MedDevDoc Pis(call2)						
Principal Investigators	**email**	**Institution**	**Titel**	**Abstract**	**Pillar**	**Keywords**
Abhay Pandit	abhay.pandit@universityofgalway.ie	Galway	Designing the next generation of implants through immuno-modulatory biomaterials	The role of lectins in biomaterial response is an interesting research question that could unlock critical features of successful material delivery and integration. Lectins are a family of proteins that recognise and bind specific sequences of glycans and have essential roles in recognition, energy metabolism, signalling and cell structure. Lectin activation is critical in the material-host response. Galectins, C-type lectin-like receptors and Sialic acid-binding immunoglobulin-type lectins are the major lectins that play a vital role in immunomodulation, neuroinflammation apoptosis, phagocytosis, oxidative bursts, and the regulation of the immune balance in inflammatory diseases. However, we don't have a comprehensive view of lectin expression at the tissue-biomaterial interface. Furthermore, we lack lectin-targeting biomaterial technology platforms that can be tuned. The project proposes designing a biomaterial to target lectin activation/inhibition to modulate the implant tissue response. Given our recent identification of the N-glycome in multiple disease targets and ongoing research in lectin characterisation in human disease, this proposal is an excellent opportunity to integrate newly found lectin targets into materials sciences via unconventionally modified biomaterials. This integration of lectin and glycan characterisation will allow for cross-domain synergism, with discoveries in one domain informing and concentrating investigations in the other and vice versa.	Immuno-Engineering /cancer and inflammatory disorders	Biomaterials, Immunoengineering, Glycomodulation, Drug Delivery
Aideen Ryan/Michael O'Dwyer	aideen.ryan@universityofgalway.ie	Galway	Developing novel NK cell therapies to target sialylation in tumours	Immunotherapies for the treatment of cancer have revolutionised the field of oncology and shown remarkable success in some cancers. Understanding how the tumor microenvironment regulates immune cell function is necessary to develop effective immunotherapeutic strategies and overcome resistance. This proposal is based on the premise that hyper-sialylation in the tumor microenvironment disables adaptive and innate anti-tumour immunity.Alterations to the biosynthesis of glycans occur in cancer and lead to altered sialylated terminal structures – termed hyper-sialylation. Sialic acid is a common component of glycan molecules and its presence can result in altered protein function. Sialic acid containing ligands are recognised by unique Sialic acid binding immunoglobulin-type lectins (Siglecs) found on the surfaces of both innate and adaptive immune cells. Inhibitory Siglecs have tyrosine-based inhibitory signalling motifs (ITIMs) within their cytoplasmic tails, similar to that of the well-known immune checkpoint, PD-1. In fact, hyper-sialylation of glycoproteins and glycolipids has been linked to increased immune evasion, drug resistance, tumour invasiveness and metastasis.In this project we propose to assess the level of hyper sialylation in aggressive B cell lymphoma. We will assess the levels of NK cell Siglec receptor expression using in vitro and ex vivo models. We will assess the effects of Sialic acid/Siglec receptor interactions on NK cell function in lymphoma using a variety of approaches. We will then explore approaches to enhance NK secretion of sialidase using genetic engineering approaches. Collectively, we aim to target hyper sialylation in lymphoma using immunoengineering approaches to enhance anti-tumour NK effector functions.	Immuno-Engineering /cancer and inflammatory disorders	Natural killer cells, sialylation, anti-tumour immune response, tumour microenvironment

Andrew Kellett	andrew.kellett@dcu.ie	DCU	Directing Anticancer Metallodrugs to Glioblastoma Multiforme and Triple-Negative Breast Cancer	Glioblastoma multiforme (GBM) and triple-negative breast cancer (TNBC) rank among the most complex and deadly cancers affecting millions of people annually. Current treatment regimens include surgery, radiotherapy, and chemotherapy, are non-curative and result in damage to surrounding healthy tissue. Recent advances in medical device fabrication have offered new opportunities to localise treatments directly in or near the tumour bed.