**Workshop Programme**

**9.55-10.00** Welcome from Morgan Alexander, Professor of Biomedical Surfaces and director of the EPSRC Programme Grant in Next Generation Biomaterials Discovery.

**10.00-10.50** María Vicent, Centro de Investigatión Príncipe Felipe, Valencia.

**Polypeptides as versatile Drug Delivery Carriers**

**10.50-11.40** Matt Dalby, University of Glasgow.

**Nanoscale control of mesenchymal stem cell growth and differentiation.**

**11.40-12.00** Break with Posters

**12.00-1.00** Molly Stevens, Imperial College London.

**Exploring and Engineering the Cell-Material Interface**

**1.00-2.00** Lunch with Posters

**2.00-2.50** Paul Stoodley, University of Southampton/Ohio State University.

**Challenges and opportunities in Anti-Biofilm Surface Modification, Design and Control Strategies.**

**2.50-3.40** Ruth Cameron, University of Cambridge.

**Biomaterials in Three Dimensions.**

**3.40-4.30** Glenn Prestwich, University of Utah

**Propelling Chemically Modified Glycosaminoglycans**

**4.30-5** Posters: The winner and runner up of the *RSC Biomaterials Science Discovery Poster Prize* will be announced.

**Molly Stevens, Imperial College London**

**Title**: Exploring and Engineering the Cell-Material Interface

**Abstract**: Understanding how cells interact with surfaces is key to a host of applications in biomedical science from regenerative medicine and drug delivery to biosensors. This talk will highlight both exciting advances in engineered biomaterials and in state of the art imaging approaches to enable exploration and engineering of the cell-material interface for regenerative medicine and biosensing.

Molly Stevens is currently Professor of Biomedical Materials and Regenerative Medicine and the Research Director for Biomedical Material Sciences in the Institute of Biomedical Engineering at Imperial College. She joined Imperial in 2004 after a Postdoctoral training in the laboratory of Professor Robert Langer in the Chemical Engineering Department at the Massachusetts Institute of Technology (MIT). Prior to this she graduated from Bath University with a First Class Honours degree in Pharmaceutical Sciences and was then awarded a PhD in biophysical investigations of specific biomolecular interactions and single biomolecule mechanics from the Laboratory of Biophysics and Surface Analysis at the University of Nottingham (2000).

**Chair**: Morgan Alexander

**María Vicent, Centro de Investigatión Príncipe Felipe, Valencia**

**Title**: Polypeptides as versatile Drug Delivery Carriers

**Abstract**: María is head of Polymer Therapeutics Laboratory at CIPF. Currently, she is the scientist responsible for the Screening Platform and also coordinates the Advanced Therapies Program at CIPF. She is the coordinator of the Valencian Community Strategy on Innovative Medicines becoming one of the Specialist site in the ERIC EU-OPENSCREEN. María’s research group focuses on the development of novel nanopharmaceuticals for different therapeutic and diagnostic applications, in particular Polymer Therapeutics for unmet clinical needs. María received several prizes including the IVth and the IXth Idea awards, and 8 patents, 2 of them licensed to the pharmaceutical industry and a third one used as foundation of the spin off company ‘Polypeptide Therapeutic Solutions SL’ in 2012. She was the Spanish President of the Spanish-Portuguese Chapter of the Controlled Release Society up to end 2013 and the chair of key conferences on the nanomedicine field such as, the International Symposium on Polymer Therapeutics: From Laboratory to Clinical Practice.

**Chair**: Cameron Alexander

**Matt Dalby, University of Glasgow**

**Title:** Nanoscale control of mesenchymal stem cell growth and differentiation

**Abstract**: Bone and the bone marrow niche are regenerative tissues comprising multiple cell types. This presentation will focus on using nanoscale approaches to drive bone regeneration and to bioengineer niche environments to allow enhanced self-renewal and retention of immune suppressive mesenchymal stem cell (MSC) phenotype.

For bone formation, we have used nanoscale topographies to show that physical cues alone can drive osteogenesis1. This data highlighted that integrin/growth factor receptor co-localisation is critical for efficient MSC osteogenesis2. Thus, we have developed a simply-engineered polymer (polyethylacrylate, PEA) system that facilitates integrin/BMP-2 co-localisation for the cells with the aim to further enhance osteogenesis3. With this bioengineered system, it is easy to upscale and move to 3D as the polymer can be applied via spin coating or plasma polymerisation. Recently, we successfully trialled bone graft coated with the PEA - BMP-2 in a compassionate veterinary case, a giant Münsterländer, Eva, who had suffered a major non-union fracture and was facing amputation; she now enjoys a normal quality of life with enhanced bone regeneration allowing her to retain her foreleg. Finally, from understanding that as cells adhere, they vibrate their focal adhesions, we have developed a nanovibrational bioreactor that uses 1000 Hz, 40 nm vibrations to drive osteogenesis in 3D hydrogels; the Nanokick4. This non-invasive and non-chemical differentiation protocol is allowing us to prepare lab-grown graft in readiness for a human trial in 2021.

