Introduction to Advanced Polymers in Medicine

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Polymeric materials, which can exhibit multiple functions, are desirable. Their synthesis, characterization, and successful clinical use requires the collaborative efforts from experts of multiple fields, such as chemists, material scientists, physicists, biologists, and clinicians.[1,2] Such efforts provide fruitful knowledge that can enable scientists to create the next generation of materials. The *Advanced Functional Polymers for Medicine* conference was held at the University of Twente campus in Enschede, the Netherlands, from June 15–17, 2011 and provided such an open environment for interdisciplinary discussion. This issue of *Macromolecular Symposia* is dedicated to the research highlights presented at this conference. This Introduction summarizes the articles by topic: *surface chemistry and fibers*, *synthetic polymers*, *porous scaffolds*, *nano- and microparticles*, *shape-memory polymers*, and *biopolymers*.

The surface chemistry of polymeric materials is important for their applications in medicine. Materials coming into contact with blood need to be hemocompatible so that they may be safely implemented in the clinic. For example, polyurethanes possess mechanical integrity, which is needed for long-term performance as an implant material, but these materials are limited in their applicability when in contact with blood as thrombus formation often occurs after an extended period of time. Multiple strategies of incorporating groups on material surfaces *via* functionalization to enable hemocompatibility are currently being developed. An approach of surface-initiated atom transfer radical polymerization and photoinduced polymerization of 2-methacryloyloxyethyl phosphorylcholine onto polycarbonateurethanes is described by Feng *et al.* [DOI: 10.1002/masy.201100034]. The zwitterionic phosphorylcholine groups of the grafted chains decreased the adhesion of platelets from rabbit blood onto the material (i.e. the hemolytic rates of the grafted systems were <5%, which is a requirement for blood-contacting materials). Microprinting represents another approach of attaching molecules to the surface of biomaterials to create functional systems. One such system is reported by Teixeira *et al.* [DOI: 10.1002/masy.201100035], which is comprised of crosslinked poly(trimethylene carbonate) (PTMC) with surface patterns of biotin, which may be useful for creating specific cell interactions. Another method of varying materials is by altering the amount of charged groups present on the surface, which was used to create charged poly(D,L-lactide) (PDLLA)-based electrospun nanofibers (Croisier *et al.* [DOI: 10.1002/masy.201100037]). PDLLA was electrospun in the presence of poly(methyl methacrylate-*b*-methacrylic acid), which introduced negatively charged groups under the specific environmental conditions. These fibers could be covered with positively charged poly(allylamine hydrochloride) to create positively charged fibers as confirmed using zeta potential measurements. In addition to the surface properties, the effects of the morphology of materials on the cellular response are of interest. Electrospun fibers and films of poly(ether)ester urethanes based on poly(*p*-dioxanone)diol and poly(ε-caprolactone)diol were investigated by Schneider *et al.* [DOI: 10.1002/masy.201100057] for their influence on the differentiation behavior of chondrocytes. All materials

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showed low endotoxin contamination and allowed the growth of primary articular chondrocytes, which maintained their differentiated phenotypes and expressed type II collagen production.

Poly(ether imide)s (PEI)s are promising for medical applications because they are non-toxic and are steam sterilizable, but they exhibit low flexibility. A synthetic method for preparing PEIs with lower glass transition temperatures, which would enable materials with higher flexibility, is presented by Lange *et al.* [DOI: 10.1002/masy.201100052]. These novel PEIs were synthesized from 4,4′-(4,4′-isopropylidenediphenoxy)bis(phthalic anhydride) or 4,4′-[(3-methoxypropane-1,2-diyl)bis(oxy)]bis-(phthalic anhydride) with 4,4′-[(3-methoxypropane-1,2-diyl)bis(oxy)]dianiline. The introduction of the methoxyglycerol unit lowered the material glass transition temperatures, resulting in a higher flexibility. A method of creating flexible polycyanoacrylate-based materials is reported by Tripodo *et al.* [DOI: 10.1002/masy.201100058]. This expanded range of mechanical properties are useful since polyalkylcyanoacrylates have shown potential for wound closure and drug delivery applications, but their inherent brittle mechanical properties create a challenge in their applicability. The incorporation of varying quantities of oligo(ethylene glycol) diglycidyl ether resulted in a polymer system in which the Young's modulus can be varied in a wide range from 0.2 to 900 MPa. A different approach of adjusting biomaterial properties is creating blends, as shown by Wischke *et al.* [DOI: 10.1002/masy.201100050], who blended poly(ε-caprolactone) (PCL) with poly[(ε-caprolacone)-*co*-glycolide] (PCG). PCG, which contained 8 wt% glycolide, showed drastically accelerated hydrolytic degradation profiles as well as decreased elastic properties (elongation at break, $\varepsilon_B = 4\%$ for PCG and $730 \pm 50\%$ for PCL). However, blending PCG with PCL homopolymer by coextrusion resulted in blends with mechanical properties similar to those of PCL, and the blends were viable substrates for L929 mouse fibroblasts. Synthetic polymer systems may show great promise as ocular implants, such as the PTMC-based cerclages presented by Wojcik *et al.* [DOI: 10.1002/masy.201100053]. The PTMC scleral buckles were inserted in rabbit models and no intra-operative problems, inflammatory issues, or otherwise negative reactions were observed. Small debris particulates from the degrading implant were taken up by macrophages and giant cells, which was indicative of a normal foreign body response.