[1] This project seeks to develop a new medical device to both assemble and direct delivery of a gene-targeted therapeutic nucleic acid (NA) to GBM and TNBC. Using exciting in vitro preliminary findings (papers 1 + 2 + 3 above), we seek to selectively couple new metallodrugs to specific NAs within a prototype convection-enhanced delivery (CED) device. The end goal is to eradicate individual cancer cell DNA, thereby avoiding damage to surrounding healthy tissue. Since CED establishes a positive pressure gradient, the device can be left in situ for extended periods of time thereby improving spatial distribution with lower amounts of the drug required. Recent advances in parallel areas of CED,[2,3] NA and hybrid chemical synthesis (e.g. papers 3 and 4 above) has only recently made it possible to consider selectively assembling and delivering these gene-selective chemotherapeutics to the primary tumour site. We will apply click chemistry to construct the hybrid, apply advanced anticancer drug screening using the AUTOPILOT system—a breakthrough robotic cancer cell screening facility located at Dublin City University and underpinned by CÚRAM—and carry out pre-clinical in vivo evaluation in collaboration with the University of Southern Denmark and Odense University Hospital where strong collaborative ties have been forged between the PI (Prof. Kellett) and collaborators within an ongoing large-scale Novo Nordisk Foundation funded project. National collaborators: Prof. Abhay Pandit (Galway) and Dr. Eddie Myers (Galway). International collaborators: Prof. Christine McKenzie (University of Southern Denmark) and Prof. Helge Thisgaard (Odense University Hospital).	Immuno-Engineering /cancer and inflammatory disorders	Metallodrugs; Convection-enhanced Delivery; Click Chemistry; Triple-negative breast cancer; Glioblastoma
Bharat Tripathi/Karen Doyle	bharat.tripathi@universityofgalway.ie	Galway	Nonlinear mechanical characterisation of blood clots	Brain stroke is a major cause of mortality worldwide. Strokes are caused due to blood clots or thrombus in arteries. Thromboinflammation, i.e., impact of the thrombus on the immune system depends on the composition of the thrombus. Prof. Karen Doyle's lab (co-supervisor) is currently investigating markers of thromboinflammation based on the composition of cardioembolic clots. For instance, clots rich in platelets and fibrin show heightened markers of thromboinflammation which necessitates the need of an accurate characterisation of blood clots. Furthermore, accurate material characterisation of thrombus will help in development of novel devices for mechanical thrombectomy, one of the treatment protocols, planned together with our industrial partner: Cerenouvus. Currently the mechanical modelling of clots is done using linear viscohyperelastic models and are inadequate for large deformations and therefore new data driven models are needed to characterise heterogeneous clots and their nonlinear properties. The models will be validated with the help of in-silico datasets and in-vitro clot mimicking gel-phantom experiments. This model discovery and calibration has the potential of creating new treatment protocol/devices and will advance the understanding of thromboinflammation.	immune-engineering /neural-musculoskeletal	Viscoelastic, nonlinear elasticity, uncertainty quantification, physics informed neural networks.

Fiona Freeman	fiona.freeman@ucd.ie	UCD	Ultrasound-Modulated Hydrogel Implant for Precision Bone Regeneration: Exploiting Immune Dynamics for Enhanced Healing	Bone, a vital tissue with remarkable self-regenerative capabilities, faces challenges in repairing large-scale defects, often leading to permanent loss and non-union fractures. While tissue engineering holds promise, its translation to clinical applications is hindered by inadequate understanding of biomaterial-immune system interactions. The complex orchestration of various cell types, particularly macrophages, underscores bone fracture healing. Macrophages transition from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, crucial for effective regeneration. Dysregulation in this transition impairs inflammation resolution, hampering bone repair.This proposal aims to develop a bone regenerative implant which exploits ultrasound-triggered hydrogels to modulate M1-M2 polarization, thus enhancing bone regeneration. Specific aims include developing a novel hydrogel for on-demand cytokine release, investigating spatiotemporal effects of M1-M2 polarization post-injury, and assessing BMP-2 mRNA nanoparticles for osteoblast differentiation. The project integrates interdisciplinary approaches to elucidate immune-regenerative dynamics and optimize hydrogel-based therapies for critically sized bone defects. By deciphering the nuanced interplay between biomaterials, immune responses, and bone regeneration, this research offers insights crucial for advancing tissue engineering strategies towards effective clinical translation, potentially revolutionizing the management of large bone defects and fracture non-unions.	immune-engineering /neural-musculoskeletal	mmunomodulation, Bone Regeneration, Biomaterials, Nanoparticles, Macrophages