For MSC self-renewal, we, again, used a nanotopography to show that MSCs could be grown with a retained MSC phenotype in the lab for prolonged periods5. This is important as out of their marrow niche, MSCs tend to quickly differentiate into e.g. fibroblasts. This makes it hard to grow large numbers of high quality stem cells in vitro. It is notable that MSCs are finding use in transplant treatments – not for their regenerative capacity per se, but for their immune-suppressive capacity. This capacity is also lost with time in vitro, but can be maintained using nanotopography. Using a metabolomics pipeline that we developed to understand MSC differentiation6, we identify key glycolytic pathways that can be modulated with drugs in order to achieve prolonged immune suppressive effects and thus generate better MSCs for use with transplant protocols. Going forwards, we are using this information to develop bioengineered MSC niche environments.

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**Chair**: Amir Ghaemmaghami

**Paul Stoodley, University of Southampton/Ohio State University**

**Title:** Challenges and opportunities in Anti-Biofilm Surface Modification, Design and Control Strategies.

**Abstract:** In this workshop Dr. Stoodley will discuss the biology of bacterial biofilms and how strategies evolved to survive in the ancient Earth environment may now be used to survive on the newest manmade materials, never before encountered by these bacteria.

Dr. Paul Stoodley is a Professor in the Departments of Microbial Infection and Immunity and Orthopaedics at The Ohio State University. He also holds an appointment at the University of Southampton in the UK as Professor of Microbial Tribology in the Department of Mechanical Engineering. Dr. Stoodley has a broad research interest in bacterial biofilms, drawn from experience in medicine, engineering and basic microbiology. His specific research focus is on biofilms in orthopedic and other device related infections, control of dental biofilms and biofilm mechanics as a surface survival strategy in the context of industrial fouling and medical devices. He has over 25 years of experience in biofilm research. Dr. Stoodley serves as a key opinion leader and consultant for a number of multi-national companies in the health care sector. Dr. Stoodley has published over 200 articles including reviews, research papers and book chapters in various clinical, engineering and microbiological journals; he has given over one 140 seminars where he has presented his research and workshops to a wide variety of academic, industrial and healthcare audiences.

**Chair**: Paul Williams

**Ruth Cameron, University of Cambridge**

**Title:** Biomaterials in Three Dimensions

**Abstract**: The talk will describe the challenges in using ice templating and other technologies to create novel, complex and biomimetic 3D environments for the control of tissue growth adaptable to a wide range of medical applications.

Professor Ruth Cameron obtained her PhD in Physics from the University of Cambridge, before joining the University's Department of Materials Science and Metallurgy. Together with Professor Serena Best, Ruth directs the Cambridge Centre for Medical Materials and is also a founder member of the board of the Pfizer Institute for Pharmaceutical Materials Science. Ruth’s research focuses on materials which interact therapeutically with the body.

Research themes in medical materials include bioactive biodegradable composites, biodegradable polymers, surface patterning and topography and tissue engineering scaffolds. Research focuses on orthopaedic and spinal applications and heart tissue regeneration with further work in breast tissue engineering, dental repair and 3D imaging. In drug delivery, research is ongoing in tabletting, inhalation devices, and release from degradable implants.

**Chair**: Felicity Rose

**Glenn Prestwich, University of Utah**

**Title:** Propelling Chemically Modified Glycosaminoglycans Into the Clinic

**Abstract:** Glycosaminoglycans (GAGs) are ubiquitous, complex, and essential components of the extracellular matrix, and have been used therapeutically for years. The focus of this talk is chemically modified GAGs, several of which are in clinical development for regenerative and reparative medicine, including wound healing, adhesion prevention, cell therapy, reduction of inflammation, and mitigation of vascular disease. To fulfill the imperative of translational medicine imperative, laboratory-scale biomaterials developed in university settings have now reached veterinary and human patients. Several examples of this bench to business to bedside paradigm will be presented for companies at different stages.

The three main research areas for the Prestwich lab are:

(i) new reagents for phosphoinositide and lysophospholipid signaling in cell biology and cancer treatment,

(ii) biomaterials for cell therapy, wound repair, cartilage repair, tissue engineering, scar-free healing, and xenograft models, and

(iii) sulfated glycosaminoglycan analogues as inflammation modulators for clinical use.

**Chair**: Cathy Merry

**Posters**

**Production of functionalized polymer microparticles using droplet microfluidics**

Adam Dundas1, Derek Irvine2 and Morgan R. Alexander1.

1 Boots Science Building, University of Nottingham, NG7 2RD

2 Advanced Manufacturing Building, University of Nottingham, NG8 1BB

Microparticles currently produced from emulsion-based techniques are often covered in commercially available surfactants such as poly-vinyl alcohol (PVA) which inherently dominates the surface chemistry of produced microparticles. This is a major problem for controlling biological responses as cellular response is known to depend partially on the sample surface chemistry. The synthesis of bespoke amphiphilic polymer surfactants through catalytic chain transfer polymerization (CCTP) is used for the production of monodisperse polymer microparticle populations in a flow-focusing microfluidic junction. Subsequent analysis of the particles using time of flight secondary ion mass spectrometry (ToF-SIMS) demonstrated how the surfactant is located at the surface of the particles and bacterial adhesion studies showed how the surface chemistry effected bacterial adhesion on 3D polymer microparticles. The development of functionalized monodisperse 3D microparticles will allow for the critical analysis of the effect of surface chemistry on more realistic 3D culture systems.

