

# **$\beta$ -sheet forming peptides: from self-assembly to functional biomaterials**

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The use of non-covalent self-assembly to construct materials has become a prominent strategy in material science offering practical routes for the construction of increasingly functional materials for a variety of applications ranging from electronic to biotechnology. A variety of molecular building blocks can be used for this purpose, one such block that has attracted considerable attention in the last 20 years is *de-novo* designed peptides. Our group work focusses on the development of a technological platform for the design of novel biofunctional hydrogels exploiting the self-assembly of so-called  $\beta$ -sheet forming peptides. The  $\beta$ -sheet motif is of increasing interest as short peptides can be easily designed to form  $\beta$ -sheet rich fibres that entangle and consequently form hydrogels. These hydrogels can be easily functionalised using specific biological signals and can also be made responsive through the use of enzymatic catalysis and/or conjugation with responsive polymers (Fig. 1). Based on the design principles developed we have constructed hydrogels for a variety of applications including functional hydrogels for the culture of a variety of cells including chondrocytes, osteoblast, embryonic and mesenchymal stem cells, injectable hydrogels for *in-vivo* cell delivery (myocardium) and sprayable hydrogel for topical (buccal) drug delivery.

## 2-Photon Degradable Hydrogels to Study Cell-Material Interactions

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Study of cells behaviour in response to different biological, chemical and physical cues has gained a lot of interest in the field of tissue engineering.<sup>1,2</sup> The dynamics of cell-cell and cell-material interaction has determining effect on cell properties and functions. For this purpose, light serves as an excellent stimulus by providing precise spatiotemporal control over the cell microenvironment.<sup>2</sup> However, several drawbacks associated with the UV and visible light wavelengths such as cytotoxicity, mutagenesis and low penetration depth has shifted the focus to more cytocompatible wavelengths. Here we present potential modified alginate hydrogels based on SPAAC (strain promoted azido-alkyne click) and PTAD (4-phenyl-1, 2, 4-triazole-3, 5-dione)<sup>3</sup> chemistries as 3D photo-responsive scaffolds for cell culture. The incorporation of *o*-nitro benzyl (with up converting Ln nanoparticles)<sup>4</sup> and coumarin moieties will allow to gain important insights into complex dynamics of cell-material interactions via 2-photon gel degradation using cytocompatible near infrared light irradiation.

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## **3DEAL: A tuneable Technique for Construction of Anisotropic Scaffolds**

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Human tissues and organs have a complex and heterogeneous composition. The possibility to recreate with high precision the biochemical and structural properties of the extracellular matrix would be of great benefit for applications in tissue engineering, regenerative medicine, and drug screening. Hydrogels offer great promise for such applications. Due to their cross-linked nature hydrogels swell (and/or de-swell) in water without dissolving gaining from 20 to 99% of their dry weight. Hydrogels mimic the physico-chemical composition and the mechanical structure of the native ECM of a tissue. Their tuneable capability, functionality, responsiveness and biomimetic properties made them ideal candidates for tissue repair/regeneration. While a number of techniques have been developed to create patterns within 3D hydrogels, many still require elaborate hydrogel materials, the use of potentially harmful UV radiation, limited capacity to pattern large or complex molecules, and chemical reactions and expensive processes. We have developed a novel 3D-Electrophoresis-Assisted-Lithography (3DEAL) platform to create patterns of multiple functional molecules, and subsequently complex anisotropic environments, within readily available hydrogels. The 3DEAL combines fundamental principles from gel electrophoresis by using electric fields to manipulate charged biomolecules within different types of hydrogels; affinity chromatography by immobilizing and anchoring the proteins to the hydrogels; and microfabrication by using a porous mask to define the patterns within the hydrogels.

Well-defined patterns of proteins of different molecular weights were obtained in 10 types of hydrogels. The molecular patterns generated anisotropic environments comprising parallel columns, curved lines, gradients of molecular composition, and patterns of various proteins ranging from tens of microns to centimeters in size and depth. NIH 3T3 fibroblasts were cultured on polyacrylamide-co-collagen and agarose-co-collagen hydrogels patterned with fibronectin and observed to recognize and adhere to the patterned regions.

In this way, an affordable, easily tuneable, and versatile device and fabrication process designed to print multiple types of functional molecules within different kinds of hydrogels with high precision has been developed. The printing platform offers a simple, accessible, and practical molecular printing method with potential widespread applications in cell studies, *in vitro* models, drug screening, and tissue engineering due to its specific spatio-temporal location of proteins to recreate anisotropic environments.

# 5,5'-Diazaisoindigo: an Electron-Deficient Building Block for Donor-Acceptor Conjugated Polymers

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The development of donor-acceptor (D-A) conjugated polymers for organic electronics have attracted great attention. However, high-performance acceptor units are still lack compared with the numerous donor units. Therefore, design and synthesis of novel acceptor units is of great importance for diversifying D-A conjugated polymer structures and further improving the polymer properties. Recently, isoindigo (IID) was explored as an excellent electron-accepting moiety for a large number of organic semiconductors in OPVs and OFETs. Unlike 7,7'-Diazaisoindigo (7DNIID), the synthesis and application of 5,5'-diazaisoindigo (5DNIID) with two nitrogen atoms at different positions have never been reported.

Recently, we develop a facile method to synthesize a novel electron-accepting unit, 5,5'-diazaisoindigo (**5DNIID-Br<sub>2</sub>**), in good yield. DFT calculations suggested that 5DNIID has a lower LUMO level than 7DNIID. Moreover, compared to 7DNIID, the two sp<sup>2</sup> nitrogen atoms in 5DNIID would not be occluded after introducing alkyl side chains, which is beneficial to the formation of intermolecular N···H hydrogen bonds and N···S interactions, leading to an ordered molecular arrangement and thus enhanced device performance.

In conclusion, we reported a facile synthesis of a new isoindigo derivative, 5DNIID-Br<sub>2</sub>, and further explored its application as an electron acceptor unit in D–A conjugated polymers. CV measurement of 5DNIID-Br<sub>2</sub> showed an ultra-low LUMO level of -3.92 eV owing to the introduction of two electron-deficient nitrogen atoms in the para-position of the amine groups in the isoindigo  $\pi$  skeleton, which was also 0.08 eV lower than that of the 7DNIID analogue. The different positions of nitrogen atoms exhibited significant effects on the photophysical and electrochemical properties of the two analogues. Moreover, an unusual polymerization condition was applied to afford the D–A conjugated polymer 5DNIID-2T, which showed typical p-type transport characteristic with hole mobilities of up to  $1.27 \times 10^{-3} \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$  under air. Our research provides a reliable approach to synthesize 5,5'-diazaisoindigo and its derivative, which could be an electron-deficient building block for high-performance organic semiconductors.

## **Analysis of challenging polymers – Characterisation of molecular weight and structure by the latest advanced multi-detector GPC system**

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The analysis of polymers is fundamental in order to successfully use them in end products. Molecular weight characteristics, relating directly to polymers bulk properties, play an important role in the applications of the polymers. Most commonly the analysis of polymers in terms of molecular weight and molecular weight distribution is carried out by using Gel-permeation chromatography (GPC), i.e. conventional and/or advanced GPC. Advanced GPC involved the use of static light scattering detectors, which allow us to overcome the limitations of conventional calibration and to obtain absolute molecular weight for the polymers analysed. In addition, the presence of the viscometer in advanced GPC can give you measurements of intrinsic viscosity, that is used to obtain structural information using the Mark-Houwink plot and size measurements in terms of hydrodynamic radius (Rh).

However, even with advanced GPC there are types of polymers that can be challenging or even not possible to measure. For example, polymers with low molecular weight and low  $dn/dc$  or with high molecular weight and high intrinsic viscosity, were not easily analysed by GPC. The introduction of the Malvern's latest integrated, multi-detector GPC system, OMNISEC, has made these measurements a reality. The high sensitivity of the light scattering and RI detectors extend the lower sensitivity limit for polymer measurements and we can now measure polymers that before were not detected by GPC detectors. Challenging polymers of this type include epoxies, PLA/PLGA, PCL, polyols, UV and adsorbing additives. Among these, polyols, for example, have a very low  $dn/dc$  that, combined with low molecular weights values, make the analysis of these polymers not possible by using an ordinary GPC system. OMNISEC with the improved sensitivity of the detectors can actually detect the polyols and calculate their molecular weight and structural information. In addition to this, the sensitivity of the system has made possible the measurement of high Mw and high IV samples without risk of column overload.

In this work the analysis of several challenging polymers by the multi-detector GPC OMNISEC system will be shown. Molecular weight and structural information have been obtained for several types of polymers previously beyond the range of standard GPC systems. The data reported will show how the new advanced detection system from Malvern can comfortably be used in difficult analyses of polymers.

# **A New Class of Bioinsecticides via the Complexation of double-stranded RNA with pH-Responsive Block Copolymers**

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Without significant advances in crop-protection, it is likely that food production will not be able to sustain an ever-increasing world population. Unfortunately, environmental concerns and the increasing frequency of pesticide resistance means our current library of insecticides is unlikely to be sufficient. As a result, it is important to consider alternatives to existing chemical pesticides. Biopesticides derived from natural sources with new modes of action, such as peptide/protein toxins, neuropeptides, insect hormones and double-stranded RNA (dsRNA) mediated RNA interference (RNAi), have been proposed as alternatives.

RNAi provides sequence specific suppression of gene expression, which can be utilised for insect pest control. RNAi mediated by dsRNA has a number of positive attributes over conventional chemical insecticides, such as its selectivity for a target pest and biodegradability. However, the efficiency of RNAi varies different species, and its wide scale use is currently limited by its rapid degradation upon oral delivery, poor gut cellular uptake and high production cost.

By complexing dsRNA to specific block copolymers containing a complexing and stabilising block, we can increase the protection of the dsRNA to degradation from extracellular nucleases, and increase RNAi efficiency. Specifically, we have utilised reversible addition-fragmentation chain-transfer (RAFT) polymerisation to produce well-defined diblock copolymers comprising poly(2-hydroxypropyl methacrylamide)-*b*-poly((dimethylamino)ethyl methacrylate) (PHPMA-*b*-PDMAEMA) and investigated their complexation with dsRNA, in order to target the vATPase proton pump in several insect species.

# **A novel interleaved carbon fibre/epoxy composite offering easy repair of interlaminar damage**

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Laminated carbon fibre/epoxy composites possess excellent specific strength and stiffness and low weight, and therefore have been widely used in aerospace and other transport applications. However, they are susceptible to interlaminar damage when impacted and this can significantly weaken the material. Conventional repair methods show good strength and stiffness recovery of the composites, but these are expensive and require considerable skill. This paper explores a novel concept in which an interleaved composite is designed to ensure that interlaminar damage can be easily, and repeatedly, repaired.

In this concept, carbon fibre/epoxy composites are interleaved with thermoplastic films. The thermoplastic interleaf material is chosen so that the interlaminar damage occurs predominantly within the interleaf but not at its interface with the carbon-epoxy plies and not within these plies. The interleaf material must be thermally bondable to itself at a temperature which will not damage the cured carbon fibre/epoxy composite.

Initial trials have been conducted with interleaves of polylactide (PLA) and of thermoplastic polyurethane (TPU). Three-point bend tests, designed to cause interlaminar shear failure, were performed and the failed specimens were repaired by heating within a vacuum bag. Results showed that after repair, shear strengths of the PLA and TPU specimens were restored by 80% and 100% on average respectively and after a further damage-repair cycle, the average recovery reduced to 66% for the PLA specimens and 97% for the TPU specimens. Results from static indentation tests on PLA specimens showed 50% strength recovery after two repairs. Both of the thermoplastics used for these trials have rather low shear strengths. Work is now progressing to identify and investigate interleaf materials which have higher shear strengths for this 'easy repair' concept.

# **A pore structure photolithography based on dynamically crosslinked hydrogels**

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Photolithography is a highly important technique to fabricate surface micro-structure, which is essential for plate making in printing industry, wafer etching in electronics industry, etc. However, common photolithography methods are costly on both time and finance aspects, and usually bring on a variety of pollutions. Herein we develop a simple, fast, yet green photolithographic method towards high water content (> 95 wt%) hydrogels crosslinked by disulfide bonds which can dynamically exchange under UV exposure. When the light was locally exposed on the hydrogels at a frozen state, the stress on the polymer chains due to the ice crystallization will be locally relaxed via dynamic bond exchange, simply and rapidly resulting in photolithographic porous regions after melting of the ice. The pore morphology can be well adjusted by exposure time, disulfide bond content, additives, etc. We furthermore demonstrated that the lithographed hydrogels can be applied as shape changeable smart plates, which would potentially contribute to a next-generation printing technique. On the other hand, the porous hydrogel plates can be regenerated into nonporous ones for cyclic photolithography processes, implying their zero-waste green nature.

# A self-assembly based supramolecular bioink with hierarchical control as a new biofabrication tool

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**Introduction** One of the major goals in tissue engineering is the capacity to recreate and control the extracellular matrix (ECM) in a hierarchical manner. Molecularly complex materials or advanced additive fabrication techniques are often used to capture aspects of the ECM. Whilst biofabrication or bioprinting can build complex tissue-like structures with micro-to-macro scale precision, many of the bioinks are constrained by stringent printing requirements, such as low viscosity, rapid gelation and structural integrity. These conditions are currently not optimal for cell culture, and therefore alternative inks or fabrication methods are needed. Self-assembling biomaterials have recently gained more attention, as these can be functionalized and tuned at the nanoscale to better mimic the extracellular matrix (ECM). We propose a new fabrication platform that integrates the benefits of bioprinting and molecular self-assembly to overcome the current major limitations.

**Methods** Our approach relies on the co-assembly of peptide amphiphiles (PAs) with biomolecules and/or proteins found in the ECM, whilst exploiting the droplet-on-demand (DoD) printing process. Four PA sequences were designed to interact with the macromolecule keratin for the basic study. A simple acoustic based print head was used (Nozzle diameter  $\leq 500\mu\text{m}$ ). PA and keratin were dissolved in cell friendly buffer at concentrations 5-20mg/mL and 10-50mg/mL respectively. A high-speed camera was used to visualise the hydrogel formation. Scanning electron microscopy (SEM) was used to characterise the gel structure. Cell viability was assessed using live/dead assay.

**Results** Either the PA or keratin solution was used as the ink, with the other forming the liquid pool to be jetted into. The method takes advantage of interfacial forces generated between solutions of the co-assembling molecules, enabling for the first time the possibility to bioprint whilst controlling biomolecular (specific proteins, biomolecules, peptides) and structural (aligned or randomly oriented nanofibres, microtopographies, gel geometries) elements of the printed scaffold. The co-assembly process can be performed during printing and in cell-friendly conditions, whilst exhibiting high cell viability (> 88 %). Moreover, multiple cell types can be spatially distributed on the outside or embedded within the tuneable biomimetic scaffolds.

**Conclusion** The combination of self-assembling materials with DoD based bioprinting, enables the possibility to use interfacial forces to direct self-assembly. The merits of the ink and the method allows the fabrication of complex bioactive scaffolds for applications such as tissue engineering, *in vitro* models, and drug screening.

# A simple method to synthesize self-immolative polymers with varying reporter molecules

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**Summary:** Self-immolative polymers (SIPs) have several application opportunities within the fields of drug delivery and material science. The main advantage of SIPs are their ability to degrade into small molecules upon a controlled triggering event in a head-to-tail manner. It is possible to control the type of stimulus that triggers the depolymerization and the speed of decomposition by the design of a suitable trigger and polymer backbone. It is further possible to install a reporter molecule, such as a fluorophore or a drug, in the tail of the SIP, which will result in reporter release when full depolymerization is accomplished. These features are attractive for medical application such as controlled drug delivery and sensing, as well as in material science. The unique properties of SIPs demonstrate the requirement for simple syntheses to be able to exploit the great potential of these polymers.

**Results and discussion:** We have synthesized a self-immolative polycarbamate with *p*-aminobenzylalcohol as the repeating unit, which results in 1,6 eliminations during the depolymerization. The synthesis apply blocked isocyanate chemistry, which is a smart strategy to synthesize polycarbamates due to the possibility of exploiting the reactivity of isocyanates in a safe manner, since the free isocyanate only exists *in situ*. This polymerization method permits the use of different triggers, and we have further developed a standard strategy to add a variety of reporter molecules to the polymer chain. The addition of reporter molecules involves blocked isocyanates chemistry making it possible to use the same conditions as during the polymerization. The strategy has proved successful and reporter molecules such as fluorophores have been synthesized as blocked isocyanates. Self-immolative polymers containing the reporters were further synthesized with success making it possible to easily monitor the depolymerization.

**Conclusion:** The studies are still on going and additional reporter molecules will be tested using the method. The research presented herein will hopefully permit the fully exploitation of the potential of SIPs since the synthesis can easily be adapted to fit the wanted application.

# **Advanced wound dressings based on nanofibres embedding therapeutic plant extracts**

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The development of advanced systems for the efficient treatment of skin wounds is becoming crucial in order to face global demographic issues (ageing population, obesity and diabetes). An ideal biomedical device for wound care should promote the complete regeneration of the injured tissue, effectively restore its biological activity and aesthetic aspect, while reducing inflammation and preventing microbial invasion. The risk of infection is one of the main concerns in wound care, where the colonisation of the wound site by bacteria can negatively affect the healing process and delay it.

Here we present the development of bioactive dressings that encapsulate natural active agents with antibacterial activity. The composite scaffolds were produced by electrospinning biopolymers, such as alginate and cellulose, and essential oils. In vitro and in vivo tests revealed that the fibers were effective in stopping the growth of bacteria and in promoting tissue repair.

The scaffolds produced have high potential in the wound healing field, because, together with antibacterial activity, their porosity is suitable for gas permeation, and their mechanical properties can be engineered. Furthermore, the mechanical flexibility of the nonwoven mat guarantees conformability to the wound site, providing protection of the injured tissue against external mechanical and thermal stresses.

