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Biomaterials
Discovery



Engineering and
Physical Sciences
Research Council

Next Generation Biomaterials Discovery Report 2019

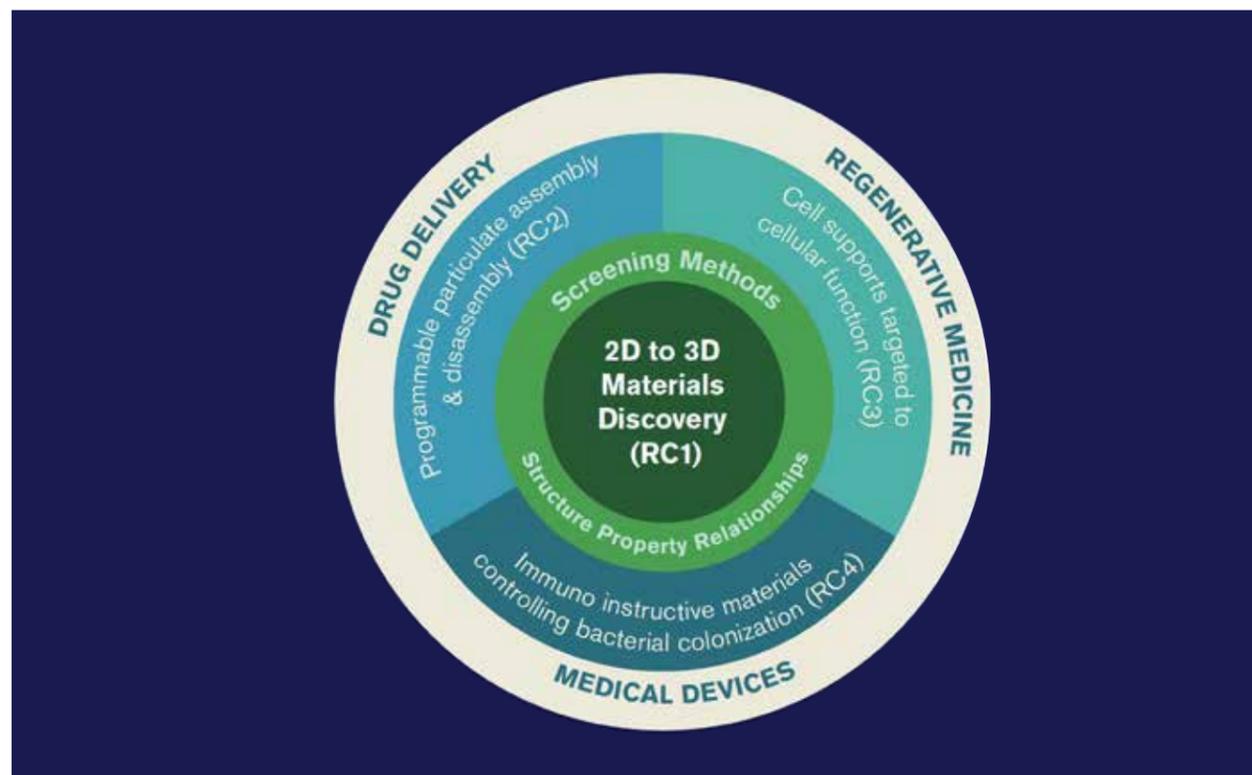
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Cover image:
Jeni Lockett and
Ana Da Silva

The Next Generation Biomaterials Discovery Programme Grant was launched in 2015 with the goal of discovering new biomaterials. The project is based around screening large and diverse polymer libraries to identify bio-instructive materials for medical devices, stem cell manufacture, cell delivery and targeted drug delivery.

Reducing medical device associated infections is a key element in the fight against antimicrobial resistance, a global challenge recognised as a priority by the UN, the WHO, and the UK government, and is also predicted to rival cancer in human and financial cost by 2050 if left unchecked.



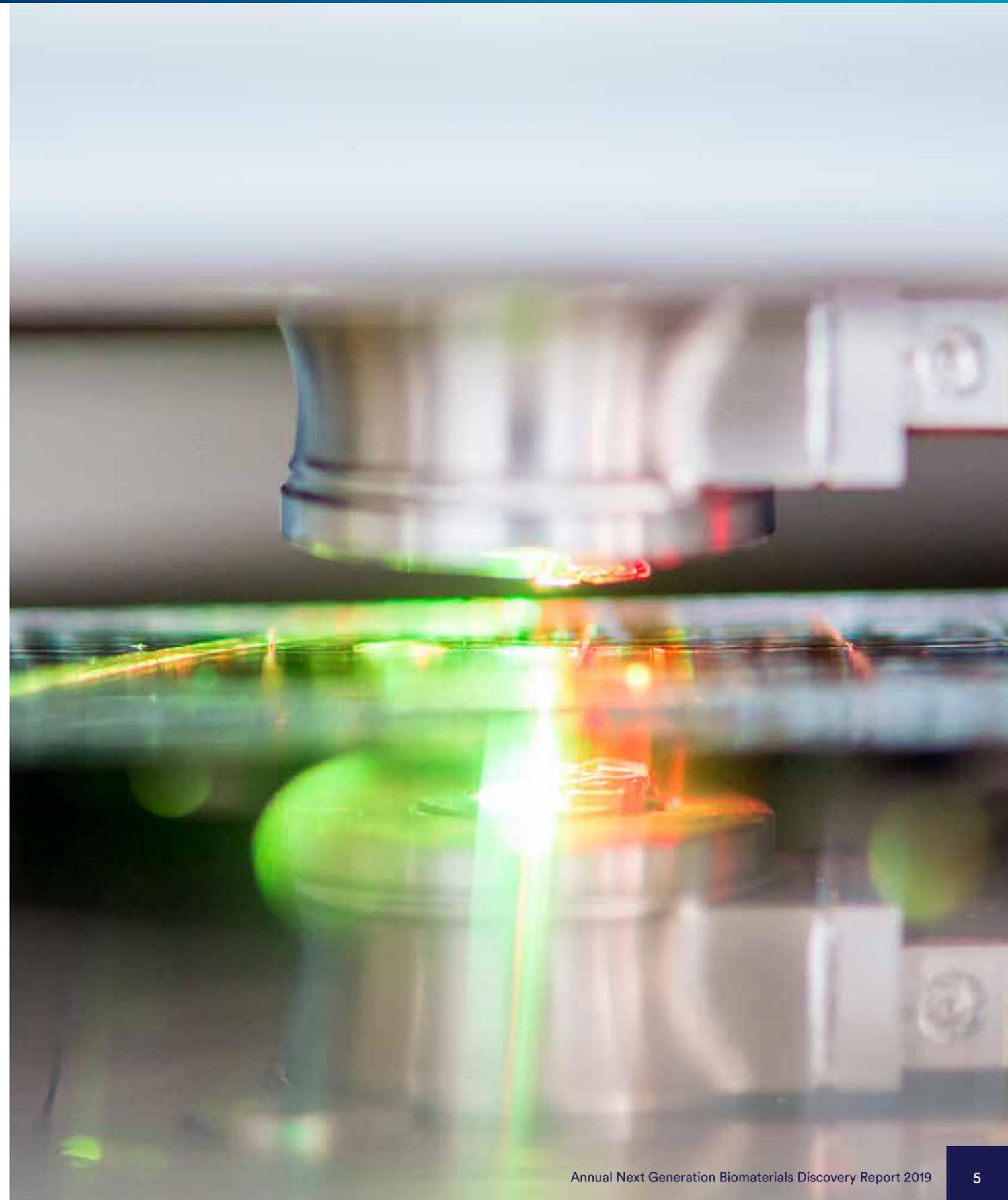
2019 has been a productive year for the grant, with large scale outreach projects such as the Royal Society Summer Science Exhibition and long term components of the project reaching the point of publication.

As we move into the final year of the grant we are completing work for dissemination by publication, conference presentation, filing patents, and exploiting our findings in partnerships with industry and through further grant funding. We will be holding an event at BIOCITY, Nottingham to engage with small and medium sized enterprises. A large number of our PhD students will be completing their PhDs and post-doctoral researchers moving on to new positions.

Research challenges overview

The grant is divided into four research challenges.

1. Moving from two-dimensions to three-dimensions material discovery methods
2. Systems based advanced drug delivery
3. Advanced materials for 3D stem differentiation and regenerative medicine
4. Advanced materials for medical devices



Materials for medical devices: better immune responses and lower infection rates



Manuel Romero



Ana Da Silva

How micro-scale topographical patterns influence bacterial attachment

A high throughput method was used to assess bacterial adhesion/attachment on 2,176 distinct micro-topographies (TopoChip)¹, using Gram-negative (*P. aeruginosa*) and Gram-positive (*S. aureus*) pathogens commonly associated with medical device-centred infections². Based on these results, a predictive model to identify key surface parameters and topographical patterns and their pro- and anti-attachment properties has been developed. Remarkably, a single strongly predictive descriptor was found, which was able to accurately predict both *P. aeruginosa* and *S. aureus* attachment to, and biofilm formation on, the micro-topographies.

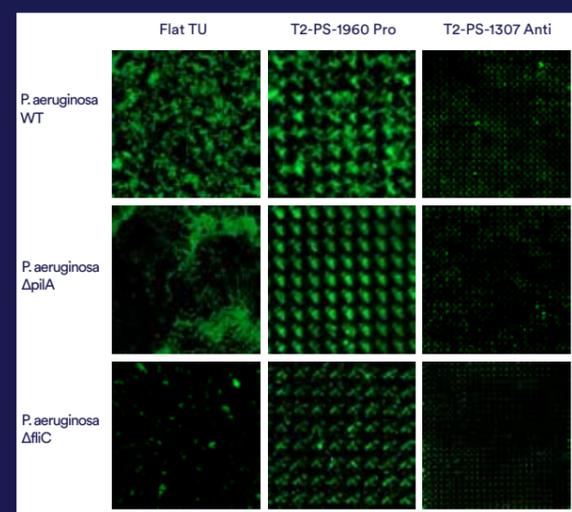
Further work provided preliminary insights into bacterial responses to biofilm resistant topographies. This new knowledge has broad applications where bacterial biofilms are a problem in medical device centred infections and more broadly in the marine biofouling and in the water, oil and food manufacturing industries.

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Figure 2

Representative images showing *P. aeruginosa* WT, Δ pilA and Δ fliC mutants attachment to flat, T2-PS-1960 and T2-PS-1307 TUs after 4 h incubation under static conditions on an oxygen plasma etched polystyrene topochip. Scale bar: 50 μ m.



Dr Laurence Burroughs

Development of the chemotopo chip screening platform

Advanced biomaterials are essential for realising the full potential of future medical devices and for production of emerging regenerative cell-based therapeutics. However, the combined influence of topography and material chemistry upon cell response has been poorly characterised to date. The ChemoTopoChip platform allows for high-throughput combinatorial chemistry and microtopography screening, facilitating the identification of chemistry-topography combinations able to control cellular phenotype.

