

This is a list of research projects currently available for PhD study.

For further information about possible funding opportunities for these projects please see

<http://www.materials.manchester.ac.uk/postgraduate/research/>

1. PhD Biomaterials

Age related macular degeneration (AMD) is one of the largest cases of registered blindness in the Western world. AMD is typically described as the disorder of the retina, with two known types; the wet, which exhibit neovascular formations, and the dry form, which exhibit drusen deposition under the retinal pigment epithelium (RPE) layer. Both forms have debilitating effects on vision and in many cases lead to blindness, by degrading the structure of the Bruch's membrane (BM) and depleting the function of the RPE cells. However the dry form, which makes up 90% of cases, has no known viable treatment. The use of non-degradable materials could be used to replace the BM and allow the growth of fresh RPE cells. The project will involve, fabricating the polymers, chemical characterisation, cell culture and biomechanical testing. The aim is to stimulate RPE cell regeneration and improve interaction at the biological/medical device interface. The output should be a **new medical device** for consideration by Industry for pre-clinical testing.

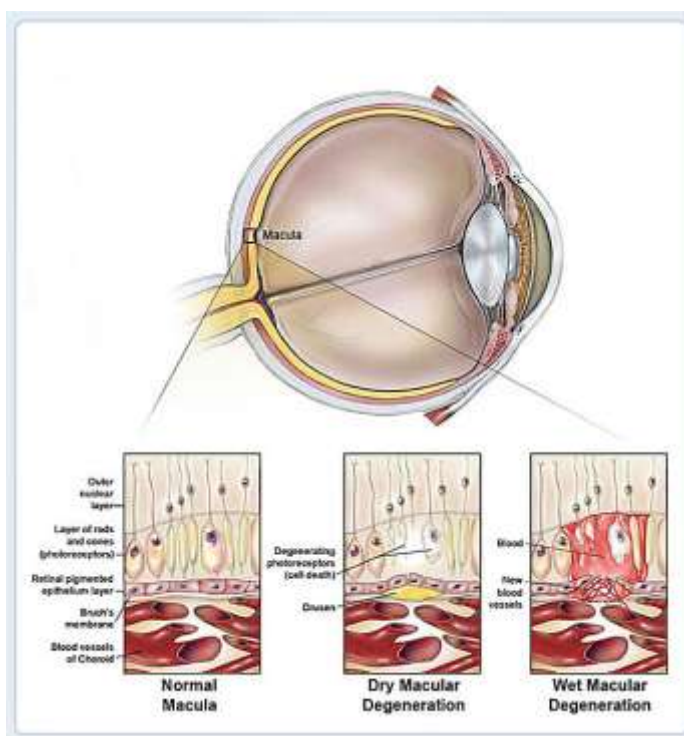


Figure 1 Comparison of the normal macula to the dry and wet forms of AMD. (Image obtained from <http://www.ahaf.org/macular>)

Supervisor: Professor Sandra Downes

2. PhD Biomaterials

Cell-matrix biology of the vascular progenitor stem cell niche

This project is focused on defining the cell-extracellular matrix (ECM) biology of the vascular mesenchymal progenitor cell (MPC) niche, and on exploiting our specialist knowledge of the cell surface-matrix interface to develop effective new MPC-based cardiovascular therapies.

MPCs offer powerful cardiovascular therapeutic opportunities, given their accessibility, their potential to differentiate along vascular lineages without provoking a host immunological response, and their paracrine contributions to the repair microenvironment. However, the osteogenic potential of MPCs can also lead to serious vascular complications such as aberrant calcification. Moreover, many fundamental aspects of their biology remain poorly defined and present a major obstacle to their exploitation in cell-based therapies. Therefore, comprehensive definition of the cell surface receptors and extracellular matrix of MPCs from different anatomical sites (bone marrow, adipose tissue, Wharton's jelly), correlated with their stemness and differentiation potential *in vitro* and *in vivo*, are an essential prelude to their effective therapeutic application in cardiovascular repair.

During the first three years, our focus is to define the molecular and cellular basis of the MPC perivascular niche, and to begin to establish how this microenvironment controls their fate. Future Centre research will exploit this specialist knowledge of the MPC niche to direct vascular remodelling. Our initial clinical target is the application of MPCs to optimise tissue-engineered small-diameter vessels for vascular access and bypass grafts, taking advantage of advanced *in vivo* imaging to assess MPC behaviour and graft function. In parallel, we will direct MPCs to contribute to revascularisation of ischaemic cardiac and peripheral tissues.

