trial of women with stage I-III breast cancer who have been prescribed endocrine therapy and clinical and support staff, to assess face validity, acceptability, feasibility and any barriers to implementation. Work-package 3 will evaluate the cost-effectiveness of potential interventions to improve endocrine therapy MTB.
Conclusion: The results of this research will directly benefit women with breast cancer prescribed endocrine therapy, through improved clinical outcomes and survival and also the healthcare professions involved in their care.
Keywords: Cancer, Population Health, Theoretical-based intervention, endocrine therapy

Research project 26: Patient-Centred Care (PCC) in Sub-Saharan Africa
Supervisors: Prof Ruairi Brugha, Epidemiology and Public Health Medicine and Dr Jakub Gajewski, Division of Population Health Science.
Research Project Description: This PhD studentship, through research undertaken in a sub-Saharan African country (Tanzania or Malawi), will investigate healthcare provider and patient dimensions of patient-centred care (PCC). Little substantive research has been undertaken in Africa on PCC, which is determined by health worker training; the structure and organisation of the health system; and the socio-economic environment in which health workers operate man (1). Given the lack of research from Africa, an exploratory mixed methods study is planned, comprising in-depth interviews of hospital staff and patients, followed by structured surveys of staff and of patients. The successful candidate will have the opportunity to develop qualitative and quantitative research skills, under the supervision of experienced researchers and working with an international research team from European and African research institutions.
The PhD comprises: 1) a systematic review of the PCC literature, 2) qualitative research to develop an understanding of PCC in an African country context; 3) development and testing of a tool to measure PCC in an African setting, 4) and survey implementation to determine the current state of PCC in the selected country. This will lead to research outputs (scientific articles), led by a candidate who has the drive to become an accomplished researcher; and who may be considering a research career on health in low- and middle-income countries. The platform of the PhD is the 4-year €6 million Horizon 2020 Scaling up Safe Surgery for District and Rural Populations (SURG-Africa) project, 2017-2020 - see www.surgafrica.eu. SURG-Africa is testing a supervision, mentoring and support intervention, in 31 district level hospitals, in Malawi Zambia and Tanzania, filling a major global health research gap.
This project will require fieldwork in Tanzania or Malawi in collaboration with, and supported by, the SURG-Africa research teams. This will provide an excellent opportunity to obtain first-hand experience in conducting studies in resource-limited settings. Structured training will be delivered through the PHS SPHERE programme, with on-the-job training by Brugha and Gajewski, the SURG-Africa research PI and lead, in: (i) qualitative methods; and (ii) quantitative methods. It is expected that findings will lead to the design of a PCC intervention that could form a post-Doc proposal for a candidate interested in a career in global health research.
Reference:
1. Man J De, Mayega RW, Sarkar N, Waweru E, Leys M, Olmen J Van, et al. Patient-Centered Care and People-Centered Health Systems in Sub-Saharan Africa: Why So Little of Something So Badly Needed? Int J Pers Cent Med. 2016 Oct 26;6(3):162–73.
Keywords: Patient-centred care, health systems, Africa

Research project 27: Solar Water Disinfection Transparent 20L Jerrycan (SODIS-TJC)
Supervisors: Prof Kevin McGuigan, Physiology & Medical Physics and Dr Fidelma Fitzpatrick, Clinical Microbiology.
Research Project Description: According to the WHO and UNICEF, in 20171:

- 2.1 billion people are without access to a safely manage source of water.
- 1.8 billion rely on either unimproved water sources or improved sources that are faecally contaminated.
- 844 million people still lack even a basic drinking water service.
- 159 million people collect drinking water directly from surface water sources.

The 2030 Sustainable Development Agenda agreed by the United Nations (UN) Member States in 2015 calls for universal access to safe drinking water. Therefore, development of sustainable and affordable point-of-use (POU) water treatment technologies to deliver safe drinking water at household or microcommunity level is a priority for achieving Sustainable Development Goal 6 (Clean Water and Sanitation).
Solar water disinfection (SODIS) 2 is a water treatment technique where transparent containers are filled with water and exposed to sunlight for a minimum of 6 h allowing the UV to kill the waterborne pathogens. SODIS is one of the most appropriate household water treatment & storage (HWTS) technologies for treating drinking water in low-income environments because it's:
1. Effective against a wide range of waterborne pathogens
2. Low- or zero-cost in areas where transparent containers are available.
3. Easy to use: very little training is required.

