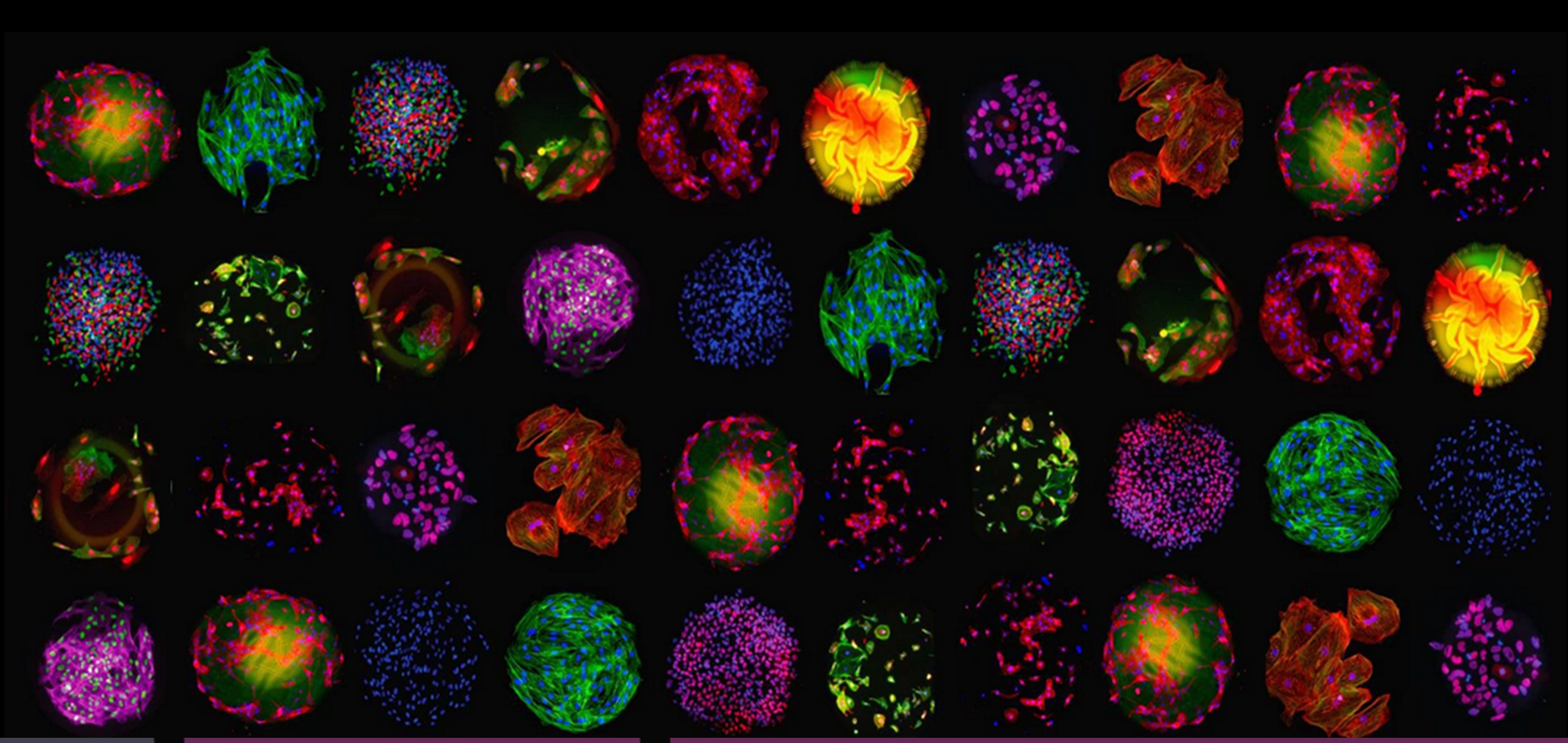

ATREUM

Advancing Tissue Engineering and Regenerative Medicine in UK MEdicine

EDITED BY: RICHARD HARRISON & CHRIS ADAMS

ABSTRACTS FROM ATREUM 2017©

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Wolfson School of Mechanical and Manufacturing Engineering

Loughborough University

Loughborough

LE11 3TU

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Preface

The UK is currently a globally competitive leader in Tissue Engineering and Regenerative Medicine (TERM). To maintain its leadership in the field, a forward looking strategy is required to ensure the future leaders in TERM research are fully equipped with the scientific skills, entrepreneurial knowledge and supportive infrastructure required to facilitate translation of their research into clinical therapies in a global market.

Between 2012 and 2013 the UK published its strategy for regenerative medicine, forming the UKRMP and initiating a burst of world-leading innovation in TERM research, and supporting the development of a closely knit network of researchers developing translational TERM therapies. Five years later, the government appointed a committee to evaluate adoption of new technologies in clinical practice. The Accelerated Access Review published their report in late 2016, highlighting the need to develop a "process for identifying and pulling transformative innovations into the NHS quickly".

This process does not yet exist.

There are large time, resource and communication gaps between our most innovative TERM research, and the clinical use of TERM therapies. In order to address these gaps, it is imperative that the UK develops a more streamlined approach to the clinical translation of innovative TERM therapies.

The timing of this is critical; by the onset of the ATREUM conference, the UK will have likely triggered Article 50 and initiated its withdrawal from the European Union. Linked to this, in early 2017, the government released a statement on "Science priorities for Brexit" and the "Building our Industrial Strategy" green paper, calling for recommendations and strategies to accelerate growth and development in the UK. The government has identified ten pillar areas as crucial for future growth in the UK, with Science, Research and Innovation included as a focus area.

In light of these developments, ATREUM brings together TERM focused researchers, regulators, funders and industrial leaders to identify the current challenges in the translation of TERM research, and develop strategies to overcome these challenges. Over the course of three days, Early Career Researchers (ECRs; including recently appointed PI's, academic clinicians, research fellows and those soon to make the transition to independence) will engage with leaders in the field to share new science, learn about the current process of TERM translation in the UK, and complete a series of workshops to probe the current barriers to ECR-led entrepreneurship and the translation of ECR research.

Using the metrics generated at the conference, we will write an ECR-led position paper describing key recommendations in policy, funding, regulation and scientific direction to improve the UK TERM Translational Landscape, which will enable future leaders to best deliver TERM research. We anticipate it may take another five to ten years to put these strategies in place, but by engaging ECRs in defining the problem and identifying the solution, we can ensure that the future leaders in TERM research are best positioned to accelerate clinical adoption of their own TERM innovations.

ATREUM is a landmark and disruptive conference, designed by ECRs for ECRs, aiming to define, direct and eventually deliver the future of translational UK TERM research. We are excited to welcome you to ATREUM and are looking forward to working together over the next few days,

Derfogail

Dr. Derfogail Delcassian

ATREUM Conference Chair

On behalf of the E-TERM Fellows

ETERM Committee

Dr. Derfogail Delcassian

ATREUM Conference Chair

University of Nottingham, Harvard Medical School, and MIT

Dr. Amanda Barnes

Workshop Session Chair

University of York

Dr. Chris Adams

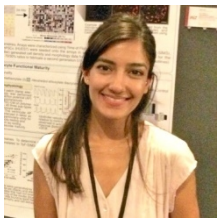
Workshop Session Chair

Keele University

Dr. Stuart Jenkins

Workshop Session Chair

Keele University



Dr. Asha Patel

University of Nottingham and MIT

Dr. Richard Harrison

Loughborough University & The University of Nottingham

Dr. Owen Davies

University of Birmingham

Dr. Antony Herbert

University of Leeds

Dr. Sandhya Moise

University of Nottingham and Kings College London

Dr. Sammy Wilson

University of Loughborough

Dr. Qasim Rafiq

University College London

Dr. Ilida Ortega

University of Sheffield

Prof. David Williams OBE FREng

Advisory Board

Loughborough University

Contact Numbers

Emergency	999
Committee Mobile (Derfogail)	+44 (0) 7947 385147
Crewe Hall	+44 (0) 1270 253 333
Local Taxi	+44 (0) 1270 211222

Venue

Crewe Hall

Address: Crewe Hall, Weston Road, Crewe, CW1 6UZ

Website: https://www.qhotels.co.uk/our-locations/crewe-hall/

Sponsorship

We are very grateful to the following sponsors who have supported ATREUM 2017:

UK Regenerative Medicine Platform

Programme

Monday 03 April 2017: Engineering Cellular Behaviour	
Arrival and registration	
17:00	**Registration and poster set up (Groups A and B)**
19:00	**ECR Networking and Drinks** An introduction to the conference and networking drinks
20:00	**Dinner**
Tuesday 04 April 2017: Engineering Cellular Behaviour	
SESSION 1- Acellular materials and constructs to direct cellular behaviour	
08:45	**Conference welcome and overview** Dr. Derfogail Delcassian- ATREUM Chair
	Bridging the Gap: Skeletal Cell Based Strategies for Repair - Opportunities and Challenges Prof. Richard Oreffo, University of Southampton
	Nanoscale approaches to control mesenchymal stem cell growth and differentiation Prof. Matt Dalby, University of Glasgow
	Regenerative Polymers for Dentistry Dr. Adam Celiz, University of Nottingham
	Functional nanomaterials for intracellular interaction to direct cell fate Dr. Ciro Chiappini, Kings College London
10.50	**Break**
SESSION 2- Cellular cues for redirecting stem cell fate/challenges in TERM with stem cells	
11:15	**Deconstructing the epidermal stem cell niche** Prof. Fiona Watt, King's College London
	Simplifying cell therapy to get it to the clinic Prof. Sheila MacNeil, University of Sheffield
	An Engineered Heart Tissue Model of the Actin-E99K Mutation Dr. James Smith, University of Nottingham
	Temporal Intracellular Characterisation of Stem Cells with External Stimulation Dr. Amy Gemi, Imperial College London
13.00	**Lunch**
WORKSHOP: Engineering Cellular Behaviour	
14:15	**Scientific and Engineering Challenges in Directing Cellular Behaviour in TERM** **Workshop Chair: Dr. Chris Adams and Dr. Derfogail Delcassian** This workshop will develop an extended classification for regenerative medicine therapies based on the "Technology Readiness Level" (TRL) system. Once TRLs have been agreed, delegates will review their scientific research area to determine at which TRL level it currently stands, and identify areas of scientific and engineering focus in future work. The workshop will allow ECRs to identify new tools and technologies required to engineer successful regenerative medicine and cellular therapies, focusing on tools to direct desired cellular behaviour, and engineering challenges in evaluating cell behaviour.
16.15	**Break**
POSTERS	
16:30	**Poster session A** Poster flash presentations and poster networking
18.30	**Free time**
20:00	**Dinner**

Wednesday 05 April 2017: Evaluating pre-clinical TERM therapies	
SESSION 3- Monitoring cellular behaviour post manipulation and delivery	
09:00	**Tracking cell therapies *in vivo*** Bill Shingleton, GE Healthcare
	Delivery of encapsulated cells inside polymer gels and their behaviour post manipulation Prof. Liam Grover, University of Birmingham
	Monitoring the fate of administered cells using whole body imaging Prof. Phillip Blower, King's College London
	Enhanced antibody computed tomography (ENACT) a novel, non-destructive, molecularly specific method for the detection of cellular populations in three dimensional samples Dr. Adam Glen, University of Sheffield
10.50	**Break**
SESSION 4- Evaluating TERM cell and material constructs	
11:15	**Nanomaterials; investigating their biological interactions to speed up clinical translation** Dr. Neill Liptrott, University of Liverpool
	Regulator's perspective on preclinical testing of advanced therapy medicinal products (ATMPs) Dr. James McBlane, MHRA
	Toward Building Complex Cellular Microenvironments via Biomicrofabrication Dr. Yan Yan Sherry Huang, University of Cambridge
	Use of companion dogs as a clinical model for regenerative medicine research John Prager, University of Bristol
13.00	**Lunch**
WORKSHOP: Evaluating pre-clinical TERM therapies	
14:15	**Preclinical modelling: assessing the potency of regenerative therapies** **Workshop Chair: Dr. Stuart Jenkins** This workshop will discuss how best to prepare the regenerative medicine industry for a successful 'moonshot' therapy. There will be a particular focus on assessing the potency of biological therapies: this aspect is more problematic to determine when compared to more generally applicable toxicity/safety measures. So, how do we most effectively develop and validate assays/models for disparate, biological products? The recent MHRA 'consultation on strategy for pharmacopoeial public quality standards for biological medicines' will be discussed, and a summary of opinions from the ATREUM delegates will be fed back to MHRA.
16.15	**Break**
POSTERS	
16:30	**Poster session B** Poster flash presentations and poster networking
18.30	**Free time**
20:00	**Dinner** **Formal Conference Dinner**

Thursday 06 April 2017: Translating TERM Research	
WORKSHOP: Translational skills and strategies	
09:00	**Skills and strategies to support translational researchers and entrepreneurs** **Workshop Chair: Dr. Amanda Barnes** This workshop will focus on identifying routes from academic led research towards ECR-led entrepreneurship. Building on the translational TRL system developed in workshop 1, there will be a focused discussion on stages of ECR-led entrepreneurship, current barriers to ECR-led entrepreneurship, and the skills required for each stage of the translational pipelines.
10.45	**Break**
Developing and manufacturing TERM products within regulatory frameworks	
11.15	**Current manufacturing facilities in the UK for cellular TERM translation** Cell Therapy Catapult
	Standardisation in TERM translational research Prof. Glyn Stacey, NIBSC
	Regulation and scale up challenges in cell therapies Dr. Amit Chandra, YposKesi
	Automated expansion of pluripotent stem cells at three international sites Dr. Maryam Shariatzadeh, Loughborough University
13.30	**Lunch**
WORKSHOP: Funding, manufacture and regulation **Overview- state of the UK landscape**	
14:30	**ECR driven TERM Translational "moonshot"** **How do we support the next generation of TERM research leaders?** **Workshop Chairs: Dr. Chris Adams and Dr. Derfogail Delcassian** Having identified the translational TRL pathway to developing TERM research products, this workshop will summarise the major challenges to developing UK TERM translational therapies and set out a road map to success. With scientific and engineering challenges identified, regulatory hurdles discussed, and an ideal skills list for translational entrepreneurship in hand, we will identify **what infrastructure and which enablers are required (scientific and resource based)** to address these challenges and support future leaders progressing along the TRL. Includes; funding sources for TERM translation, matching the funding pipeline to technology readiness levels, access to funding in the European community, and a description of the current infrastructure in place to support UK ECR TERM translation. An ECR driven direction setting exercise, in response to the UK governmental "Building our Industrial Strategy" January 2017 Green Paper, focused on advancement in and commercialisation of TERM therapies. Resulting in ECR metrics and a summary position paper.
17:00	**Conference closing remarks and ECR prizes**

Workshop Details

Alongside the scientific plenary sessions and ECR presentations we will be running several workshops. In the workshops, your input will shape an ECR position paper, which will assess the current state of the UK TERM Landscape, and suggest new strategies to manage ECR driven research across the translational pipeline. We are interested in hearing **your** opinion, and have included here some background information on the workshops we'll be running, and a list of the additional resources that will be provided throughout the workshops. These workshops will formulate ATREUM's response to the UK governmental "Building our Industrial Strategy" Green Paper (January 2017), where we will develop an outline for ECR-driven advancement in, and commercialisation of, TERM therapies.

(1) Scientific and engineering challenges in directing cellular behaviour in TERM

Workshop Chairs; Dr. Chris Adams and Dr. Derfogail Delcassian

This workshop will develop an extended classification for regenerative medicine therapies based on the "Technology Readiness Level" (TRL) system. Once TRLs have been agreed, delegates will review their scientific research area to determine at which TRL level it currently stands, and identify areas of scientific and engineering focus in future work. The workshop will allow ECRs to identify new tools and technologies required to engineer successful regenerative medicine and cellular therapies, focusing on tools to direct desired cellular behaviour, and engineering challenges in evaluating cell behaviour.

(2) Preclinical modelling: assessing the potency of regenerative medicines

Workshop Chair; Dr. Stuart Jenkins

This workshop will discuss how best to prepare the regenerative medicine industry for a successful 'moonshot' therapy. There will be a particular focus on assessing the potency of biological therapies: this aspect is more problematic to determine when compared to more generally applicable toxicity/safety measures. So, how do we most effectively develop and validate assays/models for disparate, biological products? The recent MHRA 'consultation on strategy for pharmacopoeial public quality standards for biological medicines' will be discussed, and a summary of opinions from the ATREUM delegates will be fed back to MHRA.

(3) Skills and strategies to support translational researchers and entrepreneurs

Workshop Chair; Dr. Amanda Barnes

This workshop will focus on identifying routes from academic led research towards ECR-led entrepreneurship. Building on the translational TRL system developed in workshop 1, there will be a focused discussion on stages of ECR-led entrepreneurship, current barriers to ECR-led entrepreneurship, and the skills required for each stage of the translational pipelines.

(4) ECR driven TERM Translational "moonshot": How do we support the next generation of TERM research leaders?

Workshop Chairs; Dr. Chris Adams and Dr. Derfogail Delcassian

Having identified the translational TRL pathway to developing TERM research products, this workshop will summarise the major challenges to developing UK TERM translational therapies and set out a road map to success. With scientific and engineering challenges identified, regulatory hurdles discussed, and an ideal skills list for translational entrepreneurship in hand, we will identify **what infrastructure and which enablers are required (scientific and resource based)** to address these challenges and support future leaders progressing along the TRL. Includes; funding sources for TERM translation, matching the funding pipeline to technology readiness levels, access to funding in the European community, and a description of the current infrastructure in place to support UK ECR TERM translation.

Additional Information

Extracts from the following are available in the Appendix as additional resources for you to use throughout the conference and workshops.

- Building Our Industrial Strategy- green paper (UK Government- January 2017)
- Accelerated Access Review Committee Report (UK Government- October 2016)
- Science and Technology Regenerative Medicine Report (UK Government- 2013)
- UKRMP 2012: A strategy for UK Regenerative Medicine
- Technology Readiness Levels- an overview
- The Cell Therapy Catapult UK Preclinical Research Database (as of June 2015)
- Rafiq *et al*. The early career researcher's toolkit: translating tissue engineering, regenerative medicine and cell therapy products; REGENERATIVE MEDICINE, June 2015
- The MHRA Regulatory Call "consultation on strategy for pharmacopoeial public quality standards for biological medicines"
- Bravery *et al.* Potency assay development for cellular therapy products: an ISCT review of the requirements and experiences in the industry; CYTOTHERAPY, 2013; 15: 9
- Science Priorities of Brexit (UK Government- March 2017)

Keynote Speakers

Professor Richard Oreffo

Bone and Joint Research Group, Centre for Human Development, Stem Cells and Regeneration, Institute of Developmental Sciences, University of Southampton, Southampton, SO16 6YD, UK.

Bridging the Gap: Skeletal Cell Based Strategies for Bone Repair - Opportunities and Challenges

Advances in our understanding of skeletal stem cells and their role in bone development and repair, offer the potential to open new frontiers in bone regeneration. However, the ability to harness these cells to replace or restore the function of traumatised or lost skeletal tissue as a consequence of age or disease remains a significant challenge.