A total of 2 designs of silicon master moulds have been produced for the ChemoTopoChip to date containing topographies based on human immortalised mesenchymal stem cell (hiMSC) morphology¹ and human macrophage² and bacterial cell response.³ Each ChemoTopoChip formed from these masters allows for screening of up to 35 chemistries in combination with 35 microtopographies to produce 1260 unique combinations

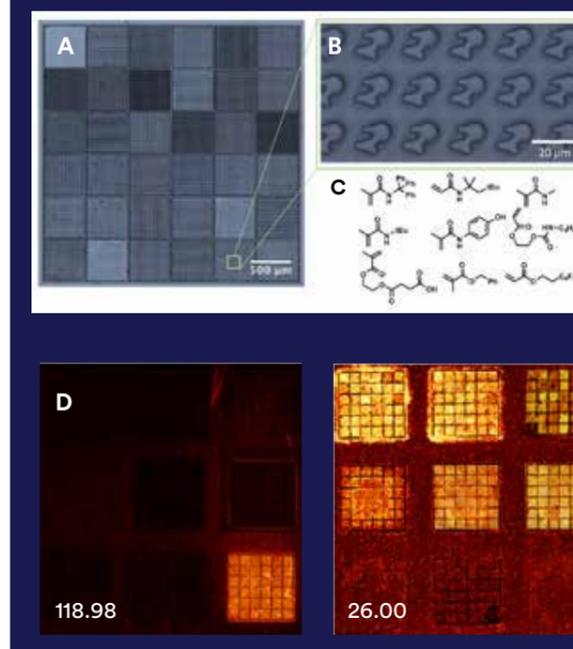
The ChemoTopoChip has been used to identify bio-instructive chemistry-topography combinations capable of polarising macrophages to pro- or anti-inflammatory phenotypes and others that direct hiMSC differentiation towards the osteoblast lineage. Surface chemistry and topography were found to equally influence human macrophage polarisation and hiMSC differentiation, with synergistic effects noted for certain topography-chemistry combinations. Analysis of the hiMSC and human macrophage datasets has highlighted a range of novel chemistry-topography combinations with promise for future applications and development using in vivo models of fibrosis and infection.

Predictive modelling of hiMSC and macrophage datasets has been used to identify aspects of features that hold promise for future biomaterials development and highlight the great potential of the ChemoTopoChip approach.

Future work will focus on bacteria and bacteria/macrophage co-culture as ChemoTopoChip also show promise as a strategy to control immune cell response to medical devices and reduce associated infections.

Figure 1

- Image showing ChemoTopo unit layout (walls of 30 μ m height are used to separate each individual Topo unit);
- Example Topo unit
- Example monomers printed on a ChemoTopoChip section;
- ToF-SIMS images showing chemistries from



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Adam Dundas



Asalan Latif

Development of microfluidic particle preparation methods for influencing response of fibroblasts

Fibroblasts are the most common cells of connective tissue in animals and have been shown to play an important role in both wound healing processes, and fibrotic capsule formation around implants.

This work is focused on controlling the differentiation of fibroblasts to myofibroblasts, as this is indicative of fibrosis and can potentially be regulated using material surface chemistry to aid wound healing.¹ Polymer microarrays identified two distinct chemistries that either promote or suppress fibroblast attachment and behaviour (phenotype). These chemistries have been synthesised into polymer surfactants to enable the fabrication of 3D polymer microparticles with surface decorated with the active functionalities.⁵

The surfactants were used to successfully form emulsions in a microfluidics set-up with 1,6 hexanediol diacrylate (HMDA) as the core material which led to the production of monodisperse particle populations seen in Figure 1.

By using time of flight secondary ion mass spectrometry (ToF-SIMS) it was possible to characterise the surface chemistry of produced particles to confirm that THFuA and EGPEA were both present on the surface. This was compared to polymer particles that had been made without any surfactant to see localized changes on the particle surface. Following production, the particles were tested for the ability to modulate fibrotic responses in human skin fibroblasts. Particles were shown to be non-toxic and able to suppress or accelerate fibroblast response depending on the surface chemistry present on the microparticles. This was monitored by observing changes in cell attachment, proliferation and fold change in gene expression of cytokines as shown in Figure 2.

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Figure 1:

c) Secondary Electron Microscopy image of polymer particles produced with a THFuA-co-mPEGMA surfactant with a size of $60.7 \pm 1.9 \mu\text{m}$ (coefficient of variation (CV) = 3.0%) d) SEM image of polymer particles produced with a EGPEA-co-mPEGMA surfactant with a size of $59.8 \pm 1.6 \mu\text{m}$ (CV = 3.0%).

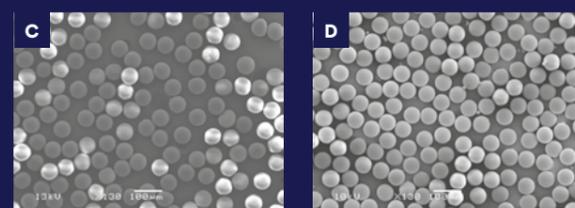
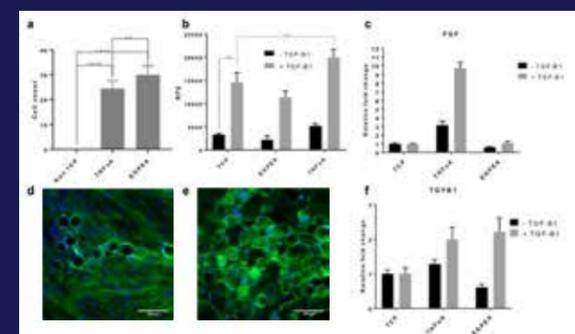


Figure 2:

a) Fibroblast attachment on polymer MPs showing significantly higher attachment to EGPEA particles. b) Fibroblast proliferation on polymer MPS in comparison to flat tissue culture plastic (TCP). c) FGF gene expression relating to cell proliferation showing a significant fold increase with THFuA particles d,e) THFuA/EGPEA MPs respectively on confluent layer of fibroblasts Blue: cell nuclei green: cytoskeleton. Results shown are from two independent experiments with three technical repeats each. f) TGFβ1 gene expression showing an increase in expression for both MPs compared to TCP.



Ana Da Silva

In vivo assessment of topographies

Biomaterial surface topography and chemistry influence extends further than just bacteria, but can also affect cellular immune cells such as macrophages, which are key factors in how a body can respond to biomaterials. Using polymer microarrays, the in vitro response of macrophages to acrylate and methacrylate polymers have been investigated, as well as macrophage attachment and differentiation using TopoChips.^{1,2}

TopoChips incorporating pro- and anti-attachment topographies were implanted subcutaneously in infected mice and their immune response was evaluated, whereupon a reduced immune response to the anti-attachment topographies was observed. (Figure 3).

Based on this work with single chemistry TopoChips³, a library has been created containing 35 micro-topographies in combination with 35 key chemistries, and will be used to investigate and understand synergistic effect of features on bacterial attachment and host immune responses. Thus, screening on this platform will allow us to determine whether the combination of topography and chemistry will facilitate the discovery of materials with the desirable anti-inflammatory, pro-healing bacterial biofilm resistant properties. These results will be evaluated using data analysis and machine learning algorithms and are anticipated to generate strong predictive models for the development of novel anti-biofilm materials.

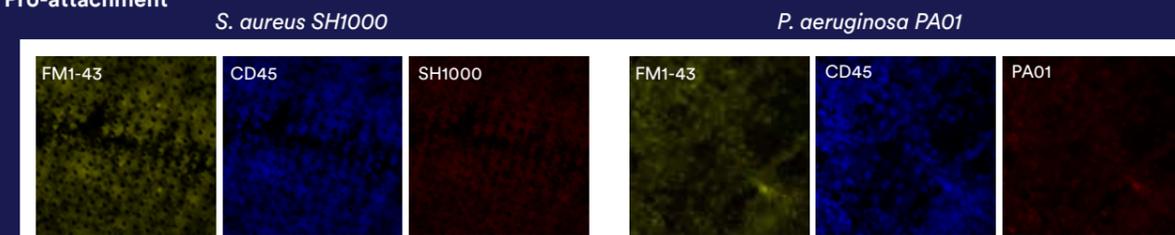
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Figure 3

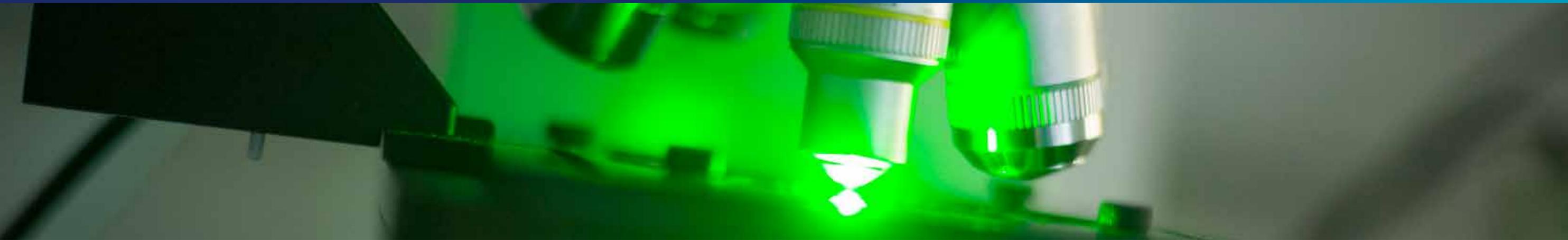
S. aureus SH1000 and *P. aeruginosa* PA01 attachment to pro- and anti-attachment scaled-up topographies on polyurethane after in vivo infection for 5 days. FM 1-43 was used to measure total biomass, CD45 was used to identify leucocytes, and specific antibodies were used to identify *S. aureus* and *P. aeruginosa* respectively. Scale bar: 20 μm.

Pro-attachment



Anti-attachment





Le Ma



Matthew Vassey

3D archichip – exploring the relationship between material geometry and chemistry on immune cell responses using two-photon printing

Biomaterials are often developed in order to restore function to diseased or damaged tissues, but following the implantation of biomaterials in vivo, a host's reaction usually includes inflammation, a foreign body reaction (FBR), and fibrous capsule development which results in implant failure.¹ These reactions are commonly due to the activation of immune cells (such as monocytes and macrophages) in the local microenvironment and play a significant role in implant biocompatibility.²

This research focuses on developing a high throughput screening approach to study the effect of structure size, geometry and complexity on phagocyte interactions and responses. By using two-photon lithography (2PL) we have been able to create 3D micro-structures with sub-micron features and intricate shapes that are impossible to create using other techniques. A wide range of 3D structures and geometries have been created, allowing efficient screening of phagocyte cell responses on a range of material chemistry that we call the ChemoArchiChip, which can hold 9 different chemistries in a variety of structured geometries.

Polymer chemistries were selected based previous studies, along with a range of simple and complex 3D geometric structures based on their biological relevance to macrophage biology, print resolution and biocompatibility. These selections were printed onto the ChemoArchiChips in arrays of features of varying dimensions using two photon lithography with different chemistries (Figure 2).

Monocytes were incubated on the ChemoArchiChip for 3 days, before being fixed, processed and analysed. Each 3D structure was independently imaged using confocal microscopy to observe the cell interactions with surface structures, before being quantified using custom analysis image software. Initial results show that complex, biocompatible structures can drive the attachment of monocytes, with spiked and polyhedron structures specifically promoting monocyte attachment. Some cells were also observed to completely remodel their morphology and cytoskeleton as part of their interaction with the 3D structures.

Systematic studies are ongoing, with a focus on understanding the effect of different geometries and chemistries on cell processes including; differentiation, cellular polarisation and morphological changes.

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Figure 1

Schematic of 2PL printing process development.



Figure 2

Illustration of 3D ArchiChip high throughput screening format.