David Brayden	david.brayden@ucd.ie	UCD	Anti-inflammatory nanoparticles in a hydrogel for administration to osteoarthritic joints	Our lab makes anti-inflammatory nanoparticle prototypes for intra-articular injection with the aim of long acting pain relief for knee osteoarthritis (OA). While efficacious to an extent in rodent models, the requirement for long acting controlled release of the anti-inflammatory cargo from nanoparticles so that injections can be reduced in frequency is difficult to achieve. Here, the candidate will combine one of our nanoparticle prototypes into a joint-injectable hydrogel delivery system made from biocompatible and biodegradable biomaterials. The concept would be to synthesise albumin-based nanoparticles based on combining them with a long-acting prodrug steroid and then embedding them in a hydrogel made from hyaluronic acid, alginate, and chondroitin. Following characterisation for loading and release, the device will be tested in vitro on a macrophage cell line (THP-1) and on primary cells from OA patients to see if they can reduce secretion of anti-inflammatory markers. If successful, in vivo testing will require IA administration to the knees of mono-iodoacetate (MIA) rat model of pain, a post-traumatic OA rat model, and a lipopolysaccharide (LPS) induced equine model. Imaging of fluorescent materials will allow assessment of the location and duration of expression. The project is in the Cancer and Inflammatory Disorder Pillar and falls under the Immune-Engineering heading as we will be examining the host response to the foreign body device in knee joints.	Immuno-Engineering /cancer and inflammatory disorders	Osteoarthritis; nanoparticles; intra-articular administration; hydrogels ; knee inflammation
Garry Duffy	garry.duffy@universityofgalway.ie	Galway	Overcoming the foreign body response using an AI-driven soft robotic drug delivery device	Implantable medical devices may unlock advanced therapeutic interventions in healthcare but a major issue holding them back is the foreign body response (FBR). The response time and severity are patient specific; meaning to overcome the FBR, drug delivery must be controlled and individualistic. Particularly in sensitive tasks, such as releasing insulin in response to changing blood glucose levels, monitoring, and adjusting device function is crucial for long-term success. By sensing in situ physiological signals, we can monitor fibrotic capsule formation for up to 7 days in a rodent model and using soft robotics (predetermined actuation regime) we can improve subcutaneous drug delivery. The ability to use this sensor signal to inform the actuation regime for enhanced drug delivery has been shown computationally and in vitro. This project will extend the technologies capabilities to monitor and overcome the FBR for 28 days in a porcine model. Using machine learning, the actuation regime will be tailored based on real time biosensor signal. The systems performance will be validated in vivo, including criteria for FBR detection accuracy, actuation requirements and drug delivery adjustments. The secondment will be carried out in a state-of-the-art preclinical facility (Explora, Rome) with the capability for large animal models.	Immuno-Engineering /cancer and inflammatory disorders	Foreign body response; Machine learning; Drug delivery; Soft Robotics; Diabetes

Gerard Wall /Daniel Otool	gerard.wall@universityofgalway.ie	Galway	Development of a bifunctional immunoengineering approach to transform treatment of Acute Respiratory Distress Syndrome (ARDS)	Acute respiratory distress syndrome (ARDS) is a life-threatening syndrome caused by neutrophil infiltration into the alveolar space and uncontrolled release of reactive oxygen species (ROS), leading to respiratory failure.Building on our established expertise in recombinant protein technology, targeting and lung biology, we will develop an innovative drug delivery approach to simultaneously suppress IL-8-mediated neutrophil infiltration and protect against ROS damage in ARDS and related diseases. The approach will utilise a recombinant fusion protein, expressed in Escherichia coli, containing a neutralising IL-8-binding antibody fragment and a human superoxide dismutase enzyme to achieve a synergistic therapeutic effect. Its effect on lung function will be demonstrated in vitro with bronchial epithelial cells and by nebulised delivery in an ARDS model – both systems in current use in our groups.	Immuno-Engineering /cancer and inflammatory disorders	ARDS; scFv antibody fragment; superoxide dismutase; nebuliser; drug delivery