One of the obstacles to SODIS uptake is the workload associated with filling, exposing and managing a sufficient number of standard 2L bottles to provide for the entire household. An objective of the EU WATERSPOUTT project (Grant no 688928 see www.waterspoutt.eu) was to develop a 20L Transparent Jerrycan (TJC) for SODIS purposes. As a result we designed the TJC and demonstrated that the optimum material for its manufacture is polypropylene (PP).
However, in WATERSPOUTT we were unable to source a manufacturer in Europe or Africa who could produce PP TJC prototypes for us. Eventually compromised and the TJCs were made of polyethylene terephthalate (PET) plastic, which is not ideal.
The EU has just awarded Prof McGuigan funding to coordinate a second H2020 Project (PANIWATER Grant no. 820718) which includes funding for the manufacture and evaluation of PP TJCs in India. The successful StAR PhD Researcher will conduct a large scale (~1000 children under 5 yrs) 18 month field trial of the public health impact of the use of 20L PP SODIS TJCs on childhood diarrhea and water quality among disadvantaged communities in Rajasthan in India in cooperation with our local Indian partners. The researcher will be responsible for:

- Conducting baseline survey of incidence of diarrhoeal illness in the study population
- Conducting regular water quality analysis at participating households
- Collection and analysis of pre- & post-implementation data on incidence of diarrhea for the duration of the study.

Almost every household without access to safe water in low-income countries has a jerrycan. If this project is successful it has the potential to replace all of these with PP TJCs which will provide safe drinking water for the most vulnerable communities across the globe.

1. WHO/UNICEF Progress on Drinking Water, Sanitation and Hygiene -2017 Update and SDG Baselines. (https://washdata.org/sites/default/files/documents/reports/2018-01/JMP-2017-report-final.pdf)
2. **McGuigan** et al. Solar Water Disinfection (SODIS): A review from bench-top to roof-top. J. Hazard. Mater. 235–236 (2012) 29–46.

Keywords: Public health

Research Theme: Respiratory Medicine

Research project 28: Using induced pluripotent stem cells (iPSC) to evaluate new CFTR-directed and microRNA-based therapies for cystic fibrosis (CF)
Supervisors: Prof Catherine Greene, Clinical Microbiology and Dr Killian Hurley, Consultant Respiratory Physician and Senior Clinical Lecturer, Medicine.
Research Project Description: The recent development of drugs that directly modulate the CFTR protein in patients with CF has delivered a paradigm shift in how CF is treated using personalised medicine. However, a significant number of patients with CF do not have the better understood and more common CFTR mutations and therefore cannot access these lifesaving medications because CFTR modulator medications are only licensed and available to patients with specific mutations (e.g. Ivacaftor for G551D). Several CF preclinical models exist but none are lung-specific and reflect an individual patient's genetic background. Here we propose to engineer a novel in vitro human system to enable the derivation of lung-specific organoids, called bronchospheres, from induced pluripotent stem cells (iPSC) isolated from the peripheral blood of patients with such CFTR mutations. Using forskolin induced swelling of these bronchospheres we will measure lung-specific CFTR function in a high throughput fashion to screen approved and experimental CF therapies. The experimental therapies that will be tested are proprietary inhibitors of microRNA that downregulate CFTR expression. In addition to the high throughput methods we will also assess CFTR function using MQAE and YFP fluorescence-based chloride ion conductance assays in air-liquid interface (ALI) cultures, and immunoprecipitation and western blotting for mature CFTR.
Aims:

- To establish iPSC-derived lung-specific models of CF from patients with rare or unknown CFTR mutations. A placement in Boston University, School of Medicine will be provided to learn the methodology.
- To interrogate these models to study CFTR protein, translation, trafficking and function.
- To test the efficiency of existing and novel CFTR-targetting drugs for patients with rare CFTR mutations.

This PhD project will be co-supervised by a scientist and a clinician-scientist. It is designed to facilitate the acquisition of in-depth cutting-edge and state-of-the-art **cell and molecular biology** skills in a **translational and personalised medicine setting.**
Keywords: Cystic fibrosis and miRNA-based medicines

Research Theme: Vascular Biology

Research project 29: Development of a novel therapeutic for the treatment of sickle cell anaemia
Supervisors: Dr Marian Brennan, Molecular & Cellular Therapeutics (MCT) and Prof Marc Devocelle, Pharmaceutical & Medicinal Chemistry.
Research Project Description: Sickle cell anaemia is a chronic condition that is expensive to treat and requires significant clinical intervention and management. Patients in crisis need acute management that often requires hospitalization. Furthermore, damage to the vasculature leads to joint and organ damage that require frequent monitoring and treatment. Currently patients can be cured by bone marrow ablation followed by a transplant if a match can be found. Unfortunately, this process is very costly, dependent on a donor match and only has a 90% survival rate. This treatment is also only available in specialized treatment centers.
Sickle cell anaemia is a disorder resulting from a mutation in the β-chain of haemoglobin. Haemoglobin is the protein responsible for carrying oxygen from the lungs to the tissues where it releases oxygen. In patients with sickle cell disease, oxygen can be successfully carried from the lungs to the tissues, but after the oxygen is released, the haemoglobin protein interacts inappropriately with other haemoglobin proteins. This results in multimers of sickle haemoglobin (HbS) forming long rigid chains which in turn causes erythrocytes to distort into the characteristic sickle shape. The sickle shaped erythrocytes are inflexible and become trapped in the capillaries causing damage to organs. The multimers are more prone to form under certain conditions such as in low oxygen conditions and during infections. The blocking of capillaries leads to severe pain in patients known as a sickle cell crisis. The crisis can cause permanent damage to organs including the brain, liver, spleen, kidneys and lungs.
In 1998 the anti-cancer treatment hydroxyurea was approved for use in sickle cell disease. Hydroxyurea increases expression of the foetal haemoglobin β-like chain. As the foetal gene is a different gene to the adult one, there is no defect in this protein subunit expressed, and therefore multimer formation is disrupted and thus the red blood cells do not distort.