**Novel biomaterials for maturation of Human Pluripotent Stem Cell-Cardiomyocytes**

Aishah Nasir1, Marta Alvarez-Paino2, Jordan D. Thorpe1,Laurence Burroughs2, Jan de Boer3, Felicity R. A. J. Rose2, Cameron Alexander2, Morgan R. Alexander2, Chris Denning1

1 Centre for Biomolecular Sciences, University of Nottingham, Nottingham, NG7 2RD

2 Boots Science Building, University of Nottingham, NG7 2RD

3 Laboratory for Cell Biology-Inspired Tissue Engineering, MERLIN Institute, University of Maastricht, Maastricht, The Netherlands.

Human pluripotent stem cell-cardiomyocytes (hPSC-CMs) are a well-established, readily available human cell source for cardiac disease modelling. However, unlike adult myocardial cells *in vivo*, hPSC-CMs cultured *in vitro* maintain an immature phenotype. In this work, we use 2.5D and 3D biomaterials with surface topographies and polymeric synthetic substrates to influence hPSC-CM maturity.

A high-throughput microarray screening approach tested 24,924 cell-polymer interactions to identify synthetic substrates capable of supporting hPSC-CM attachment. Selected polymers scaled up to 19 cm2 on glass and functionalised on 3D polylactic acid (PLA)-based microparticles with varying topographies successfully supported hPSC-CM attachment and functionality/maturity. Using TopoChip technology, high-throughput screening of over 1000 different surface features will also be tested and combined with polymer substrates to produce scalable models for hPSC differentiation and maturation of cardiomyocytes.

**Star-shaped block copolymers obtained via the Passerini reaction: biocompatible unimolecular micelles with tuneable encapsulation behaviour**

A. Travanut,1 S. Oelmann,2 D. Barther,2 M. Romero1, Prof. Cameron Alexander1 and Prof. Michael A. R. Meier2.

1 University of Nottingham, Nottingham.

2 Karlsruhe Institute of Technology, Karlsruhe.

Within the last decade the interest in novel and complex polymeric materials in advanced applications has increased. The synthesis of defined molecular weights macromolecular architectures has been studied through the investigation of several chemistries. In this scenario, multicomponents reactions gained much attention, due to their high degree of versatility and atom economy. The Passerini three component reaction (Passerini-3CR) is one of the most well-established isocyanide-based multicomponent reaction, it combines an oxo component (aldehyde or ketone), a carboxylic acid and an isocyanide to synthesize an α-acyloxycarboxamide.[1] This reaction can lead to the synthesis of polymers (by the use of monomers having two functional groups) [2] or monomers. In this work a library of star-shaped polymers was synthetized by performing the Passerini-3CR; the organic core was obtained with a degree of polymerization ranging from 5 to 10 and was then functionalized through a Passerini-3CR with PEG 950 g/mol chains leading to water-soluble star-shaped block copolymers. These polymers showed unimolecular micelle behaviour, which interestingly was considered to be more stable than the conventional supramolecular micelles. [3] The polarity of the core of these amphiphilic star-shaped block copolymers was increased by oxidizing the thioether groups to sulfone and it was accurately measured by quantifying the octanol-water partition coefficients (P) with the reverse phase HPLC method. [4] Moreover the ability of encapsulating the water soluble Orange II, the water insoluble Para Red and the Reichardt’s dye was investigated. It was found that the encapsulation ability was not only related to the polarity, but also to the number of arms of the hydrophobic core of the star-shaped copolymers. For the first time it was shown that the encapsulation behaviour could be tuned by matching core and guest polarity. These good findings led to investigate the ability of these polymers to encapsulate the antimicrobial drug azithromycin and, thus, its potential as drug delivery systems. These polymers showed good drug loading (35 mole%), biocompatibility on THP-1 macrophage differentiated cells, internalization and cytoplasm localization in macrophage and, finally, retention of drug activity against the common pathogen *Staphylococcus aureus* after its encapsulation in the unimolecular micelle. In addition to this the drug cargo was retained at pH levels found in the bloodstream, but release the drug under acidic pH values similar to those in intracellular digestive compartments.

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**Using polymer 3D architecture, size and chemistry to control nanoparticle distribution for Doxorubicin drug delivery *in vitro* and *in vivo***

Amanda K. Pearce1, Akosua B. Anane-Adjei1, Robert J. Cavanagh1, Patricia Monteiro1,Thomas M. Bennett2, Vincenzo Taresco1, Phil A. Clarke3, Alison A. Ritchie3, Morgan R. Alexander1, Anna M. Grabowska3 and Cameron Alexander1\*

1 School of Pharmacy, University of Nottingham.

2 School of Chemistry, University of Nottingham.

3 School of Medicine, University of Nottingham.

The size, shape and underlying chemistries of drug delivery particles are all key parameters which govern their ultimate performance *in vivo*. We investigate the effects of size, shape, architecture and reductive degradation on the performance of 2-hydroxypropyl methacrylamide (HPMA)-based co-polymers using *in vitro* and *in vivo* models. We synthesize polymers with linear, hyperbranched, star and micellar-like architectures, all based on core HPMA building blocks, with glutathione-sensitive points of degradation specifically placed for efficient drug delivery and effective clearance from the body. All polymers and nanoparticles are well-tolerated with low toxicity to macrophages and breast cancer cells. Biodistribution studies show that reduction-responsive hyperbranched polymers most successfully avoid accumulation within the liver, and none of the materials target the spleen or lungs. Three lead nanoparticles were selected for further functionalization with a model anticancer drug doxorubicin (DOX), HBP-HPMA-L, HBP-SS-HH and Star-SS-L. Conjugation of the chemotherapeutic drug was via hydrazone-linker onto the nanoparticles, which achieved a 2 to 10-folds increase in potency relative to free DOX in *in vitro* 2D and 3D experiments. In this regard, an *in vivo* model was established to evaluate both tolerability and tumor regression efficiency of the selected NPs-DOX conjugates. The work overall provides valuable new insight into how nanoparticle size, architecture and programmed degradation can be tailored to elicit specific biological responses for drug delivery, and the enhanced potency achieved via drug conjugation to the selected polymeric nanoparticle highlights the potential application of these delivery systems for breast cancer therapy.