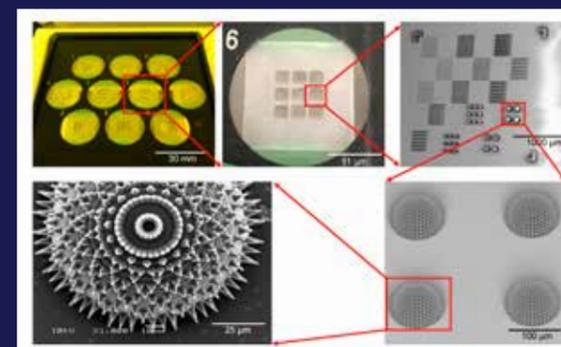
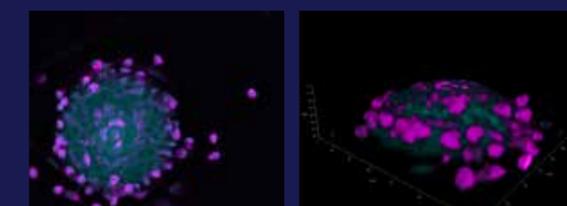


Figure 3

Confocal microscopy of macrophage attachment to 3D surface structures. Left panel – Top view maximum intensity projection from Z-stack of primary macrophages (magenta) and 2PL hemisphere structure (grey) and (right panel) a 3D rendered image of the same hemisphere highlighting cell-structure interactions. Scale bar = 20 microns.



Andrea
Alice Konta

Two-photon polymerization (2pp) 3D printing of new biodegradable polymers for ocular therapy

The aim of this project is to produce new biomaterials in order to expand the library of available materials for this technique, and to use these new biomaterials to produce a biomedical device capable of long-term drug delivery for wet-Age Related Macular Degeneration (AMD), where the current treatment is monthly injections of anti-VEGF molecules. 2PP (two – photon polymerization) is a high-resolution 3D printing technique that can create complex structures at the micro and nano scale with a great degree of design freedom, porosity, and topology. However, the lack of available biomaterials is holding the technique from reaching its full potential (1).

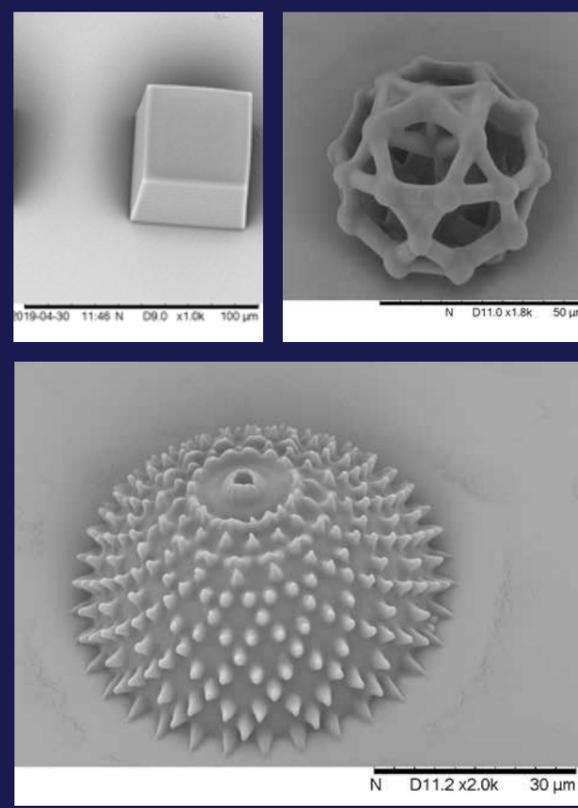
A new biomaterial (named APTMC) has been trialed at a range of molecular weights, with different concentrations of solvent, and printed using a variety of printing parameters. In addition, various geometries have been printed to show that the new polymer is capable of being printed in complex structures

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Figure 5

Cube, bucky ball and hemisphere with spikes printed with 50%wt APTMC + 50%wt PGDA.



Valentina
Cuzzucoli Crucitti

Design, synthesis and application of a novel bioactive surfactant library as a tool for the production of chemically functionalised microparticles

Polymeric microparticles are 3D structures with numerous potential healthcare applications including tissue engineering, diagnostics and drug delivery. Our research focuses on new “biologically active” surfactants suitable for use in the production and formation of microparticles (mps) as surfactants currently available often cannot be fully removed from the produced mps, resulting in alterations of the surface chemistry, leading to implications in biological applications.

In addition, topography of mps have also demonstrated effects on cell and bacteria surface attachment.¹ As a consequence, it is important to move from the design of 2D to 3D structures in order to have a deeper understanding on the interaction of cells with their immediate extracellular environment and, consequently, derive more realistic biological models/assays that mimic real conditions.²

Scanning electron microscope (sem) was used to calculate sizes of the mps as well as observe their topography, and how this was altered and influenced by a variety of new surfactants. To demonstrate how the surfactant is located at the surface of the particles, time of flight secondary ion mass spectrometry (tof-sims) was used. These techniques showed that bespoke functionalized surfactants for polymeric mps can be manufactured with specific targeted surface chemistry, and be tested on the 3D scale, which was not previously possible.

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Dara
O'Brien

Renewable epoxy/amine oligomers from terpenes with synergistic antifungal activities

Compared with antibacterial treatments, finding fungal-specific agents is challenging, partly because of the eukaryotic nature shared by both the fungal pathogens and their hosts.¹ The global fungicide market is now worth more than \$7 billion, with diverse fungi considered undesirable, be it in terms of human and animal pathogens, food spoilage, or the deterioration of materials.² However, the development of new antifungal agents has encountered numerous challenges, including antifungal resistance.³ Synergistic combinations of agents may offer a pragmatic approach to this problem, as evolution of resistance to more than one agent is much slower than with a single one.² These combination therapies allow for the development of potent new formulations without the need for specific new agents, and can be facilitated by repurposing known antifungals.³ Additionally, synergistic combinations enable lower amounts of active agents to be used, lessening concerns surrounding non-specific toxicity, and cost.^{2,3} The overall aim of this study has therefore focused on the synthesis of new, renewable materials with suitable properties for use in synergistic antifungal treatments.

So far, two new synergistic combinations with antifungal activity have successfully been identified, against the human pathogen *C. albicans*, as well as *T. virens*. We have achieved this by having repurposed known antifungal agents and coupling them with a new epoxy/amine oligomeric material. This was demonstrated using growth inhibition assays, checkerboard assays, and disk diffusion assays. In the case of both fungi, the addition of the oligomers was found to reduce the MIC of the respective antifungal agent.

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Nishant Singh

Dual bioresponsive antibiotic and quorum sensing inhibitor combination nanoparticles for treatment of pseudomonas aeruginosa biofilms in vitro and ex vivo

Many debilitating infections result from persistent microbial biofilms that do not respond to conventional antibiotic regimens. A potential method to treat such chronic infections is to combine agents which interfere with bacterial biofilm development together with an antibiotic in a single formulation. This research focuses on a new bioresponsive polymer formulation derived from specifically modified alginate nanoparticles (NPs) in order to deliver antibiotics (in this instance, ciprofloxacin - CIP) that will disrupt mature *Pseudomonas aeruginosa* biofilms.

The new polymer formulation was engineered for dual-action release of antibiotic and quorum-sensing inhibitor (QSI), designed for the low-pH regions of a biofilm. When tested in a biofilm model this concomitant release significantly reduced the viability of the biofilm compared with antibiotic treatment alone.

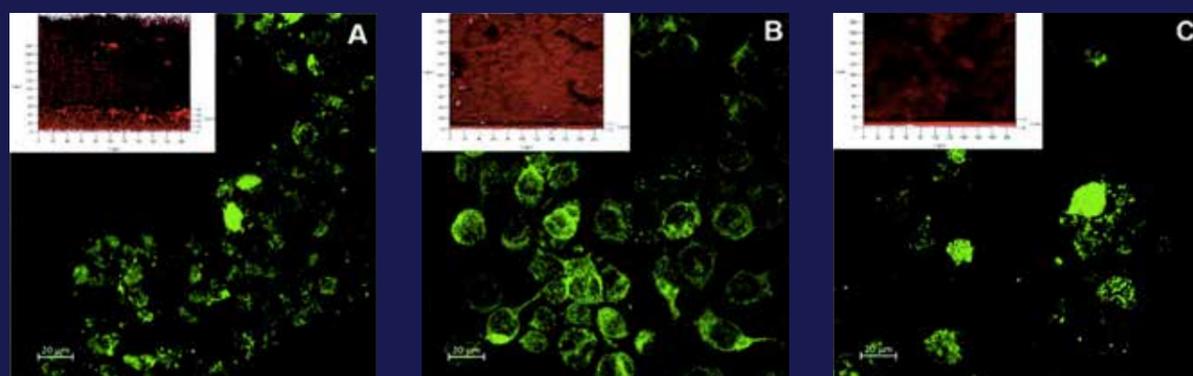
In addition, the new polymer formulation was shown to penetrate deeply into *P. aeruginosa* biofilms. Finally, the formulation was tested in both a 2D keratinocyte and a 3D ex vivo skin infection model. The dual-action bio-responsive QSI and antibiotic release effectively cleared the infection in the latter, suggesting considerable promise for combination therapeutics to prevent biofilm formation as well as effectively killing mature *P. aeruginosa* biofilms.

References

Nishant Singh, Manuel Romero, Alessandra Travanut, Patricia F. Monteiro, Elena Jordana-Lluch, Kim R. Hardie, Paul Williams, Morgan R. Alexander and Cameron Alexander; Dual bioresponsive antibiotic and quorum sensing inhibitor combination nanoparticles for treatment of *Pseudomonas aeruginosa* biofilms in vitro and ex vivo; *Biomater. Sci.*, 2019, 7,4099

Figure 1

2D Keratinocyte Infection Model. HaCat cell monolayer infected with PAO1-N for 20 h (A) and treated with ALGQSI (B) or ALGALD (C) NPs



Kiril Kalenderski

A first-in-man pilot study of bacterial resistant polymers to reduce catheter associated urinary tract infection (CAUTI)

Indwelling urethral catheters are one of the leading causes of hospital acquired infections, as well as the most commonly implanted medical device associated infection with 17.5% of patients in 66 European hospitals, and 23.6% in 183 US hospitals.^{1,2} The significant morbidity and mortality resulting from catheter-associated urinary tract infections (CAUTIs) are a major clinical problem, which is associated with a large economic burden for healthcare facilities, increasing the cost per hospital admission in the US by US\$749-1007.^{3,4}

Bacterial biofilms and their associated crystalline deposits are frequently described as causes of long-term indwelling urinary catheter failure.⁵ Following bacterial attachment to the catheter surface, biofilms and mineralization develop, which can result in complications associated with CAUTIs, such as catheter blockage and incontinence.⁶

Coating catheter devices with a co-polymer of ethylene dicyclopentenyl ether acrylate (EGDPEA) and di(ethleneglycol) methyl ether methacrylate (DEGMA), has resulted in resistance to bacterial attachment in in vitro and in vivo assays.⁷

This research has demonstrated the impact that this novel antibacterial coating for urinary catheters has had upon the reduction of biofilm formation on catheter devices and associated urinary tract infections within a clinical environment (Figure 1).