Although this reduces the number of hospitalizations in patients, approximately one third of patients are refractory to this therapy for a variety of reasons (Yahouédéhou SCMA et al., 2018). Hydroxyurea is not specific and therefore can also have severe side effects including liver and kidney damage as well as increased carcinogenic risk.
Using molecular modelling, we have designed peptides to disrupt haemoglobin multimer formation that can be delivered into the erythrocytes. We plan to test peptides for binding to HbS and assess the disruption of multimer formation in a cell free assay. A range of peptides and peptidomimetics derived from the parent peptide will be assessed to identify the lead peptide. The peptides are designed with a specific peptide tag for delivery into erythrocytes, therefore, we will assess delivery into erythrocytes and perform haemolysis assays in order to determine whether the peptides damage the erythrocyte membrane. We do not expect toxicity from the peptides, however, we will also test for toxicity in endothelial cells, erythrocytes and platelets. We will further test the peptides ex vivo using red blood cells from patients with sickle cell anaemia.
Successful development of an alternative therapy for patients with sickle cell disease will provide a much needed treatment that can prevent painful crisis and damage to patient's organs.
Keywords: Vascular biology, Chemoinformatics, Drug Discovery

Research project 30: Engineering protease-activated receptors to modulate cell signaling output
Supervisors: Dr Roger Preston, Molecular & Cellular Therapeutics (MCT) and Dr Ingmar Schoen, Molecular & Cellular Therapeutics (MCT).
Research Project Description: Protease-activated receptor 1 (PAR1) is a G protein coupled-receptor expressed on the surface of endothelial cells and platelets. It has a critical role in maintaining vascular homeostasis and its dysregulated activation has been proposed to contribute to a range of cardiovascular and inflammatory diseases. Unlike most receptors, PARs become activated not when bound by ligands, but when cleaved by specific proteases. Recent studies indicate PAR1 activation can occur via a number of different proteases, which can promote either pro-inflammatory, prohemostatic signaling activity or anti-inflammatory, cell-protective effects, depending on the activating protease.
Analogously, PAR1 activation in platelets can either potentiate platelet aggregation or aid thrombus consolidation. Despite growing recognition of its physiological importance, the molecular basis for how PAR1 signaling 'bias' is achieved by different proteases remains poorly understood. An enhanced understanding of the molecular parameters that control signaling bias is important given the early promise of drugs that tilt PAR1 towards 'cytoprotective' signaling for the treatment of inflammatory vascular disease. The objective of this study is to define how different proteases confer distinct PAR1 cell signaling outputs. To achieve this, we will utilize state-of-the-art genome engineering approaches combined with advanced microscopy techniques to decipher the structural determinants required to mediate PAR1 signaling bias in different cell types. We will assess whether specific PAR1 molecular regions are differentially altered in response to activation with different proteases, using mutant recombinant versions of PAR1 in new assays of PAR1 signaling that have been developed in our lab. In addition, we will use fluorescence resonance energy transfer (FRET) live cell imaging and super-resolution microscopy to determine PAR1 interactions with other cell surface receptors that we hypothesize contribute to skewing of PAR1 signaling output.
Finally, we propose to utilize genome-wide screening approaches to identify and subsequently characterize novel modifiers of PAR1 signaling outcomes. Collectively, the proposed study is anticipated to reveal novel insights as to how PAR1 structure, activation status and molecular interactions with co-receptors impact upon downstream signaling outcomes. Ultimately, this will enable generation of new pharmacological strategies to facilitate preferential skewing of PAR1 signaling output for therapeutic benefit. The project will be performed under the supervision of Dr. Roger Preston and project co-supervisor Dr. Ingmar Schoen. The Preston lab (www.prestonlab.com) is a large multi-disciplinary research group that is currently funded by prestigious awards from Science Foundation Ireland, Bayer Healthcare and the National Children's Research Centre. It has well-established expertise and an international reputation in the study of the mechanistic basis of PAR1 proteolysis and subsequent downstream signaling (Gleeson et al Blood 2015, Gleeson et al JTH 2017). The Schoen lab (http://schoenlab.strikingly.com) is the only dedicated super-resolution microscopy lab in Ireland and has specific expertise in FRET imaging and super-resolution microscopy techniques (Li et al Nature Methods 2018, Früh et al Nature Communications 2015) with a research focus on platelet mechanobiology. Consequently, the PhD student would benefit from a multi-disciplinary approach, with expert tuition provided in molecular biology techniques, recombinant protein generation, CRISPR-Cas9 mediated genome modification, advanced microscopy and cell labeling techniques.
Keywords: Vascular biology, Immunology and Systems Biology