To define the MPC pericellular niche, we will draw on our major international strengths in cell-matrix biology and adult MPCs, and in proteomics, phosphoproteomics and glycomics. Once the cell surface receptors, ECM molecules and glycosaminoglycans expressed by MPCs *in vitro* and *in vivo* have been delineated, the mechanisms whereby they control cell fate will be examined in functional studies such as single or combinatorial lentiviral strategies to modulate expression or test functional mutants, and validated shRNAi technology to modify glycosaminoglycan sulphation patterning. The significance of MCP receptors and ECM molecules in maintaining pluripotency, or in directing cellular differentiation, will then be validated using *in vivo* *Xenopus* and mammalian models. Our established *Xenopus* tadpole tail regeneration model, which encompasses renewal of major vessels and capillary networks alongside muscle, skin and nerves, allows real-time assessment of how MPCs and the cell-matrix environment contributes to vascular regeneration. The spatial context of cell-matrix molecules in pluripotent MPCs, and following recruitment and differentiation, will be mapped using state-of-the-art electron microscopy (Polaris 300kV FEG EM) and 3D reconstructions, both *in vivo* and *in culture*.

Supervisor: Dr Cathy Merry

3. PhD Biomaterials

Development of Functional Peptide Scaffolds for Tissue Regeneration Applications

Hydrogels and more generally “soft solids” are used in the biomedical field in a wide range of applications from tissue engineering to drug delivery. Peptidic hydrogels in particular have recently attracted significant attention as the numerous recent reviews published show [Chem. Soc. Rev., 2010, Issue 9 Chem. Soc. Rev., 2010, Issue 9]. Peptides are short amino acid sequences that form the building blocks of biological molecules (e.g.: proteins). The *de-novo* design of β -sheet forming peptide and the exploitation of their fibrilisation properties have led to the creation a new range of biomaterials [Saiani *et al*; *Soft Matter*; 193; 2009 & Guilbaud *et al*. *Langmuir*; 11297; 2010 & Tang *et al*.; *Langmuir*; 9447; 2009].

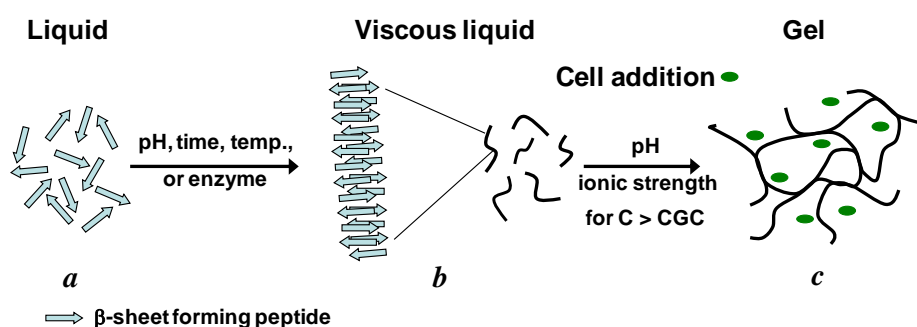


Figure 1: Schematic representation of the self-assembly process of peptide-responsive polymer conjugates

We have designed in our laboratory a range of β -sheet peptide based scaffolds (Figure 1) able to sustain the culture of a variety of cell lines. In this project we will develop functionalised scaffold that allow specific cell behaviour to be triggered e.g.: proliferation, production of extracellular matrix. The cell culture work will be carried out in 2D and 3D. In addition injectable scaffolds will also be developed and the effect of injection on cell viability and culture will be investigated. The ultimate aim being to create injectable scaffold for tissue regeneration the main focus being cartilage repair.

Supervisor: Dr Alberto Saiani

4. PhD Biomaterials

Design and characterisation supramolecular polymers matrices for composite application

Supramolecular polymers that are based on small units that self-assemble through complementary hydrogen bonds have attracted considerable attention in recent years. In this project this concept will take this concept further and in collaboration with Dr. A. Wilson (Leeds University) supramolecular block copolymer akin to polyurethanes will be synthesised and characterise to

create supramolecular thermoplastic materials. Due to their hydrogen bonded nature these materials have been shown to possess low melt viscosity which makes them excellent candidates as matrices for nano and fibre composite and therefore their use for these specific applications will be investigated. The characterisation of these novel materials will be performed using a variety of techniques including; FTIR, SAXS, WAXS, TEM, DSC, TGA and DMTA.