**Wireless Bioelectronics for the Treatment of Glioblastoma Multiforme**

Andie Shaw1, Prof Richard Hague2, Dr Ruman Rahman, Dr Frankie Rawson1

1 Pharmacy, University of Nottingham.

2 Engineering, University of Nottingham.

3 Medicine, University of Nottingham.

Glioblastoma Multiforme (GBM) is the most common and lethal primary malignancy of the central nervous system. Prognosis is poor, with most patients succumbing to the disease within a year of diagnosis. An exciting new treatment modality ‘tumour treating fields’ (TTFs) uses electric fields to disrupt cancer cell division, therefore slowing or preventing the spread of tumours. Despite reportedly increasing 5-year survival rates from 5% to 13%, TTFs is not approved by the NHS. This means patients in the UK can expect to pay £18,000 a month to receive this life changing treatment. Improvement and a better understanding of the therapy may allow the uptake in the UK and the use of TTFs to treat other forms of cancer.

We aim to improve TTFs by targeting the electric fields using *in vivo* conductive structures. This will allow electric fields to be targeted at cell surfaces, potentially permitting the use of lower electrical inputs, enhancing therapeutic benefit and lessening side effects. *In Vitro* studies show proof of concept: growing the conductive structures. Current work involves optimising growth with cells and pursuing *In vivo* proof of concept in *C. Elegans*.

**Natural-based hydrogel as a 3D platform for cell co-culture towards cartilage regeneration**

Annachiara Scalzone

Articular cartilage is a tissue that lacks the ability to self-repair and this makes it a very attractive target for exploring new bio-approaches. This work aimed to combine Tissue Engineering with Stem Cells-based therapy to obtain an innovative 3D platform for cell co-culture towards cartilage regeneration. It was based. Rheological and gelification analyses on a thermo-sensitive chitosan-based hydrogel, ionically cross-linked with the addition of β–glycerophosphate, showed a sol/gel transition occurring at 31-33°C in 5min. Mechanical tests evidenced a compressive and equilibrium Young’s modulus of 37±4.0kPa and 17.0±0.8kPa. After proving the hydrogel cytocompatibility, the influence of human chondrocytes spheroid, in close-contact with Mesenchymal Stem Cells-laden hydrogels, on the formation of new cartilage-like tissue was successfully assessed by immunofluorescence and histological analyses.

**Surface Chemistries Influence Fibroblast Differentiation into Myofibroblasts: a High Throughput Approach**

Arsalan Latif1, Laurence Burroughs2, Morgan R Alexander2, Amir Ghaemmaghami1

1School of Life Sciences, University of Nottingham, United Kingdom

2School of Pharmacy, University of Nottingham, United Kingdom

The implantation of foreign material into a host body, as used in medical devices, is known to induce an immune response known as the foreign body response1. Fibroblasts have been shown to play an important role in both healing process and fibrotic capsule formation (as part of the foreign body response) depending on the nature of biochemical stimuli, e.g. from immune cells such as macrophages, and the physicochemical characteristics of the materials. Conversion of fibroblasts to myofibroblasts is the hallmark of fibrosis2 and is associated with enhanced ECM secretion and could lead to fibrotic capsule formation if not regulated. Regulation of fibroblast to myofibroblast differentiation using biomaterial surface characteristics such as surface chemistry to control fibrosis is the goal of this work. To identify such a material high throughput screening was used to identify polymers that modulate fibroblast differentiation into myofibroblasts.Our data clearly show that some polymers are able to modulate (i.e. suppress or accelerate) fibroblast response to TGF-b, a potent stimulant of fibroblasts, as evidenced by changes in cell proliferation and myobfibroblast differentiation. Changing the surface chemistry of materials could provide a means for modulating deleterious fibrotic responses by directly influencing fibroblast differentiation and proliferation. Future work will focus on fuller characterization of fibroblast response to the identified polymers and investigating their effect on macrophages and the cross-talk between fibroblasts and macrophages on the ‘hit’ polymers.

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**Nanotherapeutics for neurosurgically applied tumour drug delivery**

Catherine Vasey

Aliphatic polyesters have gained a broad interest for biomedical application, mainly due to their biocompatibility, biodegradability and low toxicity. Access to these polymeric materials is provided through the ring-opening polymerisation (ROP) of cyclic esters, and growing these into large macromolecular frameworks provides enhanced control over polymer characteristics. Based on an increasing understanding of brain intra-tumour heterogeneity, the capability to deliver multiple therapeutic moieties from single formulations is clinically-relevant for the treatment of glioblastoma (GBM). Through formulating star-branched aliphatic polyesters with functional groups introduced into the backbone, we have shown potential to encapsulate and conjugate two therapeutic agents within the same formulation. A pre-existing biomaterial, poly(lactic-co-glycolic acid)/poly(ethylene glycol) (PLGA/PEG) microparticles, has been formulated to act as a paste at room temperature and sinter at body temperature. It is hypothesised that incorporating drug-loaded nano-polymers into the PLGA/PEG paste will lead to efficacious local delivery of chemotherapeutic agents against GBM.