We have developed protocols for the isolation, expansion and translational application of skeletal cell populations with cues from developmental biology informed by in vitro and ex vivo models as well as, nanoscale architecture and biomimetic niche development informing our skeletal tissue engineering approaches [1]. We demonstrate the importance of biomimetic cues and delivery strategies to directly modulate differentiation of human adult skeletal cells and, central to clinical application, large animal in vivo translational studies to examine the efficacy of skeletal stem and cell populations in innovative scaffold compositions for orthopaedics.

These are exciting times in skeletal cell biology and tissue regeneration. While a number of challenges remain and will be reviewed, including the need to harness multidisciplinary approaches that integrate developmental and engineering processes as well as cell, molecular and clinical techniques for skeletal tissue engineering. Nonetheless, advances in our understanding of skeletal cells and the role of environmental cues offer the potential to open new frontiers across the hard tissue interface and exciting opportunities to improve the quality of life of an increasing ageing population.

[1] Dawson JI, Kanczler J, Tare R, Kassem M, Oreffo ROC (2014). Bridging the gap: Bone regeneration using skeletal stem cell-based strategies - Where are we now? Stem Cells. 2014; 32(1):35-44. doi: 10.1002/stem.1559. Review

Acknowledgements: Funding from the BBSRC, MRC UKRMP and EU FP7 programmes is gratefully acknowledged.

Professor Matthew Dalby

Professor of Cell Engineering at the Institute of Molecular Cell and Systems Biology, University of Glasgow, UK.

Nanoscale approaches to control mesenchymal stem cell growth and differentiation

Mesenchymal stem cells are highly responsive to nanoscale cues. This talk will focus on the use of nano topography, nano fibrous hydrogels and nanoscale vibrational stimulation (nanokicking) in the control of MSC self-renewal (to deliver large amounts of high quality stem cells) and differentiation (for regenerative therapies). Further, the use of polymer scaffolds that provide growth factors to cells at ultra-low dose but with high biological efficiency will be discussed. Throughout mechanotransductive pathways will be considered.

Professor Fiona Watt FRS FMedSci

Director, Centre for Stem Cells & Regenerative Medicine, Kings College London

Director, UKRMP Immunomodulation Hub

Deconstructing the epidermal stem cell niche

The UKRMP Immunomodulation Hub Director, Professor Fiona Watt has expertise in co-ordinating a major national research project, the Human Induced Pluripotent Stem Cell Initiative (www.hipsci.org) and has a strong leadership role within the international stem cell community. She was a founder of the International Society for Stem Cell Research, of which she is past president; she is on the scientific advisory board of several international regenerative medicine initiatives, including the California Institute for Regenerative Medicine (CIRM) and the Harvard Stem Cell Institute; and she helped establish the Cambridge University Stem Cell Institute in the UK. Fiona Watt's research interests include modelling stem cell-niche interactions in vitro, epidermal stem cells, skin wound repair, inflammation and cancer is currently the head of the Centre for Stem Cells and Regenerative Medicine at King's College London.

Professor Sheila MacNeil

Department of Materials Science & Engineering, University of Sheffield, Sheffield, UK.

s.macneil@sheffield.ac.uk

Translating biomaterials and cell therapy to the clinic

I have been involved in delivering cell therapy to the clinic since 1992. This started with an interaction with the Burns Unit in a Sheffield hospital where I cultured autologous epithelial keratinocytes for patients with extensive full thickness burns. After a 10 year audit of this it became clear there was room for improvement[1]. We improved on the cell delivery system, developing a carrier system, Myskin™, through a spin out company, CellTran Ltd. The development of the carrier was only possible because of our sustained support from surgeons in the Burns Unit and then later colleagues working with diabetic ulcers – we published a small single-blind study demonstrating that MySkin offered benefit to patients with diabetic ulcers[2]. The product, Myskin™, has been used by 11 out of the 13 Burns Units in the UK and has been on the market for a decade now.

Following that I have produced tissue engineered skin and taken that to small scale evaluation in patients[3], tissue engineered buccal mucosa where we have used this for replacing scarred tissue of the urethra[4] and, more recently, I have developed an alternative to the amniotic membrane for the regeneration of the cornea working with colleagues in India[5].

[1] Hernon CA, Dawson RA, Freedlander E, Short R, Haddow DB, Brotherston M and MacNeil S. Clinical experience using cultured epithelial autografts leads to an alternative methodology for transfering skin cells from the laboratory to the patient. Regenerative Medicine 1(6):809-821. (2006). [2] Moustafa M, Bullock AJ, Creagh FM, Heller S, Jeffcoate W, Game F, Amery C, Tesfaye S, Ince Z, Haddow DB and MacNeil S. Randomised controlled single blind prospective pilot study on the use of autologous keratinocytes on a transfer dressing (Myskin) in the treatment of non-healing diabetic ulcers. Regenerative Medicine 2(6):887-902. (2007). [3] MacNeil S. Progress and Opportunities in Tissue Engineering of Skin. Nature Insights. Nature 445, 874-880 (2007). [4] Osman N. Long-term follow-up after tissue engineered buccal mucosa urethroplasty. European Urology. 66(1):790-791 (2014). [5] Deshpande P, Ramachandran C, Sefat F, Mariappan I, Johnson C, McKean R, Hannah M, Sangwan VS, Claeyssens F, Ryan AJ, MacNeil S. Simplifying corneal surface regeneration using a biodegradable synthetic membrane and limbal tissue explants. Biomaterials. 34(21): 5088-5106 (2013).

Dr Bill Shingleton

Health and Environmental Sciences Institute (HESI) Cell Therapy – Tracking, Circulation and Safety (CT-TRACS) and GE Healthcare Life Sciences' Core Imaging R&D, Amersham, UK.

Driving translation of cell-based therapies: an international consortia to develop tools for safety assessment

Cell-based therapies show great therapeutic promise, but to realize their full clinical potential there is a need for greater understanding of their mode of action, how they migrate after administration to deliver their therapeutic benefits, and whether their localization or distribution may cause safety issues. Currently, there are few recognized and established tools or approaches to monitor these cell-derived therapies to achieve such understanding. The Health and Environmental Sciences Institute (HESI) has formed an international, multi-disciplinary team of experts to address this issue.

Since its inception in December 2015, the Cell Therapy – Tracking, Circulation and Safety (CT-TRACS) committee has gathered about 50 members from 29 organizations across the United States, Europe and Japan. The focus of the group has been narrowed down to Cell Fate, i.e., distribution, survival/engraftment and phenotype, post-administration, in vivo, as well as evaluating the tumorigenic potential of cell-based therapies. The Committee's focus will be to: 1) evaluate current tools and methods employed to assess the safety of cell-based therapies; 2) develop recommended best practices for application of available tools for safety assessment of cell therapies and identify gaps in information required to assess safety; 3) promote our activities through workshops and publications. The CT-TRACS project is open to all current HESI members as well as new participants with relevant technical expertise.

Professor Liam Grover

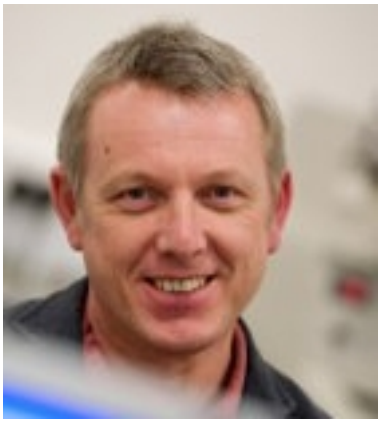
Professor of Biomaterials Science, School of Chemical Engineering, University of Birmingham, UK.

Structured soft solids as innovative medical devices

The adoption of novel materials into the clinic is a long process requiring extensive toxicological and safety assessment. As a consequence, scientists are often stuck with a small number of materials from which they can design medical devices. This talk will describe how we have used a number of different innovative approaches to structure existing medical materials so that they can be translated to the clinic relatively quickly. It will describe the production of a novel bone augmentation device using chemical gardens and how we have used self-healing fluid gels to enable additive layer manufacturing. Finally, it will describe the production of a new anti-scarring eye drop that we are taking to clinical trial for the treatment of microbial keratitis.

Professor Phillip Blower

Chair in Imaging Chemistry and Head of the Imaging Chemistry and Biology Department, King's College London, UK.



Novel imaging probes for cell imaging

Most trials of cell based therapies measure clinical end points that may take weeks to months to demonstrate efficacy, with little knowledge of the in vivo fate and behaviour of administered cells. The questions "where do the cells go after administration?" "how long do the cells survive in vivo?" "Do they proliferate and differentiate?" are now being asked in clinical trials and animal models. In principle, methods to help answer them using imaging methods have been available since the 1980, when cell tracking using gamma emitting radioisotopes became routine to detect sites of inflammation using autologous leukocytes. The advent of widely available PET offers opportunities to replace gamma emitters with positron emitters, with benefits in improved resolution and sensitivity. These methods offer the potential to track cells for several days after administration. For long term monitoring, reporter gene imaging can be used, whereby the administered cells are engineered to express a specific molecular target that can be imaged repeatedly, in principle for the lifetime of the patient or the administered cells, using a radiolabelled probe. Similar principles can be used for magnetic resonance and optical imaging. Recent progress in methodology and clinical translation of cell tracking for these methods, with a particular focus on short and long half life radionuclide methods and reporter genes, will be described and challenges for further development outlined.

Dr Neill Liptrott

Tenure Track Fellow, Molecular and Clinical Pharmacology,

University of Liverpool, UK.

Nanomaterials: Investigating their biological interactions to speed up clinical translation

Nanomaterials hold the potential to improve therapy across a number of diseases either through improved bioavailability or systemic distribution. Additionally, novel nanobiomaterials may be used to improve cell therapies or implantable constructs. However, there is a paucity of information regarding putative adverse interactions in biological systems, which is important for the development and regulation of safe and effective nanomaterials.

The interaction of nanomaterials with various components of the immune system has been well documented and therefore assessment of these interactions is vital for successful translation to the clinic. Prediction of such reactions is important for development of robust preclinical systems for selection of viable leads, but is hampered by a limited understanding of the mechanisms and signalling pathways involved in the recognition of engineered nanoparticles by the host immune system.

The mechanisms involved in this recognition are complex and varied including, but not limited to, altered cytokine expression, generation of reactive oxygen species, absorption of blood proteins (e.g. complement) which induce phagocyte activation and triggering of various signalling complexes. We are investigating these relationships in order to determine critical attributes of nanomaterials that relate to their biological interactions both to assess their compatibility and to aid in the, future, rational design of nanomaterials.

Dr James McBlane

Preclinical Assessor, Biologicals Unit, Licensing Division, Medicines & Healthcare products Regulatory Agency (MHRA),

151 Buckingham Palace Road, London SW1W 9SZ.

Regulator's perspective on preclinical testing of advanced therapy medicinal products (ATMPs)

Use of ATMPs as regenerative medicine in the UK has thus far been limited to clinical trials or to instances of use in individual patients, lacking alternatives. The current framework for market access were introduced in 2009 and thus, in 7 years, there has been no commercial use of an ATMP in the UK. Why not?

To ensure that there are no unreasonable obstacles posed by regulation of the pharmaceutical industry, regulators may need to explain those systems that developers of ATMPs need to navigate to bring such products to patients. This is what this talk is about.

ATMPs are licensed in Europe through the centralised procedure in accordance with Regulation 1394/2007, allowing for one decision for all EU member states. In this, the Committee for Human Medicinal Products (CHMP) and the Committee for Advanced Therapies (CAT) consider scientific data in relation to quality, safety and efficacy. For products with a favourable opinion, CHMP informs the European Commission who issues the marketing authorisation.

However, for clinical trials, the situation is completely different: regulation of applications for clinical trials is at the national level, currently in line with Directive 2001/20; for up to 28 EU countries, this can involve up to 28 national applications. The directive will be replaced with Regulation 536/2014 which will simplify administrative steps to allow one procedure, no matter how many EU countries are involved: this will include Ethics Committee review.

Review of clinical trial applications address whether the specific proposals are judged safe: if so, the trial can go ahead. This says nothing about whether the trial is optimal, or even relevant, for generating data to obtain a marketing authorisation. Review of preclinical data in a marketing authorisation application addresses further issues relating to the evidence supporting the claims for mode of action, and the detail of studies claiming safety.

In terms of preclinical data, principles are similar between an ATMP and conventional product: information on the mode of action, and why this is of benefit to a defined patient population should be presented, including justification of dose, complemented by evidence as to why the specific proposed intervention is considered likely to be safe in the population defined. However, the type of study used to provide this information for an ATMP can differ, with combined biodistribution and toxicity studies often used: also the timing of these studies in relation to clinical development may differ, as even from the first human dose, once the product is given, it may be that there is life-long exposure thereafter. The implication of this is that all, or almost all, preclinical safety studies are needed to support the first clinical dose.

In relation to the UK leaving the EU, firstly, the regulatory procedures outlined above will continue in the UK until the UK leaves but will thereafter continue in the 27 member states. The procedures implemented after that point in the UK are not defined but will be influenced by the nature of the UK's future relationship with the EU.

Professor Glyn Stacey

Director, UK Stem Cell Bank

Head, Cell Biology Department, NIBSC

Standardisation in TERM research

Professor Stacey joined NIBSC in 1998 as a senior scientist, progressing to director of the UK Stem Cell Bank. Glyn has over 30-years' experience in microbiology, cancer research and the development of cells for diagnostic, research and clinical use. He is the head of the cell biology department at NIBSC and also Director for the UK Stem Cell Bank.

Glyn is a microbiologist by training, with an MPhil in cancer research from the University of Southampton obtained his PhD in genetic stability in cell culture whilst at the centre for Applied Microbiology and Research at Porton Down. He also has a visiting chair at the University of Bedfordshire and lectures on numerous University post graduate courses in regenerative medicine (e.g. University College London, Kings College London).

His research interests include critical scientific issues in the acceptability cell therapies including characterisation of genetic stability and potential pluripotency in human pluripotent cell lines. Glyn has more than 100 peer reviewed scientific papers and has edited 7 books.

Abstracts

Mesenchymal stem cells in corneal wound healing

Olla Al-Jaibaji[1], Stephen Swioklo[1], Che Connon[1]

1 Newcastle University, International Centre for Life, Newcastle upon Tyne, NE1 3BZ

Corresponding email: o.m.h.al-jaibaji2@newcastle.ac.uk

Poster Number: A2

Keywords: Stem cells, Cornea, wound healing, hydrogel and Cells therapy

Background: The natural refractive properties of the cornea reflect its transparency degree, in which represent a healthier vision. The corneal epithelium and stromal layers maintain this transparency via their regenerative ability that occurs on daily basis. However, a disease or an injury can affect this ability and lead to several problems that would require medical treatment. Until now, the available medical treatments could not cover the wide range of diseases that affect the cornea. Mesenchymal stem cells (MSCs) offer a solution to many diseases that affect not only the cornea but many other diseases such as heart, liver, kidney and bone, which has been shown in the literature to be safe and hold the key to future cell therapy. However, despite its large potential in cell therapy, there are challenges that are yet to be solved in regard to storage and distribution of cells between manufacturing sites and end-user.

Objective: In here the focus will be on the ability to achieve an improved corneal wound healing process using hydrogels to encapsulate MSCs in hypothermic conditions and control/maintain their paracrine release profile before and during clinical application.

Method: The experimental study is focused on in vitro evaluation of the hypothermic stored encapsulated MSCs at 4oC and 15oC and their ability to heal corneal wounds after three days of storage.

Results: Hypothermic storage of encapsulated MSCs did not affect the cells ability to release paracrine factors in a corneal wound healing model.

Conclusion: This observation indicates the great potential of using these cells and distributing them between sites of manufacturing and the clinic.

Engineering canine olfactory cell grafts using magnetic particle mediated delivery of therapeutic genes: Implications for canine spinal injury

Christopher Adams[1], Alexander Delaney[1], Alinda Fernandes[2], Arwa al-Shakli[1], Darren Carwardine[3], Nicolas Granger[3], Divya Chari[1]

1 Cellular and Neural Engineering Group, Institute of Science and Technology in Medicine, Keele University, UK
2 Institute of Psychiatry, Kings College London, UK
3 School of Veterinary Sciences, University of Bristol, UK

Corresponding email: c.adams@keele.ac.uk

Poster Number: A1

Keywords: Neural cells, cell transplantation, magnetic particles, hydrogels, nanotechnology

Spinal cord injury (SCI) is severe and debilitating for patients and their support network. Further, with an estimated cost to the UK of £1bn per annum there is a high financial burden on healthcare providers. Currently, there are no curative treatments for SCI meaning that developing effective therapeutic strategies remains a major clinical goal for regenerative neurology. One promising strategy is the transplantation of olfactory mucosal cells (OMCs) which have demonstrated repair in animal models of SCI and are derived through straightforward procedures from the patient - overcoming many of the issues surrounding other transplant populations. However, in order to achieve effective translation their therapeutic capacity needs to be improved.

Magnetic nanoparticles (MNPs) are key translational platforms with the ability to label cells for non-invasive imaging and genetically engineer cells for release of therapeutic biomolecules. We show for the first time that application of magnetic fields can safely enhance MNP mediated labelling and genetic engineering of autologous canine OMCs (cOMCs), a key veterinary cell population shown to improve locomotion in companion dogs with spinal injury. Crucially, the developed protocols were successfully combined with advanced minicircle DNA vectors to deliver brain derived neurotrophic factor (important in promoting nerve fibre outgrowth) to cOMCs. Minicircles have distinct advantages for clinical gene delivery due to their small size, lack of bacterial backbone and duration of transgene expression. Finally, we also show that MNP labelling can facilitate imaging of cOMCs encapsulated in implantable collagen hydrogels using non-invasive magnetic resonance imaging. A combination of these methodologies could enable translation of safe and effective OMC transplantation strategies in canines, but also holds promise for future translation into humans.

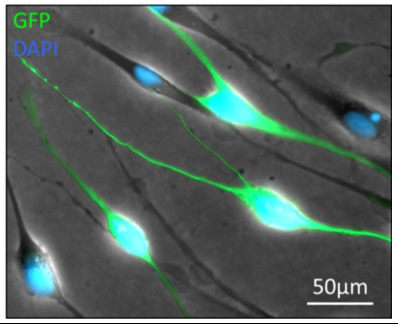


Figure 1 Representative image of green fluorescent protein expressing cOMCs after MP mediated transfection performed under application of a static magnetic field.

Investigating the effect of chondrocytes and mesenchymal stromal cell co-cultures on cartilage formation

Amanda L. Barnes[1] & Paul Genever[1]

1 Department of Biology, University of York, York Uk,

Corresponding email: amanda.barnes@york.ac.uk

Poster Number: A3

Keywords:

Early intervention in the treatment of lesions in the articular cartilage of the knee joint can help to slow down and potentially prevent progression to osteoarthritis. One example treatment is autologous chondrocyte implantation (ACI), where a patient's own chondrocytes are expanded in-vitro and re-implanted to repair the damaged tissue. However the quality of the regenerated tissue does not have the same mechanical properties of the native tissue. Furthermore a suitable source of chondrocytes may not be available from the donor. Using a co-culture of chondrocytes and mesenchymal stromal cells (MSCs) in ACI, may produce superior cartilage compared to using chondrocytes alone. This is currently under investigation in the ASCOT clinical trial, however little is known mechanistically about how these methods improve cartilage formation.