Supervisor: Dr Alberto Saiani

5. PhD Biomaterials

Designing nano-structured responsive hydrogels for biomedical applications

Hydrogels and more generally “soft solids” are used in the biomedical field in a wide range of applications from tissue engineering to drug delivery. Peptidic hydrogels in particular have recently attracted significant attention as the numerous recent reviews published show [*Chem. Soc. Rev.*, 2010, Issue 9 *Chem. Soc. Rev.*, 2010, Issue 9]. Peptides are short amino acid sequences that form the building blocks of biological molecules (e.g.: proteins). The *de-novo* design of β -sheet forming peptide and the exploitation of their fibrilisation properties have led to the creation a new range of biomaterials [*Saiani et al. Soft Matter*; 193; 2009 & *Guilbaud et al. Langmuir*; 11297; 2010 & *Tang et al. Langmuir*; 9447; 2009]. In addition the conjugation of these peptides to responsive polymer has recently opened the possibility to create responsive hydrogels for the topical delivery of drugs and/or biological signals (figure 2).

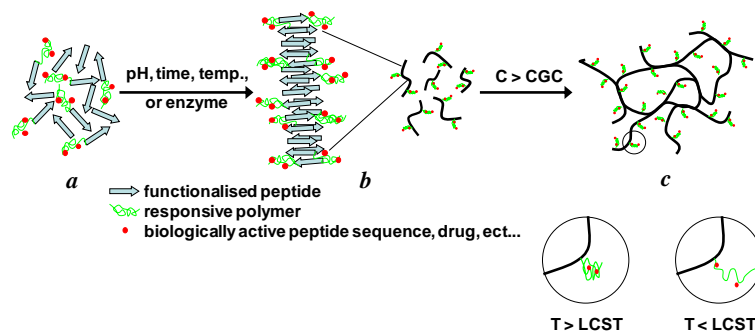


Figure 1: *Schematic representation of the self-assembly process of peptide-responsive polymer conjugates*

In order for these materials to be used in a controlled manner their properties need to be tailored to the desired application (e.g; stiff gel for cartilage tissue engineering, soft gel for injectable / sprayable systems for topical drug delivery). The control of the physical properties of these materials, in particular mechanical, is achieved through the control of their nano-structure (e.g. fibre dimensions and properties, network mesh size). In this project we will focus first of a set of simple octa-peptides and investigate their self-assembling properties. We will then use known conjugation methods to conjugate these peptide to responsive polymers (e.g.:PNIPAAm) to create responsive hydrogels [*F. Stoica et al. Chem Comm*; 4433 ; 2008] with controlled mechanical and physical properties. For this purpose a number of characterisation techniques will be used including: micro-

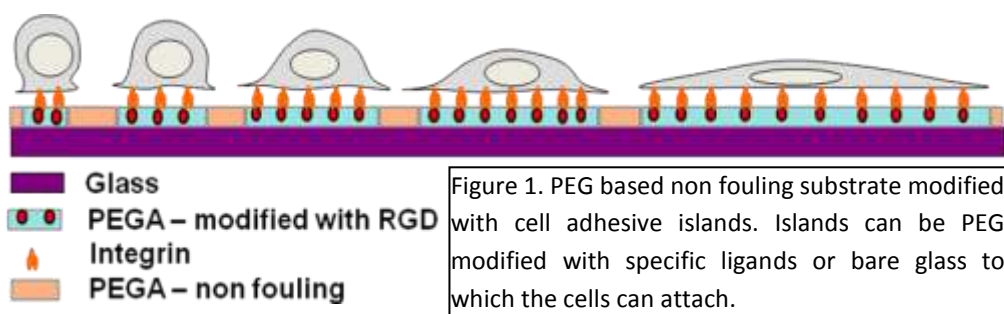
differential scanning calorimetry (μ -DSC), atomic force and electron transmission microscopy (AFM & TEM), rheology, small angle X-ray and neutron scattering (SAXS & SANS) and infrared spectroscopy.

Supervisor: Dr Alberto Saiani

6. PhD Biomaterials

Micropatterned substrate control of cell shape and effect on protein and gene expression