Catheter devices were received for analysis from various hospital facilities, following the catheterization of patients which had undergone a selection of urinary tract procedures. The samples were sectioned and analysed for biofilm biomass accumulation. Confocal fluorescence microscopy was incorporated to generate values for accumulation of biofilm along the catheter devices. Figure 1 exhibits the accumulated data over 51 samples, and the pronounced

higher biofilm biomass associated with each section of the uncoated catheter devices, in comparison to the devices coated with the EGDPEA/DEGMA co-polymer. This data has supported a granted efficacy claim for Camstent Ltd who license the polymer and developed the catheter to CE mark approval in collaboration with The University of Nottingham. The same device is under consideration for FDA approval. A full-scale clinical trial to quantify the effect of CAUTI in a tightly controlled patient cohort is being planned by Camstent Ltd.

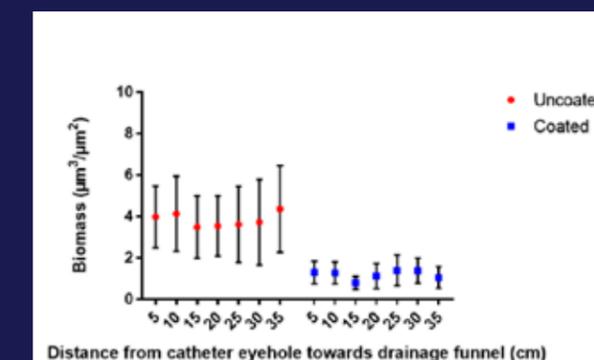
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Figure 1

Biofilm and mineral biomass accumulated on uncoated vs coated catheter samples

The mean biofilm biomass on coated and uncoated clinical catheter samples, calculated from confocal microscope images via comstat/ImageJ, for each 5 cm section, 5-35 cm, from the balloon end to the drainage funnel end of the catheter device. 51 catheters have been analysed, 28 coated and 23 uncoated. The data is normalized by the square root of the time each catheter spent in a patient. Error bars represent the mean with the standard error.





Amanda K. Pearce

Patrícia F. Monteiro

Effects of polymer 3D architecture, size and chemistry on biodistribution and drug delivery in vitro and in orthotopic triple negative breast cancer models

A drug delivery particles' performance is reliant on key parameters such as size, shape and underlying chemistries, which govern ultimate performance in vivo. Responsive particles are desirable for triggered drug release and clearance from the body, achievable through architecture change and biodegradation in the body to control in vivo fate.

This research looks at polymers both in a 'materials discovery' context, and also as therapeutics for Triple Negative Breast Cancer (TNBC), which remains a disease with unmet treatment needs.¹ We have focused here on materials based around the poly (2-hydroxypropylmethacrylamide) (pHPMA) platform, as related polymers have been evaluated in human clinical trials.²

We have investigated the effects of size, shape, architecture and reductive degradation on the performance of 2-hydroxypropyl methacrylamide (HPMA)-based copolymers using in vitro and in vivo models. Polymers have been synthesised with architectures varying from linear, hyperbranched, star and micellar-like, all based on core HPMA building blocks (Figure 1).

Current results indicate that when orthotopic tumour models dosed over specific schedules, selected polymers reduced tumour volume to a greater extent than free doxorubicin in a highly aggressive orthotopic breast cancer model.

The data shows it is possible to direct materials of the same chemistries into different cellular and physiological regions using changes to architectures, and the work overall provides valuable new insight into how nanoparticle size, architecture and programmed degradation can be tailored to elicit specific biological responses for drug delivery.

References:

1. W. T. Khaled, S. Choon Lee, J. Stingl, X. Chen, H. Raza Ali, O. M. Rueda, F. Hadi, J. Wang, Y. Yu, S.-F. Chin, M. Stratton, A. Futreal, N. A. Jenkins, S. Aparicio, N. G. Copeland, C. J. Watson, C. Caldas and P. Liu, *Nature Communications*, 2015, 6, 5987
2. R. Duncan and M. J. Vicent, *Advanced Drug Delivery Reviews*, 2010, 62, 272-282

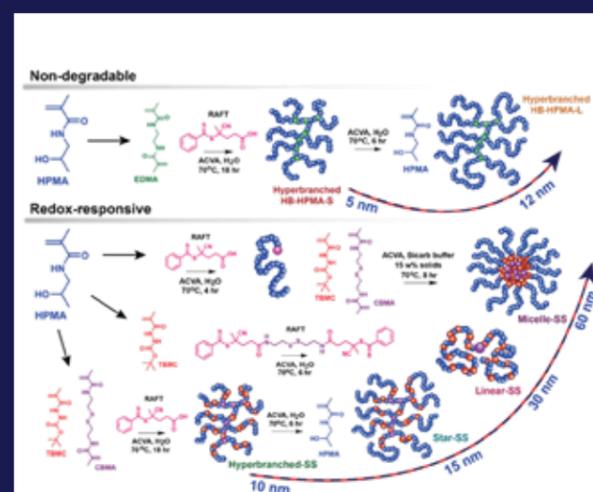
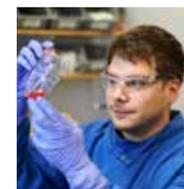


Figure 1

Parallel synthetic routes were developed using Reversible Addition Fragmentation Chain Transfer Polymerization (RAFT) of HPMA for the synthesis of materials with both varying architectures and increasing physical sizes. Hyperbranched through to micelle structures resulted in particles of a size range 5 nm - 60 nm, maintaining the same surface chemistries. Materials featuring disulfide bonds are indicated by SS in the nomenclature.



Robert Cavanagh



Thais Abelha

Varied architecture polymer pro-drug nanoparticles with efficacy in vitro and in an orthotopic triple negative breast cancer model

Triple Negative Breast Cancer (TNBC) is an aggressive disease with a typically poor prognosis. Polymer drug delivery systems offer a chance to improve therapeutic window for some existing potent but poorly-tolerated chemotherapy drugs.¹ The goal of this research is to expand on the range of biomaterials that can be utilised as drug carriers, and in particular their biodistribution and drug release properties, while retaining chemistries as close as possible to polymers already translated for non-TNBC cancer therapies.

Amphiphilic block co-polymers were synthesized in block ratios and monomer arrangements to enable assembly into nanoparticles with different sizes and architectures. These materials were based on components already in clinical use, or known to be biodegradable, and retained the same fundamental chemistry.

Three candidate polymers were taken further for therapeutic evaluation, as these were found to generate nanoparticles which were highly colloidally stable in aqueous suspension, and of size ranges (80-120 nm) deemed suitable to test for penetration into model cancer tissues and in tumours in vivo. Promising formulations have been generated with efficacy in an aggressive TNBC model. Future work will concentrate on coupling these formulations with functionality to exploit radiation-induced changes in cancer cell biology, as ~ 60% of patients receive first-line radiotherapy in breast cancers. In addition, formulations will include targeting ligands and agents to couple with ultrasound to improve accumulation and penetration within tumours.

References:

1. R. Duncan, *Journal of Drug Targeting*, 2017, 25, 759-780





Alessandra Travanut

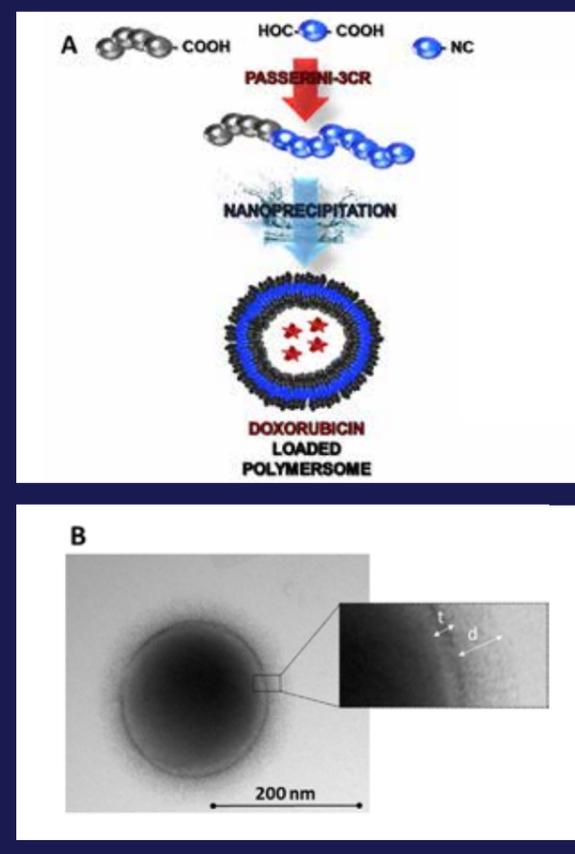
Passerini multicomponent reaction based polymeric self-assemblies: versatile biocompatible and biodegradable carriers for triple negative breast cancer treatment

This research aims to develop versatile 'platform' chemistries for biodegradable drug delivery systems with high drug-loadings via the Passerini multicomponent reaction (Passerini-3CR). The end application goal is to improve the treatment of triple negative breast cancer (TNBC), which has poor prognosis and no effective therapies.

Polyesters/amides diblock copolymers were synthesized by performing the Passerini-3CR leading to amphiphilic, biodegradable and biocompatible polymers, which, in water, self-assemble into polymersomes (P1 and P2). Interestingly, these polymers were well tolerated in triple negative breast cancer cell line MDA-MB-231 and the non-cancerous human mammary epithelial cells MCF10A. The uptake of the Passerini polymersomes was found to be concentration dependent in MDA-MB-231 cells (Figure 2). These polymers could be exploited as drug delivery systems, since these are able to encapsulate (~ 5% w/w), release and exploit the toxic effect of doxorubicin. In addition, chemistries are in place for conjugation of drug molecules via pH-responsive linkers, enabling dual-control of release profiles.

Figure 1

(A) Schematic representation of the synthesis and formulation of the Passerini amphiphilic di-block copolymers into polymersomes. (B) Transmission Electron Microscopy image of Passerini polymersome P1; entangled hydrophobic layer thickness t , hydrophilic PEG brushes d .



Patricia Monterio

Micellar-like nanoparticles with specifically-placed reductively-cleavable cross-links to overcome multi-drug resistance in tumour spheroids of triple negative breast cancer

This research aims to develop a 3D multicellular tumour spheroid model, to better mimic triple negative breast cancer cell (TNBC) interactions, therefore increasing clinical relevance. In addition, to assess the efficacy of docetaxel (DTX)-loaded micellar-like nanoparticles against the developed TNBC 3D multicellular tumour spheroids model, including the ability to overcome the multi-drug resistance (MDR) of the TNBC tumour spheroids.