# Bio-adhesive proteins from fungi: biotechnological production, self-assembly and applications

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1. Summary. Hydrophobins (HFB) are cysteine rich polypeptide chains, made of ~100 amino acids. The folded protein consists of a globular, ~3 nm, amphiphilic structure able to self-assemble at hydrophilic-hydrophobic interfaces forming amphiphilic films that are endowed with adhesive properties. HFBs play peculiar roles in fungal physiology in both the soluble and aggregated forms. Class I HFBs can self-assemble into amyloid-like aggregates able to stably coat several materials. We study the Class I HFB named Vmh2 produced by the edible fungus *Pleurotus ostreatus*, its self-assembling behaviour and applications for surface modification.

2. Results and discussion. Vmh2 was extracted from the surface of the fungal mycelium using 100% trifluoroacetic acid. The production yield was 100 mg of protein per Litre of culture broth. Its self-assembly and aggregation behaviour was affected by environmental conditions. In aqueous buffers, Vmh2 was soluble at pH  $\geq 7$ , however, it spontaneously aggregated into amyloid fibrils. In 60% ethanol 40% water solution at low pH, the pure protein was stable for more than one year. At 60% ethanol-superhydrophilic glass interface it self-assembled changing the water contact angle of the surface from  $<5^\circ$  to about  $60^\circ$ . The amount of Vmh2 produced from a Litre of culture broth was sufficient to coat 20000 glass slides (270 ng of Vmh2 per  $\text{cm}^2$ ). Interestingly, the biofunctionalized surface was able to adsorb fluorescent labelled BSA, antibodies, CdTe Quantum Dots in microarray format as well as a homogenous layer of Graphene Oxide. The functionalized glass slides were proven functional for IgG biosensing.

3. Conclusion. Vmh2 is an adhesive and amphiphilic biopolymer. Its hierarchical self-assembling is modulated by environmental conditions. It spontaneously aggregates into amyloid fibrils, robust and stable proteinaceous structures. The glass surface coated by Vmh2 mediates the adhesion of nanomaterials and proteins, which is advantageous for biomedical devices manufacturing such as optical biosensors in microarray format.

# **Biodegradable PCL-*b*-PTMC-*b*-PCL triblock copolymers and nano-hydroxyapatite composites for use in extrusion-based additive manufacturing**

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## Introduction.

Additive manufacturing based on extrusion processing of a thermoplastic polymer is of great interest in preparing designed scaffolds for tissue engineering applications. However, the number of thermoplastic materials available for extrusion is very limited. Here we developed new thermoplastic elastomers materials and their composites for additive manufacturing based on extrusion processing.

## Results and discussion.

Biodegradable PCL-*b*-PTMC-*b*-PCL triblock copolymers were synthesized by sequential polymerization of trimethylene carbonate (TMC) and  $\epsilon$ -caprolactone (CL). Composites with nano-hydroxyapatite (n-HA) were prepared from solution and evaluated for their physical properties. The prepared triblock copolymers have physical properties characteristic of the respective TMC- and CL homopolymers. Reinforcement of the triblock copolymers with n-HA resulted in increased tensile modulus and toughness values, and decreased elongations at break.

Using ethylene carbonate (EC, water soluble, m.p.=37 °C) as a crystallizable solvent, micro-porous (composite) structures were prepared by 3D printing using an extrusion-based additive manufacturing technique (BioBots, USA) and extraction with water. The PCL-*b*-PTMC-*b*-PCL triblock co-polymer and n-HA mixtures in ethylene carbonate were extruded at 60 oC, the structure was solidified by cooling to -20 °C.

## Conclusions.

Using low-melting ethylene carbonate as a benign crystallizable solvent, structures with macro- and micro-pores could readily be 3D printed using PCL-*b*-PTMC-*b*-PCL triblock copolymers. These biodegradable thermoplastic elastomers and their n-HA composites may find wide use in tissue engineering.

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## Catalytic Activity of the Co/Cu Carbon Nanofibers Electrode for Methanol electrooxidation

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At present, Pt/C in the anode and cathode of polymer electrolyte fuel cells, and PtRu/C, in the anode of direct methanol fuel cell are known to be the most active materials. Pt catalysts suffer from several drawbacks including slow kinetics and high cost. Thus in this work we focused on the development of catalyst materials with low cost, high performance, high stability and durability. The electrospinning process can be efficiently utilized to produce carbon nanofibers decorated by metallic nanoparticles. Polyvinylpyrrolidone (PVP) based nanocomposite fibers containing CoCu have been successfully fabricated by an electrospinning technique. The formed nanofibers mats were initially dried for 24 h at 80°C under vacuum and then calcined in a tube furnace at 750°C for 5 h in argon atmosphere and holding time of 2 h. Scanning electron microscopy (SEM) and energy dispersive X-ray (EDX) measurements were carried out to show the surface morphology and the metal state of both of produced carbon nanofibers and nanocomposites. Information about the phase and crystallinity was obtained by using x-ray diffractometer with Cu K $\alpha$  ( $\lambda = 1.540 \text{ \AA}$ ) radiation over Bragg angle ranging from 10° to 90°. Also, the electrochemical measurements were recorded using conventional three electrode electrochemical cell at room temperature in 1 M KOH solution. Investigation of the electrocatalytic activity of the introduced nanofibers toward methanol oxidation indicates good performance, as the corresponding onset potential was small compared to many reported materials. Therefore, based on the above investigations, carbon nanofibers composite

# Cellulose Nanopaper Characteristics and their Influence on Composite Properties

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Cellulose nanofibrils (CNF) have received great attention in recent years as reinforcement in nanocomposite materials due to their excellent mechanical and chemical properties. One promising approach to produce CNF based nanocomposites is to utilize nanopapers as reinforcement in laminated composites. Cellulose nanopapers can easily be produced by filtering a suspension of nanocellulose, followed by consolidation in a hot-press. The utilization of nanopapers enables better exploitation of the outstanding mechanical properties of CNF compared to composites in which CNF are introduced conventionally.

In this regard, the characteristics of the nanopapers show a significant impact onto the final composite-properties. Thereby not only the mechanical properties of the nanopaper are of importance. One parameter that is anticipated to significantly influence the properties of composites is the porosity of the nanopaper utilized. Whereas low porosities are usually preferred for achieving good mechanical properties of the nanopapers, low porosity nanopaper also show high resistance for a resin to enter into the nanopaper structure. This leads to suboptimal adhesion and the creation of voids resulting in lower mechanical properties of the composite as potentially possible.

Our approach was to adjust the porosity of cellulose nanopapers by solvent-exchanging the CNF suspension with various types of organic solvents for papermaking to allow for a better infiltration of the resin. To produce composites, layers of nanopapers were infused with an epoxy resin by lamination and subsequent hot-pressing. From these composites, specimens for thermo-physical and mechanical measurements were prepared and tested. Results indicated a major impact of the characteristics of the nanopapers on the physico-chemical and mechanical properties of the composites.

# **Characterization of Biopolymers and Synthetic Polymers using Asymmetric Flow Field-Flow Fractionation (AF4) and Thermal Field-Flow Fractionation (TF3) coupled to Multi-Angle Light Scattering (MALS)**

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Field-Flow Fractionation (FFF) has become a reliable analytical tool for the separation and comprehensive characterization of polymers, biopolymers, proteins and nanoparticles. Four different FFF techniques are commonly used today: asymmetric flow FFF, centrifugal FFF, thermal FFF and gravitational FFF. By coupling the FFF systems to suitable light scattering detectors, such as multi-angle light scattering (MALS) and dynamic light scattering (DLS) and concentration detectors such as UV and refractive index, the molecular weight distribution of synthetic polymers and biopolymers can be measured together with the molecular structure (degree of branching, copolymer composition and aggregation) of these samples.

In this poster the application of asymmetric flow FFF (AF4) for the characterization of biopolymers in aqueous solvents and thermal FFF for the characterization of synthetic polymers in organic solvents will be demonstrated. Several application examples will show the possibilities of the FFF techniques and the results that can be achieved when FFF separation methods are coupled to multi-angle light scattering (MALS) detection.

# Chemistries for Self-Assembling Polymer-Drug Nanoparticles

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**Summary:** For disease targets such as cancer, there is a need to identify new polymer carriers that are compatible with and capable of co-assembly with drugs. These delivery systems should release payloads at levels above the therapeutic threshold rapidly and site-specifically and degrade predictably to known components. In this work, the effect of varying size and architecture of drug delivery polymers formulated from hydroxypropyl methacrylamide (HPMA) on *in vitro* and *in vivo* performance is investigated.

**Results and Discussion:** 1<sup>st</sup> generation hyperbranched polymers (HBPs) were synthesised from HPMA and PEGMA via RAFT polymerisation, with molecular weights and particle sizes from 36 kDa and 3.5 nm to 94 kDa and 12 nm. Cell viability assays in MDA-MB-231 cells showed the HBPs were not toxic at all concentrations tested. The biodistribution of the 1<sup>st</sup> generation HBPs were assessed through an *in vivo* study in healthy mice. The polymers were found to be biocompatible and did not induce any adverse effects *in vivo*. 2<sup>nd</sup> generation polymers were synthesised from HPMA in varying architectures, with the inclusion of degradable monomers for both polymer degradation and stimuli-responsive drug release, which were varied between 5-20 mol% with HPMA to create a diverse polymer library. These had molecular weights and particles sizes from 75 kDa to 107 kDa and 6.0 to 10.6 nm, and up to 40 nm for micelles. Anti-cancer drugs were conjugated to the polymers through a hydrazone linkage, allowing for stimuli-responsive drug release. Preliminary *in vitro* and *in vivo* experiments demonstrate consistent findings to the 1<sup>st</sup> generation library, where all polymers were able to be cleared through the kidneys, and showed minimal liver and spleen accumulation.

**Conclusions:** HPMA polymers demonstrate suitability for *in vivo* applications due to their lack of toxicity both *in vitro* and *in vivo*. Degradable polymers of various architectures are able to be synthesised and facilitate stimuli-responsive drug delivery through an acid-labile hydrazone bond. The library of polymers allows for important investigations into the effects of size, shape and molecular weight on drug delivery performance.

# Clicked Gelatin Hydrogels - Multifunctional Networks Showing Enzymatic Surface Degradation

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Tailoring material properties of biopolymers such as proteins or polysaccharides in a physiological environment typically requires network formation by establishing covalent and/or physical netpoints. We have formerly demonstrated that copper-catalyzed azide-alkyne cycloaddition of functionalized hyaluronic acid and bifunctional crosslinkers is a suitable strategy for tailoring the elasticity of the resulting hydrogels, and that copper removal by washing with EDTA solution is effective for the synthesis of non-toxic materials [1]. Here, it is shown that a similar strategy can be adopted for the synthesis of gelatin-based networks. Alkyne functionalized gelatin was reacted with 4,4'-diazido-2,2'-stilbenedisulfonic acid (DSSA) or 1,8-diazidooctane (DAO) as diazides to give hydrogel networks with properties tailorable by diazide amount and rigidity. DSSA yielded hydrogels with Young's moduli  $E$  of 50-390 kPa, storage moduli  $G'$  of 1-10 kPa, and swelling degrees  $Q$  of 150-250 vol.%, while the more flexible DAO resulted in hydrogels with  $E = 125$  kPa to 280 kPa, storage moduli  $G'$  of 1-25 kPa, and  $Q = 225$ -470 vol.%. Variation of the ratio of alkyne and azide groups furthermore resulted in networks, in which the reactive groups could be used for a subsequent covalent functionalization of the hydrogels, which was demonstrated by functionalization with dexamethasone. So, the copper catalyzed azide-alkyne cycloaddition reaction is suitable for synthesizing multifunctional gelatin-based networks with tailorable properties, which combine degradability, potential for covalent attachments, and provision of cell adhesion sites. In hydrolytic degradation studies the DSSA networks proved to be more resistant to degradation than the DAO networks. The rate of degradation was ruled by the crosslinking density of the network and proceeded via a bulk degradation mechanism. Addition of *Clostridium histolyticum* collagenase resulted in a much enhanced rate of degradation, which interestingly occurred via surface erosion. The hydrodynamic radius of the enzyme (4.5 nm) was smaller than the mesh size of the hydrogels determined in rheological experiments (>7 nm). This shows that even in hydrogels with large mesh size enzymes may be used as switch to change from a bulk to a surface degradation mechanism, which is furthermore much faster than the observed hydrolysis. Such a knowledge of the degradation mechanism is pivotal for predicting a material performance in vivo and design the polymer network according to this prediction.

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# Combating Multi-Drug Resistance Bacteria with Polymer Coatings and Hydrogels

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NTU

In the recent year, the appearance of multiple resistances of the antimicrobial agent toward the different types of pathogenic bacteria is the most prominent threat to the global public health. The invention of antibiotic to the medical field has great impact on human mortality and morbidity. However, the multi drug resistance (MDR) effect of the pathogenic bacterial towards commonly used antibiotics has impeded the treatment of bacterial infections.

In the recent few decades, the Antimicrobial polymers (AMPos) have been widely used as a promising antimicrobial alternative to combat the infectious disease caused by MDR bacterial. Hence, unlike traditional antibiotics, AMPos interact with the bacterial membrane through non-specific electrostatic interaction. This electrostatic mode of interaction offers the AMPos to progressively interact with the bacterial with a less likely hood of bacterial resistance.

We have developed a series of antibacterial hydrogel based on AMPos that is intrinsically antibacterial and non-leachable. For example, in a wound infection mice model to compare the efficacy of our hydrogel with commercial antimicrobial wound dressings (Allevyn Ag and Algisite Ag, Smith & Nephew), NTUWound1 hydrogel performed better by killing 4.3 log order (>99.99%) of Methicillin-resistant *Staphylococcus aureus* (MRSA USA300) and 4.1 log order (>99.99%) of *Pseudomonas aeruginosa* O1 (PAO1) in a 0 h infection model, and 3.8 log order (>99.9%) of MRSA USA300 and 3.2 log order (>99.9%) of PAO1 in a 24 h infection model. The *in vivo* bacterial killings were much higher than the commercial antimicrobial wound dressings. Our **NTUWound1** hydrogel is also non-inflammatory and non-pyrogenic, as it significantly reduces the number of inflammatory cells in infected mice skin to a non-infected wounded level.

We have developed a catheter antibiofilm coating that is non-leachable and *in vivo* anti-biofilm. Catheters are indispensable tools of modern medicine but catheter-associated infection is a significant clinical problem, even when stringent sterile protocols are observed. When the bacteria colonize catheter surfaces, they tend to form biofilms making them hard to treat with conventional antibiotics. Hence, there is a great need for inherently antifouling and anti-bacterial catheters that prevent bacterial colonization. The *in vivo* anti-bacterial and anti-biofilm effect of our non-leachable covalently linked coatings (using a mouse catheter model) can be tuned to achieve about 99% reduction clinically relevant pathogenic bacteria (specifically with Methicillin-resistant *Staphylococcus aureus* (MRSA)).

# Complex Movements Enabled by Triple-Shape Hydrogels

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Stimuli-sensitive hydrogels provide the ability to store large amounts of water, exhibit soft tissue-like mechanical properties, and are capable to respond to a stimulus like temperature, changes in pH, or a variation of the concentration of ions.<sup>[1]</sup> The strategy to incorporate crystallizable switching segments as side chains in a hydrophilic polymer network resulted in hydrogels with on demand directed movements when heat was applied, whereby constant degrees of swelling during shape switches were obtained.<sup>[2]</sup>

Here we report about hydrogels providing complex movements of soft materials with two almost independent shape changes, which were triggered by a thermally-induced triple-shape effect.<sup>[3]</sup> Triple-shape hydrogels (TSHGs) with two different semi-crystalline switching segments integrated as side chains were designed, whereby interferences of volume changes could be avoided as the degrees of swelling were almost independent of different shapes and temperatures. Two distinct shapes were implemented by a two-step programming procedure resulting in shape fixity ratios of generally > 50%. While shorter side chains orient perpendicular to the hydrophilic main chain, side chains with a higher molecular weight gain lower orientation after deformation as detected by means of X-ray scattering. Furthermore, it was observed that the orientation of the switching domains is not a key requirement for adequate shape fixity and recovery ratios of TSHGs. Therefore, these soft materials, which provide complex directed movements, are potential material candidates for two-step self-unfolding devices or soft temperature-sensitive actuators, e.g. smart valves for flow rate control in an aqueous media.

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# Conjugated Polymers for Photocatalytic Hydrogen Evolution

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*University of Liverpool*

Photocatalytic hydrogen production from water is a research area of immense interest as hydrogen has been identified as a potential energy carrier of the future. Most of the studied photocatalysts are inorganic and organic materials have been far less studied. In this contribution, we will present the application of conjugated microporous polymers (CMPs) as catalysts for photocatalytic hydrogen evolution. The optical band gap of the polymers was fine-tuned over a broad range by varying the amount of co-monomer incorporated in a Suzuki-Miyaura type copolymerization. These polymer networks exhibit apparent Brunauer-Emmet-Teller (BET) specific surface areas in the range 500–1000 m<sup>2</sup>/g as measured by nitrogen adsorption at 77 K. The CMPs were found to be highly active for photocatalytic hydrogen evolution from water in the presence of a sacrificial electron donor, without the need for an added metal co-catalyst. The introduction of planarized fluorene, carbazole, dibenzothiophene, or dibenzothiophene sulfone units into poly(*para*-phenylene)s (PPP), greatly enhanced the hydrogen evolution rates of PPP-derived co-polymers. A dibenzothiophene sulfone co-polymer has a UV photocatalytic activity that rivals TiO<sub>2</sub>, but is much more active under visible light also outperforming platinized commercial carbon nitride. Here, we will discuss how transient absorption spectroscopy was used to monitor the temporal evolution of photogenerated reaction intermediates on slow and ultrafast timescales. This allowed us to draw a comprehensive picture of the processes that take place upon photoexcitation and to correlate the anion transient signal with the activity of the respective polymer.