We have developed an immortalised clonal cell line from primary MSCs, Y201, which displays tri-potent differentiation, enabling studies of the chondrogenic pathway in-vitro and alleviates donor variability. In QPCR studies investigating the effect of a 1:1 co-culture of primary chondrocytes with Y201 MSCs, expression levels of the pro-chondrogeneic transcription factor Sox9 and matrix genes, Collagen II and Aggrecan were lower than using chondrocytes, but superior to MSCs alone, with increases of 2.1, 1.4 and 3.9-fold respectively. Whereas the change in expression level of Lubricin in the co-cultures was 49 fold higher. In addition to using the Y201 cell line, the experiments have also been repeated with primary cells from the same donor to assess whether an autologous source of cells improves the cartilage produced.

Mechanically optimised tissue-engineered constructs for spinal cord repair

Richard D Bartlett[1,2], David Choi[2], James B Phillips[1]

1 Biomaterials & Tissue Engineering, Eastman Dental Institute, University College London
2 Brain Repair & Rehabilitation, Institute of Neurology, University College London

Corresponding email: richard.bartlett.11@ucl.ac.uk

Poster Number: B4

Keywords: Neural tissue engineering; spinal cord injury; CNS repair; biomechanics; cell therapy

BACKGROUND: The role of mechanical properties in influencing cell behaviour has become increasingly apparent. This is particularly pertinent in CNS tissue engineering, where mechanical properties not only influence therapeutic cell behaviour, but they also have the potential to mediate an adverse host response through mechanically-responsive astrocytes. However, given the soft viscoelastic nature of the brain and spinal cord tissue, reliable mechanical characterisation has so far been challenging. Thus, the aim of this project was to develop a novel method to mechanically characterise spinal cord tissue, and ultimately one which could be applied to screen the mechanical properties of candidate biomaterial for CNS repair.

METHODS: Rodent spinal cord was extracted from male Wistar rats. This was placed in iced tissue-preservation media, cut into ~5 mm sections, and measured using a goniometer. Height measurements were used to generate size-independent mechanical deformation values. Unconfined compressive dynamic mechanical analysis (DMA) was then performed using an ascending frequency sweep with minimal displacement.

RESULTS: Rat spinal cord had compound modulus values ranging between 4.9 - 22 kPa over the 1 - 100 Hz testing range. This varied with compression orientation. Modulus was strain-rate dependent and stiffness increased non-linearly with frequency. Tan delta values revealed that the viscous phase of modulus (E") became increasingly dominant towards higher strain-rates. The testing protocol was minimally destructive to tissue and suitable for testing other soft substrates such as hydrogels.

CONCLUSIONS & FUTURE DIRECTIONS: DMA is a powerful method to reliability profile the mechanical properties of soft tissues and substrates. In turn, it facilitates 'mechanical benchmarking' of CNS biomaterials against native spinal cord, and may offer a novel tool to explore the effects of stiffness tuning on the cell response. Overall, this work represents an important step-forward in developing mechanically appropriate repair strategies for spinal cord injury.

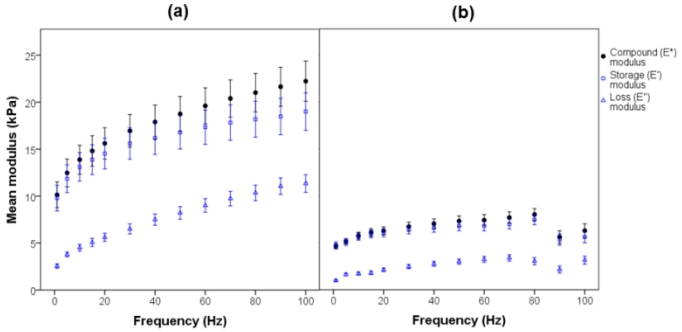


Figure 1. Moduli of spinal cord tissue after mechanical testing with unconfined compressive DMA. Panel a) represents radially compressed spinal cord; panel b) represents longitudinally compressed spinal cord. Error bars represent +/- SEM (n = 6, triplicated per spinal cord).

Creating biomimetic composites for cartilage repair and regeneration

Lucy A Bosworth[1], Michelle L Oyen[2]

1 School of Materials, University of Manchester, Sackville Street, Manchester, M1 3BB
2 Department of Engineering, University of Cambridge, Trumpington Street, Cambridge CB2 1PZ

Corresponding email: lucy.bosworth@manchester.ac.uk

Poster Number: A5

Keywords: Electrospinning; hydrogels; composites; biomimicry; cartilage

The incidence of degenerative diseases, such as osteoarthritis, is increasing as a result of population ageing and rising obesity. These conditions have a profound negative effect on the quality of life of sufferers. Consequently, there is increased demand in the field of regenerative medicine to provide targeted strategies to restore quality of life and reduce the associated social and economic costs (1,2). Biomaterial scaffolds fabricated from electrospun fibres or hydrogels are under investigation as implantable therapeutics due to their potential to replicate and temporarily restore the extracellular matrix (ECM) of the tissue requiring repair (3). An engineered replica ECM provides functional stimuli to cells instigating normal cell behaviour and neotissue formation to promote regeneration. Despite a valid rationale and a significant volume of published research, few of these scaffolds actually translate into bedside solutions for clinical problems. This is due to inherent disadvantages of fibres (poor cell infiltration) and gels (weak mechanical strength) when used alone. This research focuses on the combination of both techniques to create composite structures that more closely mimic the ECM, which itself is a composite structure of nanofibres within a gel-like matrix, and determine the response of seeded cells in terms of viability, morphology and matrix deposition. Preliminary data demonstrates preferable cellular morphologies and interactions within composite scaffolds compared to cells cultured within hydrogels or nanofibres alone.

References: (1) Regenerative medicine report. House of Lords, Science and Technology Committee, July 2013. (2) Taking stock of regenerative medicine in the United Kingdom. Department of Health, July 2011. (3) Bosworth LA, et al. Nanomedicine: Nanotechnology, Biology and Medicine. 2013, 9(3): 322-335.

Placental mesenchymal stem cells for the treatment of bronchopulmonary dysplasia

J. Bratt[1], A. El Haj[1], N. Forsyth[1], P. Wu[1]

1 Institute for Science and Technology in Medicine, Guy Hilton Research Centre Keele University, Stoke-on-Trent, UK

Corresponding email: J.Bratt@Keele.ac.uk

Poster Number: A6

Keywords: Mesenchymal Stem Cell, Lungs, Bronchopulmonary Dysplasia

Bronchopulmonary Dysplasia (BPD) is a neonatal disease affecting the lungs of premature infants. The disease disrupts the lung development leading to an arrest in alveolar maturation and vascularization. Despite advances in neonatal care the incidence of BPD has remained unchanged with about 50% of infants born under 26 weeks gestational age being diagnosed with BPD. Currently there are no treatment options, only preventative and supportive measures. BPD is the most common complication of prematurity and therefore represents the biggest burden on financial resources. Mesenchymal stem cells (MSCs) offer a promising therapeutic agent for the treatment of BPD patients as observed in hyperoxia induced rodent and murine models. MSCs derived from gestational tissue has the potential to provide an advantageous source of MSCs since they possess fewer ethical concerns, they are easily attained and have a high capacity for self-renewal and differentiation. Currently we are developing a 3D in vitro model (figure 1) to accurately represent the human lung alveoli and BPD disease progression. Rodent animal models do not follow the same lung development pathway as humans and therefore provide limited insight into BPD pathology. We aim to use this novel in vitro model to assess the suitability of placental derived MSCs for the treatment of BPD. Comparisons will be made between term and preterm placental MSCs and chorion membrane versus amniotic placental membrane MSCs.

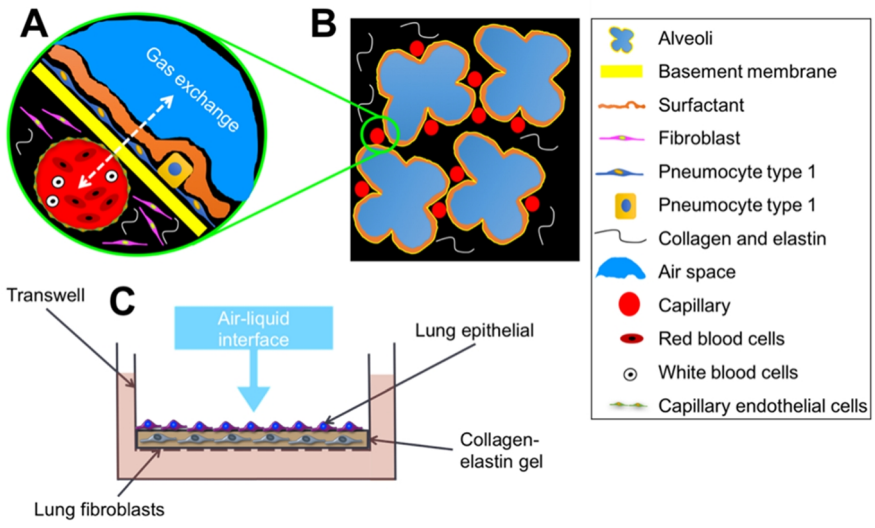


Figure 1: The development of an in vitro model to represent the BPD lung alveoli. A magnified representative image of the alveoli wall (A) which resides with the lung interstitium tissue (B). An in vitro model (C) will be developed to represent the lung alveoli wall and BPD disease pathology.

Manipulation of the extracellular matrix for liver tissue engineering

Rhiannon Grant[1], David Hay[2], Anthony Callanan[1]

1 Institute for Bioengineering, School of Engineering, The University of Edinburgh, Scotland.
2 Scottish Centre for Regenerative Medicine, The University of Edinburgh, Scotland.

Corresponding email: anthonycallanan@ed.ac.uk

Poster Number: B7

Keywords: Kidney, Liver and Cartilage Tissue Engineering, Extracellular Matrix Materials,

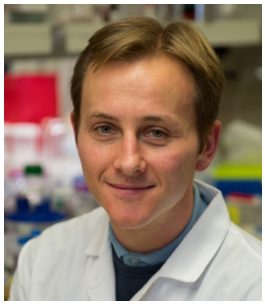
Liver disease in the under-65s has risen by 500% since 1970, with mortality increasing by 400% in the same time period. A treatment is sought in the form of liver 'organoids'; lab grown devices which support the survival and function of hepatocytes. While scientists can maintain liver organoids in the lab, decade's worth of research has failed to translate this into a fully functional organ. This in part is due to the complexities of recapitulating a vital part of the in vivo environment; the extracellular matrix [ECM]. Tissue engineering novel scaffolds provides a strategy to tackle the problem of mimicking the ECM. This study aims to demonstrate that manipulating cell derived ECM via chemical means improves scaffolds for liver tissue engineering. Poly-capro-lactone [PCL] scaffolds were created by electrospinning. Epithelial cells seeded onto the scaffold were subjected to drug treatment using histone deacetylase inhibitors to encourage protein production. These cells were stripped from the scaffolds to leave behind their ECM. The resulting hybrid ECM-PCL scaffolds were then seeded with HepG2s, and cultured for 3/5 days before being used for analysis. Scanning electron microscopy [SEM], mechanical and biochemical quantification, histology, and gene expression analyses were performed on the scaffolds. SEM demonstrated markedly different scaffold topography. Additionally, gene expression was altered between conditions. The production of extracellular matrix is significantly altered by drug treatment. Cytochrome P450 [CYP] genes are significantly upregulated, as is albumin. Exposure to the drug induced decellularized ECM influences the gene expression profile of the HepG2s Collagens I & IV, Fibronectin, Albumin and Cyp 1A2 & 3A4. These results demonstrate the great value of these drugs for the production of bespoke ECMs; and their potential for liver tissue engineering.

Regenerative polymers for dentistry

Adam D. Celiz[1,2], Kyle H. Vining[1,3], Jacob C. Scherba[3], Alaina Bever[4], Morgan R. Alexander[1], David J. Mooney[1,3]

1 Advanced Materials and Healthcare Technologies Division, School of Pharmacy, University of Nottingham, NG7 2RD
2 Wyss Institute for Biologically Inspired Engineering at Harvard University, Cambridge, MA 02138
3 Department of Mechanical Engineering, Seat

Corresponding email: adam.celiz@nottingham.ac.uk



Poster Number: B8

Keywords: Tissue Engineering, Biomaterials, Polymers, Regenerative Medicine, Dentistry

Dental disease is one of the most prevalent chronic diseases in the world and affects millions of patients annually. Thus, novel therapeutic strategies to treat dental disease would greatly improve healthcare. This work aims to discover and investigate a therapeutic biomaterial that promotes dentin regeneration by stimulating endogenous dental pulp stem cell (DPSC) proliferation and differentiation. We applied high throughput screening using polymer microarrays to rapidly identify polymers polymers that supported adhesion of DPSCs isolated from a donor's extracted third molar. We employed thiol-ene click chemistry to polymerize multifunctional acrylate monomers with minimal residual monomer. DPSC adhesion to these polymers over 48 hours was not statistically different from the tissue culture plastic, while no viable cells adhered to Bis-GMA. Bis-GMA is the most widely used monomer in resin-based dental materials, but is toxic to cells and not compatible with dental pulp tissues. Cell adhesion to our polymers was reduced compared to TCP with the addition of an anti-ITGb1 blocking antibody, suggesting that adhesion to these materials depends on ITGb1 signaling. Confluent monolayers were cultured with osteogenic inductive media for 21 days. DPSCs cultured on our polymers expressed elevated markers of early odontogenesis, COL1A, SPP1, ALP, compared to the TCP control. Our work presents a novel strategy that could significantly impact the practice of dentistry by promoting healing of dental tissues and, thus, establish a new paradigm for regenerative dental treatments.

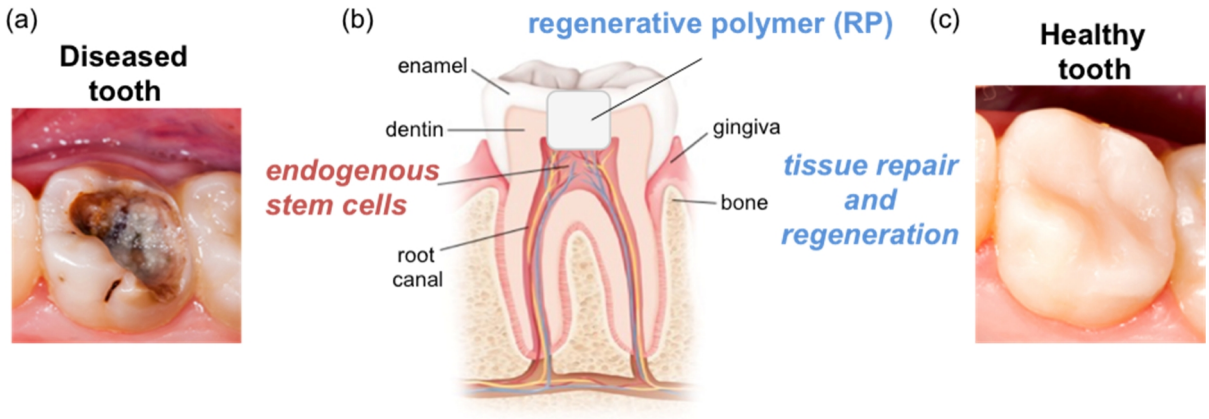


Fig. 1. a) A diseased tooth that has undergone significant decay into the pulp. b) Regenerative polymers (RPs) placed in contact with the endogenous stem cell population found within the tooth can harness these cells for tissue repair and regeneration and restore vitality to the tooth (c).

Functional nanomaterials for intracellular interaction to direct cell fate

Ciro Chiappini[1], Enrica de Rosa[2], Jon Martinez[2], Paola Campagnolo[3], Spencer Crowder[4], Catherine Hansel[4], Sahana Gopal[4], George Hanna[5], Ennio Tasciotti[2], Molly Stevens[5].

1 Division of Craniofacial Development and stem Cell Biology, King's College London, London, SE1 9RT
2 Department of Nanomedicine, Houston Methodist Research Institute, Houston, USA
3 School of Biosciences and Medicine,University of Surrey, Guilford
4 Department of Materials, Imperial College London, SW7 2BP
5 Department of Surgery and Cancer, Imperial College London.

Corresponding email: ciro.chiappini@kcl.ac.uk

Poster Number: B9

Keywords: nanotechnology, biointerfaces, material science, mechanosensing, engineering

Direct material interaction within the intracellular space has broad enabling potential across biomedicine, with transformative impact in tissue engineering, precision medicine and fundamental cell and molecular biology. Efficiently accessing and sensing the intracellular milieu with minimal cell perturbation are key aspects of direct intracellular interaction in that they enable detection, study and control of biological processes at the molecular level inside living cells. The development of a versatile platform that can efficiently handle delivery, sensing and collection processes to mediate diagnosis and localised treatment in vivo still represents a major bioengineering challenge. High aspect ratio nanostructures (nanowires/nanoneedles) have recently risen to prominence as an effective approach to safe, minimally invasive access to the intracellular space on the large scale with resolution approaching that of a single cell.

This talk will report on the contribution to direct intracellular interaction of the recent development of porous, biodegradable nanoneedles1 for tissue engineering in vivo and molecular diagnostics in clinical tissue samples. These nanoneedles efficiently (>90%) delivery nucleic acids and nanoparticles to the cytosol. Used in vivo they do not induce detectable cell death, alter tissue architecture or elicit immune response. They mediate in vivo delivery of a VEGF expressing plasmid in vivo that yields local VEGF expression and induces neovasculature formation, in proof or principle for highly local in situ gene therapy2. A nanoneedle-based sensor3 detects single-cell protease activity to discriminate cancer and healthy clinical samples of esophageal mucosa resections.

The ongoing development of this platform technology involves applications for neural differentiation, cardiac reprogramming, and multimodal spectroscopy analysis of molecular tissue replicas, alongside fundamental investigation of the role of nanoneedles as biophysical cues in epigenetic remodelling.

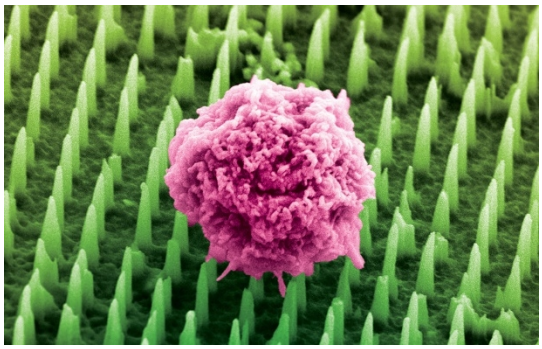


Figure 1: A human cell in the early stages of interaction with nanoneedles.