A 3D TNBC cell culture model was developed for assessing the cytotoxicity, penetration and efficacy of reduction-responsive crosslinked and un-crosslinked micellar-like nanoparticles, which were developed to exploit the inherent hypoxia reported in solid tumours for site-specific drug release¹ (Figure 1). These polymers were based on functional monomers similar to those in the clinically used Genexol formulation,² but with additional responsive cross-links to ensure stability in transit in the body but in situ tumour activated breakdown.³

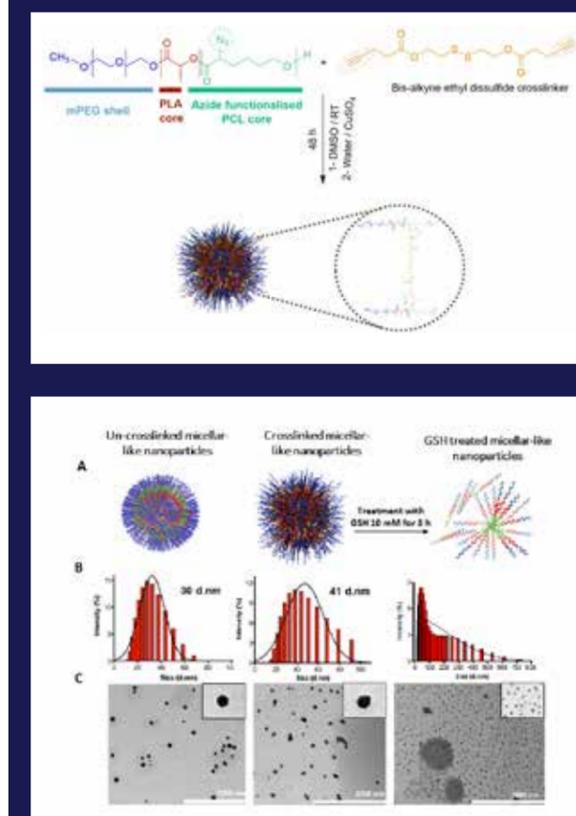
These materials and models show promise in the development of effective anti-TNBC formulations. Current work is building in fibroblast and other tumour stroma cells into the 3D models, and establishing metabolomics assays to evaluate further the mechanism of action of the polymers in complex tissue mimics.

References

1. M. Bazan-Peregrino, R. C. Carlisle, R. Hernandez-Alcoceba, R. Iggo, K. Homicsko, K. D. Fisher, G. Hallden, V. Mautner, Y. Shen and L. W. Seymour, Human Gene Therapy, 2008, 19, 873-886
2. T.-Y. Kim, D.-W. Kim, J.-Y. Chung, S. G. Shin, S.-C. Kim, D. S. Heo, N. K. Kim and Y.-J. Bang, Clinical Cancer Research, 2004, 10, 3708-3716
3. M. Gulfam, T. Matini, P. F. Monteiro, R. Riva, H. Collins, K. Spriggs, S. M. Howdle, C. Jerome and C. Alexander, Biomaterials Science, 2017, 5, 532-550

Figure 1

Reduction-responsive polymer nanoparticles, designed to be activated by TNBC hypoxia, showing (left) synthetic route and schematics (A), DLS measurements (B) and TEM (C) of the nanoparticles evaluated for this study.





Mahetab Amir



Francesco Pappalardo



Marta Alvarez-Paino

Differentiation by design: tailoring microparticle topography and elasticity for bone regenerative engineering

Microparticles have gained significance over the past few decades. In addition to their use as drug delivery systems, microparticles have been utilized as cell carriers, scaffolds for tissue engineering strategies, in bioinks for three-dimensional bioprinting and for large-scale expansion of anchorage-dependent cells¹. Understanding the correlation between microparticle-based cues and associated cellular responses is critical to elucidate underlying mechanisms of cell response and achieve predictable outputs for translational applications. Tailoring surface properties of microparticles to direct cell differentiation provides the opportunity to transform these cell delivery systems from passive mechanical supports to functional components of stem cell expansion and regenerative therapies.

Textured PLA microparticles were produced, and by varying emulsion settings microparticles of two key surface topographies were produced: dimpled 'golf ball'-like and angular morphologies (Figure 1).

In the absence of osteoinductive supplements, cells on dimpled microparticle displayed significantly higher levels of osteocalcin relative to smooth microparticles. Metabolomics revealed that the dimpled microparticles-cultured samples were significantly separated from the smooth microparticles group, with PCA scores and orthogonal partial least-squares discriminant analysis models indicating that metabolic state of hMSCs cultured on dimpled microparticles was changed relative to smooth ones.

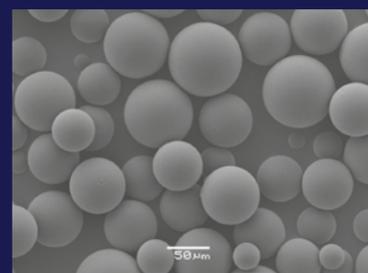
Surface elastic properties of gelatin methacrylate (GelMA) microparticles and their ability to induce the differentiation of hMSCs towards specific lineages was also explored. Low polydispersity, spherical GelMA microparticles were produced and studied, and the ease of production of GelMA in a microparticle format shows the possibility to translate findings into the 3D perspective. This constitutes a novel translational approach using microcarriers with fine-tuned mechanical properties towards high-throughput generation of differentiated progenitors, highlighting its applicability in tissue engineering and regenerative medicine.

Figure 1

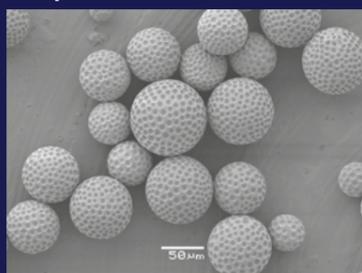
SEM images of microparticle designs, including smooth microparticles and textured surfaces with varying microscale features (scale bar=50 μm).

Surfaces with microscale features

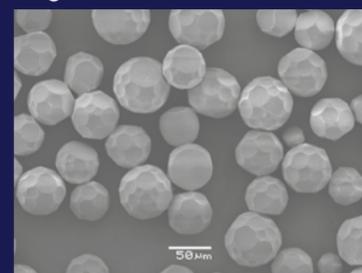
Smooth



Dimpled



Angular

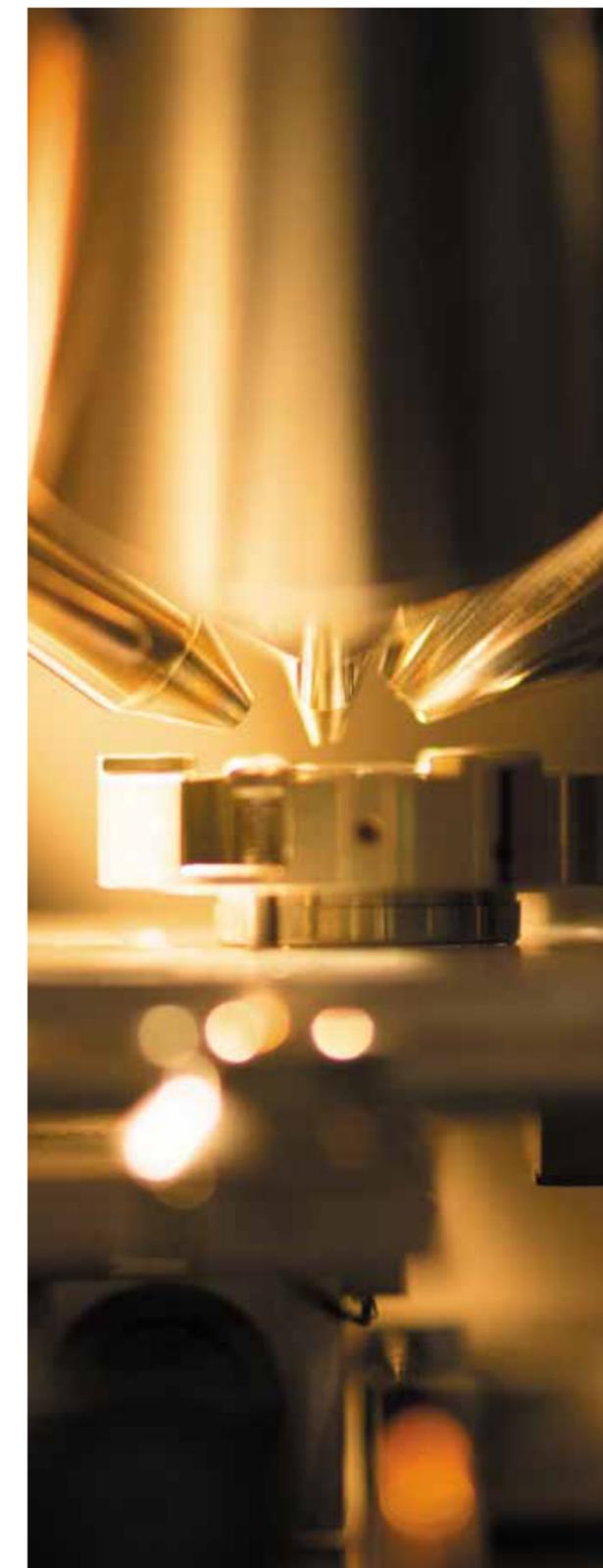
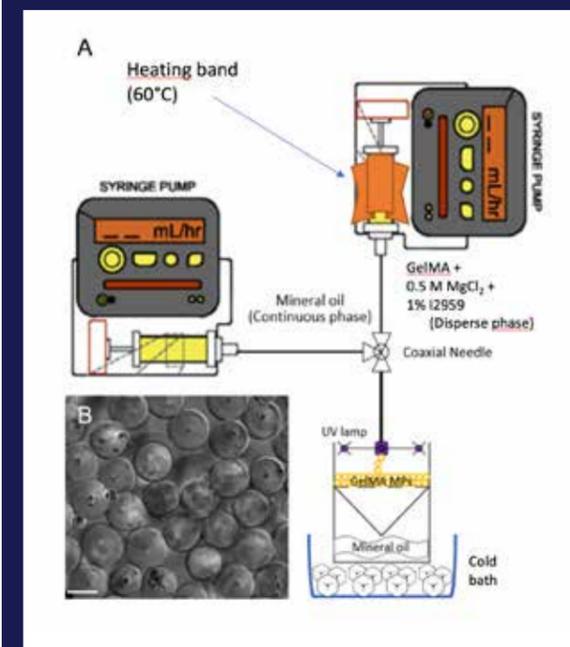


References:

1. Neto, MD., Oliveira, MB. & Mano, JF. (2019) "Microparticles in Contact with Cells: From Carriers to Multifunctional Tissue Modulators"; Trends Biotechnol 37 (1011-1028)

Figure 1

Setup for production of GelMA microparticles using the co-current flow system.





Aishah Nasir

Discovery of novel polymer substrates for xeno-free long-term culture of human pluripotent stem cell expansion

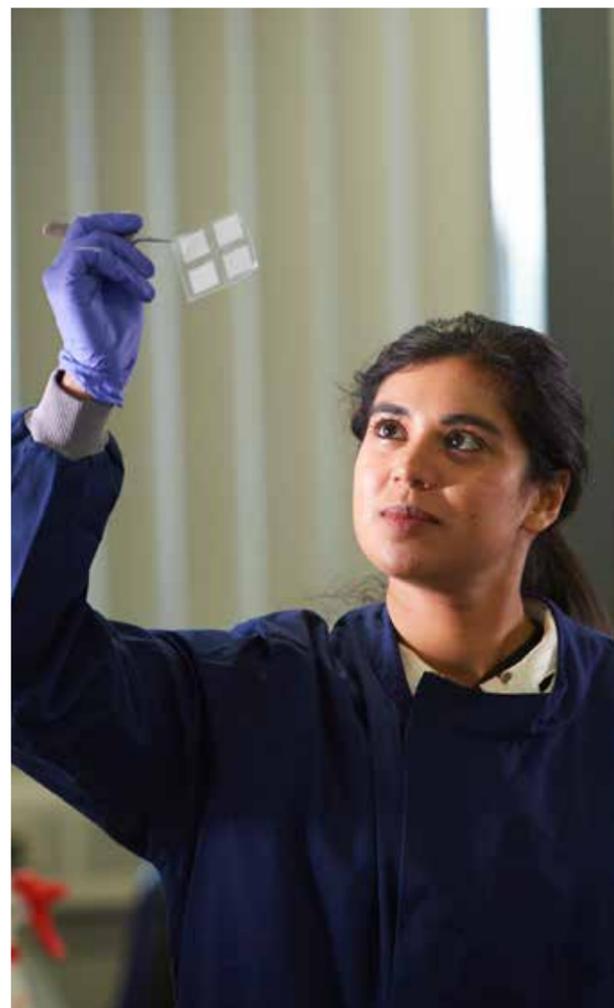
Human pluripotent stem cells (hPSCs) have the ability to self-renew and differentiate into the three germ layers to form any adult tissue type.¹ Their versatility and capability of providing a rapid turnover of cells make them excellent tools for disease modelling and precision medicine. In recent years, in vitro hPSC culture has moved away from the use of animal-derived feeder layers to fully-defined xeno-free culture systems. High-throughput screening platforms have been successfully utilised to identify alternative growth substrates.² However, the most successful commercially available peptide based surface, includes biological substrates which increases costs and creates problems in the scaling up process.