# **Continuous-Flow Synthesis of Block Copolymer Nanoparticles via RAFT Dispersion Polymerisation**

S. Parkinson, N. Warren, R. Bourne

*University of Leeds*

As an alternative to batch synthesis, continuous-flow synthesis is becoming much more popular since it is also often faster, cleaner, cheaper and safer. Furthermore, laborious processing and purification steps can be avoided since it allows multi-step syntheses to be conducted in series through the rapid progression of intermediates. Recently continuous flow reactors have been used to synthesise a range of controlled structure block copolymers via RAFT polymerisation. Herein, we develop a wholly aqueous continuous flow process designed for RAFT synthesis and self-assembly bio-relevant block copolymers. We evaluate the effects of various parameters on the reaction kinetics and compare the resulting material with that prepared in batch.

# **Contraction and alignment of bioengineered anchored fibrin constructs as functional skeletal muscle models**

I. Roberts, C. Valdivieso, R. Donno, F. Galli, A. Tirella, G. Cossu, N. Tirelli

*The University of Manchester*

We aim to study biomaterial instructed differentiation in the generation of connective tissue with the ultimate aim of developing functional skeletal muscle fibres. A preliminary model using human dermal fibroblasts within fibrin hydrogels is used to prove and study cell-mediated contraction and alignment. These constructs are produced with defined geometries and fibrin concentration (with variation of mechanical properties, varying the elastic modulus up to 2.3 kPa). In particular, different seeding strategies were studied to optimise the construct contraction, exploring the role of 2D vs 3D in vitro systems cultured for up to 2 weeks.

An additional variable to these constructs, was the treatment TGF- $\beta$  (supplementing media with 10 ng/ml of TGF- $\beta$  for 2 days), evaluating its effect on contraction and on fibroblast-myofibroblast differentiation. Light-microscopy and image analysis are used to measure the contraction and alignment of these constructs over time. The expression of markers associated with myofibroblastic differentiation (e.g.  $\alpha$ -smooth muscle actin and ED-A fibronectin) are investigated using immunofluorescence imaging and qPCR. Masson's Trichrome and Picrosirius red histological staining are used to study the collagen deposition within the constructs. Having profiled the optimal cell culture conditions e.g. fibrin concentration, seeding method, cell density,  $\pm$ TGF- $\beta$ , time points, we are now progressing to the development of functional skeletal muscle constructs using human muscle progenitor cells.

# Critical Dependence of Molecular Weight on the Thermo-Responsive Properties of Diblock Copolymer Worms

N. Warren

*University of Leeds*

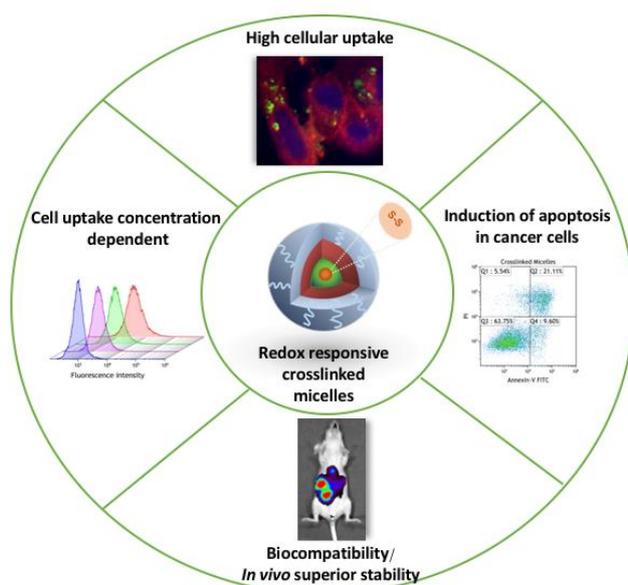
Aqueous dispersions of poly(glycerol monomethacrylate)-*b*-poly(2-hydroxypropyl methacrylate) (PGMA-PHPMA) block copolymer worms have attracted significant attention recently due to their ability to form thermo-responsive free-standing gels. Furthermore, their similarity to natural mucins enables them to be used as a synthetic medium for storage of human embryonic stem cells. For such a high profile applications, it is imperative that these materials are fully understood, but until now, the effect of the overall molecular weight of this diblock copolymer on the material properties has not been studied in detail. Herein, we use the fine control afforded by RAFT polymerisation-induced self-assembly (PISA) to prepare a series of PGMA-PHPMA block copolymer worm gels with varying molecular weight, while maintaining relative block volume fractions required to form worms. In addition to qualitative observations, we use SAXS to measure specific parameters such as cross-sectional diameter (a.k.a. worm thickness), worm contour length and the degree of hydration in the core. Variable temperature DLS, SAXS and rheology are used to characterise the thermo-responsive behaviour. In addition, a relatively novel rheo-optical shear induced polarized light imaging (SIPLI) technique is used to visualise alignment of the worms under shear. This technique is also used to compare the relaxation times for the various systems. Overall, it is shown that the molecular weight is critical in determining the material properties and should be a major consideration when designing any block copolymer worm gel.

# Crosslinked redox-responsive micelles for treatment of triple negative breast cancer

P. Monteiro, M. Gulfam, C. Monteiro, A. Grabowska, D. Heery, P. Gershkovich, C. Alexander

*University of Nottingham*

There is an urgent need to develop effective treatments for triple negative breast cancer (TNBC). The disease is characterised by aggressive progression, lack of standard therapies and low overall survival of the patients. Existing targeted therapies are not applicable to TNBC; thus, chemotherapy remains the standard of care for the treatment of TNBC. Here, we developed docetaxel (DTX)-loaded redox responsive crosslinked micelles using biocompatible and biodegradable functionalised mPEG-b-poly(D,L-lactide-co- $\alpha$ -N<sub>3</sub>- $\epsilon$ -caprolactone) for the treatment of TNBC. The empty micelles did not show cytotoxicity *in vitro* in any of the three cell lines used (MDA-MB-231, MCF7 and MCF10A), whereas DTX-loaded reducible crosslinked micelles had higher cytotoxicity against TNBC cells. Crosslinked and non-crosslinked micelles showed high cellular uptake in MDA-MB-231 (TNBC) cells which was found to be concentration-dependent. The crosslinked micelles induced higher levels of apoptosis in MDA-MB-231 cells. They also promoted an increase in the activity of caspase-3/7 in comparison to the cells treated with DTX-loaded uncrosslinked micelles and free docetaxel. Biodistribution results in healthy mice showed that crosslinked micelles have an increased stability *in vivo* in comparison to their non-crosslinked counterpart. Moreover, both formulations were found to be biocompatible and did not promote any adverse effect *in vivo*. These data demonstrate that crosslinked micelles can potentially have efficient distribution and accumulation at the tumour sites. Taken together, these results suggest that reducible crosslinked micelles may be an effective and promising nanocarrier for forthcoming clinical applications to TNBC.



## Digital Polymers: a new class of man-made macromolecules

J-F. Lutz

*Institut Charles Sadron*

Information-containing macromolecules are polymers that contain a message encrypted in their comonomer sequences. For example, digital polymers store binary information using two comonomers that are intentionally defined as 0- and 1-bits. A given digital sequence is synthesized using multistep-growth solid-phase approaches that allow exact placement of the coded monomers in the chains. Using such strategies, our group has described the synthesis of different digital polymers, such as polyphosphodiesteres, poly(alkoxyamine phosphodiester)s, poly(alkoxyamine amide)s, poly(triazole amide)s and polyurethanes. In all cases, the information stored in the polymer can be efficiently read by a sequencing technique; for example using tandem mass spectrometry. In addition, digital polymers containing thermo-cleavable backbones (e.g. alkoxyamine-containing polymers) allow erasing of information. Consequently, digital polymers are promising macromolecules for applications in the fields of product traceability, anti-counterfeiting materials, long-term storage and molecular data storage. However, in the latter case, additional research is needed before attaining a real molecular memory. Although the fact that information can be written, read, erased and stored in polymer single chains has now been clearly demonstrated, the preparation of a molecular storage device requires further developments that are not only related to polymer science but also to materials science, nanotechnology and computer science. In this lecture, I will highlight future directions in this important emerging area of research.

# Dual-stimuli responsive injectable nanogel/solid drug nanoparticle nanocomposites for the long-term sustained release for poorly soluble drugs

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*University of Liverpool*

## Summary

Solid drug nanoparticles (SDN)s (also known as nanosuspensions or nanocrystals) have been shown to be an attractive approach for the delivery of poorly water soluble drugs, with eight clinically approved medicines currently available. SDNs consist of particles composed entirely of solid drug and have been shown to give enhanced saturation solubility and increased dissolution rate.<sup>5</sup> Given these characteristics, SDNs offer great potential as drug reservoirs for implanted, sustained release drug delivery devices.

## Results and Discussion

We have developed a novel system in which SDNs are contained within an injectable, responsive, polymer matrix. This dual-stimuli responsive nanocomposite material, which gels upon injection into the body, allows the rate of drug release to be controlled and may prove beneficial in the treatment of long term conditions as an *in situ* forming drug delivery implant. We have shown that the thermally-responsive behaviour of PNIPAM nanoparticles can be tuned to form aggregates under dual-responsive conditions; increased temperature and ionic strength. Heating of the PNIPAM nanoparticles to body temperature (above their lower critical solution temperature) at physiological ionic strength, resulted a well-defined aggregate of PNIPAM nanoparticles. This aggregate was capable of entrapping up to 40% w/w a range of payload nanomaterials (including SDNs) to form nanoparticle/gel composites.

## Conclusion

These nanocomposites show controlled drug delivery over sustained periods of time (<120 days) with the rate of drug release controlled by the polymer composition. This makes the system a suitable candidate as an *in situ* forming drug delivery implant for hydrophobic drugs and SDNs, where injections could possibly be given as infrequently as twice a year to improve adherence rates in the treatment of long term and particularly chronic conditions.

## Dynamic Covalent Shape Memory Networks

T. Xie

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In contrast to thermoplastic shape memory polymers (SMP), thermoset SMP exhibit robust shape memory behaviours, but their permanent shape is not reconfigurable. In addition, the permanent shapes of both thermoplastic and thermoset SMP are defined by traditional molding process, which limits the geometric complexity of SMP based devices. Our recent work has established a third class of SMP with dynamic covalent crosslinkers that overcomes the above limitations. At relatively low temperatures, the covalent linkages remain dormant, the SMP exhibits the classical elasticity-based thermoset shape memory behaviours. At sufficiently high temperature such that the dynamic linkages are activated, the permanent shape can be reconfigured repeatedly via solid-state plasticity in a mold free manner. The talk will overview the physical principle, molecular designs, and practical benefits of this new class of SMP with regard to potential applications on flexible electronics.

# **Effect of sulfur content on properties of the dynamic vulcanized natural rubber and poly(lactic acid) blends**

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*Chulalongkorn University*

Thermoplastic vulcanizates (TPVs) based on poly(lactic acid) (PLA)/natural rubber (NR) blends were prepared through a melt blending with sulphur cure system. The objective is aimed to promote flow ability and strength for this biobased TPV as a result of high strength but low viscosity of PLA and high elasticity of natural rubber. Sulfur cure system is selected to promote crosslinking only in the natural rubber phase to build up its rigidity. The dynamic vulcanization was thus carried out in the variation of sulphur content and at the two polymer compositions (40/60 and 50/50 wt% of PLA/NR). Moreover, compatibilizer (poly(ethylene-co-glycidyl methacrylate), EGMA) at 10 phr was used to improve the mechanical properties of the blends. The effect of sulfur content (1, 1.5, 2 and 2.5 phr) on morphology, thermo-mechanical properties and mechanical properties of the TPVs were investigated. The phase morphology of TPVs showed co-continuous structure at 50/50 wt% and PLA dispersed domains at 40/60 wt%. In the presence of 1 phr sulphur, the morphology of phase inversion with large rubber particles was observed but disappeared when EGMA was added. The results in mechanical properties found that TPVs with EGMA showed the good mechanical properties, especially the tensile strength. The highest elongation at break (576%) obtained at NR 60 wt% and sulfur content at 1 phr while hardness of the TPVs with and without EGMA increased with increasing sulfur content.

# Elastin-like Polymers as an avenue for Hierarchical Biomineralization

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## 1. Summary

A major goal in materials science is to develop biomimetic functional materials that can offer precise control of building blocks across multiple length-scales towards hard tissue regeneration. Elastin-like polymers (ELPs) solution was crosslinked to form thin films, which then were mineralized at physiological conditions to develop hierarchical mineralization. We used a comprehensive suite of advanced multi-scale imaging techniques including TEM, FIB-SEM, and FEGSEM to investigate the mechanism of hierarchical mineralization and its relation to the distinctive structure at multiple length-scales ranging from crystallographic, to nano-, to micro, and up to the macro-scale.

## 2. Results and discussion

Here we report a novel biomineralization system based on a tuneable organic-inorganic bulk environment that controllably nucleates and grows hierarchically-ordered apatite structures as coatings or membranes with remarkable multi-scale organization. The structures exhibit elongated apatite nanocrystals of about  $85\pm 22$  nm in cross-section that are aligned and organized into approximately  $3.8\pm 0.9$   $\mu\text{m}$  thick prisms that resemble those found in human dental enamel. These prisms assemble further into hierarchical structures hundreds of microns in diameter that come together to fill macroscopic areas. The hierarchical structures can be grown in the presence of the organic matrix as thin mineralized membranes or coatings over irregular rough surfaces. The hierarchical structures can be grown as thin mineralized coatings over irregular rough surfaces. The potential of the system towards dental applications has been investigated by growing the hierarchical apatite structures as conforming acid resistant coatings that can conform to dentine while blocking the dentinal tubules. These results demonstrate the potential applicability in early treatment of dental caries, erosion, and dentine hypersensitivity.

## 3. Conclusion

We report on the discovery of a distinctive physicochemical environment, comprising a tuneable organic matrix with specific molecular composition, conformation, and physical conditions, which promote nucleation and hierarchical growth of apatite structures resembling those found in human dental enamel. The system has a potential for dental applications resembling those found in human dental enamel. The system has a potential for dental applications.

## Electrical and Dielectric behaviour of thin film of Poly(aniline-co-m-fluoroaniline)

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<sup>1</sup>*Qatar University*, <sup>2</sup>*Wollo University*

Semi-Transparent and conducting thin film like poly(aniline-co-m-fluoroaniline) has been synthesized by conventional oxidative polymerization by using aqueous solution of aniline, m-fluoroaniline and ammonium persulfate as oxidising agent. The copolymer has been characterised by XPS and XRD studies. The morphological and surface profile characterization has been performed by Atomic Force Microscopy (AFM) and the thickness of the thin film (50-100 nm) has been studied by transmission electron microscope (TEM). The electrical ac conductivity of these copolymers is measured to be of low magnitude in the low and high frequency region. The copolymer PA-co-m-FA50 has higher permittivity than polyaniline in the high frequency region. The composition of the copolymer has been confirmed from the binding energies of C-C, C-N and C-F in the XPS study. The dielectric behaviour of PA-co-m-FA50 copolymer is entirely dissimilar from polyaniline at high frequency.

**Keywords:** Polyfluoroaniline; Permittivity; Particle size; XPS; Binding Energy; XRD; AFM; TEM.

# Enabling alternative stimuli in shape-memory polymers

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Center for Regenerative Therapies*

Shape-memory polymers (SMPs) can switch their shape in a predefined manner upon application of a specific external stimulus. Accordingly, they have a high potential for applications ranging from electronic engineering, textiles, aerospace, and energy to biomedical and drug delivery fields based on the perspectives of new capabilities arising with such materials. Most SMP are triggered by heat. In this presentation other stimuli like magnetic fields, ultrasound and humidity are explored for inducing shape shifting effects. The mechanisms for these functions are explained and specific examples for shape shifting materials are given.

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# Exchange Transfusion with Red Blood Cell Substitute "Hemoglobin-Albumin Cluster" into Anesthetized Rats

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## Summary

Hemoglobin (Hb)-based O<sub>2</sub>-carriers (HBOCs) have been manufactured and evaluated in the last few decades, however side-effects have prevented their practical application. For instance, the increase in systemic blood pressure observed after the infusion is probably caused by vasoconstriction induced by Hb diffusion into the extravascular space followed by scavenging nitric oxide (NO), endothelial-derived relaxing factor.<sup>1,2)</sup> We have synthesized covalent core-shell structured protein clusters composed of Hb in the center and human serum albumin (HSA) at the periphery as a unique HBOC.<sup>3,4)</sup> The average HSA/Hb ratio of one cluster is  $3.0 \pm 0.2$  (Hb-HSA<sub>3</sub>). The obtained Hb-HSA<sub>3</sub> is expected to be a promising artificial O<sub>2</sub>-carrier in transfusion medicine.<sup>5)</sup> In this paper, we report physiological responses to exchange transfusion with Hb-HSA<sub>3</sub> solution into rats.

## Results and discussion

In order to evaluate the preclinical safety, the physiological responses to a 20% exchange transfusion with Hb-HSA<sub>3</sub> ([Hb]=5 g/dL) were investigated using anesthetized rats. The circulation parameters, blood gas parameters, and blood cell numbers were carefully monitored for 6 h after the injection. Time course changes in all parameters essentially showed the same features as those of the control and HSA group. Blood biochemical tests of the withdrawn plasma at 6 h after the exchange transfusion have also been carried out.

## Conclusion

The results of the 20% exchange transfusion with Hb-HSA<sub>3</sub> revealed the preclinical safety of this solution. The blood biochemical tests after exchange transfusion with Hb-HSA<sub>3</sub> showed no acute toxicity.

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# Exploring Dynamic Equilibrium of Diels-Alder Reaction for Solid State Plasticity in Remoldable Shape Memory Polymer Network

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*Zhejiang University*

The reversible and click nature of Diels-Alder (DA) reactions has made them ideal candidates to design materials with non-conventional properties. Most commonly, the reversibility of DA is utilized for designing thermosets that can be liquefied for reprocessing and/or self-healing, yet the dynamic equilibrium nature has been largely neglected. In this work shape memory polymers (SMP) containing DA moieties in the networks were synthesized. In addition to its remoldability at the liquid state at sufficiently high temperatures (above 110 °C), we show uniquely and surprisingly that such a network can undergo plastic deformation in its solid state at intermediate temperatures (60-100 °C) by taking advantages of its dynamic equilibrium for network topological rearrangement. The liquid state remoldability and solid state plasticity represent two distinct yet complementary mechanisms to manipulate the permanent shape of an SMP, leading to unprecedented versatility that can benefit a variety of applications in the future.