Suspended manufacture of biological structures

Samuel R Moxon[1], Megan E Cooke[2,4], Sophie C Cox[2], Martyn Snow[2,3], Lee Jeys[3], Simon W Jones[4], Alan M Smith[1], Liam M Grover[2]

1 Department of Pharmacy, University of Huddersfield, Queensgate, Huddersfield, HD1 3DH
2 School of Chemical Engineering, University of Birmingham, Edgbaston, B15 2TT
3 Royal Orthopaedic Hospital, Bristol Road, Northfield, Birmingham, UK
4 Institute of Inflammation and Ageing, MRC Musculoskeletal Ageing Centre, QE Hospital, University of Birmingham, Edgbaston, UK

Corresponding email: mec110@bham.ac.uk

Poster Number: B10

Keywords: osteoarthritis; biofabrication; hydrogels; cartilage regeneration; ex vivo modelling

Here we present a novel method of extrusion-based ALM for the production of cell-laden strucutres from low viscosity polymers. The traditional planar print bed is replaced with a bed of micoparticulate fluid gel. During the extrusion process, the fluid gel is displaced whilst providing a support strucutre for the low viscosity material. The extruded structure can then be easily removed from this self-healing fluid bed. Using this technqiue relatively complex geometries can be manufactured. For this study, a bi-layered cell-seeded construct was produced to model the osteochondral junction. ***Methods:*** Defects were introduced into femoral condyle tissue donated by patients undergoing joint replacement surgery. Condyles were scanned using microCT to determine and reconstruct the defect geometry. Cartilage and bone from the contralateral condyle were used to isolate chondrocytes and osteoblasts respectively. These were added to 1.5% w/v gellan with (osteoblasts) or without (chondrocytes) 5% nano-hydroxyapatite. Cell-gellan solutions were then extruded consecutively into the fluid bed to form the defect geometry. 200mM CaCl2 was added to further crosslink the bi-layered constuct. Constructs were reimplanted into the defect space and cultured for 30 days. ***Results:*** Cell viability following extrusion was confirmed using calcein AM/PI live/dead staining showing excellent viability. Following this, constructs were sectioned, and qRT-PCR was performed, showing a native collagen phenotype across the construct as well as evidence of matrix markers in the cartilage-like region which were also identified using fluroescent-IHC. Constructs were also tested for their bulk relaxation properties. The addition of nano-hydroxyapatite in the bone-like region resulted in a faster, more elastic relaxation than gellan alone, something that has previously been reported to favour osteogenic differentiation. ***Conclusions:*** We have demonstrated the efficacy of suspended manufacturing to maintain viability and phenotype of two populations of human primary cells in a single construct thus emulating the structure of the osteochondral junction.

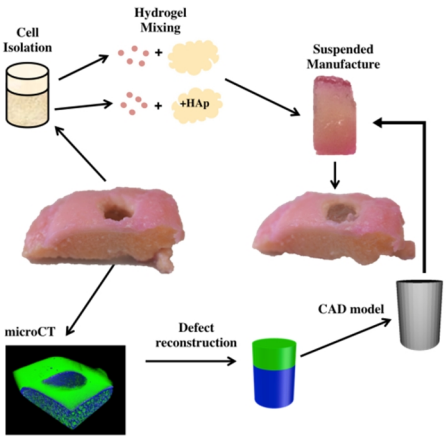


Figure 1. The suspended manufacturing process for osteochondral tissue

Osteoblast-derived extracellular vesicles are effective alternatives to traditional cell-based approaches for bone regeneration

Owen G Davies[1,2], Sophie C Cox[1], Richard L Williams[1], Mark P Lewis[2], Liam M Grover[1]

1 School of Chemical Engineering, University of Birmingham, Birmingham, B15 2TT
2 School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, LE11 3TU

Corresponding email: O.Davies@bham.ac.uk

Poster Number: A11

Keywords: Vesicle, Bone, MSC, Acellular, Nano

Osteoporosis affects over 3 million people in the UK. Over 300,000 osteoporosis-related fragility fractures are reported annually with an associated healthcare cost of more than £1.5 billion. Alarmingly, these numbers are expected to double by 2020, placing tremendous strain on healthcare systems in the UK and beyond. The last decade has seen considerable attention focused on the development of regenerative cell-based approaches to this problem. Although these methods have yielded promising results their translation is frequently hindered by often insurmountable regulatory hurdles. We show that by harnessing the regenerative capacity of osteoblast-derived extracellular vesicles (EVs) we can develop an acellular yet entirely biological therapy for hard tissue regeneration. In the present study, EVs were isolated from mineralising osteoblasts using differential centrifugation and comprehensively characterised using AFM, TEM, nanoparticle tracking analysis and flow cytometry. The effects of EVs on MSC differentiation were assessed against a clinical gold-standard, BMP-2. Mineralisation was analysed using alizarin red calcium staining, alkaline phosphatase (ALP) quantification and X-ray fluorescence (XRF) elemental mapping. Infrared spectroscopy (IR) was applied to define the mineral phase. To elucidate possible mechanisms governing vesicle-induced mineralisation, the EV proteome was profiled using LC-MS/MS with subsequent Gene Ontology enrichment analysis. We found that electron-dense EVs (~160nm) were able to significantly enhance ALP levels, mineralisation rate and mineral volume beyond the current gold-standard BMP-2. Alizarin red staining identified a significantly increased calcium presence in EV-treated cultures. XRF elemental mapping confirmed that calcium was co-localised with phosphate. IR analysis of the mineral component showed a mineral phase that appeared to be transitioning from an amorphous to a more stable state. Proteomic analysis of EVs showed that they were enriched in calcium-binding annexins, osteoblast-bridging collagen (type-VI) and osteopontin. Our data suggest that EVs may have considerable utility as an alternative to cell-based approaches for hard tissue regeneration.

Stem-cell transplants- a transplant matrix to control the host immune system and enhance graft survival

Derfogail Delcassian[1,2], Matt Bochenek[1], Amanda Facklam[1], Omar Qatachi[2], Crystal Shuo Shan[1], Reed Hausser[1], Collin McGladrigan[1], Kevin Shakesheff[2], Robert Langer[1], Daniel Anderson[1]

1 Koch Institute for Integrative Cancer Research, MIT, USA
2 Division of Regenerative Medicine and Cellular Therapies, University of Nottingham, UK

Corresponding email: Ddelcass@mit.edu

Poster Number: B12

Keywords: Immunoengineering, transplant, biomaterials, cell therapy

The rapid development of stem cell therapies in TERM offers the potential to revolutionise cell, organoid and organ transplantation therapies for a range of diseases, however, a major limitation to these therapies is the need to carefully control host immune response to prevent graft rejection. Currently, transplant patients are required to take immunosuppressive drugs, often daily, for the remainder of their lives. These drugs are required to prevent the host immune system from destroying the newly transplanted tissue, yet can impact the quality of life for the patient and may lead to a globally impaired immune system at risk of opportunistic pathogens and lymphomas. Our research focuses on designing new materials to control immune cell behaviour, developing new ways to deliver localised and targeted immunosuppression in cell transplant therapies. Focusing on diabetes-1, we have developed a hydrogel transplant niche that can protect functional beta-cell islet clusters, or stem cell derived islet clusters, from host immune attack. These transplant matrices provide a 3D environment to support transplanted cells, and can control localised immune cell behaviour in the transplant site through the controlled release of immunomodulatory factors and presentation of anti-fibrotic ligands on the matrix surface. We demonstrate that islet graft survival is enhanced in materials possessing immunomodulatory properties compared to control materials; these transplant matricies can support transplanted cell function, and restore glycemic control in a clinical diabetes model (measured using GSIS, IVGTT and blood glucose levels) in vivo for up to 3 months.

The importance of being functional: an in vitro microfluidic model of the basal ganglia

Matthew Dunn[1], Munyaradzi Kamudzandu[1], Rosemary Fricker[1], Paul Roach[1]

1 Life Sciences, Keele University, Keele, Staffordshire, ST5 5BG, 4 Chemical/Physical Sciences, Loughborough University, Epinal Way, Loughborough, LE11 3TU

Corresponding email: mattdunn64@gmail.com

Poster Number: B15

Keywords: Parkinson's, neural, model, microfluidics, functional

Parkinson's and Huntington's diseases are both caused by select damage to neurons of the basal ganglia. The basal ganglia is very challenging to study in vivo, resulting in a lack of pre-clinical progress or effective treatments for both diseases. The solution, and the aim of this project, is to create an in vitro model of the basal ganglia to be used as a platform for study.

Our model exhibits five separate areas for culture of primary cells from five main functional areas of the basal ganglia: cortex, striatum, substantia nigra (pars compacta and pars reticulata) and the globus pallidus. These areas, or 'ports' are connected by tapered micro-channels through which axons can grow, mimicking the circuitry of the in vivo basal ganglia. The model also features functional testing in the form of a multi-electrode array (MEA) for continuous extracellular recording of spontaneous electrophysiological activity.

The model is fabricated using photolithography and thus accurate to the micron level, with the micro-scale channels between ports tapering from either 15, 25 or 50 μm to 5 μm, intended to encourage axons to preferentially grow unidirectionally. Primary E16 rat neural cell attachment and axonal morphology were assessed via immunocytochemistry and electron microscopy. Processes were counted to determine the optimum micro-channel width to promote unidirectional growth. The device was also subject to different chemical coatings designed to promote attachment and limit migration, as well as continuous assessment of neural function from the MEA.

The optimum channel width were 5-15 μm channels, and the optimum chemical coating was polyethylenimine (PEI) with poly-D-lysine (PDL). All five cell types were successfully cultured within the device and connected via axonal outgrowth through channels, exhibiting electrophysiological activity as in vivo. Thus, this device represents a powerful pre-clinical experimental platform for study of an otherwise inaccessible area of the brain.

Anterior cruciate ligament reconstruction in an ovine model using an acellular human bone-patellar tendon-bone graft

Jennifer H Edwards[1], Anthony Herbert[1], Hazel L Fermor[1], John N Kearney[2], Paul Rooney[2], John Fisher[1], Eileen Ingham[1]

1 University of Leeds, Leeds, UK
2 NHS Blood and Transplant Tissue and Eye Services, Liverpool, UK

Corresponding email: j.h.edwards@leeds.ac.uk

Poster Number: A16

Keywords: Acellular scaffolds, bone-tendon, knee, shoulder

Current anterior cruciate ligament (ACL) replacement strategies involve cellular autograft or allograft tissue. Removal of the cells from allografts prior to implantation has the potential to improve graft integration and regeneration. This study investigated the in vivo regeneration and biomechanical function of a decellularised human bone-patellar tendon-bone (hBTB) graft in an ovine model of ACL repair.

Decellularised hBTB were produced following an established method (low concentration SDS and nuclease treatment) before sterilisation by gamma irradiation (minimum dose 25 kGy). Ovine bone-patellar tendon-bone (oBTB) controls were harvested aseptically and irradiated as for hBTB grafts. Grafts were used to replace the ACL in skeletally mature sheep, following human surgical procedures. At 4, 12 and 26 weeks following implantation, grafts were analysed macroscopically and histologically. Biomechanical analysis was carried out by tensile testing to failure at 26 weeks only, with data analysis through one-way ANOVA and Tukey's post-hoc testing ($p < 0.05$).

After 4 weeks, signs of inflammation and peripheral cell infiltration were seen for both graft types. These local tissue effects were reduced at 12 weeks and absent at 26 weeks. Graft ligamentisation and Sharpey's fibre formation were observed in both groups at 12 weeks, with further improvements by 26 weeks. By 26 weeks, osseous bridging and calcification of the ligament within bone tunnels was evident for both groups. Biomechanically, both groups were significantly different to the native ovine ACL (load at failure, linear stiffness; $p<0.05$), but not to each other.

These results suggest progressive cellular infiltration, remodelling and bony integration of both groups over 26 weeks. hBTB grafts showed similar biomechanical performance and local tissue structure to oBTB in this xenogeneic model of ACL repair. This study demonstrated the regenerative potential of the central portion of decellularised hBTB following ACL reconstruction.

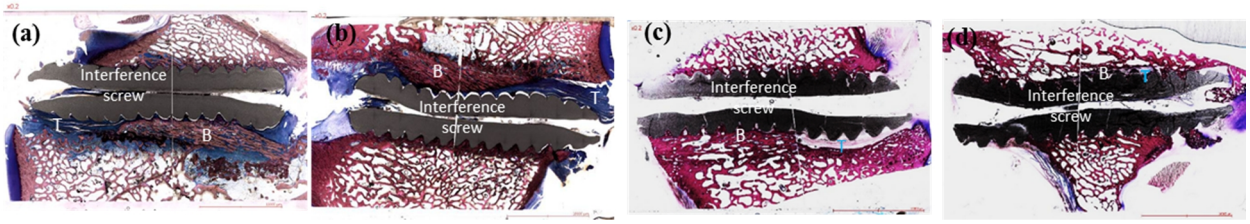


Figure 1: Modified Paragon staining of femoral tunnels following ACL reconstruction using hBTB (a, c) and oBTB (b,d). Images show representative examples from 4 (a, b) and 26 (c, d) weeks functional implantation. T denotes the location of the tendon portion of the hBTB or oBTB graft, B represents the patellar component.

The in vivo compatibility, integration and regeneration of a decellularised porcine bone scaffold

Hazel Fermor[1], Anthony Herbert[1], Gemma Jones[1], John Fisher[1], Eileen Ingham[1]

1 Institute of Medical and Biological Engineering, University of Leeds, Leeds, LS2 9JT

Corresponding email: h.l.fermor@leeds.ac.uk

Poster Number: B17

Keywords: Musculoskeletal, decellularisation, scaffolds, knee, osteoarthritis

Introduction: Achieving adequate fixation of regenerative decellularised musculoskeletal scaffolds has proved challenging. Incorporation of bony attachment sites may enable superior soft tissue anchorage into the skeleton and improve integration/regeneration. Here we investigate the biocompatibility and osteointegration of decellularised porcine bone scaffolds in an ovine model. ***Methods:*** Porcine bone plugs (6mm diameter, 10mm long; n=6) were decellularised using low concentration SDS and protease inhibitors. Tissues were analysed by histology. Quantitative analysis of DNA and tissue fat content was performed. The biomechanical/material properties of the bone were assessed by µCT and tested under compressive load. Cytotoxicity was determined using BHK and L929 cells. In vivo biocompatibility was determined by subcutaneous implantation of native and decellularised bone (n=3) in mice for 4 and 12 weeks, followed by histological assessment. Osteointegration was assessed through implantation of decellularised porcine bone plugs (n=6) and allograft bone controls (n=6) into an ovine condyle for 4 and 12 weeks. Explants were assessed by histology. ***Results:*** Decellularisation of porcine bone resulted in removal of cell nuclei. Decellularised bone contained 20.2±8.5ng.mg-1 DNA/dry weight and no fat could be detected. Decellularised bone had reduced mineral content (817±13mgHA.cm3) compared to native porcine bone (917±12mgHA.cm3), which resulted in significantly reduced elastic modulus (227±52MPa native, 55±30MPa decellularised; $p<0.05$, student`s t-test). Decellularised bone was not cytotoxic. No adverse tissue reaction occurred after implantation in mice. In sheep, scaffolds showed signs of osteointegration at 4 weeks with osteoconduction occurring after 12 weeks, at a slower rate but to the same extent as allograft controls. A lymphocytic response to the scaffold was present at 4 weeks but had subsided by 12 weeks. ***Discussion:*** Following the demonstration of osteointegration this process can now be transferred to develop acellular bone-soft musculoskeletal tissue composite scaffolds as well as acellular bone scaffolds for clinical regeneration of musculoskeletal tissues.

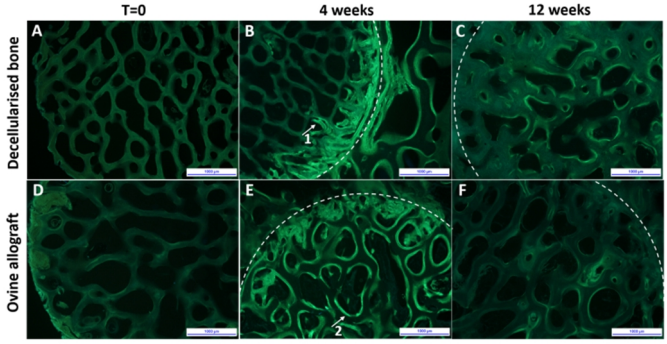


Figure 1. Histological assessment of regeneration performance. Fluorescent oxytetracycline labelling of new bone deposition between 15 and 5 days prior to sacrifice. a) decellularised porcine bone, b) decellularised porcine bone following 4 weeks implantation, c) decellularised porcine bone following 12 weeks implantation, d) ovine allograft bone, e) allograft following 4 weeks implantation, f) allograft following 12 week implantation. Dotted lines indicate the graft:host bone margin. Arrows indicate osteoconduction. Scale bar = 1000 µm.

Temporal intracellular characterisation of stem cells with external stimulation

A. Gelmi[1], S.W. Crowder[1], M. J. P. Cruz[1], A. N. Peña[1], A. Maziz[2], E.W.H. Jager[2], M.M. Stevens[1]

1 Stevens Group, Imperial College London, United Kingdom
2 Centre for Biosensors and Bioelectronics, Linköping University, Sweden

Corresponding email: a.gelmi@imperial.ac.uk

Poster Number: A18

Keywords: stem cell, biomaterial, characterisation, conductive, mechanotransduction

The control of stem cell fate via external stimulation is a vital contribution to the advancement of tissue engineering for regenerative medicine and there are many external factors at play when cells interact with biomaterials. Highly sensitive real-time characterisation using Atomic Force Microscopy AFM and micro-Raman spectroscopy RMS of living human mesenchymal stem cells hMSC elucidates the cellular response and mechanisms during applied external electrical stimulation. Real-time characterisation using AFM can directly measure single cell elasticity changes due to mechanics such as reorganisation of the cytoskeleton and RMS of living cells can determine the progression changes in biomolecular composition. The external stimulation is provided by biocompatible conductive polymer electrodes which are capable of electrical and mechanical stimulation.

The hMSC were able to successfully adhere and spread on the conductive polymer electrodes with no adverse effects over long time periods 14 days. A biphasic pulse stimulation is applied to the conductive polymer electrodes with the cultured hMSC in a live cell arrangement in order to deliver the external stimulation to the cells whilst also simultaneously performing AFM and Raman measurements. Initial experiments demonstrate changes in the elasticity of hMSCs was observed during and post-stimulation.

Using conductive polymer actuating microchips we are also able to deliver both electrical and mechanical stimulation to individual hMSC. Direct electrical or mechanical stimulation combined with cell modulus measurements and cell biochemistry spectra is a novel type of measurement in understanding the immediate response of living cells to external stimulation and how this response may be appropriated to control stem cell fate. Once these response mechanics are better understood the process can be improved and finely-tuned creating a more efficient approach to tissue engineering via smart biomaterials.

3D printed hydrogels as a novel method for the generation of 'off the shelf' cell models

Maaria Ginai[1], Anthony Callanan[1]

1 Institute for BioEngineering (IBioE), Kings Buildings, University of Edinburgh, Edinburgh, EH9 1JL

Corresponding email: m.ginai@ed.ac.uk

Poster Number: A19

Keywords: Hydrogels, scaffolds, cryopreservation, biofabrication, 3D printing

Hydrogels are routinely used in tissue engineering applications due to their high water content, excellent permeability, and their ability to be manipulated for cellular and non-cellular applications. Cell laden alginate hydrogels have a wide range of uses including encapsulation for bioartificial organs, drug testing models and as scaffolds for cell culture. And whilst alginate beads and discs are easy to produce, other shapes and thicker gels require the use of special moulds before cross linking, and a subsequent increase in the time or concentration of the cross linking solution. This in turn can have a detrimental effect on cells, creating heterogeneous models, and highly variable results. Furthermore, an increase in the amount of cross linking can have an effect on the cooling profile of the gel, presenting another issue for cryopreservation of these models for long term storage. The aim of this research is to overcome these issues using biofabrication methods such as 3D printing to produce cell laden hydrogels directly onto a cold surface. Our results indicate that using sub microliter droplets of 2.5 % alginate allow fast cooling rates required for vitrification. We then show that THLE-3 cells can then be printed in bespoke shapes, stored long term and cross linked on thaw. This offers a novel and rapid off the shelf method for cell laden hydrogel generation.