The first-generation microarray developed for this research consisted of 284 chemically diverse monomers pin-printed onto poly(2-hydroxyethyl methacrylate) (pHEMA) coated spots (figure 1i). REBI-PAT hPSCs were seeded on the arrays for 24hrs, fixed, and stained. From this initial screen, 24 materials with low to high REBI-PAT hPSC attachment with broad OCT4 expression were selected and mixed pairwise to form a second generation array of 576 unique materials (figure 2ii). Polymer structural properties and protein adsorption analyses are being explored using computational modelling, and mass spectrometry strategies including liquid extraction surface analysis-tandem mass spectrometry (LESA-MS/MS) respectively to further explore these interactions.

9 co-polymer surfaces that supported hPSCs beyond 24hrs were polymerised in situ onto 2D tissue-culture plastic (TCP) 96 well-plates using UV irradiation. Co-polymers that supported and maintained high hPSC attachment consisted of diacrylates mixed with monoacrylate, corroborating with the highest performing co-polymers from the second-generation co-polymer screen.

References:

1. Thomson, J.A., et al., Embryonic stem cell lines derived from human blastocysts. *Science*, 1998. **282**(5391): p. 1145-7
2. Jin, S., et al., A synthetic, xeno-free peptide surface for expansion and directed differentiation of human induced pluripotent stem cells. *PLoS One*, 2012. **7**(11): p. e50880



The highest performing co-polymer mixed with butyl acrylate (TCDMDA:BA) was selected for long-term culture based on its scalability to laboratory-scale plastic ware and ability to maintain colonies up to 72hrs. Surface characterisation using time-of-flight secondary-ion mass spectrometry (ToF-SIMS) and atomic force microscopy (AFM) imaging of in situ UV polymerised TCDMDA:BA coatings on TCP showed the presence of both compounds with concentration of one material dispersed within another material creating a poly-TCDMDA-blend-BA surface.

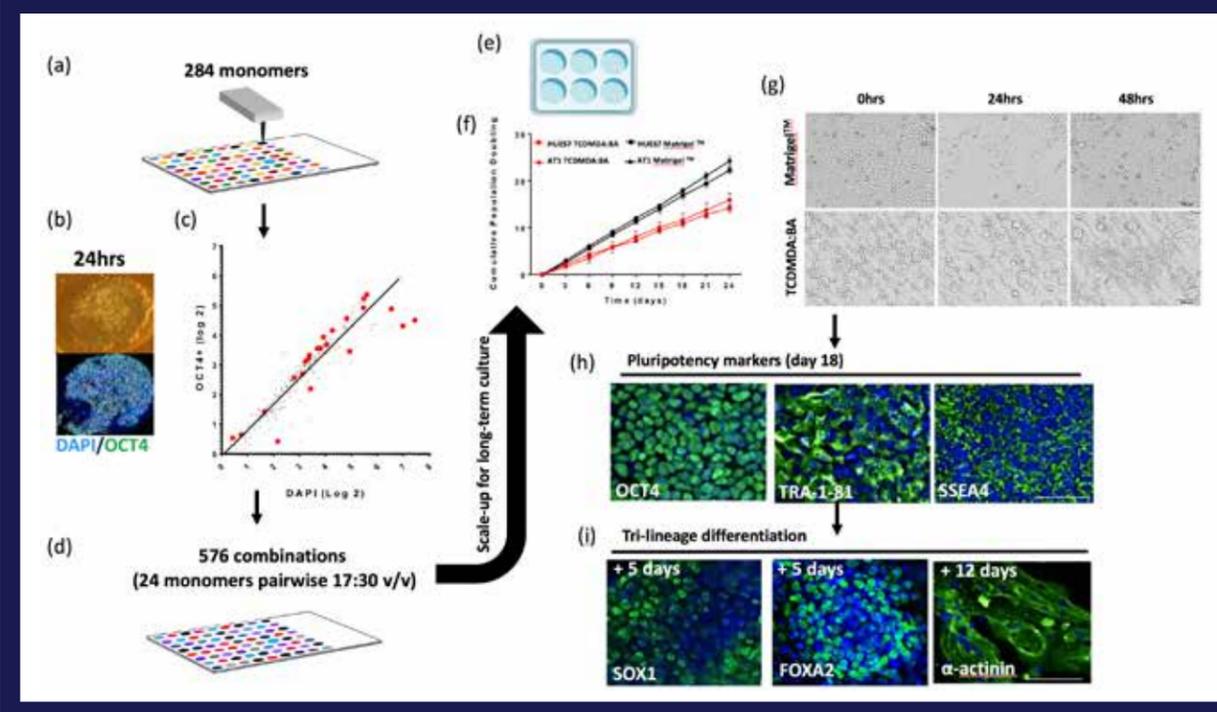
This study provides the first characterisation of a fully defined, xeno-free (using E8 medium), scalable polymer surface for hPSC research. The poly-TCDMDA-blend-BA coating has great potential to provide a cost-effective way of producing GMP-grade hPSCs without the need for expensive biological substrates.

Figure 1

Identification of polymeric surfaces for long-term hPSC culture.

(a) Contact printing was used to fabricate polymer microarrays on a glass slide coated with pHEMA. A first generation of 284 chemically diverse monomers (commercially available and photocurable) were screened with hPSCs cultured in E8™ medium for 24hrs. (b) Polymer spots (9 replicates/polymer) were ranked by OCT4+ hPSC attachment using CellProfiler (Broad Institute; ver 2.2.0) open source imaging software. (c) Materials with diverse OCT4+ hPSC attachment (red spots) were selected for combinatorial pairwise mixing. (d) Materials were mixed pairwise (70/30% v/v) to produce 576 unique materials which were ranked by OCT4+ hPSC attachment (24hrs).

(e-g) hPSCs (AT1 and HUES7) were cultured on tissue culture plastic (TCP) 6 well plates coated with Poly-TCDMDA-blend-BA (UV in-situ polymerisation) or Matrigel™. (f) Growth comparison was calculated by cumulative population doublings of hPSCs AT1 and HUES7 over 8 serial passages (72hr/passage; 24 days) and (g) time-lapse brightfield images 48hr growth follow-up of hPSCs (day 15 at seeding). Scale bars represent 100µm. (h) hPSCs (day 18) stained positive for pluripotency markers OCT4, TRA-1-81 and SSEA4 and (i) were capable of differentiating to early ectoderm (SOX1+), early endoderm (FOXA2+) and cardiac (alpha-actinin) cell types. Scale bars represent 50µm.





Aishah Nasir

Using high-throughput screening of polymers and micro-topographies to improve human pluripotent stem cell cardiomyocyte maturation

The use of human pluripotent stem cell-cardiomyocytes (hPSC-CMs) have prompted a paradigm shift for studying cardiovascular diseases. However, current differentiation protocols often produce hPSC-CMs which lack maturity and functionality of adult cardiovascular cells in vivo. Recent xeno-free differentiation protocols using recombinantly derived matrix substrates and small molecules offer a fully-defined culture system with varied degrees of hPSC-CM attachment that also compromises structural integrity. Previous studies conducted at the University of Nottingham have demonstrated the use of polymeric surfaces for improved hPSC-CM functionality¹. This study explores the use of micro-topographical surfaces with surface chemistries for hPSC-CM models for improved maturation and has identified polymer substrates capable of improving hPSC-CM function as well as being amenable for scale-up. These substrates will be combined with micro-topographical patterns in future work to investigate topo-chemical interactions for hPSC-CM maturation in a 2.5D platform.

References

1. Patel, A.K., et al., A defined synthetic substrate for serum-free culture of human stem cell derived cardiomyocytes with improved functional maturity identified using combinatorial materials microarrays. *Biomaterials*, 2015. 61: p. 257-65



Jamie Thompson

Investigating glycosaminoglycans in development and disease using fully defined 3D cell culture environments and human pluripotent stem cells

Aim: Human development is tightly regulated by components of the extracellular matrix (ECM), including glycosaminoglycans (GAGs) such as heparan sulphate (HS). Mutations in genes for enzymes in HS synthesis disrupt normal GAG production and GAG-related function. These mutations lead to Multiple Osteochondroma, MO, a developmental disease which is poorly understood. In vivo mouse models that are currently used to study MO fail to replicate disease progression in humans and impede our ability to define the specific mechanistic basis of this disease. To address the need for defined, GAG-free culture conditions to investigate the ECM and GAGs in early development and diseases such as MO, we aim to combine human induced pluripotent stem cell (hiPSC) models and an optimised a “blank slate” 3D culture environment.¹

This research has optimised a self-assembling peptide hydrogel that allows cell encapsulation in a matrix-free 3D environment. Human induced pluripotent stem cells (hiPSCs) formed round, well-defined colonies by day 4 within the peptide gels, when seeded as single cells in commercial Essential 8 medium (figure 1). hiPSCs produce and secrete sulphated glycosaminoglycans within the gels (heparan sulphate, chondroitin sulphate, keratan sulphate), and the deposition is predominantly around the periphery of the cell clusters, in contrast to the pluripotency marker OCT4 which is nuclei-associated (figure 1).

To test differentiation in the peptide gels, stem cell aggregates (embryoid bodies, EBs) were generated and differentiated for 22 days in Essential 6 medium in the peptide gels. Changes in cell morphology were observed as expected for differentiating colonies (figure 2). RNA was successfully extracted from the encapsulated hiPSC EBs and used to perform qRT-PCR for quantification of pluripotency and lineage-specific differentiation. Differentiation towards specific lineages (e.g. cardiomyocyte/neural progenitor cells) in the peptide gels has also been optimised and differentiation confirmed by qRT-PCR and immunostaining. This therefore supports the application of the peptide gels as synthetic, fully-defined 3D environments to support hiPSC differentiation.

References

1. Ashworth, J.C., et al., Peptide gels of fully-defined composition and mechanics for probing cell-cell and cell-matrix interactions in vitro. *Matrix Biol*, 2019

Figure 1

End-point immunostaining and microscopy of pluripotency marker (OCT4) and sulphated glycosaminoglycans (heparan sulphate, keratan sulphate and chondroitin sulphate) expressed by wild-type hiPSCs. hiPSCs were seeded in pluripotency E8 medium within the matrix-free peptide gels and stained and imaged on day 4.