# Fabrication of Poly(PEGMA) Grafted Graphene Oxide and Polysulfone Based Porous Films via Breath Figure Method

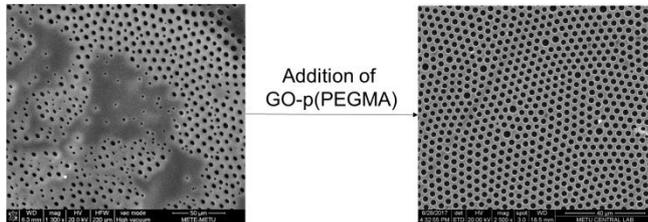
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*Orta Dogu Teknik Üniversitesi (ODTÜ)*

Porous polymer films are used in various different fields such as electronics, sensors, biomedical, catalysis, and separation. Breath figure (BF) method is a way of obtaining porous polymers via a self-assembly process based on water condensation. It became popular in scientific community after François obtained the first honeycomb patterned polymeric porous films in 1994. When compared to other fabrication methods, BF method has the following main advantages: It is a versatile technique and requires simple apparatus. Also, it allows tuning of pore sizes in a single step production. Briefly, in this method a solution of a polymer in an organic solvent is casted onto a substrate and then, it is placed under humid air flow. As the solvent evaporates, the surface of polymer/air interface gets colder. When humid air contacts the cold surface, water droplets are formed and may be regularly arranged on surface depending on process conditions. Formed water droplets act as a sacrificial template and they continue to grow or sink until all solvent is evaporated. After complete evaporation of solvent and water, a honeycomb shaped porous polymeric film is obtained. It is difficult to form regular honeycomb patterned polysulfone (PSF) films via BF method as PSF itself is not very effective in stabilizing water droplets during BF process even though such films could be very useful for membrane based separation applications. In this work, a small amount of poly(PEGMA) grafted graphene oxide (GO) was added to PSF/chloroform solution to stabilize water droplets during BF process and to obtain PSF microsieves with highly regular and through pores for microfiltration applications. As poly(PEGMA) grafted GO is anticipated to assemble at the pore surface, this is expected to increase the flux through and reduce fouling of the membrane too. In order to improve hydrophilic property of GO (synthesized via Tour Method) and to increase its dispersibility in chloroform, poly(PEGMA) chains were grown from a GO macroinitiator via Atom

Transfer Radical Polymerization (ATRP).

Obtained products were characterized with ATR-FTIR, TGA, GPC, <sup>1</sup>H-NMR, and XPS. The surface morphology of obtained porous films was examined using SEM analysis. Our results showed that poly(PEGMA) grafted GO facilitated regular pore formation



during BF process and resulted in highly uniform honeycomb patterned PSF films (See figure on the left). Average pore sizes of the obtained porous films could be varied from 2 to 6 microns depending on process conditions. The filtration performance of porous films was tested by filtering yeast solutions. The obtained porous films are considered as low cost microsieves for microfiltration applications.

## Green synthesis of long chain polyesters from agro-wastes catalyzed by SnO<sub>2</sub> nanoparticles

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Tomato peels are an abundant raw material for multifunctional fatty acids. In fact, we have depolymerized them by using NaOH solutions and have analyzed their chemical composition, being the main components the 10,16-dihydroxyhexadecanoic (43.2 wt.%), 9,12-octadecadienoic (16.1 wt.%), and 9-octadecenoic (11.9 wt.%) acids. Such monomers have been polymerized by a free-solvent melt-polycondensation method in the presence of SnO<sub>2</sub> nanoparticles (NPs), producing free-standing films.

SnO<sub>2</sub> NPs were synthesized following the 'benzyl alcohol route' assisted by microwave irradiation. The obtained NPs presented a narrow size distribution between 3 and 4 nm as revealed by morphological inspection. Structural characterization pointed out NPs crystallinity with SnO<sub>2</sub> in the characteristic cassiterite polymorph.

The conditions of the polycondensation were optimized in terms of temperature (150, 175, 200, and 225°C), time of reaction (1, 2, 3, 4, 5, 6, and 7 hours), and load of nanoparticles (0, 100, 200, and 300 ppm). The kinetic and thermodynamic parameters of the reaction were calculated by infrared spectroscopy of the resultant samples synthesized in the above conditions. Mechanical, hydrodynamic and thermal properties of free-standing films were related to the degree of polymerization and the presence of NPs inside the polymer matrix.

# Heated solution blow spinning of poly(vinylidene fluoride) Fibres: Mechanical, morphological and structural effects

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Poly(vinylidene fluoride) (PVDF) has piezoelectric, hydrophobic and chemically resistant properties and wide ranging applications. When processed into membranes of nanofibers, PVDF has potential for lightweight energy scavenging, air filtration and water filtration. The most widely used method of fabricating PVDF nanofibers is by electrospinning, however low fabrication rates and the high costs of industrial scale electrospinning systems limit the upscaling of production. Solution blow spinning (SBS) is an industrially scalable alternative nanofiber fabrication technology which uses compressed air to produce nanofibers from a polymer solution an order of magnitude faster than electrospinning. However, the presence of large beads in SBS PVDF sheets significantly decreases the mechanical and piezoelectric properties when compared to pristine electrospun sheets. The formation of these beads in SBS PVDF is poorly understood. One of the factors that influence the formation of these beads in electrospinning systems is the formation of PVDF microgels within a PVDF/*N,N*-dimethylformamide (DMF) spinning solution when below a the sol-gel temperature. In this work the morphological, mechanical and structural properties of PVDF nanofibers spun via SBS from solutions heated to different temperatures are determined. PVDF/DMF solutions were heated via an in-line SBS feed tube running through a mineral oil bath immediately prior to spinning, and their mechanical, morphological and structural properties analysed. The results indicate that an increase in polymer solution temperature from 30 to 130°C immediately prior to spinning results in an increase in the strain at break from  $50 \pm 7\%$  to  $88 \pm 8\%$ , an increase in the ultimate tensile strength from  $0.9 \pm 0.3$  MPa to  $2.5 \pm 0.4$  MPa and a decrease in the area of beads visible in SEM images from  $\sim 30\%$  to 3%, determined by image analysis. The overall crystallinity of the polymer is not affected by this process, however, the ratio of piezoelectric crystalline beta phase to non-piezoelectric alpha phase also appears to decrease concomitant with increasing polymer solution temperature, however PVDF fibers can be treated to increase beta phase. The production of PVDF nanofibers with little to no bead content and increased mechanical properties via SBS is significant as it provides a more rapid alternative to electrospinning, and will allow for easier upscaling of PVDF nanofiber fabrication.

# **How Pluronic block copolymers interact and modulate the response of lipid membranes to mechanical stress**

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Block copolymers are largely used in pharmacological formulation and may represent a breakthrough in the development of controlled drug/gene release systems or cell activities regulators. The identification of the key molecular interactions responsible for the destabilization of the cell membrane represents the first milestone towards a rational design of these biomaterials. Modelling can guide the understanding of the effect that biological active copolymers have on the structure and stability of lipid membranes. In this talk we will focus on a specific family of amphiphilic block copolymer known as Pluronic and will clarify the mechanism of membrane adhesion and breakage.

# Implantable Biodegradable Polymers for Drug Delivery and Tissue Separation and Marking

A. Domb

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Biodegradable polymers should possess specific physical, chemical, biological, functional, biomechanical, and degradation properties that fit the biomedical application at hand.

Biodegradable polymers have been synthesized from natural components: fatty acids, amino acids and saccharides to form compounds with tailored properties that fit the intended application. Injectable pasty polymers were synthesized from castor oil and used for the delivery of agents to diseased sites such as infected bones and solid tumors. Polyesters derived from amino acids have been used as scaffolds for tissue engineering and cationic polysaccharides were used as transfection agents for plasmid DNA and siRNA. Biodegradable balloons have been applied for separation of the prostate from the rectum for irradiation protection and for treating massive rotator cuff tear. Stent coating by crystallization of rapamycin and paclitaxel onto stent struts releasing the drug for weeks have been developed.

The preparation of biodegradable polymers and their applications for human wellbeing.



# **Materials science of advanced drug delivery systems: future generations of medicines?**

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## Summary

This paper will discuss materials science aspects of novel drug delivery systems in development for oncology therapeutics. There has long been the need for delivering challenging active molecules to treat a wide variety of diseases, including different types of solid tumour cancers. The latest technologies used for targeting tumours use the enhanced permeation and retention (EPR) effect to allow penetration of active ingredients into the leaky vasculature, enabling a preferential uptake into this tissue versus normal healthy tissue. Two different types of technology will be discussed; polymeric nanoparticles and stealth dendrimer conjugates. The potential effect of input materials variability will be presented, as will the benefits of using newer separation techniques and detection technologies to determine molecular weights and study self-association and behaviour in delivery vehicles.

# Matrix-free Graphene Oxide Nanocomposites by Surface-Initiated Polymerisation

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We present the synthesis of hydrophobic ‘matrix-free’ composites of graphene oxide (GO), in which all of the polymer matrix phase is composed of surface-grafted polymer brushes grown from the GO by ARGET ATRP.

For the first time, a cationic macroinitiator (MI) was immobilised on anionic GO and subsequently grafted with hydrophobic polymer grafts. Dense grafts of PBA, PBMA and PMMA with a wide range of average graft lengths were polymerised by surface-initiated controlled radical precipitation polymerisation from the statistical MI. Extremely stable solvent dispersions of grafted GO in the isotropic state were obtained. Transparent and translucent matrix-free GO-composites could be melt-processed directly using only grafted GO. After processing, birefringence due to nematic alignment of grafted GO was observed as a single giant Maltese cross, 3.4 cm across. Permeability models for composites containing aligned 2D-fillers were developed, which were compared with the experimental oxygen permeability data and found to be consistent with isotropic or nematic states. The storage modulus of the matrix-free GO-composites increased with GO content (50 % increase at 0.67 wt.%), while the significant increases in the thermal stability (up to 130 °C) and the glass transition temperature (up to 17 °C) were dependent on graft length. The tuneable matrix-free GO-composites with rapid thermo-responsive shape-memory effects are promising candidates for a vast range of applications, especially selective membranes and sensors.

Our latest work on surface modification of graphene-type materials will also be presented.

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## **Mechanically-tailored Fibrin Matrices for Wound Healing Applications**

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*The University of Manchester*

In wound healing applications, fibrin sealants are considered ease-to-use glues compared to sutures/staples due to their main advantages of fast healing and following minimum scarring. In fact, scars are produced by fibroblasts migration and consequent collagen deposition to the wound bed (causing an increase in the rigidity of the tissue). It has been demonstrated that wound-healing, hence tissue remodelling, is also influenced by the mechanical and structural properties of the final hydrogel network. In this work we describe the use of fibrin's native knob-hole affinity interactions to incorporate poly(ethylene glycol) (PEG)-peptide conjugates into the hydrogel, as a macromolecular model compound to modulate the matrix properties through altered fibrin polymerisation.

Hydrogels, varying fibrinogen concentration between 6.25 and 50 mg/mL and their hybrid versions, with PEGylated fibrin-interacting knob-A and knob-B mimics (GPRPGCG and GHRPGCG, respectively) used at different fibrinogen:PEGylated knob molar ratios (1:10 and 1:20), were evaluated in terms of rheological and compressive mechanical properties, and structural parameters (e.g. fibre diameter, fibre mass-to-length ratio). The migration of adult Human Dermal Fibroblasts (HDFa) was finally investigated in some of the characterised fibrin gels (6.25 and 12.5 mg/mL fibrinogen concentration with or without PEGylated knobs) by quantifying the HDFa radial invasion (as a function of time) from a confined cell-loaded clot in the network.

The inclusion of PEGylated-knob-A mimic in fibrin network returned greater fibroblasts migration rate compared to control gels and to its homologous knob-B mimic; notably, the migration rate inversely correlates with the Young's modulus of such gels. These results suggest that modulation of thrombin-mediated polymerisation can improve the migration of fibroblasts in fibrin gels, a condition that will potentially lead to speed-up wound healing and reduced scarring side effects.

# Medicinal polymer chemistry : From polymer design to therapeutic benefit and back

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Antiviral macromolecular prodrugs, innovative bioconjugation techniques, and engineering of biocatalytic materials for biomedicine - these areas of research are in the focus of our lab and during this presentation, we will discuss our recent findings on these avenues. I will present the development of biocatalytic implants as novel tools for site-specific drug delivery. We will also discuss the design of macromolecular prodrugs as broad-spectrum antiviral agents. Finally, I will outline our recent successes in delivery of latency reversing agents against HIV and the design of long circulating, high payload pools of antiviral drugs. Presentation aims to be of interest for diverse audience, specifically scientists in the fields of polymer science and engineering and biomaterials.

## Key recent publications

“Prodrugs in medicinal chemistry and enzyme prodrug therapies”, *Adv. Drug Deliver. Rev.* DOI 10.1016/j.addr.2017.06.013

“Substrate mediated enzyme prodrug therapy”, *Adv. Drug. Deliver. Rev.* 10.1016/j.addr.2017.04.013

Macromolecular antiviral agents against Zika, Ebola, SARS and other pathogenic viruses”, *Adv. Healthcare Mater.* Early view

“Synthetic polymer with a structure-driven hepatic deposition and curative pharmacological activity in hepatic cells”, *ACS Macro Lett.* ASAP

“Albumin-polymer-drug conjugates: long circulating, high payload drug delivery vehicles”, *ACS Macro Lett.* **2016**, *5*, 1089-1094.

“HIV anti-latency treatment mediated by macromolecular prodrugs of histone deacetylase inhibitor, panobinostat”, *Chem. Sci.* **2016**, *7*, 2353-2358.

“Polyanionic macromolecular prodrugs of ribavirin: antiviral agents with a broad spectrum of activity”, *Adv. Healthcare Mater.*, **2016**, *5*, 534-540.

“Self Immolative Linkers Literally Bridge Disulfide Chemistry and the Realms of Thiol-Free Drugs”, *Adv. Healthcare Mater.* **2015**, *4*, 1887-1890

# **Melt Reprocessable Polymer Networks and Network Composites with Full Property Recovery Associated with Cross-link Density after Multiple Recycling Steps: Dynamic Cross-links Based on (1) Nitroxide-Mediated Polymerization and (2) Cyclic Carbonate Aminolysis**

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Two different one-step synthetic approaches have been developed to prepare cross-linked polymer networks and network composites with dynamic cross-links that allow for multiple melt-reprocessing steps with full recovery of cross-link density. In one case, we use nitroxide-mediated polymerization, with the strongly temperature-dependent reversible capping-uncapping step as the basis for the dynamic cross-links. By combining a polymerizable monomer containing a stable nitroxide radical with a bifunctional radical initiator and monomer and/or polymer with carbon-carbon double bonds amenable to radical polymerization, melt-reprocessable networks have been produced that have been recycled multiple times with full recovery of properties (e.g., rubbery plateau modulus) related to cross-link density. This approach has also been extended to polymer network composites containing as much as 20 wt% carbon black dispersed polymer such as polybutadiene and natural rubber, also leading to full recovery within error of properties related to cross-link density. Thus, this approach has potential for use in developing rubber tires that can be recycled for high-value applications, including use as recycled, reprocessed tires, and providing a method to overcome a decades-old problem of spent rubber tires being discarded, burned for energy content, or recycled in other low-value uses. In the second case, cyclic carbonate aminolysis is done in the presence of appropriate catalyst to prepare polyhydroxyurethane networks that can be melt-reprocessed multiple times with full recovery of cross-link density. These materials also exhibit properties that are competitive with polyurethane networks that cannot be effectively melt-reprocessed because of the lack of effective dynamic cross-links. Additional sustainability and human-health benefits are associated with the non-isocyanate based polyhydroxyurethane networks in comparison with the isocyanate-based polyurethane networks. Factors important in achieving full property recovery in melt-reprocessed dynamic polymer networks will also be discussed.

# Microfluidic biomaterials - Reactive polymeric surfactants for chemical library diversity

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**Background:** Advanced biomaterials are an important part for a lot of medical applications, e.g. drug delivery, regenerative medicine and novel medical devices.<sup>[1]</sup> Biomaterials, nowadays, are mainly investigated with two-dimensional screening methods, which is not an accurate representation of the *in vivo* environment they will be applied to later on.<sup>[2]</sup> Therefore, we want to advance the existing biomaterial libraries into the third dimension, investigating the influence of 3D structured biomaterials in comparison to their 2D counterparts.

**Methodology:** One methodology to achieve 3D biomaterials is the preparation of particles in a microfluidic approach.<sup>[3,4]</sup> Microfluidics gives us access to homogeneous particles with low polydispersity in a highly reproducible manner. Additionally, it possesses a high versatility regarding the large variety of materials, which can be processed, with minimal adjustments in the microfluidic setup.

**Results and Discussion:** By utilising different chip designs we created a large library of microparticles with variation in size and chemistry. However, during the characterisation of these particles, the crucial role of the used surfactant on the surface chemistry of the particles became apparent. To avoid this “contamination” of the particles’ surface we developed novel polymeric surfactants (surfmers) containing the target chemistry. This approach guarantees the particles surface to contain only the chemistry we targeted for without adding any other contaminant into the system.

**Conclusion:** With the combination of microfluidics and tailored polymeric surfactants, we gain access to a large variety of three-dimensional polymeric particles, excluding any contamination by additional chemistries in the system. Therefore, any biological response can only be caused by the chemistry and morphology of the particulates, but not by a contamination from additional reagents.