Patterned surfaces will be developed by photolithography to precisely control cell shape and 3-dimensionality and the effects on cell behaviour will be determined. Controlling and understanding cell shape will provide important new insights for the molecular design of new biomaterials as well as further the understanding of fundamental processes in cells. Adhesive islands will be prepared in a range of sizes from 5 to 80 μ m in diameter. Square islands will be prepared with corresponding areas (to compare round to sharp corners – differences in cytoskeletal arrangement and cell signalling well documented [1]). Photolithography can routinely fabricate micro-features of $\sim 1\ \mu$ m on substrates and this will be used to generate our micropatterns. Silanisation chemistries will be used to immobilise different functionalities e.g. PEG on glass substrates which has excellent resistance to protein and cell adhesion, thus providing an ideal inert background [2]. Adhesive islands will be bare glass (i.e. non specific) and also specific cell adhesion ligands including peptides and sugars (Figure 1). Cell responses to the prepared graded geometry will be quantified in terms of cell shape using confocal microscopy, interferometry and image analysis. Protein production and candidate marker gene expression will also be analysed. Cells studied will be human osteoblasts and chondrocytes and also stem cells. Osteoblasts and chondrocytes have a specific morphology in vivo which is challenging to maintain in vitro, therefore this study will determine the effect of cell morphology on aspects of bone and cartilage tissue formation. This will provide information on the strong relationship between cell morphology and cell behaviour, typically observed during processes such as healing, development, progression of diseases including cancer. The main context of this research is for biomaterials/tissue engineering and understanding how biomaterial surfaces can further control cell behaviour and tissue formation.



[1] Kilian KA, Bugarija B, Lahn BT, Mrksich M. Geometric cues for directing the differentiation of mesenchymal stem cells. PNAS 2010;107: 4872-4877.

[2] Zourob M, **Gough JE**, Ulijn RV. A micro-patterned hydrogel platform for chemical synthesis and biological analysis. *Advanced Materials* 2006;18:655-659.

Supervisor: Dr Julie Gough

7. PhD Biomaterials

Multi-composition bioceramics via combinatorial chemistry and their analysis via high-throughput cell culture techniques

The focus of this project is the exploration of a wide range of cations for the synthesis of new bioceramics which may have potential for bone repair and bone tissue regeneration. This is to allow the development of new materials not necessarily based on the calcium or titanium standards. We will utilise combinatorial robotics (based at UCL with Prof Julian Evans) to produce arrays of ceramic pillars of differing compositions (Figure 1) and then use high-throughput robotic facilities (based at Manchester) to analyse osteoblast and mesenchymal stem cell responses. The objectives are as follows: 1. Preparation of zirconias with different stabilizers: Combinatorial source of oxides. 2. Mechanical testing of multi-sample materials. 3. Autoclave testing for degradation. 4. Identification of bone-forming compositions using Thermo Scientific Momentum platform and robotics to perform multiwell deposition of cell cultures (osteoblasts and mesenchymal stem cells) and assays.

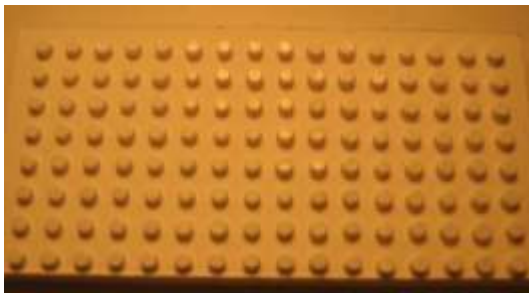


Figure 1. A 25x50 mm alumina plate with pillars; each pillar can have a different composition; droplets of cell culture medium can be positioned on each pillar and retained in a controlled atmosphere.

Supervisors: Dr Julie Gough, Dr Sarah Cartmell, Professor Ping Xiao

8. PhD Biomaterials

Self-assembled peptide gels for intervertebral disc tissue engineering

Disorders of the intervertebral disc cause low back pain, resulting in disability, limitation, and economic loss affecting 70-85% of people at some time in life. For severe disorders and degeneration of the IVD, removal and subsequent spinal fusion is the main surgical procedure. This has many disadvantages and therefore tissue engineering and regeneration strategies are being developed. Surfaces can further control cell behaviour and tissue formation. This project focuses on the development of self-assembled peptide hydrogels for intervertebral disc (IVD) tissue engineering, in particular the central nucleus pulposus (NP) region. The physical properties of these hydrogels combined with the nanofibrous architecture are proposed to mimic the extracellular matrix of the NP.

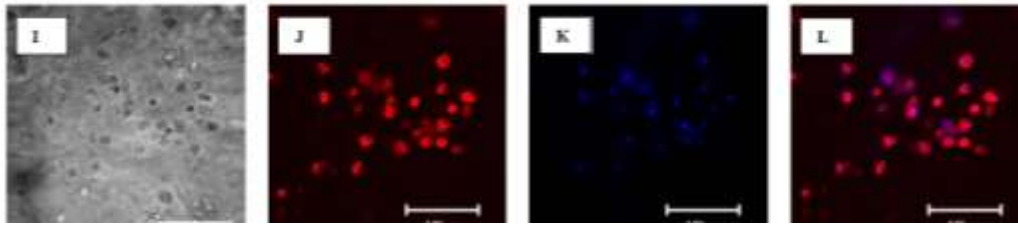


Figure 1. Fluorescence microscopy of NP cells grown in Fmoc-FF/Fmoc-GG peptide gels.