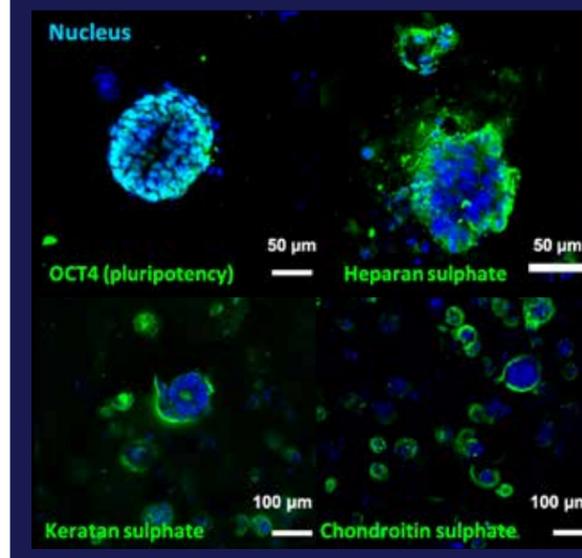
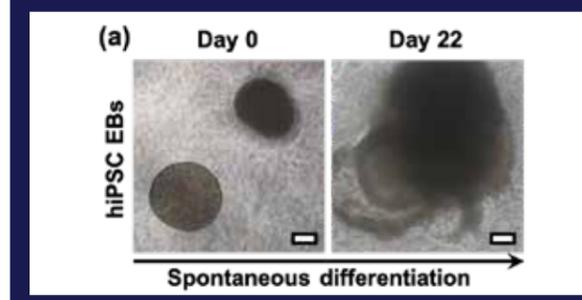


Figure 2

hiPSC differentiation in matrix-free peptide gels (a) embryoid bodies (EBs) seeded at 8–10 EBs/gel and differentiated in E6 medium. Scale bar 100 µm.





Joris
Meurs

High throughput surface proteomics for examining cellular response on biomaterial surfaces

Pluripotent stem cells are a valuable source for cell production and have a huge potential to serve a multitude of applications in regenerative medicine. Biomaterials have been discovered that assist as synthetic substrates for pluripotency maintenance during expansion, but the mechanism by which they achieve this is not well understood due to poor characterisation of the biointerface. The pre-adsorption of proteins from the culture medium is believed to be a crucial element. In this project, the focus is to develop a high throughput surface analysis strategy for quantitative analysis of proteins adsorbed to biomaterial surfaces. This provides important information in understanding the behaviour of cells on complex biomaterial surfaces.

On-surface MS analysis of proteins can be readily performed using a 2-hour in situ digestion at 37°C reducing the required digestion time about 10-fold compared to previous employed digestion strategies. With optimised digestion, extraction, and mass spectrometry parameters, initial quantitative protein screening of a small set of homopolymers has been carried out after incubation with Essential 8™. It was found that the amount of adsorbed FGF-2 (fibroblast growth factor 2) correlates well with pluripotent stem cell count. This may suggest FGF-2 plays a role in the response mechanism of stem cells on biomaterials surfaces. However, repetitions and screening of an increased number of homopolymers is necessary to confirm the role of FGF-2 and other proteins present in Essential 8™.

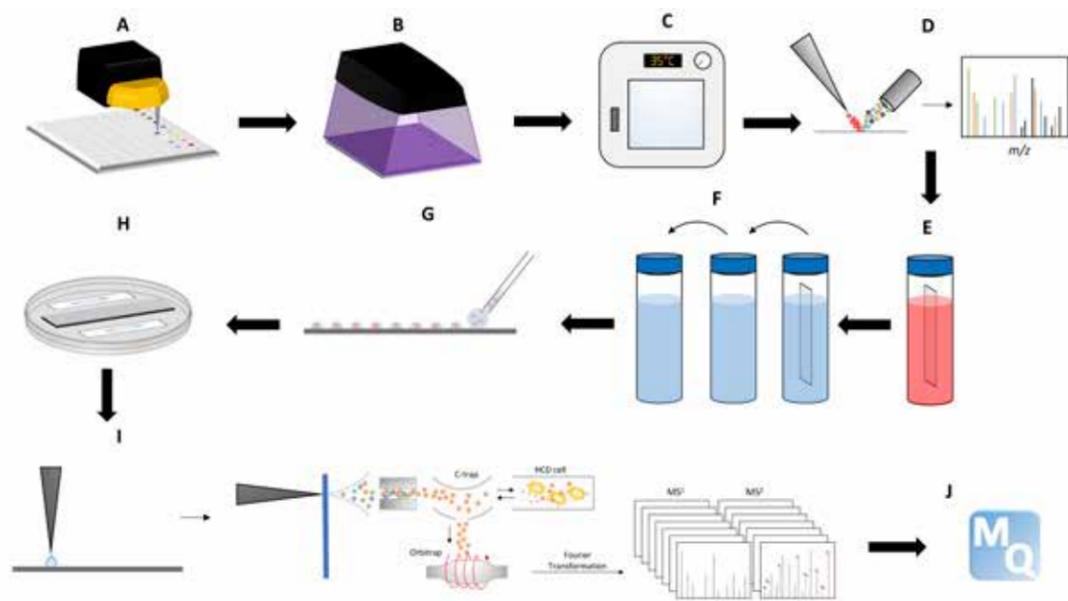


Figure 1

Schematic high throughput workflow for the analysis of proteins on biomaterial surfaces. Monomer solutions (50% w/v or v/v) mixed with 1% photoinitiator are a) printed onto a Droplet Microarray (Aquarray, Karlsruhe). Printed monomer solutions are b) in situ polymerised using a long wave UV light source. The array is allowed c) to dry under vacuum at 35°C for 7 days for removal of residual solvent and monomer. d) TOF-SIMS analysis is carried to confirm the presence of polymers. After, the array is e) incubated in cell culture medium for 1 hour at 37°C and subsequently f) immersed three times for 10 seconds in DI H₂O to remove non-adsorbing components. Then, g) a trypsin solution in DMSO/100 mM AmBic 1:9 v/v is dispensed onto each spot via the rolling droplet technique. The array is subsequently h) incubated for 2 hours at 37°C in a humidified Petri dish after which the array is dried under vacuum at 30°C. The next step the analyse the surface digests using i) LESA-MS/MS to obtain fragmentation spectra of the peptides which are then submitted to j) MaxQuant for protein identification and quantification

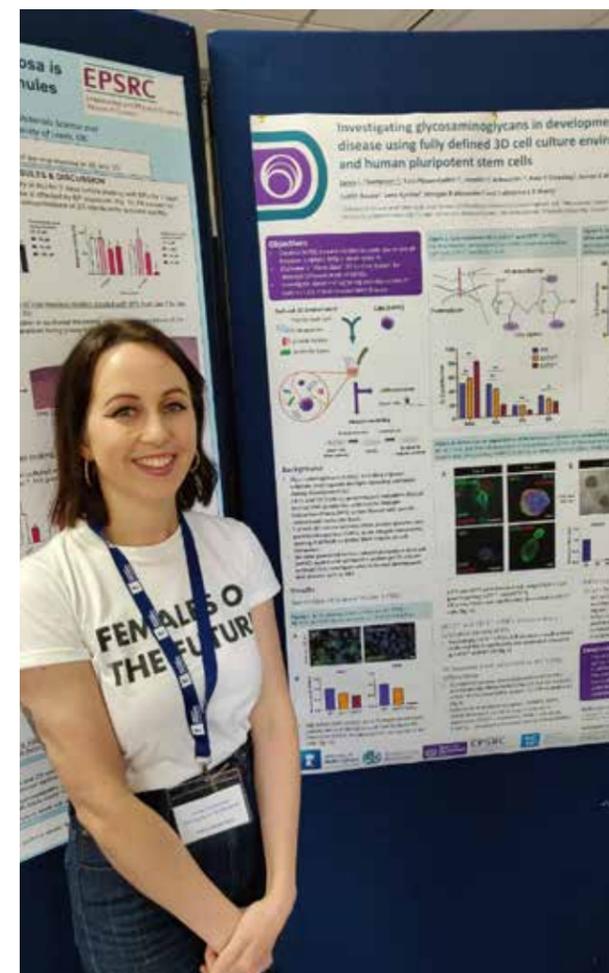


Outgoing

11th International Meeting on Proteoglycans, Japan September 2019	Oral presentation by Jamie Thompson
Proteoglycans Future Leaders Symposium, Japan September 2019	Oral presentation by Jamie Thompson
Uppsala University, Sweden Jan 2019	Jamie Thompson – invited speaker
Invited seminar talk University of Genova, March 2019	Robert Cavanagh – Invited speaker
United Kingdom and Ireland Controlled Release Society (June 2019 – Poster and Oral presentation, Poster prize awarded)	Oral presentation and Poster by Robert Cavanagh
PharmSci 2019 - The Academy of Pharmaceutical Sciences.	Oral presentation by Robert Cavanagh
European Polymer Congress 2019 (EPF2019)	Poster presentation by Valentina Cuzzucoli Crucitti
2018 UoN Polymer Science and Engineering meeting	Poster presentation by Valentina Cuzzucoli Crucitti
TERMIS EU Conference 2019, Greece, May 2019	Oral presentation by Mahetab Amer
Macro Group YRM, University of Canterbury July 2019	Poster presentation by Patricia Monteiro
Annual CRS Meeting and Exposition, Valentia, July 2019	Poster presentation by Alessandra Travanut
European Society of Biomaterials 2018, Maastricht, September 2018	Attended by Arsalan Latif
Asian Chemical Congress Taipei, Taiwan, December 10th 2019.	With Cameron Alexander as Invited International Keynote speaker
UK PharmSci 2019, Greenwich, UK, September 11 2019.	With Cameron Alexander as Invited International Keynote speaker Attended by Andrea Alice Konta
14th International Conference on Materials Chemistry (MC14), 8 – 11 July 2019, Aston University, Birmingham, UK.	With Cameron Alexander as Invited International Keynote speaker
2019 Cancer Nanotechnology Gordon Research Conference, Mt Snow, VT, June 23-28, 2019.	With Cameron Alexander as Invited International Keynote speaker
OxCD3 2019, Oxford September 24th 2019.	With Cameron Alexander as an invited speaker
Interpharm 2019, Coventry, May 6th 2019.	With Cameron Alexander as an invited speaker
“Polymer Therapeutics” – University of Bath, March 20th 2019	With Cameron Alexander as an invited speaker
Antimicrobials Meeting – London November 29th 2018.	With Cameron Alexander as an invited speaker
Ambient MS Special Interest Group Meeting, Huddersfield, 30 January 2019	Attended by Joris Meurs
Mass Spectrometry Imaging Special Interest Group Meeting, Sheffield 01 May 2019	Attended by Joris Meurs
East Midlands Proteomics Workshop, Sheffield, 30 October 2019	Attended by Joris Meurs
RSC Twitter Conference	Most of the grant researchers participated in the twitter conference, either through submitting a poster or by voting and retweeting others.
3D OrbiSIMS in Biomaterials Discovery” Kyoto SIMS conference, October 2019	Presentation by Morgan Alexander
Workshop for the Opening of the Therapeutic Biomaterials Discovery Platform, Technical University Eindhoven – September 2019	Presentation by Morgan Alexander
“Biomaterials Discovery: a personal tale from tribulations to trials” Cape Town, September 2019	Presentation by Morgan Alexander
3D Materials in Biomedicine” Added International, Nottingham, July 2019	Presentation by Morgan Alexander
Biomaterials Discovery: a personal tale from tribulations to trials” Engineering Better Health, Nottingham, June 2019	Presentation by Morgan Alexander
Biomaterials Discovery: a personal tale from tribulations to trials” School of Pharmacy, Queens University Belfast, May 2019	Presentation by Morgan Alexander