Enhanced antibody computed tomography (enact) a novel, non-destructive, molecularly specific method for the detection of cellular populations in three dimensional samples

A Glen[1], R Owen[1] & JW Haycock[1]

1 Department of Materials Science and Engineering, The University of Sheffield

Corresponding email: dradamglen@gmail.com

Poster Number: B20

Keywords: Nerve regeneration, computed tomography, stem cells, zoonotic viruses, tissue engineering

Introduction: Common tools for assessing tissue engineered (TE) scaffolds such as histology and optical microscopy, are limited by their destructive processing methods and limited depth penetration. X-ray micro-computed tomography (xmCT) computationally reconstructs scanned specimens without destructive processing. Currently, xmCT cannot detect specific cellular populations. We sought to overcome these limitations by combining lanthanide conjugated antibodies (L-ABI) and xmCT in order to non-destructively label specific cellular populations within engineered synthetic scaffolds for neuronal and bone tissue engineering applications.

Methods: Whole dorsal root ganglion (DRG) were harvested from wild type adult male Wistar rats and cultured within nerve guidance conduits (NGC) in a 3D culture system. Neuronal processes were labelled via: a) injection of a retrograde tracer or b) direct labelling for beta-III tubulin, then L-ABI before visualisation by xmCT. Polyurethane (PU) porous foam sheets, cut into cylindrical 98mm3 shapes, were seeded with MLO-A5 osteoblasts, labelled with phalloidin-FITC and subsequently L-ABI before visualisation by xmCT and compared to epifluorescent and two-photon microscopy.

Results: DRGs cultured in hollow NGCs regenerated processes and could be non-destructively visualised in both retrograde and directly labelled samples relative to L-ABI only controls. Within the PU scaffolds, MLO-A5 cells were orientated throughout the scaffold as observed by epifluorescent and 2-photon microscopy. Optimal depth penetration by these techniques was ~1.2mm. Cellular material labelled and subjected to xmCT could be seen in the same locations throughout the entire scaffold (5mm depth), with a concomitant increase in Hounsfield units relative to controls.

Discussion: ENACT is a novel approach utilising xmCT to detect specific cellular populations, providing specific molecular contrast to cellular material, whilst permitting concurrent 3D imaging of adjacent TE scaffolds. ENACT overcomes the destructive shortcomings of histology and depth limitations of optical microscopy and is applicable to any field that seeks non-destructive imaging of specific cellular populations in 3D samples.

The cell therapy landscape for Parkinson's disease

Emma Green[1], Stuart Jenkins[1], Rosemary Fricker[1]

1 ISTM, Keele University

Corresponding email: e.l.green@keele.ac.uk

Poster Number: B21

Keywords: Stem Cells, Neuroscience, Regeneration, Vitamins

Cell transplantation to replace the dopaminergic neurons that are lost in Parkinson's disease (PD) has been attempted for decades, with signs of efficacy, but also some unwanted side effects. These trial data are being reassessed, resulting in more clinical trials, with the hopes of identifying the most suitable patients. Early trials involved foetal tissue, which was biologically variable, including containing multiple cell types at different stages of development. The variability in tissue source and delivery techniques resulted in disparate patient outcomes, prompting research into identifying the parameters required to make cell therapy a viable option.

One of the most promising refinements to cell replacement therapy (CRT) for PD is the development of protocols that reproducibly and efficiently generate populations of dopaminergic neurons (or at least cells destined to become dopaminergic). These cell populations need to reliably produce large numbers of dopamine (DA) neurons containing no other cell types. Protocols are being developed using embryonic, induced pluripotent and various adult stem cells.

Some of the barriers to CRT for PD include: proliferating cells within grafts, inefficient production of DA neurons or inefficient production of DA by these neurons, poor survival of transplanted DA neurons, and a safe and economical source of stem cells.

By developing these protocols, a defined, reproducible source of dopaminergic neurons may become available on demand, representing the basis of a commercially viable cell therapy.

Drug loaded biodegradable hydrogels for personalised medicine to treat Pernicious Anaemia

T.Elliott[1], S.A.Rahman[1], A.L.Guildford[1]

1 Brighton Centre for Regenerative Medicine, School of Pharmacy and Biomolecular Science, University of Brighton.

Corresponding email: a.l.guildford@brighton.ac.uk

Poster Number: B22

Keywords: Inflammation, cell phenotype, cobalamin, invitro model, hydrogel

Pernicious Anaemia (PA) is an autoimmune condition characterised by an inability to adsorb vitamin B12 (cobalamin) due to the destruction of gastric parietal cells and a subsequent deficiency in the intrinsic factor carrier protein. This condition is associated with the thinning of the gastric mucosa, gastritis and inflammation. Treatment in the UK is by intramuscular injections of hydroxocobalamin (hCob) every 12 weeks. Cobalamin is essential for the methylation of DNA and the Krebs cycle and is available as the active form, methylcobalamin (mCob), and the inactive hCob, both of which exhibit low bioavailability within 72 hrs, up to 66% of the injected dose is excreted. Consequently, 64% of sufferers report symptom recurrence before their next injection, many resort to self-injecting the drug.

This study aims to elucidate the impact of cobalamin on inflammatory cells and to increase its bioavailability by developing a cobalamin modified hydrogel for sustained delivery. Activated macrophage cells (U937) were incubated with a range of hCob and mCob concentrations (0, 200, 500, 750 and 1000pg/ml) for 48hrs. Nitric oxide release was reduced in cells incubated with both cobalamins. hCob promoted a significant reduction in the expression of the pro-inflammatory marker CD86 (86%) when compared to cells incubated with mCob (96%) and the control (94%). Interestingly, hCob promoted an increase in mitochondrial activity. hCob and mCob modified Fibrin hydrogels were produced by combining fibrin (20mg/ml) suspended in hCob or mCob with CaCl2 loaded thrombin (4U/ml) into disc moulds. Hydrogels were optimised with the addition of the trypsin inhibitor Aprotinin, allowing the modulation of the degradation of the hydrogels promoting a slow release of the hCob and mCob. This work characterises the distinct effect of hCob and mCob on different cells associated with PA, and highlights the increased bioavailability of the cobalamins when encapsulated in a hydrogel matrix.

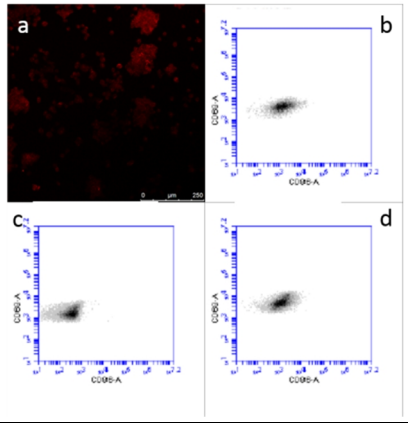


Figure 1. Confocal and FACs demonstrating the U937 cell phenotype, a) Control U937 CD86 stained confocal image, b) FACs plot confirming the pro-inflammatory (CD86+) macrophage (CD68+) phenotype of the control cell, c) FACs plot of cell phenotype post hCob incubation, d) FACs plot of cell phenotype post mCob incubation.

Informed Decision-Making for Decentralised Manufacturing of Cell and Gene Therapies

Richard P Harrison[1], Steven Ruck[1], Qasim A Rafiq[2] and Nicholas Medcalf[1]

1 Centre for Biological Engineering, Holywell Park, Loughborough University, Loughborough, LE11 3TU, UK

2 Department of Biochemical Engineering, Faculty of Engineering Science, University College London, Gower Street, London, WC1E 6BT, UK

Corresponding R.P.Harrison@Lboro.ac.uk

Poster Number: B23

Keywords:

Regenerative medicine has promised solutions for many of the health issues facing the world's population in the form of tissue engineered products as well as cell and gene therapies CGTs. Current reliance on large cell doses poses sourcing and manufacturing challenges which many research groups and companies are working to overcome.

Despite some successes, key questions remain around the feasibility of manufacturing CaGTs. What scale is appropriate, should we pursue autologous, allogeneic or partially patient matched and how will worldwide healthcare systems reimburse these expensive therapies. Without answers to these critical questions, the stunning breakthroughs we have witnessed will remain isolated examples, unable to be embraced by the wider population.

Decentralised or 'redistributed' manufacturing represents an attractive choice for production of some cell and gene therapies (CGTs), in particular personalised therapies. Decentralised manufacturing splits production into various locations or regions and in doing so, imposes organisational changes on the structure of a company. This confers a significant advantage by democratising supply, creating jobs without geographical restriction to the central hub and allowing a more flexible response to external pressures and demands.

Decentralisation presents unique challenges that need to be addressed including, a reduction in oversight, decision making and control by central management which can be critical in maintaining quality in healthcare product manufacturing. The unwitting adoption of poor business strategies at an early stage in development has the potential to undermine the market success of otherwise promising products. To maximise the probability of realising the benefits that decentralised manufacturing of CGTs has to offer, it is important to examine alternative operational paradigms to learn from their successes and to avoid their failures.

Whilst no other situation is quite the same as CGTs, some illustrative examples of established manufacturing paradigms share a unique attribute with CGTs which aid understanding of how decentralised manufacturing might be implemented for CGTs in a similar manner. We present a collection of paradigms which together represent a roadmap to success for decentralised production of CGTs

Combining growth factors with mechanical stimulation in tissue engineered bone and cartilage

James Henstock[1] Joshua Price[2] Michael Rotherham[2] Alicia El Haj[2]

1 Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK.
2 Institute for Science and Technology in Medicine, University of Keele, Staffordshire, UK

Corresponding email: j.r.henstock@liverpool.ac.uk

Poster Number: B24

Keywords: Bioreactors; Mechanotransduction; hMSC; Musculoskeletal; Manufacturing

Physical activity results in lasting changes in the musculoskeletal system and active lifestyles are generally associated with better bone and joint health. Cells in these tissues exist in an information-rich environment with guidance cues coming from the extracellular matrix, constant signals from growth factors, hormones, metabolites and external stimuli coming from the mechanical forces they are exposed to.

Evidence now suggests that the mechanical forces that the cells detect are a major regulator of how these many biochemical signals are integrated into a coherent response that can lead to tissue formation. This is particularly clear in the highly dynamic environment in the developing joint, which is an interesting model which tissue engineers try to recapitulate in regenerative medicine approaches to restoring damaged bone and cartilage. Conversely, changes in our joint biochemistry occur as we age which coupled with changes in lifestyle and reduction in exercise lead to a gradual decline in musculoskeletal function over time, and can eventually result in diseases like osteoarthritis.

Research in my lab concentrates on the interface of mechanobiology, matrix biology and cell-cell signalling to investigate how complex real-world environments drive stem cell differentiation and new tissue synthesis. My specific focus is on the interactions of growth factors with compressive mechanical loading, and uses bioreactors with 3D scaffolds to provide controlled mechanical forces in realistic, lab-grown tissues.

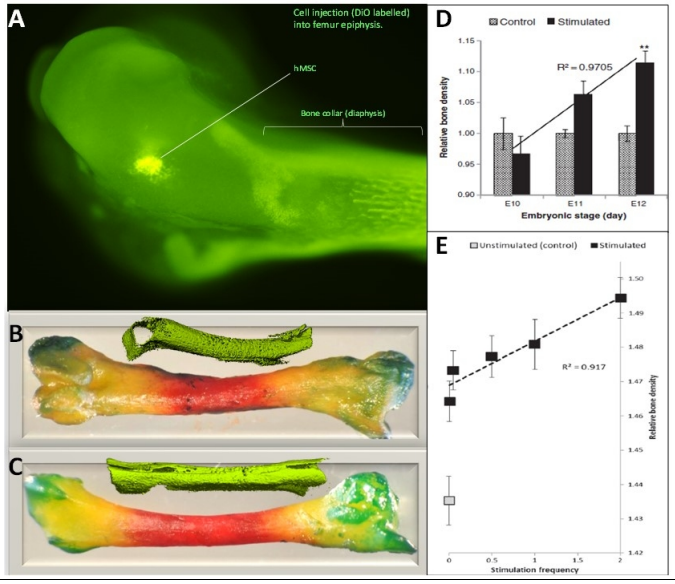


Fig.1. Mechanical loading (hydrostatic pressure) effects bone and cartilage development. Using an ex vivo chick foetal femur culture system (A) and compared to static-cultured controls (B), dynamic hydrostatic pressure was shown to increase the size and density of the bone formed (C). The effect was dependent on both foetal age (D) and stimulation frequency (E).

Manufacture, stratification and preclinical evaluation of acellular biological scaffolds for musculoskeletal repair

Anthony Herbert[1] Jennifer H Edwards[1] Eileen Ingham[1] John Fisher[1]

1 Institute of Medical and Biological Engineering, University of Leeds, Leeds.

Corresponding email: a.herbert@leeds.ac.uk

Poster Number: B25

Keywords: Acelular scaffolds, musculoskeletal repair, stratification

The most common surgical solution for the treatment of damaged tendons/ligaments is the use of autograft (healthy tissue harvested from elsewhere in the patient) as a replacement. Allografts (tissues harvested from human donors) provide an option in some cases since they eliminate the need to harvest autologous tissue whilst reducing the overall surgical time, but may elicit adverse immunological reactions and are limited in quality and supply. Acellular tendon/ligament grafts (produced by novel decellularisation bioprocesses) are an attractive alternative to replace the damaged structures without any of the current disadvantages of autologous or allogeneic grafts. The timeliness of this technology is reflected in the ongoing UK clinical trial with OrthoPureTM XT, an acellular tendon product for anterior cruciate ligament (ACL) replacement in the knee (Tissue Regenix Group, PLC) and pending CE mark.

For a number of years, the author has been involved in and then leading at an advanced level of exploration, the use of acellular porcine superflexor tendon (pSFT) and human bone-patellar tendon-bone (hBTB) grafts for ACL replacement through biomechanical, biochemical, biocompatibility and sterilisation investigations, with both approaches having successfully completed pre-clinical large animal trials. More recently, investigations into acellular porcine bone-patellar tendon-bone (pBTB) for ankle applications have also begun, and pBTB has also been targeted for use in the shoulder. However, the pathway to successful clinical translation on a global scale to meet potential market demands of over 900,000 interventions per year by 2020 (EPSRC MTIKC year four market report) requires further development of the manufacturing process, implementation and consideration of in-vivo performance at the intended sites of implantation to be realised.

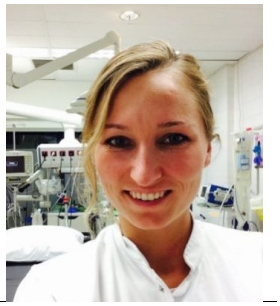
Three distinct, specialised levels of product development (stratification, implementation and function/performance) are employed to meet the manufacturing and validation challenges in product development and enhanced translation of novel acellular biological scaffolds for musculoskeletal repair.

Advances in keratinocyte delivery in burn wound care

B. ter Horsta[1] G. Chouhan[1], N.M. Moiemen[2], L.M. Grover[1]

1 School of Chemical Engineering, University of Birmingham, Edgbaston, B15 2TT, United Kingdom
2 Queen Elizabeth Hospital Birmingham, Burns Unit. Mindelsohn Way, B15 2TH, Birmingham, United Kingdom.

Corresponding email: BXT564@student.bham.ac.uk



Poster Number: B26

Keywords: Spray cell delivery; hydrogels; wounds

This review gives an updated overview on keratinocyte transplantation in burn wounds concentrating on application methods and future therapeutic cell delivery options with a special interest in hydrogels and spray devices for cell delivery.

To achieve faster re-epithelialisation of burn wounds, the original autologous keratinocyte culture and transplantation technique was introduced over 3 decades ago. Keratinocyte delivery was the first skin cell transplantation successfully translated to the clinical burn care. In the last nearly 4 decades this method has been investigated widely and numerous researchers have contributed to a variety of improvements. Further enhancement of cell culture, cell viability and function in vivo, cell carrier and cell delivery systems remain themes of interest.

Application types of keratinocytes transplantation have improved from cell sheets to single-cell solutions delivered with a spray system. Nevertheless, some shortcomings of the suspension application technique have yet to be addressed. For example, an uneven wound bed (that often also occurs on a curved body contour), can result in uneven spreading of the of the cell suspension or dripping off the wound bed. To improve the application method of spray cell delivery, hydrogels are introduced as cell carriers. Hydrogels such as chitosan, alginate, fibrin and collagen are frequently used in burn wound care and have advantageous characteristics as cell carriers. First in vitro results of our research group show that gellan gum hydrogel is a good candidate for both cell encapsulation and spray application without dripping of a tilted surface coated with gelatin. Furthermore, a novel way of assessing spray characteristics of the hydrogel has been performed based on spray analysis methods used in the agriculture section. Future approaches of keratinocyte transplantation involve spray devices, but optimisation of application technique and carrier type is necessary.

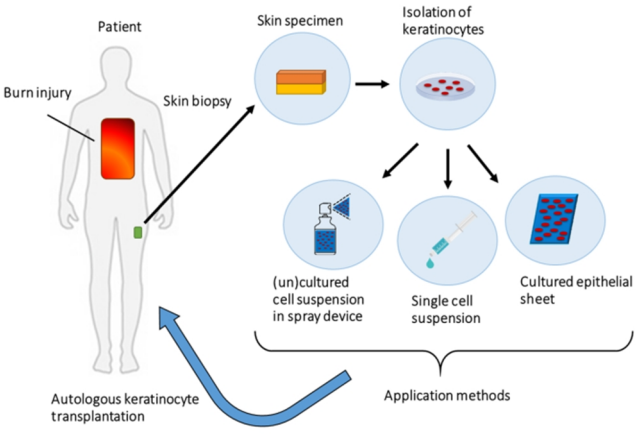


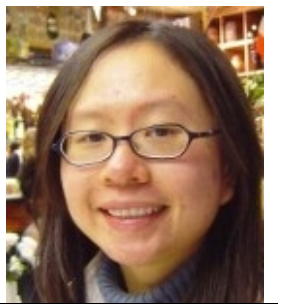
Figure 1 Methods of autologous keratinocyte transplantation to burn wounds in patients with burn injury keratinocytes can be isolated from a small skin biopsy as illustrated above. The autologous keratinocytes can be cultured and delivered to the wound bed of the patient by several methods. First to be developed was a sheet of cultured epithelial cells thereafter a single cell.