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# **Microfluidic technology for the reproducible and controlled production of polymer microparticles**

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Controlling diameter of PLGA, PCL or other polymer particles while maintaining a narrow particle size distribution is a challenge when encapsulating drugs into polymer spheres. On top of that, reproducibility and minimising API losses are essential parameters to consider when planning to scale up production.

Microfluidic technology is emerging as a method of choice for highly controlled drug encapsulation as it significantly improves on yields and quality achieved by traditional batch methods. Recent innovations in microfluidics have overcome frequent drawbacks associated with microfluidic systems, such as scaling up capabilities, and there are now machines able to produce tons of particles per month.

In this presentation, we are going to present microfluidic solutions for drug encapsulation and polymer particle synthesis, discuss results and introduce a multi-chip parallel system for seamless high throughput production.

# Miniaturized Polymeric Micro-Cuboids Prepared from Crystallizable Copolymer Networks Investigated on the Nano- and Micro-Level

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Non-spherical polymeric micro-devices with tuneable surfaces are exciting materials with attractive potential applications in biological and medical analysis, drug delivery, bioimaging or microfluidic systems and could lead to new developments.[1] Miniaturization of shape-memory materials can be achieved for example by soft-lithography approaches leading to micro-cuboids of dimensions of 25x25x10  $\mu\text{m}$  of crosslinked semi-crystalline poly[ethylene-co-(vinyl acetate)] (PEVA).[2] Due to the small dimensions of the particles optical microscopy (OM) and atomic force microscopy (AFM) was used for the quantification of temperature-triggered shape-memory effect at a micro- and nano-level for programmed cuboids. Individual micro-cuboids were programmed by compression with different degrees of deformations (in the range of 20 to 80%) and analyzed concerning their respective recovery behavior. The programming step influences the shape on two different levels including the overall shape change on the micro-level and the surface roughness of the cuboids top face on the nano-level (Scheme 1). The surface roughness of cuboids in the programmed state was significantly lower with  $R_q \sim 5$  to 8 nm while it recovered to the original roughness ( $R_q \sim 17$  to 19 nm) after heating independent on the PEVA composition and the compression rate (CR). While on the micro-level a CR dependent recovery trend was observed, as here the lowest compressions (CR: 20 to 40%) lead to the best recovery ratios (almost 100%), while the effect is reduced upon increasing the CR (> 60%). Additionally a more detailed study of the projected area observed by OM opened an insight into recovery kinetics which indicates a fast recovery process in the first seconds by a release of the stored stress. The following entropy driven shape change of the cuboids are influenced by the adhesion to the surface reducing the recovery rate. Tunability of surface roughness on the nano-level and shape changes on the micro-level in combination could lead to changes in wettability or surface area enabling future perspectives on the field of nano-technology.

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# Monomer/catalyst tuning for selective ring-opening polymerization to deliver tailored polyhydroxyalkanoates (PHAs) architectures

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Poly(hydroxyalkanoate)s (PHAs) are a class of natural or synthetic aliphatic polyesters which feature the same three-carbon backbone structure, only differing by their substituent (R) in  $\beta$ -position. PHAs have attracted considerable interest as “green” engineering plastics. These biodegradable and biocompatible polymers represent a targeted choice for in particular packaging, and biomedical applications in tissue engineering and as drug delivery systems.

Recent highlights of research at Rennes University in the field of 1) tunable catalytic systems for the ring-opening (co)polymerization (ROP) of  $\beta$ -lactones (e.g.  $\beta$ -butyrolactone (BL; R = Me), benzyl  $\beta$ -malolactonate (MLA<sup>Be</sup>; R = CO<sub>2</sub>CH<sub>2</sub>Ph),...) into their corresponding PHAs (poly(3-hydroxybutyrate) (PHB), poly(benzyl  $\beta$ -malolactonate) (PMLA<sup>Be</sup>),..., respectively),<sup>1</sup> 2) original sequence controlled PHAs featuring a high degree of control over molecular and microstructural characteristics,<sup>2</sup> and 3) amphiphilic PHA-based copolymers self-assembly towards drug delivery nanoobjects,<sup>3</sup> will be presented. Our most significant achievements in this endeavor include the development of strategies that enable the synthesis of alternated PHA-based copolymers, and the evidence of the relationship between the chemical structure/composition, self-assembly and *in vitro* cytotoxicity of the macromolecules.

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# Morphological analysis of surface functionalized porous poly(ether imide) microparticles by mercury porosimetry

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Highly porous poly(ether imide) (PEI) microparticles are discussed as candidate absorber materials for apheresis applications, e.g. the removal of uremic toxins from the blood of renal failure patients. The internal pore structure can be altered by variation of the solvent applied in the spraying/coagulation process [1], and by surface modifications. To avoid the attachment of serum proteins to the surface of the hydrophobic PEI materials, a hydrophilic modification of the porous microparticles by nucleophilic reaction with either low molecular weight polyethylene imine (Pei) or potassium hydroxide (KOH) was recently applied [2]. The spraying process provides PEI particles with a broad size distribution ranging from 20 to 800  $\mu\text{m}$ .

In this study, we first explored whether mercury intrusion porosimetry (MIP) is a suitable method to characterize particle size and intraparticle porosity of PEI microparticles. By an analytical wet sieving procedure, the obtained PEI microparticles were separated into five size fractions, which were analyzed in detail by MIP, but also by nitrogen absorption and scanning electron microscopy (SEM). MIP data allowed reliable size distribution for PEI particles in monodisperse powders with diameters up to about 150  $\mu\text{m}$ . In this particle size range, MIP may be a faster analysis technique compared to SEM. Furthermore, MIP reveals for all size fractions high porosity values in the range from 78% to 84% with pore diameters in the range from 10 to 1000 nm. A bimodal pore size distribution was found having a first peak at around 100 nm and a second pronounced peak at higher pore sizes. Finally, MIP was used to characterize the morphological changes of size fractionized PEI microparticles after surface modification with amino-functionalized components. The functionalization of imide bonds on the surface of PEI-particles was detected with XPS. While treatment of particles with PEG-diamine did not alter both particle size and pore size distribution, the reaction with diethanolamine resulted in a slight reduction of averaged particle size and significant increase in the number of pores in the size range of 50 to 500 nm.

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## **Nanomanufacturing through microfluidic-assisted nanoprecipitation: advanced analytics and structure-activity relationships**

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We have used microfluidics (cross-shaped chip) for the preparation of drug-loaded poly(lactic acid-co-glycolic acid) (PLGA) nanoparticles. The polymer precipitates from an acetone solution upon its controlled laminar mixing (flow focusing) with an aqueous solution of a surfactant, allowing for an operator-independent, up-scalable and reproducible preparative process of nanoformulations.

Firstly, using PEGylated surfactants we have compared batch and microfluidic processes, and showed the superior reproducibility of the latter and its strong dependency on the acetone/water ratio (flow rate ratio). We have then focused on the issue of purification from free surfactant, and employed advanced characterization techniques such as flow-through dynamic light scattering as the in-line quality control technique, and field flow fractionation (FFF) with dynamic and static light scattering detection, which allowed the detection of surfactant micelles in mixture with nanoparticles (hardly possible with stand-alone dynamic light scattering). Finally, we have shown that the choice of polymer and surfactant affects the release behaviour of a model drug (paclitaxel), with high molecular weight PLGA (RG756) and low molecular weight surfactant (tocopheryl poly(ethylene glycol) 1000 succinate, TPGS) apparently showing higher burst and accelerated release.

# Nanopatterning with homopolymers: from planar substrates to nanoparticles

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Further progress in nanoscience and nanotechnologies is intimately linked to the ability to form surface nanostructures with characteristic dimensions in the range from several nanometers to tens of nanometers. Such nanostructures have a plethora of applications in microelectronics, optics, memory storage, tribology, coating industries and biotechnologies.<sup>[1]</sup>

Self-assembly of block copolymers at interfaces is a versatile bottom-up patterning approach,<sup>[2]</sup> however surface patterning with homopolymers offers several crucial advantages, e.g., direct access to a substrate without the need to etch one of the blocks and the ability to pattern substrates with complex shapes. We present a surface nanopatterning strategy that utilizes homopolymers end-grafted to either a planar substrate, or the surface of inorganic nanoparticles. Following the reduction in solvent quality, an originally smooth polymer layer undergoes surface segregation into pinned micelles. This process is reversible, however the surface pattern can be permanently preserved using a photocrosslinking step. The strategy offers the ability to control the pattern type, the characteristic feature size of the pattern, and the number of surface micelles per nanoparticle, in agreement with a theoretical model. A broad parameter space controlling these properties includes polymer type, molecular weight and grafting density, as well as the quality of the solvent.

For planar substrates, we show controllable transitions from spherical micelles to worm-like features, to surface networks and porous structures. We use these patterns for nanolithography applications.<sup>[3]</sup> For nanoparticles, the versatility of the patterning is demonstrated for nanoparticles with different dimensions, shapes and compositions, tethered with various types of polymers and subjected to different external stimuli.<sup>[4]</sup> These “patchy” nanoparticles have potential applications in fundamental research, the self-assembly of nanomaterials, diagnostics, sensing and colloidal stabilization.

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## **Network-PIM-1 as a novel filler for incorporation into PIM-1-based mixed matrix membranes (MMMs)**

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Polymers of intrinsic microporosity (PIMs) are a class of high free volume glassy polymers with rigid contorted macromolecular backbones and interconnected free volume. These properties allow for the formation of microporous films with promising performance for energy-efficient gas separations. However, microporous polymers such as PIM-1 are prone to physical aging, *i. e.*, gradual loss of the free volume over time, which eventually limits their long term application as membrane materials. In recent years, there has been a growing volume of research on introducing a small amount of a porous material to a PIM-1 matrix to design innovative mixed matrix membranes (MMMs) with enhanced separation performance. To tackle the common issues with MMMs such as the poor polymer/filler interfaces, a possible approach is to use organic fillers which should offer a better compatibility with the PIM-1 matrix.

In this work, for the first time, a novel filler, network-PIM-1, with very similar chemistry to PIM-1, has been synthesized in order to use it as the dispersed phase in PIM-1-based MMMs. Similar to PIM-1, network-PIM-1 was prepared by a double nucleophilic aromatic substitution reaction and showed high Brunauer-Emmett-Teller (BET) surface area of 870 m<sup>2</sup> g<sup>-1</sup>. Free standing films containing very moderate weight fraction of network-PIM-1 in PIM-1 main matrix were prepared and the effect of this filler on the membrane structure and CO<sub>2</sub>/CH<sub>4</sub> mixed gas separation performance was studied. It was shown that addition of 0.5 wt.% network-PIM-1 to the membrane matrix improved the permeability by 66% with almost no loss in CO<sub>2</sub>/CH<sub>4</sub> selectivity compared to pure PIM-1 membranes. The results suggest a good perspective for network-PIM-1 as a selective and permeable filler with good compatibility with the polymeric matrix for incorporation into PIM-1-based MMMs.

# **New Amine Based Silicones with Intrinsic Anti-fungal Activity: Inhibiting Biofilm Growth**

S. Holder, K. Belsey, V. Makarovaite, C. Gourlay, J. Batchelor

*University of Kent*

Biofilm growth (particularly that of *Candida albicans*) on silicone voice prostheses can have significant post-operative implications for patients, often requiring multiple further surgeries and frequent prostheses replacements. A number of modifications to silicone surfaces have been shown to reduce biofilm growth, but significant difficulties have been encountered with each potential approach [Talpaert et al., *J Med Microbiol*, 2015, 64, (3)].

Here we present a new type of silicone elastomer, formed by the cross-linking reaction between an alkyl-halide terminated siloxane and the alkyl-amine branches of another siloxane. By modifying the ratios of these two components, and thus leaving different proportions of amine groups unreacted, it was possible to change the properties of the elastomer. The fewer the cross-linked groups, the greater the mobility of the chains within the siloxane and the greater the rearrangement potential. The surfaces of the samples were shown to be able to switch from hydrophobic to moderately hydrophilic in the presence of water. Results from the mechanical, calorimetric and wettability measurements will also be presented for these novel materials.

The elastomers were subsequently shown (both by halo and viability tests) to have inherent antifouling and antimicrobial properties with regards to *Candida albicans*, and preliminary data has been collected for other common biofilm components, such as *Streptococcus* and *Staphylococcus* species. The reduction in biofilm growth in comparison to standard polydimethylsiloxane was seen to be proportional to the number of amine groups left unreacted within the network. The mobile amine/ammonium groups at the silicone surface are thought to behave as cell membrane disruptors and hence kill fungal cells and inhibit biofilm formation.

The ease of synthesis of this elastomer together with its mechanical and intrinsic antifouling properties highlight its potential to be used in prostheses whilst also reducing some of the existing problems with antimicrobial silicones.

# New nanocomposite chemoresistive sensor for ethylene detection: highly tunable porosity and electrical resistance for high sensing performances

G. Mechrez

*Institute for Postharvest and Food Sciences Volcani Center*

**Summary:** Uncontrolled ethylene emission in growth chambers, greenhouses, storage facilities and during transportation leads to fast degradation of fresh produces and consequently to a significant amount of postharvest losses. To predict the shelf life, optimize the fruit quality, and reduce in-storage losses it is of paramount importance to monitor and control the ethylene emission along the supply chain. The development of miniaturized, portable, low-cost, and real-time detection chemical gas sensors for ethylene, therefore, evokes strongly rising demand. Chemoresistive Sensing technology rely on the direct reversible chemical interaction between sensing material and analyte. Due to their extraordinary mechanical and electrical properties and high aspect ratio, carbon nanotubes (CNT) are an emerging class of materials for chemical sensing of gases and volatile organic compounds. The current research presents a new chemoresistive gas sensor based on CNTs, embedded into porous polymeric structure. This offers rapid, low cost, reversible detection of ethylene at sub-ppm concentrations.

**Results and discussion:** Major challenge in this context is the dispersion of CNTs within the polymer matrix; due to their relatively large van der Waals interactions, CNTs show a strong agglomeration tendency. Recently, we have presented *latex technology microfiltration fabrication approach* as a new and promising approach for the fabrication of nanocomposite thin films with high CNTs dispersion level. The CNTs are finely dispersed in a polymeric latex, via ultrasonication, followed by a microfiltration process. The later step allows preserving the homogeneous dispersion structure in the resulting solid nanocomposite. The combination of microfiltration and proper choice of the polymer latex allows for the design of complex nanostructures with tunable properties e.g., porosity, mechanical properties.

**Conclusion:** Sensing devices which were fabricated based on the resulting tunable thin films enabled us to obtain significant and clear reversible ethylene sensing. The sensor is operational at room temperature, and is highly stable in terms of chemical, mechanical and structural changes, allowing high mechanical integrity and durability.

# Novel Organic Fluorophores for High Efficiency Luminescent Solar Concentrators

A. Pucci

*University of Pisa*

Solar energy is the preferred technology of creating electric power in the renewable energy economy being theoretically sufficient to provide for the primary energy needs of the world. An easy but promising path to cost-effective photovoltaic (PV) systems is therefore sunlight concentration. Over classical non-imaging geometrical concentrators, luminescent solar concentrators (LSCs) possess several advantages: low cost and weight, elevated theoretical concentration factors, aptitude to efficiently work with diffuse light without requiring tracking or cooling equipment. Conventional fluorescent collectors are made of poly(methyl methacrylate) (PMMA) or polycarbonate (PC) slabs doped with red-emitting fluorophores that are generally preferred since their fluorescence well matches the Si-based PV cells band gap. However, their fluorescence is strongly quenched in condensed phase, thus strongly limiting the generation of electric current.

This study reports the use of novel red-emitting organic fluorophores for the realization of efficient LSCs based on PMMA and PC thin films ( $25\pm 5$   $\mu\text{m}$ ). Fluorophores with D-A features that absorb visible light in the range between 400-550 nm and emit fluorescence at 600-650 nm with a maximum quantum yield (QY) of at least 50% are utilized and dispersed (0.1-1.5 wt.%) in PMMA and PC films. QY and lifetime investigations illustrate the effect of fluorophore concentration on fluorescence quenching and autoabsorption phenomena, which are typically addressed to inner filter effects. Study of the LSCs performances yields excellent optical efficiencies of 9.5%. i.e. at the top level respect to the current state-of-art of similar devices based on perylene-based fluorophores such as Lumogen Red.

## Aknowledgements

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# Overcoming drug bioavailability issues with branched polymer stabilised nanoemulsions

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*University of Liverpool*

## Summary

Many drug compounds are subjected to efflux transporters after oral dose that decrease absorption into the bloodstream. This leads to a number of potential problems including the need to administer large doses to achieve therapeutic concentrations. The masking of drugs that are efflux substrates through dissolution into nanoemulsions has been the subject of our research for a number of years.

## Results and discussion

The formation of branched polymers using multi-vinyl-monomer strategies has led to new opportunities to control the architecture, chemistry and function of a range of macromolecules and here we, present the design and synthesis of one-pot amphiphilic emulsion stabilizers. The emulsifiers have been used with mixed oil phases of varying volatility to generate stable nanoemulsions with controlled diameters containing dissolved drug compounds within the dispersed oil phase. Nanoemulsions containing antiretrovirals for HIV therapy, have been studied on storage, for inherent toxicity and utilized in *in vitro* gut permeation models to simulate oral dose.

## Conclusion

It is clear that drug absorption may be aided by the nanoemulsions but also that the potential to overcome efflux pumps and encourage poorly-absorbed drugs to enter the systemic circulation may also be achieved.

# Passerini multicomponent reaction: a versatile route for the synthesis of biodegradable monomers and polymers

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*University of Nottingham*

Within the last decade the demand of complex and novel polymeric materials in advanced applications has increased. Several methods for the synthesis of macromolecular architectures with defined molecular weights and end groups have been investigated. Well defined polymers can be synthesised by controlled radical polymerizations, such as RAFT (reversible addition-fragmentation chain transfer) or ATRP (atom transfer radical polymerization). Polycondensation reactions such as acyclic diene metathesis, (ADMET), where the monomers selectively react with the polymer chain ends can also be performed. In addition, step-growth polymerisation, such as multicomponent reactions (MCRs), can lead to high atom-efficient and straightforward polymers synthesis. The Passerini-3CR and the Ugi-4CR are the most well-established isocyanide-based multicomponent reactions, especially for the polymers synthesis.