Fmoc gels (Figure 1) and also octapeptide gels, initially based on FEFEFKFK and FEFKFEFK compositions will be the focus. Variations in amino acid sequences will be explored and their effect on the physical properties of the gels determined. Characterisation will be performed using TEM, cryoSEM, FTIR and oscillatory rheology.

NP cells will be cultured within the gels and their viability, proliferation and matrix production analysed using immunocytochemistry, confocal microscopy and biochemical assays.

Effects on gel stiffness and NP cell matrix production will be determined. Addition of specific bioactive ligands and effects on nanofibrous architecture and cell responses will be explored.

Supervisors: Dr Julie Gough, Dr Alberto Saiani

9. PhD Biomaterials

A Study of Cationic Polymer Particles for Enzyme Responsive Microgels

On-demand and reversible swelling and macroscopic gelation of aqueous microgel dispersions under constant conditions is not yet possible. It is the objective of our EPSRC funded collaborative project with the University of Strathclyde to construct microgel particles functionalised with enzyme-responsive peptide derivatives to trigger swelling or de-swelling in response to enzymes under constant, aqueous conditions for the first time. This project will involve construction of a new series of amine-functionalised, cationic, microgel particles for this purpose as well as a study of their responsive properties.

Supervisor: Dr Brian Saunders

10. PhD Biomaterials

DOUBLE CROSSLINKED MICROGELS AS INJECTABLE SCAFFOLDS FOR INTERVERTEBRAL DISC REPAIR

A major problem encountered during ageing is the degradation of the intervertebral disc (IVD). The IVD contains a hydrogel membrane termed the nucleus pulposus (NP). A degraded NP is compressed and this leads to accelerated wear and eventually incapacity. In this project the feasibility of using double crosslinked intelligent microgel particles as a structural support capable of facilitating repair

of damaged / worn portions of the NP will be investigated. A microgel particle is a crosslinked latex particle that is swollen in a good solvent. The approach to be used here is to prepare a concentrated microgel dispersion that is fluid in one state and then to trigger a fluid-to-gel transition using external stimuli. They will then be double crosslinked to provide long term structural support.

Supervisor: Dr Brian Saunders

11. PhD Biomaterials

Tailoring the morphology of hybrid polymer composites for application in solar cells

Hybrid-polymers solar cells offer considerable long-term potential to provide low-cost renewable energy. Hybrid quantum dot (QD)-polymer solar cells offer a number of important advantages over conventional solar cells. However, their power conversion efficiencies (PCE) are relatively low. These low PCEs are due in large part to poor control of the QD phase morphology within the QD-polymer film that forms the photoactive layer. We have recently shown that the morphology of the QD phase can be controlled by addition of difunctional ligands. This project will build on that work with the aim of producing optimum morphologies for PCEs within hybrid polymer composites.

Supervisor: Dr Brian Saunders

12. PhD Biomaterials

Use of statins for bone tissue engineering

It has been recently demonstrated that statins (widely used cholesterol lowering drugs) have significant effects on bone turnover. This project will be furthering data we have already obtained in optimising a controlled release system of statins using degradable polymers for effective local delivery to orthopaedic sites for treatment of diseases such as osteoporosis. The mechanism of effects of statins on the local tissue environment will also be analysed.

Supervisor: Dr Sarah Cartmell

13. PhD Biomaterials

Use of mechanical forces to direct mesenchymal stem cell differentiation

It has been widely documented that cells respond to mechanical forces. However, little is understood about the effects of mechanical forces on the activity, in particular differentiation, of mesenchymal stem cells. This project will investigate the use of mechanical force application (tensile strain and shear stress) in 2D and 3D situations for tissue engineering applications.

Supervisor: Dr Sarah Cartmell

14. PhD Biomaterials

Ligament tissue engineering

This project will investigate the use of novel degradable, elastic fibres for mesenchymal stem cell guidance for ligament tissue engineering applications. Cells will be cultured on fibres for guidance purposes. Cell seeded fibres will then be loaded in dynamic conditions using a BOSE biodynamic instrument to provide daily 10% strain regimes to promote ligament differentiation.

Supervisor: Dr Sarah Cartmell