Manus Biggs	manus.biggs@universityofgalway.ie	Galway	Electromechanical Conditioning for T-cell expansion	Adoptive T cell therapy (ATT) has revolutionised the treatment of cancer patients. Critically, T-cells must undergo expansion in vivo before patient infusion, and a sufficient number of functional T cells are indispensable for ATT efficacy. In vitro, T cell activation is a cornerstone in manufacturing T cell-based therapies, and precise control over T cell activation is important in developing the next-generation T cell-based therapeutics. This need cannot be fulfilled by currently available methods for T cell stimulation, which utilise biochemical activation protocols; in particular, expansion is typically slow and high-cost.In this study, the development of an electrochemical bioreactor to expedite and improve T-cell expansion is proposed. Previous work by the group has optimised the design and development of an oscillating bioreactor to provide kHz-range vibrational stimulation. We previously showed that this bioreactor can be employed to direct MSC fate1 and maintain the tendon cell phenotype in vitro2,3. In this study, we propose to investigate optimal electromechanical stimulation to induce rapid T-cell activation and proliferation in vitro and will examine the role of electromechanical stimulation in modifying T-cell function and the differentiation of effector and regulatory T-cell populations.	Immuno-Engineering /cancer and inflammatory disorders	
Thi Nga Tran	thinga.tran@universityofgalway.ie	Galway	Modulating the Immunosuppressive Nature of Tumour MicroEnvironment in Glioblastoma by siRNA Therapeutics (INTERNAs)	Glioblastoma (GBM) is refractory to immunotherapies due to a highly immunosuppressive tumour microenvironment (TME), impairing the infiltration and function of immune cells into the tumour mass. The hypersialylation of GBM cells significantly contributes to an immunosuppressive TME in GBM. siRNA is appealing as it can help to silence the genes that produce sialyltransferase enzymes in GBM cells, leading a more immunogenic TME. This project will focus on the synthesis of rationally designed amphiphilic polymers for efficient loading and delivery of siRNA to modulate the TME in GBM. We will seek to synthesize functional polycarbonates with well-defined structure using advanced polymer chemistry. The side groups of polycarbonate segments will be modified with ionizable groups (tertiary amine) and short alkyl chains, which offer the obtained polymers with the capability of complexing with siRNA to form stable polyplex nanoparticles and excellent endosomalytic performance. We will elucidate how polymer structures impact the stability of polymer/siRNA complex and their gene silencing efficacy. As proof of principle, we will exploit the optimal polymer structures to deliver sialyltransferase siRNA to GBM cells. This, in turn, will reduce the hypersialylation in such cells, reducing their immunosuppressive nature of GBMs.	immune-engineering /neural-musculoskeletal	Immunotherapy, polycarbonate, brain cancer, siRNA delivery, nanoparticle

Oran Kennedy	orankennedy@rcsi.ie	RCSI	Immuno-engineering Subchondral Osteocytes in Post-Traumatic Osteoarthritis (PTOA) using Intra-articular Microneedle Devices.	Osteocytes are the most ubiquitous cell-type in bone, comprising 90-95% of its cellular component. Their role transitioned spectacularly from originally being considered inactive 'placeholders', to their current elevated status as primary controllers of bone-remodelling during many regenerative processes. Osteocytes were also recently shown to generate the potent inflammatory cytokine Interleukin-1 (IL-1). This is a function normally associated only with innate immune cells. Production of this cytokine, in those cell types, is a specific process involving intra-cellular inflammasomes – which has been shown to occur following acute joint injuries such as ACL rupture of the knee. ACL rupture is a strong predictor of Post-traumatic Osteoarthritis (PTOA) within 10-15 years of injury. However subchondral osteocytes are difficult to target with current therapeutic approaches, such as standard intra-articular injections, which are rapidly cleared from the joint. To allow for long-duration dwell time for effective drug-delivery, we have developed microneedle-based intra-articular microneedle patches, to allow secured controlled slow-release of prophylactic/therapeutic agents within the joint space. Thus, our aim is to characterise the role of IL1- in subchondral osteocytes, in response joint injury (ACL rupture) and to target this population in situ using long-acting intra-articular microneedle devices to develop new immuno-engineered therapeutics for PTOA.	immune-engineering /neural-musculoskeletal	Microneedles, Osteocytes, Inflammatory factors, Joint injury, Osteoarthritis