Hosted

TCES-UKSB, Nottingham June 2019	Flash presentation and poster presentation by Jamie Thompson Oral presentation by Mahetab Amer Attendance by a large portion of the programme grant researchers
Cancer and Stem Cells Research Day, Nottingham June 2019	Poster presentation by Jamie Thompson
CBS Annual Research Symposium, Nottingham Jan 2019	Poster presentation by Jamie Thompson
Sue Watson PGR Oral Presentation Event, Nottingham October 2019	Oral presentation and poster presentation by Jamie Thompson
Women in Chemistry, University of Nottingham, March 2019	Co-organised by Dara O'Brien
Third Annual Biomaterials Workshop, January 2019	Attended by the majority of the Programme Grant's researchers, with most showing poster presentations



Grants



- KTP with The Electrospinning Company – Felicity Rose PI, C Alexander Co-I. 2018-2020. £107,544
- “SPI-CLOPS” EPSRC – Cameron Alexander – PI. (Helen Byrne (Oxford), Ioan Notingher, Serhiy Korposh, Steve Morgan, Poulam Patel Co-Is). £59,796
- EP/R013764/1: – Cameron Alexander – Future Vaccine Manufacturing Hub: Advancing the manufacture and deployment of cost effective vaccines. 01 December 2017-31 March 2021 £9,947,570. Co-I, ~300k to Nottingham
- EPSRC EP/R035563/1 Experiencing the micro-world – a cell’s perspective. Amanda Wright PI), Cathy Merry and Cameron Alexander (Co -I). 1 Apr 2018 - 31 Mar 2021, £752, 573
- EP/S021434/1 High resolution, cryogenic analytical and transfer scanning electron microscope (HR-CAT-SEM). Principal Investigator: Andrei Khlobystov, Cameron Alexander (Co -I). 01 January 2019 – 31 December 2023 Value £1,564,542
- AstraZeneca iMED PostDoc Project. Distribution and cargo release profiles of dendrimer-based nanocarrier formulations, designed for inhaled delivery of oligonucleotides. Dr Martin Hemmerling PI, Cameron Alexander Academic Lead 2019-2021
- Royal Society International Exchange Award IES\R2\192256– Cameron Alexander – New Neuroprotective Therapies – 1 Feb 2020 – 31 Jan 2022. £12,000.00
- Smith & Nephew award for proof of concept study to investigate the applicability of immune-instructive polymers in wound healing – Morgan Alexander – Amir Ghaemmaghami
- Jamie Thompson – Nottingham Cancer RPA 4* Accelerator Fund £2k, funded collaboration with Uppsala University
- Jamie Thompson – Nottingham NanoPrime Scheme £15k, “Testing dependence of matrix deposition on hydrogel stiffness”, funded collaboration with Cathy Merry, Kenton Arkill, Zubair Nizamudeen, David Scurr

Conference awards



- **Jamie Thompson** – First prize for best Oral presentation, Sue Watson PGR Oral Presentation Event
- **Jamie Thompson** – ISMB International Travel Grant for attendance at 11th International Meeting on Proteoglycans, Japan 2019 (€650)
- **Jamie Thompson** – Nottingham Graduate School Travel Prize for attendance at 11th International Meeting on Proteoglycans, Japan 2019 (£600)
- **Andrea Alice Konta** – 2nd Place Conference Poster Award - PharmSci2019 conference
- **Robert Cavanagh** – 1st place poster prize – United Kingdom and Ireland Controlled Release Society (UKICRS) symposium 2019
- **Dara O’Brien** – Received the Oral Presentation prize in the Materials Chemistry division at the University of Nottingham’s Postgraduate Research Symposium in the School of Chemistry, June, 2019
- **Valentina Cuzzucoli Crucitti** – Poster presentation prize for the 2018 University of Nottingham Polymer Science and Engineering meeting
- **Patricia Monteiro** – Poster presentation prize for the Macro Group YRM 2019
- **Alessandra Travanut** – RSC Biomaterials Science Discovery Poster Prize at the Third Annual Biomaterials Workshop 2019



Royal Society Summer Science Exhibition

July 2019

The Next Generation Biomaterials Discovery Programme grant was awarded a place at the prestigious Royal Society Summer Science Exhibition which took place in the first week of July. Volunteers from across schools within the Science Faculty were involved, including Pharmacy, Life Sciences and Engineering, as well as external support from Queen's Medical Centre and the National Physical Laboratory. The Grant's exhibition was entitled "Super Biomaterials to Fight Superbugs", and received hugely positive feedback from both visitors and the Royal Society staff.

The event was immensely successful with over 12,500 visitors attending the summer event, and the grant receiving press and media attention, including a radio interview with BBC Health Check, and print articles in the Telegraph and The Times.

Three activities were available to engage the public, sharing knowledge about biofilms and the novel biomaterials being developed at the University of Nottingham to combat them. Participants were able to race against each other to clear tubes filled with sticky biofilms of bacteria, dip real catheters into a bowl of "bacteria" and see how much sticks to different materials, as well as take part in the live experiment of observing bacteria transfers on hands during common greetings such as a handshake and high five.

Wonder

June 2019

The Programme Grant took part in the University of Nottingham's annual Wonder event on the 15th June which attracted an estimated 5,000 visitors. Members of the grant were involved in a variety of stands around the campus, including "Super Biomaterials to Fight Superbugs" and "A Sweet Discovery".

Pint of Science

May 2019

Morgan Alexander gave a talk entitled "Biomaterials Discovery: a personal tale from tribulations to trials" at Parliament Bar in Nottingham this May, as part of the "Scratching the Surface of Material Science" 2019 Pint of Science event – where scientific talks are given to the general public in pubs across the country.

Andrea Alice Konta is also currently involved with the organisation of the 2020 Pint of Science Nottingham events.

Nottingham Festival of Science and Curiosity

February 2020

The grant will also be involved in the Nottingham Festival of Science and Curiosity which will take place across the city in February 2020. The festival celebrates STEM subjects with free interactive events, and the Next Generation Biomaterials Discovery grant will be exhibiting their work with support from other grants and schools within the University.



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Amanda Pearce

Left in March 2019 after working in RC2 on Chemistries for Self-Assembling Polymer-Drug Nanoparticles and now works at the University of Birmingham as a Senior Research Fellow and PERCAT rep for the School of Chemistry.



Jordan Thorpe

Jordan has come to the end of his and in 2020 will travel to Australia to work at the Victor Chang Cardiac Research Institute in Sydney.



Marta Alvarez Paino

Left in July 2018 after working in RC3 with polymer microparticles for regenerative medicine, and now works in a pharmaceutical company in Spain.



Manuel Romero

Left in the grant in September 2018 having worked within RC4 on microbiology, and continues to work within the University of Nottingham.



Elizabeth Hufton

Left position as Project Manager of the grant in November 2018 to become Project Manager of the Precision Imaging Beacon within the University of Nottingham.



Paulius Mikulskis

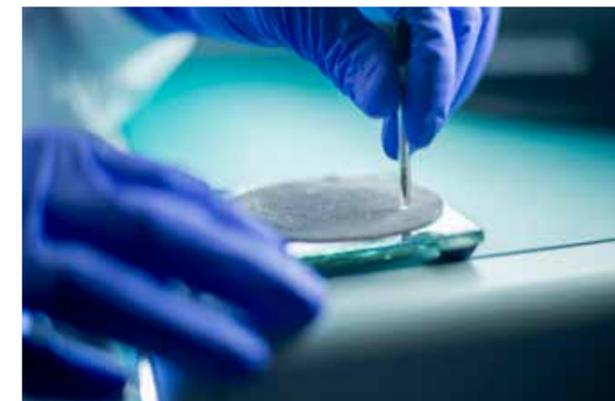
Left in November 2018 having worked in RC1 on biomaterial design rules to look for a position in Sweden.

Summer placements

Thomas Paterson and Lucy Scullard were selected for an 8-week summer placement working on a project entitled "Optimisation of polymer microarrays for the discovery of novel biomaterials" with Laurence Burroughs acting as their supervisor.

Nojus Cironis also worked on an 8-week summer placement with Valentina Cuzzucoli Crucitti supervising, on her project "Generation and Characterization of Novel Biologically Active Functional Surfactants".

All summer placement workers presented their research and work at the Programme Grant's July Quarterly Meeting.



Visits

Adam Dundas

Adam Dundas was successful in his application to the Innovation to the Commercialisation of University Research (ICURE) scheme. Conversations were had with over 125 companies over 3 months to investigate the possibility of creating a spin-out company based around the anti-biofilm coating technology BACTIGON® developed at the University of Nottingham and its application to market sectors including healthcare, marine biofouling and water processing systems.

Dave Winkler

Dr Winkler from La Trobe University in Australia visited the grant in July of this year to continue the collaborative work with regards to Research Challenge 1, focussing on material discovery methods.

Laurence Burroughs

Laurence spent one week working with the group of Prof. Jan de Boer in Eindhoven. Laurence carried out the entire procedure used to create TopoChip samples with Phani Sudarsanam, in order to learn how the process works and to translate to new biomaterials production techniques in Nottingham. Laurence also discussed ongoing research being carried out in both groups.

Chenjia Zhao

Chenjia Zhao is a visiting researcher from Tsinghua University in China, currently focussing on applying 3D printing technologies and biomaterials to construct tissue biomimetic substitutes with drug sustained release function. Her project is based on constructing an implantable cervical equivalent with long-term release of protein through 3D printing. She will be with the grant until April 2020.

Federica Sodano

Federica Sodano was a visitor for 3 months from the University of Turin and who also worked in the Universities of Naples and Catania. She worked on polymer NPs for combination photo-chemotherapy of TNBC with Rob and Amanda. This work led to a paper that was submitted to Biomaterials Science which should be published soon. Her work also led to a Royal Society International Exchange Award of £12,000 – New Neuroprotective Therapies (IES\ R2\192256, Feb 2020 – Jan 2022)





Annex A – people and roles

Name	Role
Morgan Alexander	Director
Cameron Alexander	Co-Directors
Felicity Rose	
Amir Ghaemmaghami	
Richard Hague	
Kevin Shakesheff	Project Manager
Sian Rankin-Turner	
Derek Irvine	Investigators
Anna Grabowska	
Chris Denning	
Ricky Wildman	
Steve Howdle	
Paul Williams	
Phil Williams	
Cathy Merry	
Hyun Kim	
Christopher Tuck	
Adam Dundas	Post Docs
Le Ma	
Laurence Burroughs	
Robert Cavanaugh	
Thais Abelha	
Patricia Monteiro	
Aishah Nasir	
Mahetab Amer	
Matthew Vassey	
Ana da Silva	
Graziela Figueredo	PhD
Alessandra Travanut	
Dara O'Brien	
Valentina Cuzzocoli Crucitti	
Joris Meurs	
Leonardo Contreas	
Francesco Pappalardo	
Kiril Kalenderski	
Arsalan Latif	
Eduardo Pernaut-Leza	
Jamie Thompson	PhD CDT
Charlotte Henshaw	
Elisa Tarsitano	
Andrea Alice Konta	PhD CDT
Akosua Anane-Adjei	



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