Due to the high degree of versatility and atom-economy of the Passerini reaction, it has been utilized for a diverse range of application in chemistry. Here, a promising strategy to synthesize tunable ester-amide monomers and polymers through Passerini multicomponent reaction has been demonstrated.

In this work we have performed the Passerini three component reaction combining carboxylic acids, aldehydes and isocyanides in one-pot to form ester-amide products in a one-step and mild process. Here we showed the Passerini reaction as a useful tool for the synthesis of multifunctional monomers and polymers bearing sites that can hydrolytically or enzymatically be cleaved. As a consequence, these molecules are of great potential interest as biodegradable materials with applications ranging from structural components to medical devices and therapeutics.

The work overall thus demonstrates a versatile and facile synthetic route to multifunctional and biodegradable monomers and polymers.

# Phosphorous containing Flame Retardant Polymers

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A significant drawback to many polymers is their flammability. Flame-retardant additives are often used and necessary for the finished commercial polymer based materials. Today, halogenated compounds for flame retardancy are mainly used in the industry. Halogenated organic molecules, such as brominated or chlorinated compounds, are particularly effective flame retardants. However, they cause environmental and health hazards that are restricting their continued use in the industry[1].

Due to health and environmental causes new flame retardant compounds are significant. Halogen-free flame retardants for polymeric materials have attracted increasing attention in recent years. Especially, phosphorus-containing flame retardants give off less toxic combustion products, influence the reaction in the condensed phase, and become an important replacement for halogen flame retardants [2].

Some phosphorous containing additives are used as flame retardant materials. However, the use of additives has several disadvantages such as poor compatibility, migration, reduction of the mechanical properties, transparency, and electrical properties[3]. This research focuses on the design and synthesis of novel polymer materials which has phosphorus monomer in their structure. This work is centered around synthesis flame retardant polyesters with 9,10-dihydro-9-oxa-10-phosphaphenanthren-10-oxide (DOPO) in their backbone and DOPO based polyester resins are planning to use varnish and paint applications.

**Keywords:** flame retardance , polymer, DOPO

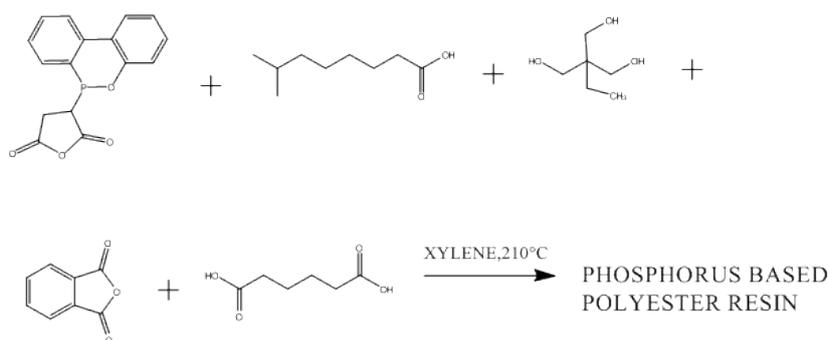


Figure 1: Schematic representation of unsaturated polyester based flame retardant polymer

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# **Poly High Internal Phase Emulsions For The Effective Encapsulation of Chemical Warfare Agents**

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Utilizing a poly(styrene-co-vinyl benzylchloride-co-divinylbenzene) lightly crosslinked polymer network, the unexceptional absorption capacities of a small selection of chemical warfare agents (CWAs) was observed. However, by altering the synthetic procedure of the polymerisation to move the morphology of the polymer from a traditional bulk network, into what is now commonly known as a poly high internal phase emulsion (polyHIPE), the absorption capacities of a wide range of CWAs was improved considerably. Following the variation of both the vinylbenzylchloride content and internal phases of the monomeric emulsions, the absorption capacities of many of the CWAs was observed to exceed a swelling degree of  $Q=40$  (weight/weight, 4400%). In addition to the significant swelling capacity now seen across a broad range of CWAs; the optimum polyHIPEs also showed impressive rates of swelling (<5mins) and the ability to absorb from both an unmodified monolithic state, and also from a highly compressed state to equal levels. These properties demonstrate the ability of this system to be a practical candidate for CWA immobilisation.

# Poly(acrylic acid) Solutions - 50 Years Of Use. What Could We Possibly Not Know Yet?

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Poly(acrylic acid) has long been considered the model example of a pH stimuli responsive based polymer. Since it was patented in 1966 it has found usage in a range of industrial, commercial and household consumer products, and is copolymerised into a range of advanced polymer structures to impart a triggering mechanism. However fundamental studies of this polymers solution properties are still revealing new information about its behaviours that were previously unexpected.

Introduction of covalently bonded fluorophores allows direct study of polymer conformation in solution. As the polymer shifts between low and high pH there is a conformational re-orientation between collapsed and swollen structures due to electrostatic interactions (Fig. 1) however it was found that in de-ionised solutions the pH response was limited under a certain molar mass threshold.

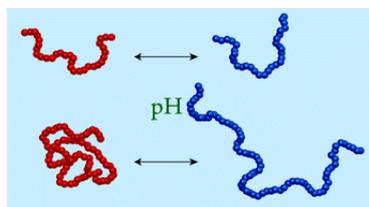


Fig. 1 – pH response of poly(acrylic acid)

Furthermore when exposed to compatible hydrogen bonding donor-acceptor polymers it is assumed the complex will form an extended ribbon/ladder structure. This model has been accepted for decades however new high resolution analysis casts doubt on the validity of this model, suggesting collapsed co-globules are a much more likely set of interactions.

**Published:** Swift et al, Soft Matter, 2016... **Upcoming:** Swift et al, 2017 (final revisions)

# Polyelectrolytes for the purification of industrial wastewater

A. Domb, M. Daife

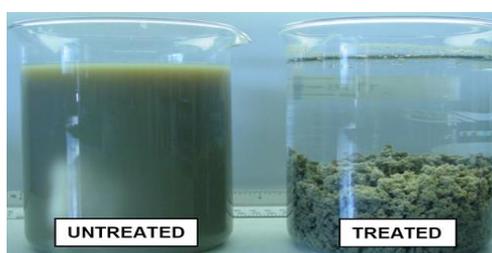
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Wastewater formed by different industries usually contain different types of suspended solids, dissolved solids, inorganic and organic particles and molecules, heavy metals, microbial agents and other impurities. Due to the charge of small particles, removal of these particles is affected by the addition of coagulants-aluminum or iron salts and flocculants-charged polymers.

Coagulation and flocculation refers to a two consecutive processes in which addition of di and trivalent metal ions, is followed by addition of high molecular weight charged polymer as flocculant aid. Using inorganic coagulants alone are not preferred due to the formation of small fragile flocs that precipitate slowly. Anionic/cationic polymer flocculants in combination with inorganic salts, are widely used to form larger and dense flocs and higher sedimentation rate of the produced flocs. Settling rate of the flocs, sediment volume (sludge volume index, SVI), percent of total suspended solids removal, turbidity, color and heavy metals removal are the main variables for determination of the efficiency of the coagulation-flocculation process. Bigger and denser flocs are preferable for good sedimentation, easy filtration and high clarification.

The purpose of this study was to develop formulations and methods for the treatment of Scrubber Water (SW) and Produced Water (PW). SW is wastewater generated on large ships that use low quality oil for the engines and PW is wastewater generated in the process of producing oil and gas from oil sand wells. To achieve this goal, first alum (aluminium sulfate water solution) was used as coagulant, followed by addition of cationic and anionic flocculants, Poly(diallyldimethylammonium chloride) and Poly(acrylamide-co-acrylic acid), respectively. Additionally, attempts were made to improve the flocculation activity of the commercially available anionic flocculant by converting the amide groups in the polymer chain to hydroxamic acids (HA). Hydroxamic acid containing polymers are known for their chelation of metal ions, particularly  $\text{Fe}^{+3}$  and  $\text{Cu}^{+2}$ . The conversion into hydroxamic acid groups was achieved by the reaction of the amide groups with hydroxylamine in high basic pH (pH=14). The formed poly(hydroxamic acid) was characterized by FTIR,  $^{13}\text{C}$ -NMR and chelation capacity with  $\text{Fe}^{+3}$  and  $\text{Cu}^{+2}$ . The flocculation activity of all samples were: total suspended solids(TSS) and turbidity (FAU) and UV/VIS absorbance. Heavy metals removal, carbon oxygen demand (COD) and color removal were also determined.

The purification of SW and PW was affected by increase the pH and applying aluminium sulfate solution, followed by the addition of a cationic and anionic flocculants. The hydroxamic derivative of poly(acrylamide) was a better flocculant than the starting material and SLES metal salts were found effective as flocculants.



# **Polymer matrix membranes (PMM) modified with electrospun woven fibres/ carbon nanofibers by nanofiltration for boron rejection**

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*University of the Punjab*

In this study, Polymer matrix membranes (PMM) were fabricated in two steps, first the formation of modified PSf substrate and woven electrospun fibrous layer with varying concentration of carbon nanofibers. ATR-FTIR spectroscopy, SEM, dead end nanofiltration tests, was employed to examine the influence of carbon nanofibers addition to the membrane performance characteristics. FTIR results verified the covalent and hydrogen bonding among the PMMs components. The performance results exhibited that the PMM4 has shown maximum boron rejection (98.9%) with corresponding flux of 40.8 L/m<sup>2</sup>.h. The resistivity of membranes also increased towards chlorine content by decreasing the active sites responsible for chlorine attack.

## Polymer, particle, vesicle? - The new challenge for analytical separation technologies in polymer characterisation

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The characterisation of polymers in solution for molecular weight and size/structural information by size exclusion chromatography (SEC or GPC) is somewhat restricted by the requirement that the polymer is dissolved in the mobile phase and has no interaction with the column packing material. More importantly, SEC cannot be used after the formation of polymer latex, polymer particles or other supramolecular structures such as vesicles (polymersomes) and we must resort to batch techniques such as static (MALS) or dynamic light scattering (DLS). Of course, these batch techniques yield very limited information about the distribution of molecular weight or size and furthermore may give misleading information due to the weighting of the data by larger species.

This paper describes and present a flow technique to complement SEC that can separate polymers and polymer structures in solution or suspension and can be coupled on-line to DLS or MALS to get accurate distribution information. Figure 1 shows a separation of a styrene acrylic latex where the particle size can be accurately determined as ranging from 46 to 50 nm across the distribution. We will show several examples of how unique analytical data can be obtained from polymers, polymer latex, polymer particles and vesicles.

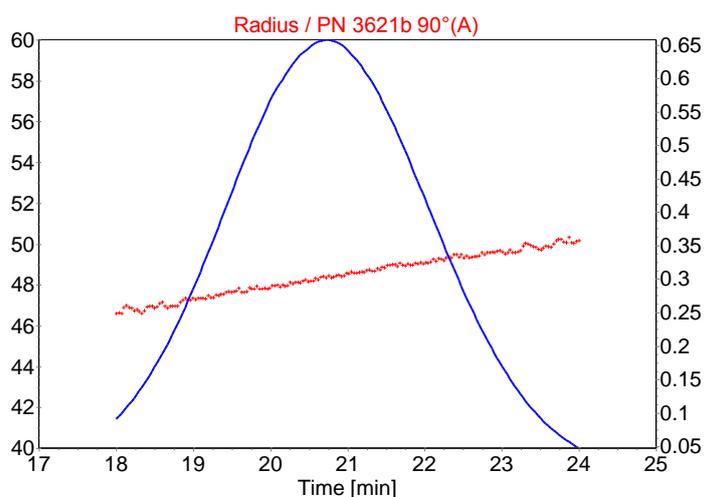


Figure 1. Separation of styrene acrylic polymer latex showing the measured radius (Rg)

## **Polymers at hard and soft surfaces**

H.A. Klok

*EPFL*

Surface-initiated polymerization (SIP) techniques are powerful tools for the preparation of thin, surface tethered polymer films. Surface grafted polymer films produced via SIP are often colloquially referred to as polymer brushes. SIP techniques are characterized by a number of unique features, which include the ability to (i) prepare polymer brushes with precise control over chemical composition and film thickness; (ii) generate polymer films that present very high surface concentrations of functional groups; (iii) conformally coat both simple, planar substrates as well as complex, 3D structured or porous substrates and (iv) tune the conformation of the surface grafted polymer chains by engineering the average distance between neighboring anchoring points. This presentation will highlight recent work from our laboratory that illustrates the use of SIP to generate thin polymer films with sensory or responsive properties as well as results from recent work, which shows that the stretched conformation of these surface grafted polymer chains also has an impact of their chemical reactivity, potentially opening avenues towards novel mechanically responsive surfaces.

## **Polymers for Advanced Technologies by ATRP**

K. Matyjaszewski

*Carnegie Mellon University*

Precise macromolecular engineering has been enabled by many controlled radical polymerization procedures. Copper-based ATRP (atom transfer radical polymerization) catalytic systems with polydentate nitrogen ligands are among most efficient controlled/living radical polymerization systems. By applying new initiating/catalytic systems, Cu level in ATRP was reduced to a few ppm. The activators are regenerated by light, reducing agents, electrical current or mechanical forces. By employing these systems, ATRP of acrylates, methacrylates, styrenes, acrylamides, acrylonitrile and other vinyl monomers was employed for macromolecular engineering of polymers with precisely controlled molecular weights, tuned dispersities, designed shape, composition and functionality. Examples of polymers for advanced technologies, including block, graft, star, hyperbranched, gradient and periodic copolymers, molecular brushes and various hybrid materials and bioconjugates prepared with high precision will be presented. Special emphasis will be on nanostructured multifunctional hybrid materials for application related to biomedicine, environment, energy and catalysis.

## **Polyoxazoline-modified lysine dendrimers as carrier molecules to improve the therapeutic index of SN-38, the active metabolite of irinotecan**

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<sup>1</sup>AstraZeneca, <sup>2</sup>The University of Nottingham

Dendrimer-drug conjugates, typically in the range of 2-25nm in size, are increasingly popular choices because they are water soluble, have near-monomodal molecular weight distributions, reproducible synthesis steps and have large numbers of surface functional groups available for drug loading and other modifications. We have explored the idea of using polyoxazolines (POZ) as dendrimer modifiers to improve the biocompatibility and systemic residency time of the dendrimer in order use it as a drug delivery system. Poly(2-methyl-2-oxazoline) was synthesised with a functional  $\alpha$ -chain end group that were then used to conjugate the polymer to a generation 5 lysine dendrimer. Residual unreacted terminal amino groups from the dendrimer were then used for conjugating the drug substance, SN-38 through a variety of linkers in order to control the release of the drug. We discovered one linker that could provide sustained drug release over a period of 96 hours (*in-vivo*) and in anti-tumour studies in mice (SW620 tumour model), this conjugate demonstrated superior efficacy over irinotecan (I.V. and I.P.), the standard of care (SOC), at a lower dose. Subsequently, because the maximum plasma concentration of the drug was reduced over the SOC, there was an improvement in tolerability with only mild gastrointestinal toxicity observed for the dendrimer-SN38 conjugate compared to moderate toxicity for the SOC. Further investigation into the dose-dependent efficacy identified the optimum dose and schedule for this conjugate to achieve significant tumour regression. Regrowth periods of 75 days after the final dose showed little tumour regrowth for the optimum dosing regimen and all of the mice in this treatment group survived throughout this regrowth period. We have demonstrated that the therapeutic index of SN-38 can be significantly improved by conjugating it to a PMOx-modified dendrimer *via* a linker, leading to both a well tolerated and highly efficacious therapy.

# **Polystyrene core/polyglycidol rich shell spheroidal microparticles – preparation, structure and their assemblies on hydrophilic surfaces**

S. Slomkowski, T. Basinska, M. Gosecka, P. Komar, M. Gadzinowski, T. Makowski, D. Mickiewicz

*Polish Academy of Sciences*

Preparation of spheroidal microparticles opens a way to materials suitable for application in medicine as new types of carriers of bioactive compounds and elements of biosensors. Preliminary studies indicate that spheroidal microparticles interact with cells differently than the spherical ones. One may expect also that their assemblies would differ from the assemblies of microspheres. In our studies we concentrated attention on the polystyrene core/polyglycidol rich shell spheroidal microparticles in which polyglycidol ensured controlled hydrophilicity of microparticles and, upon activation of hydroxyl groups, makes them suitable for covalent binding of (bio)molecules.

The title microparticles were obtained by: (i) emulsion copolymerization of styrene and  $\alpha$ -tert-butoxy- $\omega$ -vinylbenzyl-polyglycidol macromonomer yielding P(S/PGL) microspheres, (ii) elongation of polyvinylpyrrolidone (PVP) film with embedded P(S/PGL) microspheres and (iii) isolation of spheroidal microparticles by dissolution of PVP matrix in water and their multifold washing with fresh water portions. Depending on elongation the process yielded spheroidal microparticles with aspect ratio ranging from 1.8 to 6.5. Shape of microparticles was investigated by SEM. Their interfacial layer by XPS and AFM. We found that within the investigated range of elongation performed at temperatures above the softening temperature of polystyrene and polyglycidol the microparticles had perfect spheroidal shapes. At temperatures below the softening point of polystyrene but above that of polyglycidol the particles were partially stripped of the shells. The close relation between the aspect ratio of microparticles and elongation of the PVP matrix was established.

The spheroidal microparticles were deposited from water suspensions on bare and modified (by introduction of hydroxyl and amine groups) silicon wafers and glass. Relation between morphology of formed particle assemblies on particle aspect ratio, chemical structure of support and condition of particle deposition was investigated.