**Combining induced pluripotent stem cells and a defined, bespoke 3D culture model to probe the mechanistic basis of diseases impacting the cell-matrix interface.**

J.L. Thompson, J.C. Ashworth, K.S. Dowding, S. Pijuan-Galito, M.R. Alexander, C.L.R. Merry

The extracellular matrix (ECM) is a complex, dynamic 3D microenvironment providing physical and biochemical instruction to cells. Current models of ECM-related disease frequently involve irrelevant matrix and fail to adequately probe the mechanistic basis of dysregulated cell-ECM interactions, preventing development of matrix-targeting therapeutics. We have optimised a “blank slate” 3D culture environment that can be functionalised with specific matrix components, mimicking abnormal ECM. In a complementary approach, we have developed induced pluripotent stem cell (iPSC) disease models that, when encapsulated in these gels, create their own disease-specific microenvironments. Using multiple osteochondroma (MO), a disease associated with a tissue-specific phenotype linked to disrupted synthesis of heparan sulphate (HS) as an exemplar, we will combine ECM- and cell-based tools to probe the mechanistic basis of this disorder. We will present data demonstrating the creation of iPSC models together with directed differentiation within the hydrogels to identify key steps at which the abnormal HS in the MO models disrupts essential signalling.

**Micropipette Manipulation of Microparticle Components: An Insight Into “Golf Ball” Particle Formation**

Charlotte Henshaw (UoN School of Pharmacy, NGBD PG PhD Student)

Supervisors: Prof P. M. Williams, Prof M. R. Alexander and Prof F. R. A. J Rose

Particles with topographies such as the “Golf ball” microparticles could be of interest in a range of medical applications. However, to be fully utilised, their formation kinetics must be understood so the final properties (topography, etc.) can be controlled. The micropipette manipulation technique offers a unique opportunity to analyse properties, such as interfacial tension, at the scale of the particles by monitoring the formation of single particles from solutions to final solid microparticles in real time. Robust analysis techniques have been developed to allow reliable measurements of these properties; these have been demonstrated on solutions of Dichloromethane (DCM) with increasing concentrations of poly(Lactic Acid) (PLA), and water with increasing poly(Vinyl Alcohol) (PVA) concentrations, the components of the smooth microparticles and precursors to the “Golf balls”. Increasing the PVA concentration reduced the interfacial tension between water and DCM, but had no significant effect on the dissolution. Work is ongoing to understand the effect of adding PLA.

**Epoxy-Amine Resins from Terpenes with Applications in Synergistic Antifungal Treatments**

Dara O'Brien

School of Chemistry, University of Nottingham

The biomaterials-based healthcare industry has been revolutionised by polymer systems; their technologies are currently employed in a variety of applications from synthetic blood vessels to implants.1 However, there is now a drive to find new, renewable polymer feedstocks, to alleviate the environmental, and subsequent economic, impact of using petrochemical-derived systems.2 Terpenes comprise a diverse family of hydrocarbon-rich molecular biomass,3 potentially making them an attractive source of novel, sustainable monomers. This work investigates the use of a common terpenoid, (*R*)-carvone, in the synthesis of a bis-epoxide monomer using sustainable chemistry. The terpene-based bis-epoxide was then co-polymerised with a commercially-available secondary diamine. Initial investigations have yielded oligomers up to approximately 3500 Da. Growth inhibition assays were performed in broth to investigate synergistic antifungal activity of these oligomers, with major antifungals iodoproylnyl butylcarbamate (IPBC) and amphotericin B, against *Trichoderma virens* and *Candida albicans*, respectively. Checkerboard analysis found that the presence of the terpene-based oligomers decreased the MIC of IPBC ≥64- fold in the case of *Trichoderma virens*, and decreased the MIC of Amphotericin B ≥4- fold in the case of *Candida albicans*. These results indicate the potential use of these carvone-based oligomers in the synthesis of biomedical, or other, material devices.

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**Screening Combinatorial Material Microarrays to identify inducers of Epithelial to Mesenchymal Transition.**

Eduardo Pernaut-Leza

University of Nottingham

Epithelial-Mesenchymal Transition (EMT) is a process involved on gain of malignancy on cancer cells. While undergoing EMT cancer cells experience a loss in epithelial markers and phenotype and a gain in mesenchymal features that increase invasiveness and malignancy, requirements that make metastasis possible.

Currently a variety of 3D culture models are being utilized to study EMT induction in cancer cells by recreating different aspects of the tumour microenvironment (TME), as well as to test the effectiveness of anticancer drugs. However, as each model focuses on specific aspects of the TME, cancer cells lack the influence of important other components. Also, malignant properties of cancer cells are highly variable depending on features of the TME like the cell passage number, stage in the cell cycle or cell density of supporting stromal cells, as well as composition of the extracellular matrix.