Toward building complex cellular microenvironments via biomicrofabrication

Yan Yan Shery Huang[1], Xia Li1[2], Cristina Bertulli[2], Zhaoying Li[1], Elisabeth Gill[1]

1 Department of Engineering, University of Cambridge, CB2 1PZ
2 Department of Physics, University of Cambridge, CB3 0HE

Corresponding email: yysh2cam@gmail.com



Poster Number: A27

Keywords: Bioprinting; Organ-on-chips; Biomicrofabrication; Biomaterials; Bioelectronics

Recent advances in biofabrication technologies offer promising new strategies to create tissue scaffolds and tissue models that could address the pressing need for more sustainable drug screening platforms, and personalised tissue and organ part replacements. The creation of a support matrix that recapitulates the bioactive and structural roles of the extracellular matrix (ECM) may hold the key in making functional, complex tissues. Existing biomaterial fabrication techniques (e.g. 3D printing, electrospinning, and templating) fall short in building the complex combinations of chemical and structural elements, with limited feature resolution. Our recent development in low-voltage electrospinning patterning (LEP), and its combination with additive manufacturing, opens up new avenues in the creation of geometrically defined biomaterial matrices. Compared with electrospinning which operates with an applied voltage ~10kV, LEP operates with an applied voltage in the range of 100 V, and simultaneously allowing fibre patterning on a range of substrates. The versatility of LEP is shown using a wide range of combination of polymer and solvent systems for thermoplastics and biopolymers. Novel functionalities are also incorporated when a low voltage mode is used in place of a high voltage mode, such as direct printing of living bacteria; and the construction of suspended single fibers and membrane networks in microfluidics. The LEP technique reported here should open up new avenues in the patterning of bioelements and free-form nano- to microscale fibrous structures.

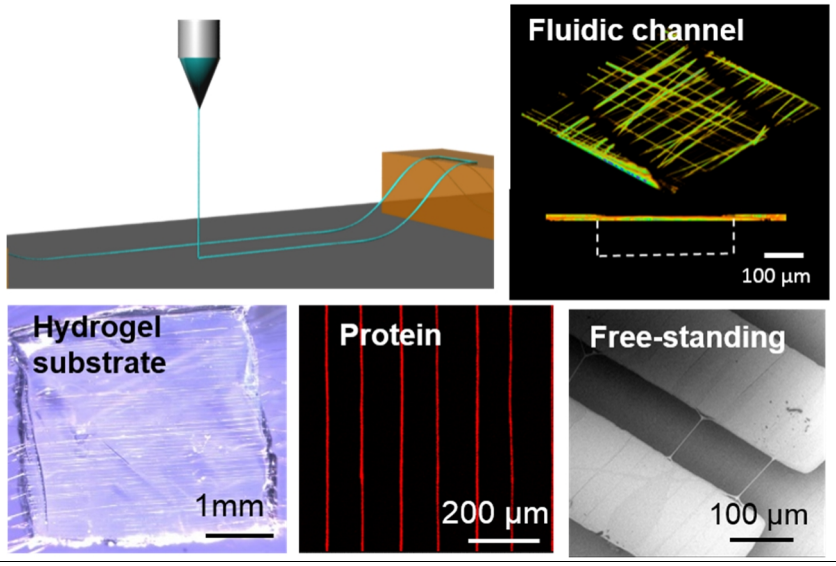


Figure 1: Low voltage electrospinning as a versatile, nano-micro fibre patterning technique supporting multi-material, flexible substrate, and room temperature deposition.

'Stealth' nanoparticles evade neural immune cells but also evade major brain cell populations: Implications for PEG-based neurotherapeutics

Stuart Jenkins[1], Daniel Weinberg[2], Arwa Al-Shakli[1], Alinda Fernandes[3], Humphrey Yiu[4], Neil Telling[1], Paul Roach[5], Divya Chari[1]

1 Institute for Science and Technology in Medicine, Keele University, Keele, Staffordshire ST5 5BG
2 Salford Royal Hospital, Manchester M6 8HD
3 Maurice Wohl Clinical Neuroscience Institute, King's College London, SE5 9RX
4 Chemical Engineering, School of Engineering and Physical Sciences, Heriot-Watt University, Edinburgh EH14 4AS
5 Department of Chemistry, Loughborough University, Leicestershire LE11 3TU

Corresponding email: s.i.jenkins@keele.ac.uk

Poster Number: A28

Keywords: Neuroscience, Biomaterials, Nanoparticles, Neurodegeneration,

Surface engineering of nanomaterials to control cell behavior is of high interest across the chemical engineering, drug delivery and biomaterial communities. Defined chemical strategies are necessary to tailor nanoscale protein interactions/adsorption, enabling control of cell behaviors for development of novel therapeutic strategies. Nanoparticle-based therapies benefit from such strategies but particle targeting to sites of neurological injury remains challenging due to circulatory immune clearance. As a strategy to overcome this barrier, the use of stealth coatings can reduce immune clearance and prolong circulatory times, thereby enhancing therapeutic capacity. Polyethylene glycol (PEG) is the most widely-used stealth coating and facilitates particle accumulation in the brain. However, once within the brain, the mode of handling of PEGylated particles by the resident immune cells of the brain itself (the microglia) is unknown. This is a critical question as it is well established that microglia avidly sequester nanoparticles, limiting their bioavailability and posing a major translational barrier. If PEGylation can be shown to limit microglial clearance, then this information will be of high value in developing tailored nanoparticle-based therapies for neurological applications. Here, we have conducted the first comparative study of uptake of PEGylated particles by all the major (immune and non-immune) brain cell types. We demonstrate for the first time that PEGylation limits nanoparticle uptake by major brain cell populations — a phenomenon which will enhance extracellular bioavailability. Data reveal changes in protein coronas around these particles within biological media, and we discuss how surface chemistry presentation may affect this process, and therefore subsequent cellular interactions.

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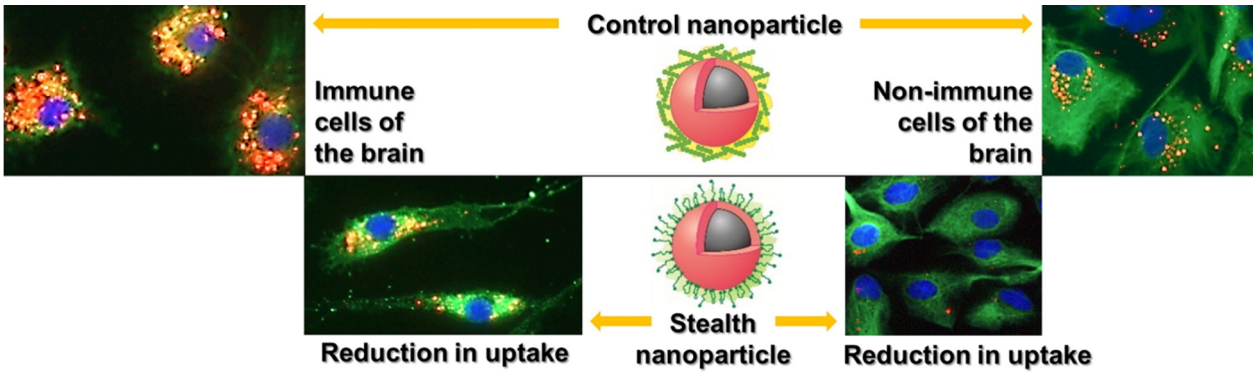


Figure 1. Stealth nanoparticles exhibit reduced clearance by brain immune cells, but also reduced uptake by major non-immune brain cell types. These data suggest PEGylation may extend bioavailability within the brain, potentially prolonging extracellular drug release, but that additional targeting strategies are likely required if delivery to specific cell types is intended.

Perspectives on additive manufacturing for functional prototyping of tissue model systems

Prosper Kanyong[1], Mathew Wilson[1], Adrian Boyd[1], George Burke[1], Brian J. Meenan[1]

1 Biodevices Lab, NIBEC, Ulster University, Shore Road, Newtownabbey BT37 0QB

Corresponding email: p.kanyong@ulster.ac.uk

Poster Number: A29

Keywords: Additive Manufacturing, Tissue Model Systems, Novel Medical Products, 3D Scaffolds, 3D Printing, Functional Prototyping

Additive manufacturing consists of technologies that utilise the interaction of mass and energy to manufacture complex 3D objects layer-by-layer. In this way, the limitations of conventional and formative manufacturing processes are overcome and products with high value, high complexity, and customisation but low volume can be produced.

Ulster University has established a Biodevices Laboratory with capability to develop functional prototypes of novel medical products in a way that will assist manufacturing companies to accelerate their time to market. By using a multimodal approach that encompass electronics, communications and materials technologies new products in a faster and more cost-effective manner; thus, removing critical delays and wasted effort during the iterative development cycle.

A core element of the work plan is the use of tissue engineering approaches to create functional ex vivo tissue models for the study of disease states and associated therapeutic interventions. The work presented here addresses the provision of hybrid 3D scaffolds and their potential applications in the study of cardiac and bone tissues.

Material-driven fibronectin nanonetworks as efficient BMP2 microenvironments for bone repair

V. Llopis-Hernandez[1], C. Gonzalez-Garcia[2], M. Cantini[2], A. Alba[2], M. Dalby[1], M. Salmeron-Sanchez[2]

1 Centre for Cell Engineering, Institute of Biomedical and Life Sciences, University of Glasgow, UK
2 Biomedical Engineering Research Division, School of Engineering, University of Glasgow. UK.

Corresponding email: Virginia.Llopis-Hernandez@glasgow.ac.uk

Poster Number: A30

Keywords: Tissue engineering / growth factors / bone / in vivo / MSCs

Material-based strategies seek to engineer synthetic microenvironments that mimic the characteristics of physiological extracellular matrices for applications in regenerative therapies, including bone repair and regeneration. We have identified a specific chemistry, poly(ethyl acrylate) (PEA), able to induce the organization of fibronectin (FN) into fibrillar networks upon simple adsorption of the protein from a solution. This process has been called material-driven fibrillogenesis due to its similarity to the physiological one, leading to enhanced cellular response, in terms of cell adhesion and differentiation. Recently, we have exploited these FN networks to capture and present growth factors (GF) in combination with the integrin binding domain of FN to promote bone healing, after finding that fibrillar conformation of FN adsorbed on PEA favours the simultaneous availability of the GF binding domain next to the integrin binding region. The combined exposure of domains improved the osteogenic differentiation of mesenchymal stem cells (MSCs). A higher expression of bone markers was found when BMP2 presented from the material interface versus its soluble administration in the culture media in vitro. The potential of this system as a recruiter of GFs was also investigated in a critical-size bone segmental defect in mouse. The synergistic integrin-GF signalling, induced by fibrillar FN, promoted bone formation in vivo with lower BMP2 doses than current technologies. Furthermore, we optimized the system for its potential use in translational research, seeking to enhance the bioactivity of materials already used in clinics applications (e.g. poly ethyl ether ketone, PEEK). Also, biocompatible and biodegradable material implants (polycaprolactone) were studied. The material-driven FN fibrillogenesis provides a new translational strategy to efficiently reduce the GF doses administrated in bone regenerative therapies.

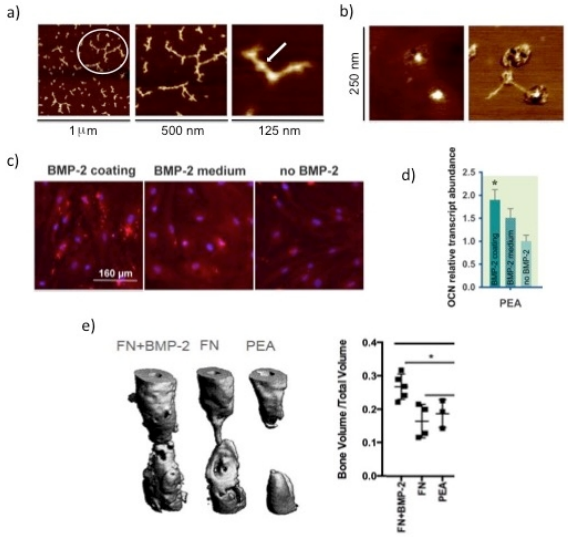


Figure 1 a Atomic force microscopy (AFM) images of FN on PEA substrate with BMP-2. BMP2 is located at the GF domain b AFM of BMP-2 immunogold on BMP-2 and FN pre-adsorbed PEA substrates c&d Osteocalcin staining and RNA expression in human MSCs grown 14 days on the different substrates e Bone segmental defect model after 8 weeks of implantation.

Delivering the immunomodulatory properties of mesenchymal stem cells

Sandhya Moise[1,2], Luigi Dolcetti [2], Paul Roach [3], Francesco Dazzi [2]

1 School of Pharmacy, Centre for Biomolecular Sciences, University of Nottingham, NG7 2RD, UK
2Department of Haemato-oncology, Rayne Institute, King's College London, SE5 9NU, UK
3 Department of Chemistry, Loughborough University, LE11 3TU, UK

Corresponding email: sandhya.moise@nottingham.ac.uk

Poster Number: A35

Keywords: Stem cell, Immunomodulation, Hydrogels, Translation, Cell therapies

Mesenchymal stem cells have been extensively investigated for exploiting their trilineage potential in regenerative medicine therapies. Emerging research shows that these cells apart from their trilineage potential also exhibit immunomodulatory behaviour that aids in wound healing and regeneration. Understanding the mechanisms through which mesenchymal stem cells regulate inflammation will help identify the best delivery routes of these cells for treating inflammatory conditions and immune diseases. In this study we investigate the different mechanisms by which mesenchymal stem cells communicate and respond to an inflammatory niche. We compare different scaffold designs to allow either direct cell-cell communication or indirect communication via signalling molecules between the MSCs and immune cells to identify the more efficient mechanism of immunomodulation. Our initial studies look at the effect of alginate-encapsulated mouse MSCs on the proliferation of concanavalin A-activated mouse splenocytes in vitro. Results obtained so far show that alginate encapsulation does not interfere with the immunomodulatory activity of the mesenchymal stem cells. Other biomaterials are also being explored including fibrin, extracellular matrix hydrogels, poly lactic-co-glycolic acid (PLGA). By comparing the effect the biomaterials have on the immunomodulatory behaviour of the MSCs the best material and design will be identified for further in vivo delivery of the cells.

The tissue-engineered vascular graft - past, present, and future

Samand Pashneh-Tala[1] Sheila MacNeil[1] Fred Claeyssens[1]

1 Kroto Research Institute University of Sheffield, Sheffield, S3 7HQ

Corresponding email: s.pashneh-tala@sheffield.ac.uk

Poster Number: B36

Keywords: vascular bioreactor scaffold 3D-culture ADSCs

Cardiovascular disease is the leading cause of death worldwide, with this trend predicted to continue for the foreseeable future. Common disorders are associated with the stenosis or occlusion of blood vessels. The preferred treatment for the long-term revascularisation of occluded vessels is surgery utilising vascular grafts, such as coronary artery bypass grafting and peripheral artery bypass grafting. Currently, autologous vessels, such as the saphenous vein and internal thoracic artery, represent the gold standard grafts for small diameter vessels (<6 mm). Synthetic vascular grafts are also available, produced from materials such as ePTFE, however these are only considered as secondary options. Autograft vessels however, are of limited availability, require invasive harvest and are often unsuitable for use. To address this, the development of a tissue-engineered vascular graft (TEVG) has been rigorously pursued. This work reviews the current state-of-the-art of TEVGs. The various approaches being explored to generate TEVGs are described, including scaffold based methods (using synthetic and natural polymers), the use of decellularised natural matrices and tissue self-assembly processes, with the results of various in vivo studies, including clinical trials, highlighted. A discussion of the key areas for further investigation, including graft cell source, mechanical properties, haemodynamics and integration, is then presented.

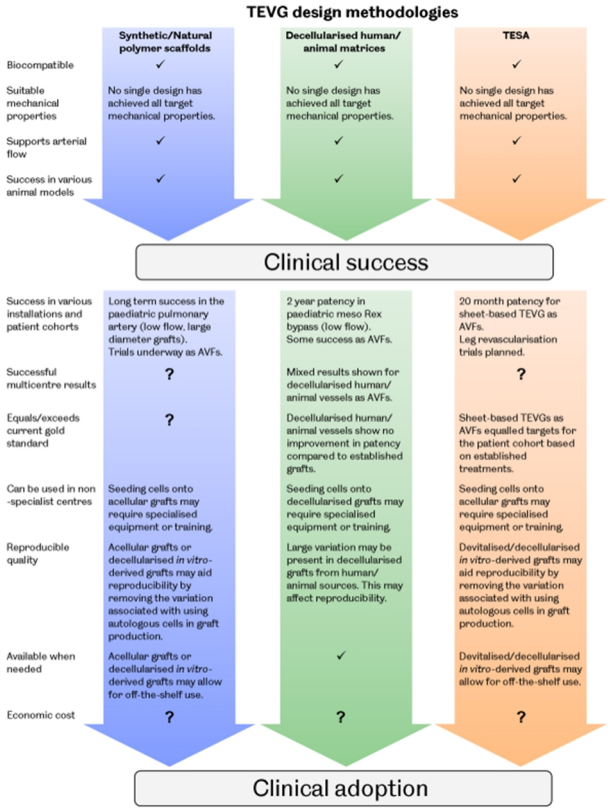


Figure 7. Pathway for the development of the TEVG from design concept to clinical success and then clinical adoption. The various criteria for achieving these milestones are detailed and discussed in relation to the three major TEVG design methodologies.

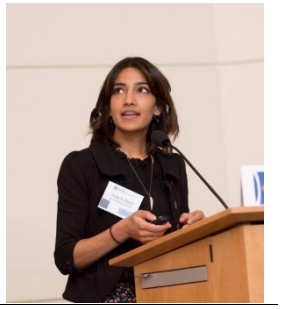
Figure 1. Pathway for the development of the TEVG from design concept to clinical success and then clinical adoption.

Developing synthetic materials for the manipulation of cellular behaviour

Asha Patel[1]

1 MIT and University of Nottingham

Corresponding email: Asha.Patel@Nottingham.ac.uk



Poster Number: A37

Keywords:

The precise control of cellular behavior underpins many goals of regenerative medicine. Various strategies have been employed to manipulate cell phenotype including cytokines, mechanotransduction and substrate properties such as patterning and elasticity. My research has focused on exploring opportunities in manipulation of underlying substrate chemistry to achieve desired cell response. A wide range of surface chemistries were surveyed to investigate their ability to act as cell culture substrates that maintain human stem cell pluripotency. Conversely, materials were also developed to promote differentiation of human stem cell derived cardiomyocytes to a more mature phenotype and utility demonstrated in an in vitro cardiotoxicity assay. A similar theme follows into my current research where I describe how changing polymer chemistry of non-viral delivery vectors for messenger RNA can have a profound effect on cellular interaction and transfection efficiency.

Use of companion dogs as a clinical model for regenerative medicine research

Jon Prager[1], Darren Carwardine[1], Alexander Delaney[2], Christopher Adams[2], Divya Chari[2], Liang-Fong Wong[3], Nicolas Granger[1]

1 School of Veterinary Sciences, University of Bristol, Bristol, UK
2 Cellular and Neural Engineering Group, Institute for Science and Technology in Medicine, Keele University, Keele, UK
3 School of Clinical Sciences, University of Bristol, Bristol, UK

Corresponding email: jon.prager@bristol.ac.uk

Poster Number: B38

Keywords: spinal cord injury, neuronal regeneration, cell transplant, cell delivery, biomaterials

Canine spinal cord injury (SCI) occurs spontaneously, and ~2 cases per day present to large veterinary hospitals in the UK. This injury provides an excellent model of human SCI with clinical heterogeneity that is lacking in rodent models, and mixed contusive-compressive lesions of comparable size to humans. There is currently no treatment for severely affected dogs and they therefore present a unique opportunity for in vivo clinical research; they allow refinement of techniques by replicating the challenges of a complex clinical scenario, with quantifiable neurological function and outcomes comparable to those used in humans. By enabling screening for treatments with a clinically significant effect, this model can help bridge the gap in translating therapies from the lab to humans.