Patricia Scully	patricia.scully@universityofgalway.ie	Galway	Biosensor for N-Terminal Pro-Brain Natriuretic Peptide Biomarker Detection: Cardiovascular Disease Diagnostics	Cardiovascular diseases (CVDs) account for 32% of global deaths, highlighting the need for precise and early detection methods. Specific biomarkers provide critical insights into physiological and pathological states, aiding in early disease detection, risk stratification, and therapeutic monitoring of cardiovascular conditions to guide clinical decisions. BNP and NT-proBNP blood levels are invaluable for screening, diagnosing, and predicting outcomes in heart failure. They indicate immune-inflammation index: elevated levels indicate a worse prognosis, left ventricular dysfunction, coronary artery disease, myocardial ischemia, and aortic valve stenosis. Monitoring BNP levels correlates with better patient outcomes; however, current methods rely on lengthy blood tests with limited innovation in bedside detection and long-term monitoring. This project proposes a low-cost, bedside-sensitive device to monitor BNP levels during a patient's critical phase continuously. The project uses novel polymer optical fibre technology embedded with an immune-engineered probe that changes light signal output by NT-proBNP levels. The core fibre sensor/ polymer technology has recently received funding from Enterprise Ireland and SFI Frontiers for the Future for translation into healthcare. The six-month placement includes clinical immersion with cardiology teams at UHG, St. James Hospital Dublin, and The Mater Hospital, as well as industry partnerships with a new fibre optics company spun out from the University of Galway.	immune-engineering /cardiovascular-renal-metabolic	cardiovascular diseases, heart failure, NT ProBNP, nanomaterials, biomarkers, biosensor

Tom Hodgkinson	tomhodgkinson@rcsi.ie	RCSI	Development of biomaterial platforms for the delivery of inflammation-responsive synthetic gene circuits to promote repair of acute cartilage injuries	Traumatic cartilage injuries are prevalent in young people and result in substantial loss-of-function and a high-risk of developing post-traumatic osteoarthritis (PT-OA). Following injury, mechanical stress drives intermittent, but persistent, local inflammation that inhibits cell repair processes and promotes the pathological cell phenotypes that lead to PT-OA. This inflammation drastically limits the efficacy of conventional surgical and regenerative medicine interventions but is highly variable between patients. Advanced biomaterial delivery of synthetic gene circuits is an emerging area that has the potential to provide on-demand local delivery of therapeutics to promote tissue repair. This project will develop synthetic gene cassettes to produce programmable, therapeutic responses to activation of key inflammatory mediators, such as NF-kB, allowing capture of diverse PT-OA relevant biochemical and mechanical inflammatory inputs. These gene circuits will be delivered using a biomaterial-controlled adeno-associated viral (AAV) vector system, which provides non-integrative, long-term transient gene expression over repair relevant timeframes. To facilitate rapid cartilage regeneration while supporting load-bearing, this gene therapy will be combined with a composite biomaterial composed of a viscoelastic hyaluronic acid-based hydrogel and a melt electrowritten microfibrous reinforcing scaffold. This approach has the potential to promote rapid cartilage repair and prevent PT-OA development through closed-loop smart therapeutic delivery.	immune-engineering /neural-musculoskeletal	cartilage repair; post-traumatic osteoarthritis; synthetic gene circuit; mechano-inflammation; smart drug delivery.
Thomas Ritter	thomas.ritter@universityofgalway.ie	Galway	Development of a biomaterial releasing immunomodulatory extracellular vesicles from mesenchymal stromal cells for treatment of ocular surface disease	Extracellular vesicles (EVs) secreted from mesenchymal stromal cells (MSCs) have shown similar therapeutic efficacy as parent MSCs but without the potential risks associated with cell therapies. Our preliminary results show significant therapeutic immunomodulatory potential of MSC-EVs in vitro and in pre-clinical ocular disease models. However, results could be further improved by prolonged/controlled MSC-EV release to the area of injury following topical application. Spatiotemporal release of MSC-EV stimulates immunomodulation and promotes enhanced corneal wound repair. The proposed project will enable the observation of their mechanism of action in-vitro and in-vivo and the evaluation of this approach as a potential cell-free therapy for treatment of inflammatory ocular diseases.Aims and Objectives:1.To isolate MSC-EV from naïve and pre-stimulated human MSC and test their immunomodulatory and pro-repair properties in-vitro,2.To develop a biomaterial loaded with therapeutic MSC-EV for spatiotemporal release and to analyze the immunomodulatory and pro-repair properties in-vitro,3.To test the optimized biomaterial releasing MSC-EV in an ex-vivo/ pre-clinical study in models of damaged ocular surface. This proposal aims to develop a novel (non)-degradable biomaterial or device for sustained release of therapeutic immunomodulatory MSC-EVs. This device will allow the controlled release of MSC-EVs and enhance therapeutic efficacy for treatment of ocular disease.	Immuno-Engineering /cancer and inflammatory disorders	Mesenchymal stromal cells, extracellular vesicles, immunomodulation, ocular disease, cornea