Next generation synthetic compounds aim to offset these disadvantages by activating the same signaling pathways described in gain of malignancy and EMT induction avoiding at the same time variability in results due to their highly reproducible process of synthesis.

**MICROPARTICLE MEDIATED DRUG DELIVERY TO MODULATE MACROPHAGE PHENOTYPE TOWARD M2 FOR APPLICATION IN SPINAL CORD INJURY**

Jasmine Z Stening1, Felicity RAJ Rose1, Lisa J White1

1Regenerative Medicine and Cellular Therapy, School of Pharmacy, University of Nottingham

**INTRODUCTION:** Currently spinal cord injury (SCI) lacks treatment capable of restoring limb function and sensation. Current strategies focus on alleviating the triggered high inflammatory environment using pharmaceuticals. Understanding macrophage behavior and the roles of their sub phenotypes in SCI has suggested a method for controlling inflammation by modulation towards a pro-immunoregulatory subgroup (M2) using cytokine IL-4. Microparticles are widely reported as drug delivery methods for controlled and sustained release in pharmaceutical strategies. We aim to determine suitable release profiles for cytokine delivery.

**METHODS:** Particles were manufactured using a double emulsion method with 50:50 or 85:15 (lactide:glycolide ratio) PLGA (52kDa). Release kinetics were tailored by: (i) incorporation of a PLGA-PEG-PLGA triblock modifier (TB) and (ii) changing the total polymer (TP) percentage. Different surface thickness particles were manufactured using 10%, 15% and 20% TP using 500mg, 750mg, and 1g PLGA dissolved in 5ml DCM respectively. Total protein loaded was 10mg/ml for 1g polymer and 5mg/ml for 500mg polymer. Protein release kinetics were analysed using lysozyme as a model protein. Release results were reported as μg protein/ mg particles with a maximum of 10 μg/mg encapsulated. Particles were characterised using scanning electron microscopy and laser diffraction for size distribution. Protein encapsulation efficiencies and release were analysed over 20 days using a micro BCA assay to detect total protein content.

**RESULTS:** Microparticles fabricated were 20-50μm in size and had a smooth morphology. In a comparison of surface thickness the fastest release was observed for 10% TP 85:15 PLGA with a burst release of 2.5 μg/mg on day 1. Less burst release was seen for 15% TP 50:50 PLGA. The slowest release occurred for 10% TP 50:50 PLGA with 1 μg/mg released by day 20. Total polymer 10% and 15% particles showed release too fast and unsustained for this application. In a comparison of triblock percentages for 20% TP 50:50 PLGA, 30% TB showed the fastest release with 10 μg/mg released by day 20. The slowest release was seen for 0% and 20% TB showing a small burst release of 1μg/mg at day 1 and only reaching 1.5 μg/mg and 3 μg/mg respectively by day 20. 10% TB showed a burst release of 3 μg/mg at day 1 as for 30% TB but showed a promising sustained and continuous release to 6 μg/mg over 20 days.

**DISCUSSION & CONCLUSIONS:** Particles prepared from 10% or 15% total polymer displayed protein release unsuitable for controlled release with a fast burst release followed by minimal daily release. Particles manufactured from 50:50 PLGA and 85:15 PLGA alone displayed release too slow for IL-4 delivery. Addition of a PLGA-PEG-PLGA triblock enabled release to be controlled with less initial burst release and accelerated overall release. Microparticles fabricated from 20%TP, 50:50 PLGA with 10% TB showed a release profile most suited to 14 days of controlled release.

**Peptide Hydrogels of Fully-Defined Composition and Mechanics for**

**Probing Cell-Cell and Cell-Matrix Interactions**

Jennifer C Ashworth1,2, Charlotte Slater1, Gillian Farnie2,3 & Cathy LR Merry1

*1Stem Cell Glycobiology Group, Division of Cancer & Stem Cells, University of Nottingham, UK; 2Manchester Cancer Research Centre, Division of Molecular & Clinical Cancer Sciences, University of Manchester, UK; 3Botnar Research Centre, NDORMS, University of Oxford, UK*

Current materials used for *in vitro* cancer models are limited by their variability, complexity, and poor similarity to human tissue. We present a “blank slate” culture environment that can be customized by incorporating matrix components specifically selected to match the target tissue, with mechanical properties controlled independently and simultaneously. As proof-of-concept, we present a panel of hydrogels designed to mimic the stages of breast cancer progression. Controlling the peptide gelator concentration allows hydrogel stiffness to be matched to normal breast (<1 kPa) or breast tumour (>1 kPa), with higher stiffness favouring the viability of breast cancer cells over normal breast cells. In parallel, these hydrogels may be modified with matrix components relevant to human breast, such as collagen I and hyaluronan. The choice and concentration of these additions control the size, shape and organisation of the breast epithelial cell structures formed in co-culture with fibroblasts. This system therefore provides a means of unravelling the individual influences of matrix, mechanical properties and cell-cell interactions in cancer and disease.