Using this model in a number of regenerative medicine approaches to SCI, we have: (i) performed autologous spinal transplant of canine olfactory ensheathing cells (cOECs) in clinical cases within a veterinary hospital, a technique known to improve locomotion after SCI in dogs and so far in phase 1 trials in humans; (ii) obtained cOECs by minimally invasive endoscopic nasal mucosal biopsy and cultured these in 3D through collagen hydrogels, a leading biomaterial for protected cell delivery in SCI; (iii) obtained novel data on the in vivo elasticity of the spinal cord using ultrasound elastography intraoperatively, which will provide a target for matched biomaterial stiffness; (iv) developed a lentiviral vector for transduction of cOECs with the chondroitinase ABC gene. Chondroitinase ABC breaks down the glial scar formed following SCI and has been demonstrated to improve functional outcomes in experimental rodent and feline models of SCI.

This work could be readily progressed to dogs with transduced cOECs expressing ChABC transplanted within hydrogel. The clinical canine model of SCI is therefore an example of the opportunities available for using veterinary cases in translational research.

Chiral nematic liquid crystal phase formation in Collagen type 1 - Engineering in vitro tissues using natures toolbox.

Joshua C Price[1], Paul Roach[2], Alicia J El Haj[1]

1 ISTM Guy Hilton Research Centre, Keele University, Staffordshire, UK ST4 7QB
2 Department of Chemistry, Loughborough University, Loughborough, Leicestershire, LE11 3TU

Corresponding email: j.price1@keele.ac.uk

Poster Number: A39

Keywords: Microscopy, Collagen self assembly, Tissue engineering, Stem cells, Biomaterials

Generating biomaterials that mimic hierarchical structures found in nature will be necessary to realize viable tissue manufacturing of a wide variety of tissues such cornea, tendon and bone. Liquid crystal self-assembly in collagen has been implicated as an important mechanism influencing the formation of hierarchical tissue structures, yet existing methods by which these properties can easily be exploited has proven challenging. In this research we detail a simple, low cost production method for highly ordered collagen bio materials containing chiral nematic textures. Substrate characterization using polarized light microscopy in combination with Raman spectroscopy allowed us identify a concentration dependent isotropic to cholesteric phase transition, as well as identifying previously unreported higher order phase transitions. The substrates are bio compatible, supporting viable cell growth and maturation over a 14 day in vitro culture period. Comparing our substrates with sectioned polarized light images of native tissues show strong correlations in the terms of tissue anisotropy and second order chiral structure, suggesting our system could represent a cell free in vitro model of hierarchical tissue formation. In conclusion, we believe these methods could be applied to a wide variety of tissue engineering protocols, as well as further our understanding of the physio-chemical mechanisms that underpin tissue formation in vivo.

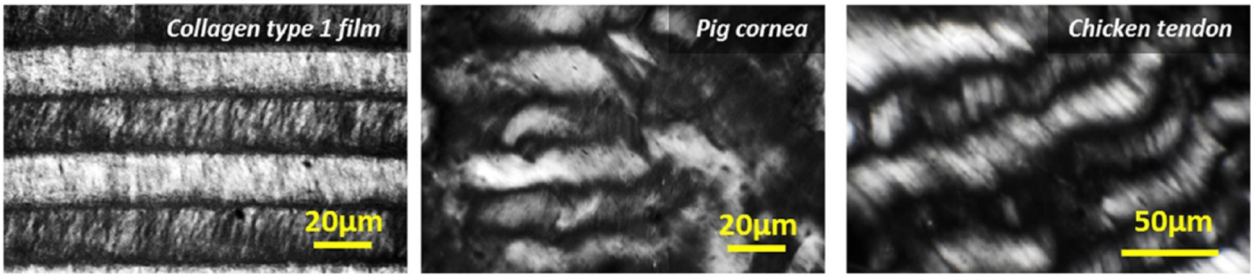


Figure 1: Cross-polarized images comparing collagen orientation in type 1 collagen films, pig cornea, and chicken tendon.

Optical measurement of oxygen concentration in melanoma spheroid and skin engineered models

A Raza[1], HE Colley[2], E Baggaley[3], NH Green[1], S Botchway[4], JA Weinstein[3], S MacNeil[1], & JW Haycock[1].

1 Department of Material Science & Engineering, Kroto reseach institute, University of Sheffield, UK.
2 School of Clinical Dentistry, University of Sheffield, UK.
3 Department of Chemistry, The University of Sheffield, UK.
4 STFC, Rutherford Appleton Laboratory, Oxford, UK.

Corresponding email: a.raza@sheffield.ac.uk

Poster Number: B41

Keywords: Skin and melanoma models, Confocal/2PE microscopy, 3D optical live imaging, oxygen measurement, in vitro invasion model

Non-invasive quantitative measurement of oxygen concentration within cells and tissues is essential for understanding of normal and pathological processes in particular tumourigenesis One of the most promising optical methods for measuring oxygen concentration is by 2-photon laser scanning phosphorescence lifetime imaging microscopy 2PE-PLIM We have used a phosphorescent dye PtLsCl that is ubiquitously but heterogeneously distributed within a whole cell and quenches in the presence of oxygen. Phosphorescence lifetime imaging PLIM has many advantages over intensity measurement for example it does not depend on fluorophore concentration and provides auto-fluorescence nullified imaging. Furthermore PLIM used with 2-photon laser excitation is useful as it allows deep imaging as the excitation light penetrates to greater depths than 1-photon excitation The aim of this study was to investigate if a PtLsCl label could be combined with 2PE-PLIM for detection of a hypoxic microenvironment in a 3D in vitro melanoma spheroid model surrounded by a normal skin epithelium.

Human melanoma cell lines C8161 were cultured in to a multicellular tumour spheroid In addition a tissue engineered model was developed this was comprised of the melanoma spheroids contained within a native human de-epidermized dermis plus cultured human keratinocytes and fibroblasts in order to mimic developing melanoma tumour. Using the resultant model, we then established a PLIM imaging method to detect the tumour by way of the oxygen concentration therein.

Our results showed a steep increase in phosphorescence lifetime in cells under hypoxic conditions compared to normoxic conditions Similarly measurements through the depth of the melanoma spheroids showed that oxygen concentrations were highest at the outer region and gradually decreased towards the core. Lifetime measurements on melanoma tissue engineered models showed short normoxic lifetime values in normal stroma and longer hypoxic values in spheroid area.

The power of bespoke biocompatible and biodegradable hydrogels

G. Saint-Pierre[1], A. Mujeeb[2], A. Saiani[3], A. Miller[4]

Dr A. Mujeeb, PeptiGelDesign Technologies Ltd, The Biohub, Alderley Park, Alderley Edge, SK10 4TG
Prof A. Saiani, School of Materials & Manchester Institute of Biotechnology, The University of Manchester, Oxford Road, M13 9PL, UK
Prof A. Miller, Universit

Corresponding email: g.saint-pierre@peptigeldesign.com

Poster Number: A50

Keywords: IVD, Tissue Engineering, Biomaterials

PeptiGelDesign has developed a family of self-assembling peptide based hydrogel that mimics the cell microenvironment and provides a natural physiological environment for 3-dimensional (3D) cell culture. In addition to its standard formulation PeptiGelDesign also offer a design service, which allows it to deliver hydrogel with tailored properties. These systems have tunable mechanical strength to suit a range of different cell types and can be functionalization with biological epitopes or formulated with small or large molecules such as growth factors. Example areas of use include 3D cell culture, stem cell culture and directed differentiation. These products have also great potential for applications in the regenerative and medical field as they are animal free, biocompatible and biodegradable. They can therefore potentially be used as primary packaging for the in-vivo delivery of drugs, cell or other biological factors. Our hydrogels can be designed to be injectable, sprayable and are naturally mucoadhesive. Our synthetic extra cellular matrices can therefore readily be used as bioink for cell encapsulation and bioprinting. To summarize the material design translational platform that covers research and industrial needs, from in vitro to in vivo. Of tailorable properties, we demonstrated a family of synthetic extra cellular matrices to suit the needs of our customers.

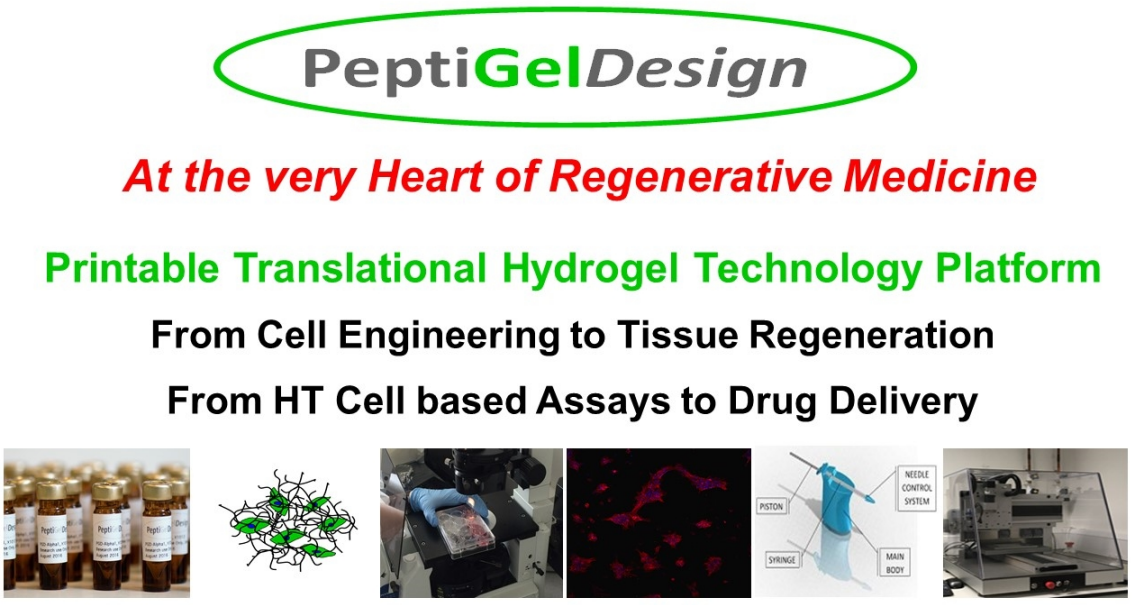


Figure 1: The Power of Bespoke Hydrogels

Manufacture of complex bioactive membranes for bone and cartilage repair

Martin Santocildes-Romero[1] Aileen Crawford[1] Ilida Ortega Asencio[1] Cheryl Miller[1] Paul Hatton[1]

1 School of Clinical Dentistry University of Sheffield, Sheffield, S10 2TA

Corresponding email: m.e.santocildes-romero@sheffield.ac.uk

Poster Number: A42

Keywords: Biomaterials; Bioactivity; Electrospinning; Tissue regeneration; Musculoskeletal

Electrospinning is a versatile manufacturing technique that offers great potential for the development of novel medical devices for tissue repair and regeneration. Briefly, electrospinning makes it possible to draw fibres with diameters in the range of micrometres to hundreds of nanometres through the application of high voltage electrical currents to polymeric solutions, resulting in the fabrication of membranes with high surface areas. However, polymers used frequently in the fabrication of medical devices intended for tissue regeneration usually lack bioactivity. Therefore, the addition of biological functionalities to the devices may be a promising approach to enhance their regenerative capacity. At the School of Clinical Dentistry of the University of Sheffield we have been investigating the development of electrospun membranes with enhanced bioactive properties for bone and cartilage repair using a range of methods, including the incorporation of bioactive glass particles and the generation of well-defined surface topographies aimed to control cellular behaviour and fate.

Strontium-substituted bioactive glass powders of demonstrated osteogenic potential were developed, and the particles were added to polycaprolactone solutions and electrospun. Membranes exhibiting three different surface topographies were produced by electrospinning polycaprolactone solutions on collectors made using advanced manufacturing techniques. All the membranes were characterised using scanning electron microscopy, showing the inclusion of the glass particles within the fibres and complex topographies. Membrane biocompatibility was studied in vitro by measuring the metabolic activity of mesenchymal stem cells isolated from bone marrow and synovial fluid and cultured on the membranes. All compositions were shown to support viable cellular populations successfully. Furthermore, fluorescence microscopy studies showed that cellular morphology and distribution was affected by the topographies.

These outcomes demonstrated the great potential and versatility of electrospinning as a manufacturing technique for the development of bioactive membranes, which may facilitate the tailoring of the properties of medical devices to specific conditions.

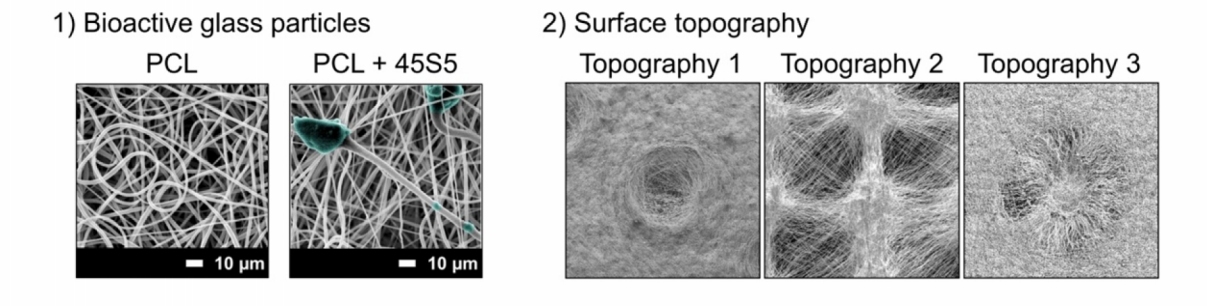


Figure 1. Methods used in this study for the incorporation of bioactivity on electrospun membranes via the addition of bioactive glass particles and the development of surface topography.

Automated expansion of pluripotent stem cells at three international sites

M Shariatzadeh[1], S L wilson[1], S sebastian[1], A Chandra[1], D J Wilson[1]

1 Loughborough University

Corresponding email: M.M.Shariatzadeh@lboro.ac.uk

Poster Number: B43

Keywords: Stem cell, tissue engineering, regenerative medice, 3D cell culture, automation system for stem cell culture

Designing manufacturing processes to consistently produce process sensitive pluripotent stem cells (PSC) and cells derived from PSC of sufficient quantity and quality for clinical application is challenging and complex. The manual production of cell therapies in flask based processes is controlled primarily through adherence to SOPs which can allow variations in process by individual operators. This can lead to clinical production processes with little direct control of critical quality attributes, significant reliance on endpoint quality testing and subsequent high wastage costs, and overly large banking requirements. Demonstrating equivalence when manufacturing across multiple sites is required to ensure comparability and is considered "difficult for cell-based medicinal products". Researchers from the UK RMP PSC Platform (Cambridge, Sheffield and Loughborough Universities and NIBSC) are working with product and process developers including Lund University, I-Stem and Fraunhofer-IBMT to conduct scaled up experiments to:

a. Understand the stability and variation of pluripotent stem cell cultures where different PSC lines are expanded and differentiated over multiple passages starting from independent vials.

b. Demonstrate product equivalence when performing end-to-end production of a therapeutic from PSC where the production is done at the developer site, a second biological variation demonstrator site and the manufacturing protocol optimisation site.

c. Automated expansion of PSC at three international sites emulating manufacture of cell therapies for global markets using the National Institute of Health "standard ruler cell line". The paper will report initial results of the application of a novel quality framework to permit manufacturing at multiple sites.

An engineered heart tissue model of the actin-E99K mutation

James Smith[1], Tom Owen[2], Diogo Mosqueira[1], Jamie Bhagwan[1], Asha Patel[1], Steve Marston[2], Sian Harding[2] and Chris Denning[1]

1 Wolfson Centre for Stem Cells, Tissue Engineering and Modelling, Centre for Biomolecular Sciences, University of Nottingham.
2 National Heart and Lung Institute, Imperial College London

Corresponding email: james.smith@nottingham.ac.uk

Poster Number: B44

Keywords: iPSC, Cardiomyocytes, Disease Model, Hypertrophy

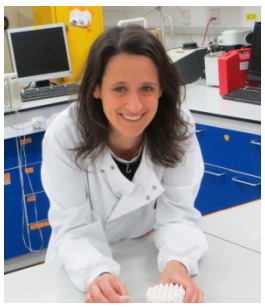
Background: Hypertrophic cardiomyopathy (HCM) is a thickening of the ventricles that can lead to devastating conditions such as heart failure and sudden cardiac death. HCM is linked to mutations in genes encoding cardiac sarcomeric proteins, such as ACTC1 encoding for actin. The E99K mutation is a single base pair mutation resulting in an amino acid change from glutamic acid to lysine in the ACTC1 gene linking to HCM. AIM This study aims to investigate the relationship between the E99K ACTC1 mutation and the contractile phenotype of HCM. ***Methods***: Punch biopsies were taken from E99K patients and heathy relatives. Fibroblasts were isolated and iPSC lines were generated using sendai virus reprogramming. Corresponding isogenic controls were created for each line by correcting or introducing the mutation using CRISPR/Cas9 gene editing technology. Each isogenic pair was differentiation to cardiomyocytes and used to generate 3D engineered heart tissue to model the contractile phenotype of the disease. ***Results***: The engineered heart tissue successfully recapitulates the hypercontractile phenotype seen in patients, with increased force generation in mutant tissue (independent of beat rate). Disease constructs also recreate the blunted response to β-adrenergic stimulation, modelling the sudden cardiac death seen in patients. ***Conclusions*** : We have successfully generated a 3D engineered heart tissue model of the ACTC1 E99K mutant that recapitulates the disease phenotype. In the future we aim to use this model to screen pharmaceutical interventions that help to modulate the hypercontractile phenotype and prevent sudden cardiac death.

3D extrusion printing of sol-gel hybrids for cartilage regeneration

Francesca Tallia[1], Laura Russo[2], Siwei Li1[3], Xiaomeng Shi1[4], Peter D. Lee[4], Molly M. Stevens[1,3], Laura Cipolla[2], Julian R. Jones[1]

1 Department of Materials, Imperial College London, London, SW7 2BP, UK
2 Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, 20126, Italy
3 Department of Bioengineering, Imperial College London, London, SW7 2BP, UK
4 Research Complex at Harwell, University of Manchester, Harwell Oxford, OX11 0FA, UK

Corresponding email: f.tallia@imperial.ac.uk



Poster Number: A45

Keywords: Tissue regeneration, hybrids, sol-gel, 3D printing, scaffold

Damage in articular cartilage can occur as consequence of a trauma, excessive wear in the joint or degenerative diseases. Nowadays articular cartilage defects have an extensive impact on the society; however, cartilage is an avascular tissue with limited self-repair ability. The repair can be supported by a scaffold, which is a 3D porous temporary template that substitutes the damaged tissue and guides the regeneration of healthy tissue while bioresorbing. Successful scaffolds should: have an interconnected porosity for tissue ingrowth and nutrient diffusion; resorb at the same rate as native cartilage is repaired; match the mechanical viscoelastic properties of cartilage and maintain them over bioresorption; have a bespoke shape that matches the defect margins in order to ensure stable fixation onto the underlying bone.