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# Polystyrene encapsulated DNA Nanoparticles for Subsurface Tracer Technology

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<sup>1</sup>University of Vienna, <sup>2</sup>Imperial College London

Robust chemical flow tracer systems to map fluid flow and fluid distributions<sup>[1]</sup> for various geological reservoirs or to trace wastewater effluent leakage<sup>[2]</sup> from landfill sites or contaminated surface water are in increasing demand. Chemical flow tracers are often used in oil & gas industry, for instance for hydraulic fracturing treatments, to map fluid flow or to obtain information about the reservoir geology, connectivity and efficiency of drilling sites. Well-specified tracers can be added to hydraulic fluid systems but have to survive the hydraulic fracturing conditions. These tracers should give a complete picture about the connectivity and efficiency of different drilling sites. We present our efforts to develop a robust DNA-based tracer system. Therefore DNA was encapsulated in cross-linked polystyrene. To do so, synthetic single stranded DNA (ssDNA) was protected, transferred from the aqueous phase into a monomer phase, which was emulsified, and subsequently polymerised to yield nanoparticles. The DNA tracer can be selectively recovered from the cross-linked polymer nanoparticles by Raney-Nickel mediated hydrogenation of the cross-links. The released ssDNA was qualified and quantified using quantitative real-time Polymerase Chain Reaction (qPCR).

# **Porous dressings of chitosan/modified chitosan IPNs for topical wound delivery of chloramphenicol**

E. Christodoulou, G. Michailidou, S. Nanaki, D. N. Bikiaris

*Aristotle University of Thessaloniki*

Skin damages are of high importance in clinical practice as they are rapidly being colonized by bacteria. Emerging antimicrobial resistance of bacteria wound pathogens limits the therapeutic options for the effective treatment of infections. It has been proposed that when the amount of bacteria is reduced in the wound, the infection can be more easily handled. The topical administration of the antibiotics has been evaluated as an effective treatment for wound infections and a wide variety of topical wound dressings has been already produced in order to deliver active ingredients in targeted sites. Controlled drug delivery systems in form of dressings provide various advantages due to their ability to deliver the antibiotic in a sustained rate without the need for frequent dressing change.

Chitosan (CS), a natural biopolymer soluble in acidic aqueous environment is widely used in such dressings systems due to its low toxicity, its haemostatic ability, its biodegradability and biocompatibility. Drug delivery vehicles consisting of CS have been used for antimicrobial drugs and other drugs.

Interpenetrating polymer network (IPN) hydrogels, as a particular category of composite materials, received a great attention due to their improved responsiveness and mechanical properties, which differentiate them on the single network hydrogels.

In this work, two grafted chitosan derivatives, one with trans-aconitic acid (CS-tAcon) and the other with trimellitic anhydride (CS-TRM) have been synthesized. Neat CS and each modified derivative were then mixed in a single homogeneous solution to form the IPN. The mixed solution was poured into a glass tube and was freeze-dried to obtain the porous sponges which were further loaded with chloramphenicol drug (a broad-spectrum antibiotic that is active against a variety of organisms) in order to increase their antimicrobial ability.

Morphological characterization of the drug loaded dressings was performed by scanning electron microscopy, while drug–matrix interactions were evaluated by FT-IR spectroscopy. X-ray diffraction studies were carried out for the identification of the physical state for both neat and drug loaded materials. Swelling and mechanical properties were tested and the in vitro drug release was also studied.

# Production of Reduced Graphene Oxide and Polymer based Aerogels for Oil-Water Separations

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In order to preserve nature as well as the future, people are prompt to seek for remediation strategies for water, especially for removal of oil from water. There are increasing number of research to find new water purification methods that cost less, spend less energy, minimize use of chemicals, and minimize the effect of chemicals on the environment. Among all the materials suggested for this purpose, aerogels are preferable in terms of commercial viability, performance criteria and cost aspects. Aerogels are very similar to hydrogels and they can be obtained by removing water from the precursor hydrogel using supercritical drying, freeze-drying etc. They have open pore structure, low density and high surface area which also make them preferable in many applications in addition to oil-water separations. In order to increase the absorbance capacity as well as to increase surface area of the aerogels, carbon based materials including activated carbon, carbon nanotube, and graphene oxide have been used for the production of aerogels. In this study, graphene oxide based aerogels were prepared by using random copolymers of glycidyl methacrylate and styrene as a crosslinker and as an oil absorption enhancer. Graphene oxide was synthesized using Tour Method and characterized with ATR-FTIR, XPS, SEM, TEM and TGA analyses. Two copolymers of glycidyl methacrylate and styrene were synthesized using free radical polymerization and characterized with ATR-FTIR, GPC,  $^1\text{H}$  NMR, and TGA analyses. Copolymers of glycidyl methacrylate and styrene were prepared and used along with graphene oxide in order to synthesize the precursor hydrogels. Graphene oxide concentration in the hydrogels was kept at 5.0 mg/mL while copolymer concentrations were ranged from 0 to 5.0 mg/mL. After freeze-drying and thermal reduction, morphologies of the aerogels were assessed using SEM analysis. To determine the oil absorption capacity of the prepared aerogels, organic solvents (chloroform and toluene) and vegetable oil were used. The prepared aerogels were found to have absorption capacities in the range of 90 to 175 g/g for toluene and 90 to 200 g/g for vegetable oil. In the case of chloroform, aerogels with higher styrene content had absorption capacities ranging from 170 to 315 g/g, whereas this range was between 145-260 g/g for aerogels with lower styrene content. Higher styrene containing copolymer containing aerogels in general showed higher oil absorption capacities. The highest oil absorption values were obtained with aerogels having initial concentrations of 1.5 to 2.0 mg/mL of copolymer.

# Protein Nano- and Micro-tubes as Functional Biomaterials

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Synthesis of cylindrical hollow structures in nanometer- or micrometer-scale using biomolecules, such as proteins, peptides, DNAs, and amphiphilic lipids, has attracted considerable attentions because of their potential applications. This paper presents highlights of the latest results from our studies directed at developing protein-based nanotubes (NTs) and microtubes (MTs) as functional biomaterials.<sup>1-5</sup> These biocylinders were prepared using an alternating layer-by-layer assembly of protein and oppositely charged poly(amino acid) into a nano- or micro-porous polycarbonate membrane (pore diameter: 0.4~1.2  $\mu\text{m}$ ), with subsequent dissolution of the template. The tubular wall typically comprises several layers of human serum albumin (HSA) and poly-L-arginine (PLA).<sup>1</sup> The obtained NTs and MTs can be dispersed in aqueous medium and are hydrated significantly. A variety of guest molecules can be encapsulated into their one-dimensional (1D) pore space selectively *via* biospecific interaction. The hybrid NTs bearing an antibody layer as an internal wall captured human hepatitis B virus into the central channel.<sup>3</sup> The NTs with a fetuin glycoprotein surface interior entrapped influenza virus.<sup>4</sup> Furthermore, protein MTs with an outer diameter of 1  $\mu\text{m}$  showed an efficient trapping ability of bacteria.<sup>5</sup> Confocal laser scanning microscopy measurements revealed that *Escherichia coli* was trapped into the hollow. More recently, we found that protein microtubes with an interior surface composed of Pt nanoparticles are self-propelled in aqueous  $\text{H}_2\text{O}_2$  medium.<sup>6</sup>

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# Robot Assisted Synthesis of Alternating Multiblock Copolymers Based on Oligo( $\epsilon$ -caprolactone)/Oligotetrahydrofuran

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The design of polymeric materials is guided by the requirements of specific applications. A versatile polymer system allowing to tailor properties and functions are multiblock copolymers (MBCs). We speculated that the block length of integrated building blocks and the sequence structure would be a parameter to control mechanical and thermal properties. In MBCs composed of polylactide (PLA)/poly(ethylene glycol) (PEG)<sup>[1]</sup> and poly( $\epsilon$ -caprolactone) (PCL)/PEG<sup>[2]</sup> segments providing an alternating and random block structure nano structures via self-assembly were observed attributed to the amphiphilic character.

In this work, well-defined MBCs based on two semi-crystalline blocks providing a similar hydrophobicity were designed, which exhibited separated melting temperatures ( $T_m$ s). Therefore, alternating and random MBCs (MBCs<sub>alt</sub> or MBCs<sub>ran</sub>) were created by means of high-throughput synthesis by coupling oligo( $\epsilon$ -caprolactone) (OCL) of different molecular weights (2, 4, and 8 kDa) and oligotetrahydrofuran (OTHF, 2.9 kDa) via Steglich esterification. MBCs<sub>alt</sub> with a weight average of molecular weight of  $M_w = 70,000 \text{ g}\cdot\text{mol}^{-1}$ ,  $160,000 \text{ g}\cdot\text{mol}^{-1}$ , and  $190,000 \text{ g}\cdot\text{mol}^{-1}$  were obtained when the chain length of OCL was increased. This increase in maximum of  $M_w$  was also observed for the series of MBCs<sub>ran</sub>, which exhibited  $M_w$ s of  $100,000 \text{ g}\cdot\text{mol}^{-1}$ ,  $130,000 \text{ g}\cdot\text{mol}^{-1}$ , and  $160,000 \text{ g}\cdot\text{mol}^{-1}$ . For all MBCs a decrease of the melting temperature ( $T_m$ ) of domains from OCL and OTHF was observed when  $M_w$  increased. Furthermore,  $T_m$  (OTHF) of MBCs<sub>ran</sub> was always higher than  $T_m$  (OTHF) of MBCs<sub>alt</sub>, which was related to a confined crystal growth of OTHF incorporated in MBCs<sub>alt</sub>. In addition, the storage modulus  $E'$  of MBCs<sub>alt</sub> was almost half as high when compared to MBCs<sub>ran</sub>. In this way this study demonstrates the important role of the control of the sequence structure in MBCs and enables a quantitative elucidation of the structure-property relationship in alternating and random MBCs.

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## Self-plasticized Cellulose Acetate Oleate mixed Ester: Improving of Hydrodynamic and Barrier Properties

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The synthesis of cellulose acetate oleate (OLA/CA) ester via a mixed anhydride (trifluoroacetic acid (TFA)/trifluoroacetic anhydride (TFAA)), chloroform co-solvent system has been investigated. The acylation of free hydroxyl groups from cellulose acetate with oleic acid was confirmed by nuclear magnetic resonance (NMR) and Fourier transform infrared (FTIR) spectroscopies. The presence of oleate groups increased the solubility of the polymer in common solvents in comparison to pure cellulose acetate (CA). Furthermore, the mechanical behavior of OLA/CA was ductile instead of rigid as CA, indicating that oleate groups can effectively plasticize the polymer chains. Interestingly, the wettability was significantly improved displaying an increase of  $45^\circ$  for the water contact angle (WCA) from  $61^\circ$  for CA to  $106^\circ$  for OLA/CA. Moreover, the value of surface energy for OLA/CA was  $16 \text{ mJ/m}^2$  with no contribution of polar dispersive component. This value is very low if compared to other conventional cellulose derivatives. On the other hand, water and oxygen barrier properties were also improved. Indeed, the water transmission rate (WTR) decreased from  $2803 \text{ g m}^{-2} \text{ d}^{-1}$  for CA to  $668 \text{ g m}^{-2} \text{ d}^{-1}$  for OLA/CA (*i.e.*, a variation of  $\sim 76\%$ ) while the oxygen transmission rate (OTR) was reduced from  $105065 \text{ mL m}^{-2} \text{ day}^{-1}$  for CA to  $10221 \text{ mL m}^{-2} \text{ day}^{-1}$  for OLA/CA (*i.e.*, a variation of  $\sim 90\%$ ). This behavior is attributed to the chemical interaction of water and oxygen with free hydroxyl and oleate groups and the morphology of the films' cross-section.

# Self-Propelled Protein Microtubes with an Interior Surface Composed of Pt Nanoparticles

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## Summary

Metal-based tubular micromotors modified with protein, antibody, and DNA have attracted great interest as smart biological devices. We have prepared several cylindrical hollow structures composed of proteins and demonstrated various functionalities using their internal pore space.<sup>1)</sup> In this report, we synthesized protein MTs with nanoparticles (PtNPs) in the interior surface and magnetite nanoparticles (MNPs) in the tubular wall. The MTs were self-propelled in aqueous hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) medium while being direction controlled with magnet. Furthermore, *Escherichia coli* (*E. coli*) was efficiently captured on the outer surface of the MTs.

## Result and Discussion

The MTs were prepared by unique alternating layer-by-layer (LbL) assembly technique using a nanoporous track-etched polycarbonate (PC) membrane. Poly-L-arginine (PLA), human serum albumin (HSA), and MNP were deposited on the pore wall of a PC membrane with a pore size of 1.2  $\mu\text{m}$ , followed by injection of citrated PtNP dispersion.<sup>2)</sup> The PC membrane was dissolved and removed to obtain PLA/HSA/MNP(PLA/HSA)<sub>5</sub>PLA/PtNP MTs (HSA-MNP-PtNP MTs). The length of HSA-MNP-PtNP MT measured from SEM and TEM observation was  $23.4 \pm 0.4 \mu\text{m}$ , the outside diameter was  $1.20 \pm 0.02 \mu\text{m}$ , and the tube wall thickness was  $124 \pm 15 \text{ nm}$ . The soft HSA-MNP-PtNP MTs were self-propelled smoothly in 5% H<sub>2</sub>O<sub>2</sub> aqueous solution (containing 0.2% TritonX-100) by spouting out of O<sub>2</sub> microbubbles from the end of the tube. The MNP layer at the intermediate of the cylindrical wall can allow magnetic control of the moving direction of the tubes. Because the exterior surface is positively charged, the bubble-propelled microtubes adsorbed *E. coli* with high efficiency. When self-propelled MTs were added to the *E. coli* suspension, 99% of *E. coli* can be removed within 15 minutes.

## Conclusion

We have shown the template-assisted synthesis of multilayered MTs of PLA, HSA, MNP and citrated PtNPs. In H<sub>2</sub>O<sub>2</sub> solution, the HSA-MNP-PtNP MTs were catalytically self-propelled by jetting O<sub>2</sub> bubbles from the open-end terminus. A common pathogen, *E. coli*, is adhered onto the self-propelled microtube with high efficiency. The moving motion enhanced the contact frequency with *E. coli*, leading to achievement of 99% isolation of the bacteria from the sample solution.

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# **Simulation of reduced graphene oxide-reinforced chitosan/polydimethylsiloxane bio-inspired morphing composite**

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This work presents a finite element analysis (FEA) model that predicts morphing of a bio-inspired morphing composite. The model simulates the deformation of the material due to differential thermal strain by application of thermal stimuli. The morphing composite modelled consists of an upper layer of reduced graphene oxide (rGO)-reinforced chitosan and a lower layer of polydimethylsiloxane (PDMS). Its bi-layered structure is inspired by natural morphing systems, for instance pine cone scales and wheat awns. Having a model that predicts morphing behaviour can aid in the design of morphing composites for applications such as soft robotics, energy harvesting, biomaterials, actuators and sensors.

The model created represents the thickness and length of the morphing composite; yielding a 2D model with low computational cost. The dimensions of the virtual sample were: 8 mm length and total thickness of 82  $\mu\text{m}$ ; in which the layer of chitosan is 10  $\mu\text{m}$  and the layer of PDMS is 72  $\mu\text{m}$ . In the model both layers are assumed to be isotropic, linear elastic and homogenous. Mechanical and thermal properties of both materials were considered to remain constant during the heating and cooling cycles. The interface of the bilayer was modelled by tying the displacement and rotational degrees of freedom at the contact edge of each interacting layer. A kinematic boundary condition constrains one end of the strip to avoid rigid motion; while the increment of temperature or trigger is applied uniformly in the virtual sample.

Experimental tests were carried out in a physical sample of the morphing composite that had the same specifications as the FEA model. Comparison of simulations and experimental results showed that the relative error of the models is 8.5 % which is reasonable due to the idealized conditions of the FEA model. As a conclusion, the model predicts the morphing behaviour of the polymeric morphing composite with sufficient accuracy to be employed in the design of functional applications.

## **Stable Poly(anhydride) Synthesized from Ricinoleic acid and Sebacic acid**

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Poly(anhydride) are unstable and prone to hydrolytic degradation and depolymerisation via anhydride interchange. They are stored at -20°C, packed under inert atmosphere until use. We synthesized a new poly(anhydride) from ricinoleic (RA) and sebacic (SA) acid that is stable at room temperature and 37°C for 18 months. The copolymerization was carried out by reacting ricinoleic acid (RA) with poly(sebacic acid) (PSA) followed by anhydride polycondensation. Dimers RA-SA and trimers RA-SA-RA, are formed during prepolymerization. Finally, the carboxylic acid terminals were activated and polycondensed under heat and vacuum, to yield the final polymer in which the monomers are incorporated through complete esterification, leading to an alternating ester-anhydride copolymer. Varying the synthetic procedure and ratio of RA:PSA, we controlled the population of ester bonds (80%-50%) in the final polymers. Purified RA-SA-RA (trimer) and RA-SA (dimer) units were polymerized, to further confirm the polymer structure. The copolymer is also stable in chloroform solution and under  $\gamma$ - irradiation. The polymer hydrolyses through anhydride cleavage lasting ~7 days to form oligoesters which are stable for more than 30 days. The release of gentamycin from the synthesized alternate polymer matrix is sustained compared to the random copolymer.

# **Surface modified cellulose nanocrystals: gateway to materials with unique properties**

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Humanity is under increased pressure to reduce energy consumption, reduce waste disposal and increase the use of renewable materials. The development of functional nanomaterials based on renewable resources has the potential to deliver a holistic solution by increasing activity, reducing the use of depletable resources, reduction in CO<sub>2</sub> emissions, and reducing the waste at end-of-life. In this presentation I will discuss developments in our group to create a renewable nanoparticle technology platform based on cellulose nanowhiskers, rigid-rodlike single-crystal nanoparticles derived from native cellulose. We investigate a range of surface functionalisation pathways such as introduction of pH-sensitive fluorophores and ionic groups as well as electron-diffusion redox-active grafts. The combination of virtually unlimited surface functionality which can be introduced with the rigidity and hydroxyl group surface order enables the design and manufacture of materials with unique benefits and properties. Several examples will be given as well as investigated applications such as pH probes, stimuli flocculants and controlled electron conducting rods.