**Development of Novel Biomaterials for Human Pluripotent Stem Cell Culture**

JD Thorpe1, L Burroughs2, A Nasir1, S Pijuan-Galito1, J Meurs2, M Alexander2, C Denning1

1. Centre for Biomolecular Sciences, University of Nottingham, Nottingham, NG7 2RD
2. Boots Science Building, University of Nottingham, NG7 2RD

Human pluripotent stem cells (hPSCs) hold great promise for the treatment of conditions such as; heart failure, Parkinson’s disease, macular degeneration, and are increasingly being used within the drug screening process. Current hPSC expansion culture systems predominantly use Matrigel™ which is xenogenic, or human recombinant proteins such as Vitronectin or Laminin-521 which are prohibitively expensive for industrial-scale biomedicine. Here we present a cost-effective, scalable culture method for hPSC expansion using polymeric synthetic substrates.

We tested 12,503 cell-polymer interactions during a high-throughput polymer microarray screening campaign to identify synthetic surfaces capable of supporting 72-hour hPSC expansion, in Essential 8 medium. Two selected polymers from the screen have been successfully scaled-up to 9cm2 on tissue culture plastic through a simple and scalable UV polymerisation technique. hPSCs cultured on these surfaces are capable of long-term culture, retention of pluripotency makers, and differentiation in to the three germ layers.

**High throughput profiling of proteins adsorbed to biomaterial surfaces using microwave-assisted *in situ* trypsin digestion and LESA-MS/MS**

Joris Meurs1, Josephine Bunch2,3, Morgan R. Alexander1, David A. Barrett1 & Dong-Hyun Kim1

1: Advanced Materials & Healthcare Technologies Division, School of Pharmacy, University of Nottingham, Nottingham, United Kingdom

2: National Centre of Excellence in Mass Spectrometry Imaging, National Physical Laboratory, Teddington, United Kingdom

3: Department of Surgery & Cancer, Computational and Systems Medicine, Imperial College, London, United Kingdom

Pluripotent stem cells are a valuable source for cell production and have a huge potential to serve for a multitude of applications in regenerative medicine. Biomaterials have been discovered that assist as fully synthetic substrates for pluripotency maintenance during expansion, but the mechanism by which they achieve this is not well understood because of poor characterisation of the biointerface. Pre-adsorption of proteins from the culture medium is believed to be a crucial element in this process. Current analytical methodologies are limited in throughput and therefore not compatible with achieving to a broad assessment of a number of materials in high throughput biomaterials discovery. Previous research has shown the potential of liquid extraction surface analysis-tandem mass spectrometry (LESA-MS/MS) as a high throughput tool for the analysis of surface-adsorbed proteins. In this work, extraction and MS parameters were optimised for acquisition of high quality spectral data. The time-limiting step is the *in situ* trypsin digestion which takes up to 18-24 hours under ambient conditions. Here, we found that the digestion time can be vastly reduced when performing the digestion in a household microwave oven, decreasing the total run time ~100 fold. The next step is to employ the methodology on biomaterial surfaces incubated in medium.

**Altering topology of additively manufactured metal surfaces using electrochemical jet machining to limit platelet activity**

Katie Blake

The role of platelets in wound healing and blood clot formation is of vital importance to medical implants. The surface topology of parts produced using selective laser melting is rough and uneven, producing an environment in which platelets will readily activate. Whilst this benefits the integration of some medical devices such as orthopaedic implants and can encourage healing and cellular ingrowth, others such as cardiovascular devices would be negatively impacted by this activation. The potential for catastrophic thrombogenic events is already higher in cardiovascular devices and as such this risk must be controlled. In this work we investigate the role of a surface produced by selective laser melting in activating the platelet response in human blood, and modify the topology using electrochemical jet machining to limit this response.

**Exploring the relationship between material geometry and chemistry on immune cell responses using two-photon lithography**

L. Ma, M. Vassey, D. Irvine, R. Hague, A. Ghaemmaghami, M. Alexander and R. Wildman

The University of Nottingham

**‘The development of biocompatible techniques towards cellular redox fabrication of biomimetic polymers’**

*Mechelle R. Bennett, Cameron Alexander, Phil J. Hill and Frankie J. Rawson,*

*University of Nottingham*

Abstract: Iron-catalysed Atom Transfer Radical Polymerisation (ATRP), an alternative, less toxic method to copper ATRP, has great potential as a tool towards biological applications and is well studied for a variety of organic solvents.[1] Literature concerning aqueous systems is more scarce and data is mostly reported at high temperatures, indicating the need for optimisation.[2] Activator Generated Electron Transfer (AGET) ATRP exploits the redox chemistry of a transition metal catalyst which is activated by a reducing agent.[3] We hypothesised that extracellular bacterial redox mechanisms would act as a reducing agent in such experiments, leading to *in vivo* polymerisations. This may enable the construction of biomimetic polymers for cell surface modification, previously demonstrated using copper catalysts.[4] The optimisation of this method to improve biocompatibility is first presented without cells, using water soluble monomers (PPEGMA, PNHEA, PPAMPS, PMEDSA) and phosphate buffered saline (PBS) as a solvent at 37°C. Several ligands (Me6TREN, Me3TREN, Bipy) were employed for the elucidation of catalyst behaviour and were found to generate polymers at different rates. The introduction of two bacteria types (*Geobacter sulfurreducens*, and *Cupriavidus metallidurans*) were investigated as reducing agents. The data presented reveals that bacterial reduction was able to initiate the polymerisation of PPEGMA in both cases. Toxicity studies were carried out to determine the optimum concentration of reagents and adjusted accordingly, resulting in a biocompatible bacteria instructed polymer synthesis.