Novel sol-gel silica/polycaprolactone (SiO2/PCL) hybrids with interpenetrating inorganic/organic co-networks covalently linked at the molecular level were designed to act as a single material with tailored mechanical properties and congruent degradation. It was found that the sol-to-gel transition allows the SiO2/PCL hybrid material to be a suitable ink for direct extrusion printing without the addition of binders: gelation causes a gradual increase of viscosity that, in a limited window of time, allows the viscous sol to be extruded through a small nozzle and then solidify and keep the shape on the printing bed. 3D grid-like SiO2/PCL hybrid scaffolds were successfully 3D printed, with optimised parameters in order to obtain struts and channels equal or below 200 μm. SiO2/PCL hybrid scaffolds exhibited mechanical properties similar to native cartilage, showing elastomeric behaviour with the ability to recover the deformation under cyclic loading (Figure 1). Furthermore, they were proven to stimulate the production of Collagen Type II, which is typical of articular cartilage, during in vitro cell cultures. Therefore, SiO2/PCL hybrid scaffolds have great potential for the regeneration of articular cartilage.

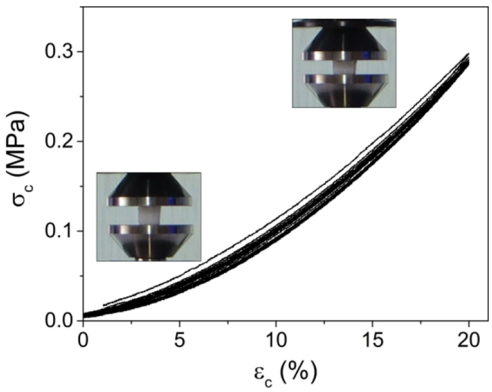


Figure 1: Cyclic loading stress-strain curves for a SiO2/PCL hybrid scaffold (10 cycles up to 20% of its original height), with photos showing as example the deformation of a scaffold going through one cycle.

Potential technologies for rehabilitation of military traumatic brain injury

Samantha L Wilson[1], Massimiliano Zecca[2,3], Matthew J Craner[4], Timothy J Hodgetts[5], David J Williams[1]

1 Wolfson School of Mechanical, Electrical and Manufacturing Engineering, Loughborough University, UK
2 Wolfson School of Mechanical, Electrical and Manufacturing Engineering, , Loughborough University UK
3 National Centre for Sport & Exercise medicine

Corresponding email: s.wilson2@lboro.ac.uk

Poster Number: B46

Keywords: healthcare manufacturing, corneal biomimetic models, toxicology models, traumatic brain injuries

Traumatic brain injuries (TBI) are heterogeneous in terms of mechanisms, pathology, severity and treatment, with widely varying outcomes. Explosive blast injuries are the leading cause of TBI amongst deployed military personnel, over 60% of blast injuries result in TBI. TBI symptoms are broad-spectrum with long-term physical, cognitive, behavioural and emotional consequences. Military injuries result in unique, clinically challenging pathologies which complicate diagnosis, classification, treatment and rehabilitation.

The aims were to: 1. Communicate clinical requirements to an engineering audience who can develop technology to meet that need with an enhanced probability of uptake by clinicians and therapists.

2. To formulate a technology strategy for improved rehabilitation of TBIs by determining the key science and technology challenges and opportunities. Specifically, to improve rehabilitation outcomes of both motor and cognitive impairments where the TBI has been sustained in a military setting.

A Loughborough University-led TBI pilot study was performed in collaboration with Royal Centre for Defence Medicine, to identify opportunities to improve and apply technologies from stroke rehabilitation and other areas to the rehabilitation of TBI, taking into account defence specific issues including blast induced neurotrauma. A broad literature study identified and established where technology, including imaging and biomarkers, bio-robotics and neuroprostheses, can assist in the diagnosis, treatment and rehabilitation strategies of military TBIs.

Eight overlapping and interrelated areas/needs were identified for further investigation. These were: Definition and classification; Insult, mechanisms and TBI injury cascades; Intervention, protection and prevention; Integrated modelling strategies to develop meaningful models; Rapid diagnosis and detection of closed-head TBIs; Biomarkers and field-deployable closed head imaging systems; Polytrauma, co-morbidities and outcomes; Personalized evidence-based rehabilitation strategies.

This work has the potential to evaluate and improve interventions and address the concerns regarding the rehabilitation of TBI military veterans for previously un-survivable conditions.

Investigating ice nucleation temperature effects on mesenchymal stem cell recovery from cryostorage

Nicholas M. Wragg[1], Alexandra Stolzing[1]

1 Centre for Biological Engineering, Loughborough University, Loughborough, LE11 3TU

Corresponding email: n.m.wragg2@lboro.ac.uk

Poster Number: A47

Keywords: Cryostorage, Expansion, Cell Engineering, Musculoskeletal

Introduction

During the cryopreservation process, cells are frozen gradually before transfer to cryogenic temperatures for long term storage. During this process, ice crystals form at nucleation sites within the storage solution. As a stochastic process, the structure of crystallisation is governed by chaos, so each time the freezing process takes place, the temperature of crystal formation and the structure changes. During crystal formulation, temperature spikes occur, linked to a change in phase, which can result in supercooling events that damage cells due to osmotic gradients and intracellular ice formation.

By controlling the ice nucleation temperature, the randomised formation effects could be curtailed potentially increasing the recovery of the cell product from storage.

Methods

Mesenchymal stem cells (MSCs) were seeded at 4500 cells/well into a 96-well plate and cultured in DMEM+10%FBS overnight. The culture medium was then replaced with growth medium+10% DMSO. A commercially available ice nucleation array (IceStart, Asymptote) was then placed into half of the 96-well plate and then the whole plate placed into a controlled rate freezing device (ViaFreeze, Asymptote). Once at -80oC the plate was removed to liquid nitrogen storage (vapour phase). Each condition was analysed using MTT, one and four days after the implementation of slow (30 minute) and fast (5 minute) thawing conditions and removal of the IceStart.

Results

The addition of IceStart moves the nucleation temperature closer to the melting point of the cryomedium. Furthermore, MTT analysis shows that IceStart Arrays enhance the viability of the MSCs significantly ($p \leq 0.05$) after just one day of culture in comparison to no-IceStart controls.

Conclusions

The addition of a known nucleation site reduces the damaging variation observed during a standard freezing process without optimisation of cryomedium and in a high throughput setting.

Committee Biographies

Dr. Derfogail Delcassian

The University of Nottingham

Derfogail.Delcassian@Nottingham.ac.uk

Derfogail is currently an EPSRC E-TERM Fellow researching biomaterials for the control of immune cell behaviour, hosted by Nottingham University and MIT. Originally, she completed an MChem with a year in Industry at the University of York, and during her time there spent a year working in the Research and Development team at GSK as an organic chemist.

In 2010 she started a PhD at Imperial College London, focusing on nanomaterials for control of T cell activation, and completed in early 2014. After this, she stayed at Imperial to complete an EPSRC Post-Doctoral Prize Fellowship focusing on nano-interfaces for immune cell behaviour, before taking on her current Fellowship at Nottingham in 2015.

Her current focus is on applying biomaterials design to the control of immune cell behaviour within tissue engineering. She is interested in developing materials and devices to manage immune cell behaviour in the transplant niche, and localised immune cell therapies for chronic auto-immune disorders.

Dr. Amanda Barnes

University of York

Amanda.Barnes@York.ac.uk

Amanda's background is in Chemistry, and she obtained her MChem and PhD, 'Tuneable Collagen and PNIPAM hydrogels for Tissue Engineering Applications' from the University of York. Her current research interests lie in the use of mesenchymal stem cells (MSC) and biomaterials for cartilage repair. Her work focuses on identifying the optimal cell population for cartilage repair by autologous chondrocyte implantation (ACI). This involves the characterisation of MSC populations for optimal repair properties and investigating co-cultures of MSCs and chondrocytes for ACI through in-vitro modelling.

Amanda also has a keen interest in the development of students and ECRs, holding the role of Employability Manager in the Biology department at York and sitting on the departmental postdoctoral society committee.

Dr. Chris Adams

Keele University

C.Adams@Keele.ac.uk

Chris has recently been appointed as Lecturer in Neuroscience at Keele University and is currently combining this with finishing his ETERM fellowship. His research has a strong neuroregeneration theme and especially in developing combinatorial therapies to effectively repair the highly complex nervous system after injury or disease. To this end, he is investigating the use of advanced implantable scaffolds for improved delivery of therapeutic cell populations and guidance of regenerating tissue and the safe genetic engineering of neural cells to enable them to release additional therapeutic factors using magnetic particles. In addition, he is examining new laboratory based models of neurological injury within which to test novel nanomedicines. This includes investigating the chick embryo as a straightforward, reductionist model of spinal injury and assessing the utility of human brain tissue slices derived from Chiari malformation patients undergoing decompression surgery as models of demyelinating disorders.

Dr. Stuart Jenkins

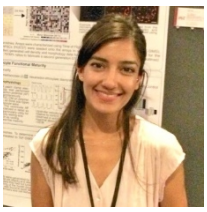
Keele University

S.I.Jenkins@Keele.ac.uk

Now a lecturer in the School of Medicine, Stuart previously gained degrees in Computer Science and Biochemistry/Neuroscience before completing a Biomedical Engineering PhD at Keele University (2013). During his PhD he developed in vitro neural culture systems to test nanoparticle-based tissue engineering of neural cell transplant populations. This encompassed genetic engineering and cell tracking applications, to promote regeneration in the brain and spinal cord.

During his PhD, he was awarded an E-TERM Landscape Fellowship by EPSRC, to test novel magnetic devices, designed by an industrial partner to enhance the utility of magnetic nanoparticles for cellular engineering. His research has highlighted the importance of the neuroimmunological component of the brain: microglia. He is currently investigating methods to evade these cells (e.g. for nanomedicine delivery), or harness their restorative potential by controlling microglial phenotype/activation to promote regeneration through immunomodulation.

Dr. Asha Patel



The University of Nottingham

Asha.Patel@Nottingham.ac.uk

Asha obtained her pharmacy degree from King's College London in 2006, achieving the MPharm award for her research into the formulation of the antifungal drug, ciclopirox. She went on to manage a team in pharmacy practice and primary care for 4 years before beginning her PhD in 2010 in regenerative medicine at the University of Nottingham. Based in the labs of Chris Denning and Morgan Alexander, she investigated the effect of surface chemistry of synthetic materials on maturity of human stem cell derived cardiomyocytes and applications in in vitro cardiotoxicity drug screening. Asha secured an E-TERM EPSRC fellowship in 2014 to begin her postdoctoral research at MIT under the guidance of Daniel Anderson, developing degradable polymers for mRNA delivery.

Dr. Richard Harrison

Loughborough University

The University of Nottingham

R.P.Harrison@Lboro.ac.uk

Rich completed his undergraduate degree in Nutritional Biochemistry and from there moved into the stem cell field with an MSc in Stem Cell Technology. He completed his PhD at The University of Nottingham investigating magnetic targeting of stem cell therapies. Over this period he developed an interest in barriers to the effective production of emerging cell therapies. He is currently interested in the manufacturing of cell therapies and cost of good modelling. In this regard, he is part of a collaborative EPSRC project investigating the challenges of manufacturing mesenchymal stem cells for cartilage therapy. This has led him to his current position as an EPSRC ETERM Landscape Fellow based at Loughborough University and The University of Nottingham investigating better ways to manufacture pluripotent stem cells.

Dr. Owen Davies

Loughborough University

O.G.Davies@Lboro.ac.uk

Owen graduated with an MRes and PhD in tissue engineering for hard tissue regeneration from the Universities of Manchester and Birmingham, respectively. He has since been awarded a personal EPSRC E-TERM Landscape fellowship at Loughborough University and an honorary visiting fellow status at the University of Birmingham's School of Chemical Engineering. His research focuses on the application of extracellular vesicles (EVs) for regenerative medicine, maintaining a particular focus on hard tissue repair. To date, he has generated evidence to show that EVs are potent inducers of stem cell differentiation. This innovative approach has already been recognised as one of the University of Birmingham's most innovative ideas (Enterprising Birmingham competition), generated an initial patent application, garnered media attention, and resulted in being awarded a highly competitive MRC Confidence in Concept grant.

Dr. Antony Herbert

University of Leeds

A.Herbert@Leeds.ac.uk

Anthony completed his Masters and Doctorate of Engineering at the University of Strathclyde, Glasgow and a Bachelor's degree in biomedical engineering at the National University of Ireland, Galway. He has always maintained a keen interest in the mechanics of biological materials such as cartilage and ligaments. From an engineering perspective, he has always found these materials are quite fascinating and understanding how biological tissues are composed and work mechanically gives insight into why they are created in the way they are. This knowledge can then be put to good use in creating replacements for these tissues should they happen to require replacement.

He was awarded the EPSRC E-TERM fellowship to continue his work on biological scaffolds for anterior cruciate ligament repair at the University of Leeds. He wants to use the knowledge he has gained so far to develop custom replacement grafts for a patient's own individual needs and to optimise how these are fixed into the body. Furthermore, he intends to rigorously assess the grafts under physiological conditions in order to develop novel metrics for assessing similar interventional devices in the future. Hence, his project is about making sure the right patient is getting the right biological scaffold for them, it's safe and that there is the right surgical strategy in place to implant it into them.

Dr. Sandhya Moise

Loughborough University

Sandhya.Moise@Nottingham.ac.uk

Sandhya graduated with a bachelor of technology degree in Biotechnology from SASTRA University, India. She went on to work on project on designing industrial scale photo-bioreactors for cultivation of marine microalgae for biodiesel production at the Department of Biotechnology, Indian Institute of Technology (IIT) Madras, India. She pursued a Master of Science degree in Cell and Tissue engineering at Keele University, United Kingdom. Following this she did her PhD at the Institute for Science and Technology in Medicine at Keele University under the EPSRC Doctoral Training Centre for Regenerative Medicine. Her doctoral research was on the characterization and application of magnetic nanoparticles to manipulate stem cell behaviour with Dr. Neil Telling and Prof. Alicia El Haj. Currently she is an EPSRC ETERM postdoctoral research fellow at University of Nottingham and a visiting fellow at King's College London. Her research focus is on identifying the most efficient delivery of the immunomodulatory potential of adult stem cells. She is assessing various biomaterials for cell encapsulation and delivery in a liver inflammation model.

Dr. Samantha Wilson

Loughborough University

S.Wilson2@Lboro.ac.uk

Samantha is a problem-led scientist comfortable working in an engineering setting. She has over 9 years of experience working in a multidisciplinary and collaborative academic research environment having completed a PhD at Keele University in Biomedical Engineering as part of an EPSRC funded Doctoral Training Centre programme. Her first (dual honours) degree was in Biology and Biological and Medicinal Chemistry and following that she was a teacher of secondary school science.

Samantha's research focuses on four aligned and reinforcing strands: healthcare manufacturing, including critical process parameters affecting cellular behaviour, alongside challenges associated with the characterisation and scale-up of cell therapies; corneal biomimetic models, including decellularised tissues as alternatives to donor tissue; toxicology models, developing animal-free and human appropriate models for industrial and pre-clinical research; military traumatic brain injuries, including evidenced based rehabilitation strategies and appropriate models specifically for use in wound healing and rehabilitative therapies.

Dr. Qasim Rafiq

University College London

Q.Rafiq@UCL.ac.uk

Qasim is currently a Lecturer (Assistant Professor) in Bioprocess Engineering at Aston University with a specific research focus on the manufacture, translation and commercialisation of cell, gene and tissue-based therapies. In his first 12 months as a Lecturer, he has established and lead the Bioprocess Engineering Research Group, a new, multidisciplinary research area within the School of Life and Health Science focusing on biomanufacture of cell, gene and tissue-based therapy production.

Since joining Aston, he has been awarded 5 research grants (Principal Investigator on 4 of them) with a total award value of ~£1M from a variety of funding sources including RCUK, InnovateUK, EU Horizon2020 and direct commercial funding. During this period, he has published 8 peer-reviewed research articles and book chapters (>15 in total) and has been invited to present his research at key cell therapy and biomanufacturing conferences in Singapore, Sweden and The Netherlands. He has been appointed to the national committee of ESACT-UK, the UK Society for Cell Culture Biotechnology where he has assumed the role of General Secretary.

He graduated with an MEng in Biochemical Engineering from University College London (UCL) in 2008 before joining as part of the first cohort of the EPSRC Centre for Doctoral Training in Regenerative Medicine at Loughborough. There he was awarded a PhD having completed his thesis on 'Developing a standardised manufacturing process for the clinical-scale production of human mesenchymal stem cells (hMSCs)' using a litre-scale stirred-tank bioreactor. The PhD was in collaboration with Lonza Cologne AG.

Following the PhD and prior to his Lectureship at Aston University, he was awarded a £250k E-TERM Landscape Fellowship to focus on 'Engineering with the cell in mind' which developed a relevant small-scale bioreactor model for hMSC microcarrier culture in addition to furthering understanding of hMSC culture through metabolomic analysis. The Fellowship was in collaboration with TAP Biosystems (now a Sartorius Stedim company). During the course of his PhD and Fellowship, he was awarded numerous oral presentation prizes including best presentation at the 1st EPSRC Manufacturing the Future conference and was shortlisted for the Malcolm Lilly award.

Dr. Ilida Ortega

University of Sheffield

I.Ortega@Sheffield.ac.uk

During Ilida's research career she has gained extensive experience working at the interface of materials and manufacturing, particularly in the manufacture, characterisation and in vitro testing of biomaterial devices for tissue engineering applications. Following her PhD at The Institute of Bioengineering at the University of Elche (Spain) she moved to the UK in order to establish her academic career. She has recently obtained a lectureship in Dental Materials and Manufacturing Science at The School of Clinical Dentistry, a post that she started on the 1st of January 2014.

During her PhD, she worked on the preparation and characterisation of nanomaterials for photothermal therapy, drug delivery applications and biomineralisation processes. In parallel to her work with nanomaterials she developed skills in polymeric device fabrication through the preparation of regenerative medicine scaffolds via manufacturing techniques including freeze-drying, microstereolithography and electrospinning. With these projects she built up expertise in scaffold manufacturing and polymer characterisation, in particular in the fabrication of biocompatible scaffolds based on polymers including polycaprolactone, polylactic acid and polyethylene glycol diacrylate. During her work at the University of Sheffield (funded initially by the Wellcome Trust prior to obtaining an EPSRC-Landscape Fellowship and subsequently her recent lectureship), she worked on the microfabrication of 3D biodegradable platforms for neural healing and corneal regeneration. Her most recent work has been focused on the fabrication of biodegradable membranes for corneal and musculoskeletal repair equipped with synthetic microenvironments emulating specific aspects of the native stem cell niche.

Notes

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