## Sweet Immunomodulators

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### Summary

Glycans mediate a range of key biological processes, which span from fecundation, to parasitisation, and the mounting of immune responses.<sup>1</sup> To exert these biological functions, however, carbohydrates typically need to be presented in multiple copies and with precise spatial orientation onto on macromolecular scaffolds. This is required to bind specific sugar-binding proteins (lectins), which often exist themselves within oligomeric structure, thus engaging with their carbohydrate ligands in a multivalent manner.<sup>2</sup> Synthetic glycopolymers – that is, synthetic polymers with carbohydrate pendant units – are increasingly utilised within this context as probes to dissect complex biological pathways involving sugar-protein recognition.<sup>3</sup> In this work we designed macromolecular carbohydrate ligands selective for CD206, receptor predominantly expressed by selected populations of macrophages, dendritic cells and non-vascular endothelium, and kidney mesangial cells - and utilized them to modulate CD206 endocytic activity both *in vitro*, using CD206<sup>+</sup>-CHO cells and murine and human macrophages, and *in vivo*. Modulation of inflammation observed in a mouse Ischaemia-Reperfusion Injury (IRI) model will also be discussed.

Taken together, this study shows that synthetic glycopolymers can be designed to bind the different lectin domains (CTLD<sub>4-7</sub> and CR) of CD206 and this can be used to modulate the *in vitro* and *in vivo* behavior of key immune cells.

# Synthesis and O<sub>2</sub>-Binding Property of Cys-93( $\beta$ ) Substituted Intramolecular Crosslinked Hemoglobins

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## Summary

It may be difficult to maintain a stable blood transfusion system several years later in Japan due to the decreasing population of blood donors accompanying the declining birthrate and aging population. Under such circumstances, development of artificial blood is greatly expected. Hemoglobin (Hb)-based O<sub>2</sub>-carrier (red blood cell substitute) of several types have been developed, such as polymerized Hb<sup>1</sup> and poly(ethylene glycol) conjugated Hb.<sup>2</sup> However, these molecules have complicated structures because of the different binding sites and number of Hbs or PEGs. In this paper, we report the synthesis and O<sub>2</sub>-binding property of Cys-93( $\beta$ ) substituted intramolecular crosslinked Hbs (R-XLHb, R=human serum albumin (HSA) or poly(ethylene glycol) (PEG), Mw: 40,000).

## Results and discussion

Intramolecular crosslinking and HSA or PEG conjugation were achieved at Cys-93( $\beta$ ) of Hb using trifunctional cross-linker, tris[4-(N-maleimidomethyl)cyclohexanoylaminoethyl]amine (TMCA). TMCA was synthesized by coupling of tris(2-aminoethyl)amine with N-succinimidyl-4-(N-maleimidomethyl)cyclohexanecarboxylate. The TMCA was reacted with Cys-93( $\beta$ ) of Hb, and the obtained intramolecularly crosslinked Hb (maleimide-activated XLHb) was subsequently reacted with free Cys-34 of HSA or thiol-PEG, yielding HSA-XLHb or PEG-XLHb. The products were purified using gel filtration chromatography. Structures of R-XLHb were characterized by electrophoresis and HPLC. O<sub>2</sub>-affinity ( $P_{50}$  value) of HSA-XLHb and PEG-XLHb were determined to be 8 Torr and 9 Torr, respectively.

## Conclusion

The HSA or PEG substituted intramolecular crosslinked Hbs were synthesized using tris-maleimide reagent. The obtained HSA-XLHb and PEG-XLHb could become promising O<sub>2</sub>-carrier as a red blood cell substitute.

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# Synthesis of dPG-based Nanogels as Carriers for Vaccines

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1. Summary: In recent years, subunit vaccines have gained interest, since they offer higher safety for immunocompromised subjects and economic advantages. Here, an antigen (antibody generator) is linked to a stronger immunogen, such as a protein or a membrane complex. Due to their unique properties (e.g. tunability in size, shape, surface charge, biocompatibility and large surface area for conjugation), nanogels (NGs) are promising candidates for vaccine delivery[1-2]. In the present study, we developed a modular, multivalent system with NGs based on dendritic Polyglycerol (dPG) as carrier[3], the Measles Virus Hemagglutinin (MV-H) protein as targeting unit and a dye for trackability. The system is based on the interaction of MV-H with the Signaling Lymphocyte Activator Molecule (SLAM), a receptor specific of immune competent cells[4-5].

2. Results and discussion: NGs in sizes around 150 nm were synthesized under mild conditions via inverse nanoprecipitation[6-7] and coupled to dye and protein by *in situ* NHS ester formation. Dye and protein coupling were verified by means of DLS, NTA, AFM as well as UV/vis and CD measurements. Bovine Serum Albumin (BSA) was used as a model protein. The protein coupling efficiency was determined with FITC-labeled BSA.

3. Conclusion: The system shows promising results as a potential subunit vaccine. Binding assays using SLAM-positive and negative Vero cells show a successful purification and binding of the soluble MV-H. and its conjugates are currently under investigation.

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# Synthesis of Polyacid-functionalized Diblock Copolymer Nano-Objects via Polymerization-Induced Self-Assembly

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Well-defined diblock copolymer nanoparticles can be prepared in a wide range of solvents via reversible addition–fragmentation chain transfer (RAFT) dispersion polymerization. During this process, a soluble stabilizer block is chain-extended using a solvent-miscible monomer. Initially, a soluble diblock copolymer is obtained, but at some critical degree of polymerization the growing second block becomes insoluble, which causes in situ self-assembly. Depending on the precise conditions, the initially-formed spheres can evolve to form worm-like or vesicular nanoparticles. Thus this approach is a powerful and versatile technique for the preparation of a wide range of bespoke organic diblock copolymer nano-objects of controllable size, morphology, and surface functionality at relatively high concentrations. In this talk, a binary mixture of anionic and non-ionic macromolecular chain transfer agents (macro-CTAs) is used to design novel polyacid-functionalized spherical, worm-like or vesicular nanoparticles with controllable anionic character and morphology. The molar ratio and degree of polymerization of the stabilizer macro-CTAs, and the mean degree of polymerization of the core-forming block are all important in determining the final morphology of the nanoparticles. The nanoparticles are characterized by electron microscopy, aqueous electrophoresis and small-angle X-ray scattering. Particular attention is paid to rheological properties of the worm-like micelles, which form free-standing gels of varying gel strengths depending on their composition.

# The Effect of Branching (Star Architecture) on Poly(d,l-lactide) (PDLLA) Degradation and Drug Delivery

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Osteoporosis is the reduction in bone formation and the ultimate weakening of bones with fractures becoming more likely; this can be highly traumatic and as well as costly for healthcare providers/insurance companies. In this study we evaluated both star (branched) and linear poly(l,d-lactic acid) (PDLLA) as degradable materials employed in the controlled release of an anti-osteoporotic drug, atorvastatin. The polymers were prepared via ring-opening polymerization initiated by decanol (linear), pentaerythritol (4-armed star) and dipentaerythritol (6-armed star), and processed both in the form of films and nanoparticles. Independent of the length or number of their arms, star polymers degrade slower than linear polymers, possibly through a surface (vs bulk) mechanism. Further, the release of atorvastatin followed zero-order-like kinetics for the branched polymers, and first-order kinetics for linear PDLLA. Using NHOst osteoblastic cells, both linear and star polymers were devoid of any significant toxicity and released atorvastatin in a bioavailable form; cell adhesion was considerably lower on star polymer films, and the slower release from their nanoparticles appeared to be beneficial to avoid atorvastatin overdosing.

# The main challenges of polymeric particles development and their physical characterization

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Many types of materials (i.e. particles, films, fibers) have been investigated over the last years for biomedical applications such as drug and gene delivery and control of cell proliferation and growth. The polymeric particles have been developed mainly to control the drug release by single emulsion process which can be affected by several factors such as rotary Brownian motion, non-Brownian behavior, shear thinning, hydrodynamic forces such as repulsion and attractive forces (i.e. van der Waals force) and equilibrium phase behavior of materials. Furthermore, varying processes development have been utilised which have made it possible to control the features of polymeric carriers including size that also determines their applicability, porosity, roughness and morphology. The particles most commonly used for drug delivery are micro and nano sized spheres and with or without porous features. In this study some physical properties of polymeric microparticles produced by single emulsion process were tested such as particle and pores morphology including size (Dynamic Light Scattering – DLS), shape (SEM, Cryo-SEM), density, surface area (BET), level of porosity by gas adsorption (BET), drug loading and encapsulation efficiency (HPLC). The proposed morphology modification to the microparticles approaches were later evaluated using different surface imaging and analytical techniques. Some of these techniques evaluated the influence of process development during particles formation, production of different level of porosity, improving drug loading and encapsulation efficiency from polymeric micro and nanoparticles as shown in Figure 1. We have developed non-porous and porous polymeric microparticles varying size range between 14 and 100 $\mu\text{m}$  and range of pores diameter between 0.36 and 7.4 $\mu\text{m}$ . Furthermore, some of polymeric materials increased the encapsulation efficiency of chemotherapeutic drug (i.e. Methotrexate) from 11 to 46%. These carriers are being investigated as potential next generation of brain tumor (i.e. glioblastoma) treatments, as they combine well established physical properties of polymeric microspheres and higher encapsulation efficiency.

# Towards new applications for responsive polymer particles

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Radical polymerisation techniques have, in recent years, allowed the synthesis of increasing complex architectures including linear and branched block copolymers, polymer particles and higher order structures such as micelles and vesicles. Control over the architecture and functionality of polymers (Fig. 1) gives us exquisite control over their solution properties, and can be achieved using commercially available starting materials.

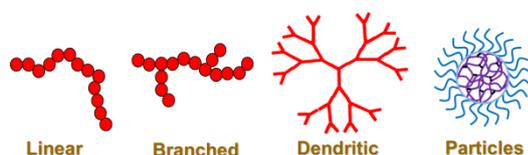


Figure 1 – architecture control in polymer synthesis

In this presentation, the synthesis of polymers by Reversible Addition Fragmentation chain Transfer (RAFT) polymerisation and dispersion and emulsion techniques will be discussed. Specifically, examples of the synthesis of zwitterionic and tertiary amine containing polymers will be presented, demonstrating how the architecture<sup>1,2</sup> and functionality<sup>3</sup> of the polymer can affect particle formation and the responsive behaviour of the polymer. It is envisaged that these biocompatible, responsive polymer particles could be used in areas such as delivery or reporting.<sup>4</sup> Current examples of the Willcock group research demonstrating the incorporation of functionality into polymeric scaffolds for applications in microfluidics, magnetic resonance imaging (MRI) and solution viscosity modification will also be highlighted.

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## Towards targeting of Salmonella-infected Macrophage using bespoke glycoliposomes

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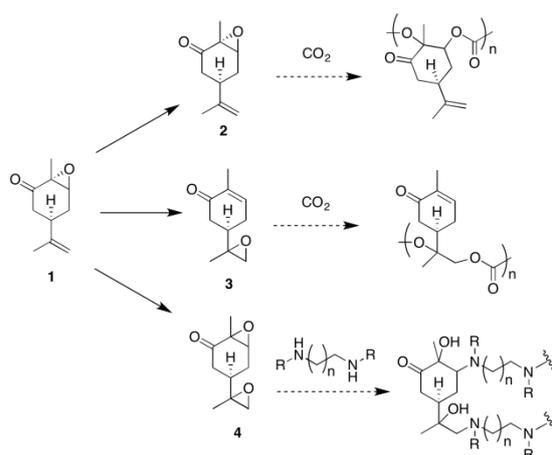
In nature, several known proteins are glycosylated and carbohydrate-cell receptor interactions mediate a plethora of key biological events, *e.g.* parasitisation and immune responses. To decipher sugar-encoded instructions, cell membranes display carbohydrate-binding proteins (lectins), which are able to selectively recognize specific sugar ligands (1). Biological systems use multivalent interactions as a way to enhance selectivity and overcome ligand-receptor low binding affinities, protein-binding sugars are typically displayed within large multivalent ligands (2). Glycoliposomes can exploit this phenomenon through the presentation of multiple glycoligands for actively targeting specific receptors, enhancing uptake of nanomedicines into target cells, or both (3). The present study focussed on the use of glycosylated liposomal systems for the treatment of intracellular bacterial infection in cells presenting lectin endocytic receptors. Antimicrobial resistance is one of the current main global healthcare challenges. In particular, antimicrobial resistance in *Salmonella Enterica* serotypes is responsible for 21 million cases of typhoid fever, 94 million cases of gastroenteritis and 600.000 deaths worldwide (4,5). *Salmonella* is able to survive in intracellular compartments of macrophages (6). Mannose Receptor (MR, CD206) is a potential access gate to *Salmonella* infected macrophages which could be selectively targeted with mannosylated-decorated liposomes. In this work, we present the design, the development and investigation of liposomal systems to deliver antimicrobials into *Salmonella*-infected macrophages. To investigate the structure/activity relationships in the interactions between glycotargeted liposomes and macrophage, two set of monovalent glycoligands and two set of multivalent polyglycosides – synthetic lipid-terminated glycopolymers – bearing a range of membrane-inserting anchors were synthesised. Liposomes coated with mannose-containing glycopolymer significantly enhanced uptake compared to uncoated liposome controls, and higher gentamicin delivery, resulting in reduction in internal infection. *References:* (1) Maupin, K. et al., *Glycobiology* 22, 2012; (2) Jayaraman, N. et al., *Chem. Soc. Rev.* 38, 2009; (3) Hillaireau, H et al, *Cell. Mol. Life Sci.* 66, 2009; (4) World Health Organization, 2015; (5) Majowicz, S. et al., *Clin Infect Dis*; 50, 2010; (6) Haraga, A. et al, *Nat. Rev. Microbiol.* 6, 2008.

# Towards the Synthesis of Novel, Renewable Carvone-Based Monomers and Polymers for Biomedical Applications

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In looking to replace crude oil as a feedstock for the synthesis of polymers, only biomass can provide renewable carbon in sufficient quantities to meet global demand.<sup>1</sup> This work has investigated the use of the terpene (*R*)-carvone (**1**) as a precursor for the synthesis of novel, sustainable monomers. A number of carvone-derived small molecules have been synthesised including epoxides **2**, **3** and **4**, which may form polycarbonate structures through their co-polymerisation with carbon dioxide.<sup>2</sup> Additionally, bis-epoxide species such as **4** have the potential to polymerise with diamine co-monomers, for the synthesis of hyper-branched networks. Following their synthesis, the suitability of these materials for biomedical applications will be investigated.



(1) *Chem. - A Eur. J.* **2016**, *22* (33), 11510–11521.

(2) *Macromolecules* **2016**, *49* (17), 6285–6295.

# Unravelling Solution-State Supramolecular Structures of A Donor-Acceptor Polymer and Their Influences on Solid-State Morphology and Charge Transport Properties

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Conjugated polymers have aroused broad interests for optoelectronic applications due to their high flexibility, good solution processability, and low manufacturing cost. Charge transport property in conjugated polymers depends sensitively on their solid-state morphologies. Remarkable improvements on the molecular design strategies have been made to obtain optimal solid-state packing and high charge carrier mobility. Polymer self-assembly in solution prior to film fabrication makes solution-state structures critical for their solid-state packing and optoelectronic properties. However, unravelling the solution-state supramolecular structures is challenging, not to mention establishing clear relationship between solution-state structure and charge transport properties in field-effect transistors (FETs).

Here, we revealed that the thin film morphology of conjugated polymer inherited the features of their solution-state supramolecular structures. We proposed a “solution-state supramolecular structure control” strategy to increase the electron mobility of a BDOPV-based polymer. By using co-solvent system to tune the solution-state structure, we found that polymer formed 1D rod-like self-assembly structure in good solvent, and 2D lamellae-like structure in poor solvent. Inspired by the dependence of solid-state morphology on solution-state structures, film with increased crystallinity without sacrificing the inter-domain connectivity was obtained by delicately controlling the solution-state structure. The electron mobility significantly increased from the original value of  $1.8 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$  to  $3.2 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ . Temperature-dependent mobility showed a significantly decreased activation energy down to 30 meV.

We revealed the detailed solution-state supramolecular structure of a BDOPV-based polymer. This is the first example of the study on detailed solution-state structure of D-A conjugated polymers, and such research methods could be generalized into many other D-A conjugated polymer systems. Interestingly, solid-state microstructures directly inherited the features of the solution-state supramolecular structures, indicating that conjugated polymer self-assembly in solutions has similar behavior as that of many supramolecular self-assembled molecules. Through a delicately control over polymer solution-state

# Vapochromic polyketone films based on aggregation induced enhanced emission

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The detection of Volatile Organic Compounds (VOCs) is a topic of great interest in various areas, including the monitoring of air quality and control of hazardous gases and vapours in industrial environments and workplaces.

Aggregachromic fluorescent organic dyes in combination with polymeric matrices have been shown to have a great potential for such applications due to their low costs, high sensitivity and ease of use.

In this work 4,4'-bis-(2-benzoxazolyl)stilbene (BBS), an aggregation-sensitive fluorescent dye was embedded in a semi-crystalline polyketone (PK) with the aim to confer interesting optical features to the matrix.

Pellets of polyketones containing 0.6% wt. BBS (obtained by hot melt extrusion) are melt-pressed into thin films and rapidly quenched in liquid nitrogen as to freeze the dispersed dye into the polymer matrix as kinetically trapped and uninteracting chromophores.

It is shown that the exposure of the semi-crystalline polymer films to vapours of well interacting solvents induce the rearrangement of the polymer chains and the subsequent increase in the extent of crystallization of the matrix. In our case, this phenomenon results in the aggregation of BBS chromophores, which in turn yields a neat variation in fluorescence emission of the whole composite. Vapours of different VOCs are investigated as well as the concentration threshold at which the designed system starts to display the chromogenic feature.

Overall, our results suggest the possibility to prepare a new class of cost-effective plastic materials sensitive to VOCs suitable for vapours detection.