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**Holographic Microscopy to image cells on a surface**

Nicola E Farthing, Martin A Bees, Laurence G Wilson

Bacterial biofilms are of increasing interest in many sectors and their growth, or lack thereof, impacts various industries. It is well known that such biofilms form on surfaces to which ‘seed’ cells attach. Many of these seed cells are motile bacterial cells and it has been suggested that the motility of cells impacts the formation of biofilms [1]. However, conventional wisdom suggests that, during biofilm formation, cells downregulate their motility. The timescale over which this downregulation may occur is not well known and we suggest that cells remain motile for some time after attachment to the surface. In this work, we present a method of using holographic microscopy to image the fluid flow due to surface attached bacterial cells in 3D. We also present a simplified model to capture the key elements of the flow using solutions to the Stokes equations. We use the simple model to suggest that the bacterial flow on a surface may impact the later stages of biofilm formation.

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**Combination of mechanical and electrical cues to improve maturity in human stem cell derived-cardiomyocytes**

Paola Sanjuan-Alberte, Jayasheelan Vaithilingam, Chris Denning, Richard JM Hague, Morgan R Alexander, Frankie J Rawson

The University of Nottingham.

Cardiac tissue is extremely sensitive to damage due to the minimal regeneration capacity of cardiomyotes. Depending on the area of damage, the consequences could lead to catastrophic heart failure where the only current solution to this situation is heart transplantation. Cardiomyocytes cultured *in vitro* from human induced pluripotent stem cells have the potential to be used in regenerative medicine and other areas such as toxicology and physiology. However, our ability to take the *in vitro* produced cardiomyocytes to a stage similar to adult cells *in vivo* is very limited. External cues such as biomimetic scaffolds and electrical stimulation have the potential to mimic physiological conditions. The ability to modulate cardiomyocyte phenotype via a combination of mechanical cues, material chemistry and topography, and electrical cues are studied herein. After development of materials, these are processed by two-photon polymerisation (2PP) in order to manufacture three-dimensional structures with human cardiomyocytes derived from stem cells. Cells were cultured on 2PP structures showing a better alignment and aspect ratio than those on control surfaces. This is also translated into a better maturation state indicated by the length of the sarcomeric units of the cells. This effect can be enhanced by the application of electrical stimulation to the cells where values of sarcomere length were similar to physiological values.

**No, these hydrogels will not turn you into Spider-Man (probably)**

Rowan Earlam

Protein hydrogels are promising materials for tissue engineering, due to their 3D structure, biocompatibility, biodegrability and controllable architecture. However, animal derived hydrogels bring the risk of infection and have batch to batch variability. Expressing proteins recombinantly in *E. coli* removes these risks to create a cheaper, more ethical and reproducible product.

The recently described recombinant spider silk protein NT2RepCT has been used to create natural protein hydrogels. Spider silk has impressive biomaterial properties as it is strong, elastic and biocompatible, making it an excellent candidate for hydrogels. Rheology, cell culture and immunological experiments are being performed to assess the compatibility of these materials for tissue engineering. Varying the concentration of NT2RepCT and method of gelation alters the mechanical properties. They can therefore be tuned to be suitable for different body tissues of varying stiffness.

Addition of functionality to NT2RepCT has been investigated under biological conditions with promising results. This technique could be used to add bioactive cues to increase cell compatibility.

**Development of an *in vivo* drug monitoring sensor**

Steven Gibney

This project aims to develop a biocompatible and biodegradable sensor for use *in vivo*. Firstly, the project will use novel biodegradable polymers in conjunction with established conductive polymers to design a combinatorial printing array capable of rapidly assessing both physical and electrochemical properties. Following this, understanding of suitable polymer composites will be paired with knowledge of therapeutic analytes to develop a sensor which is both biodegradable on a clinically relevant time-scale and can accurately detect specific analytes, such as antipsychotics, across a dynamic range.

If successful this project would act as a proof-of-concept for a novel sensor platform which would provide a step forward for translational research and contribute towards the growing field of personalised medicine.

**High-throughput Synthesis and Characterization of Surfactant Libraries via Chain Transfer-Mediated Radical Polymerization**

Valentina Cuzzucoli Crucitti, Adam A. Dundas, Shaun C. Howard, Vincenzo Taresco, Marion J. Limo, Paul Williams, Morgan R. Alexander, Ricky D. Wildman, Benjamin W. Muir\* and Derek J. Irvine\*

The University of Nottingham

The rise of combinatorial chemistry approaches and high-throughput (HT) methods has been a breakthrough for the design and screening of new materials [1]. Parallelly, polymer chemistry is very well suitable for HT combinatorial approaches due to the diversity of parameters that can be varied systematically. [2] To apply combinatorial and high-throughput chemistry to a controlled radical polymerization technique, CCTP was chosen to produce a library of polymeric surfactants. Herein, we report, for the first time, the use of CCTP to synthesize a library of smart amphiphilic polymeric surfactants adopting 19 hydrophobic monomers (HM) (showing a wide range of log P) and 1 hydrophilic PEG-based monomer. High degree of automation was reached by employing an automated synthesizer allowing synthesis mixtures preparation, NMR and GPC sampling. Finally, to assess surfactants self-assembling ability in water a HT pilot screening in terms of Critical Assembling Concentration (CAC) was performed.

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