Porous scaffolds are of great interest in biomaterial-induced regeneration.[3,4] Highly porous scaffolds were prepared from poly(ether)esterurethane copolymer synthesized by co-condensing poly(*p*-dioxanone)-diol and poly(ε-caprolactone)diol with an aliphatic diisocyanate by thermally-induced phase separation (Lützow *et al.* [DOI: 10.1002/masy.201100051]). The scaffolds possessed porosity values of 80–95 vol% with open pore geometry. These scaffolds are promising due to their biodegradability and possible angiogenic potential. Static and dynamic numerical models, which show how multilayer scaffolds with microchannels allow nutrient perfusion through the multiple layers, are presented by Papenburg *et al.* [DOI: 10.1002/masy.201100031]. Such models can be applied to understand how the interactions present within scaffolds can affect nutrient supply and therefore the fate of adhered cells. Diban *et al.* [DOI: 10.1002/masy.201100038] describes such a scaffold prepared from PCL using a phase inversion technique, which was intended for applications as an engineered blood vessel. The pore size distributions for some scaffolds were very narrow (e.g. 0.5–3.5 μm), which could allow a connected multicellular lining of endothelial cells that would enable thrombo-resistance behavior and isolate foreign material from the blood. Synthetic scaffolds can also be used as load-bearing devices, such as defect fillers in the annulus fibrosus. Scaffolds based on PTMC and poly(ethylene glycol) (PEG), which were injected and crosslinked upon illumination with visible light, are reported by Sharifi *et al.* [DOI: 10.1002/masy.201100047].

The efficiency of the crosslinking reaction, which resulted in scaffolds with compressive elastic modulus of approximately 5–20 MPa in the equilibrated swollen state, was tested in canine cadaveric IVD tissues. The crosslinking technique was sufficient to achieve adequate network formation, and the adhesion capabilities of the liquid precursors to the native tissues were examined as well.

Nano- and microparticles are becoming increasingly important and versatile in the fields of drug delivery and imaging. Creating novel nanocarriers, which can encapsulate, transport, and deliver otherwise insoluble drugs, would be beneficial for the medical field in general. Novel micelles composed of star-shaped copolymers based on PEG and PCL are reported by Cajot *et al.* [DOI: 10.1002/masy.201100044]. Specifically, three-arm (A_2B) and four-arm (A_2B_2) stars were created by coupling azide-terminated PEG with PCL chains bearing one or two alkyne groups in the middle of the chains. When dispersed in water, small particles with diameters of approximately 20 nanometers were observed. These multi-armed polymers were shown to effectively stabilize larger polylactide particles, which proved that they could be useful in multiple forms of drug delivery systems. The dynamic behavior of particles under physiological conditions is obviously of great importance in their evaluation as biomaterials. The degradation profiles and porosity changes in poly[(*rac*-lactide)-*co*-glycolide] PLGA-based microparticles were monitored and reported by Mathew *et al.* [DOI: 10.1002/masy.201100059]. Particles prepared from PLGA with varying M_n (2–13 kDa) and a PLGA-PEG-PLGA triblock copolymer were studied for their protein encapsulation efficiency using ovalbumin as a model payload. Examples of prepared microparticles from $M_n = 5$ kDa PLGA showed pore opening and closing in pH 7.4 PBS buffer solution.

Polymersomes represent another class of particulates, which are highly useful for drug delivery purposes. The binding effects of polymersomes bearing hydroxyl functional groups or carboxylic acid functional groups on human cervical carcinoma (HeLa) cells as well as the adsorption of bovine serum albumin on the two sets of polymersomes were studied by Bleul *et al.* [DOI: 10.1002/masy.201100042]. Polymersomes based on polybutadiene-*b*-PEG with the different functional end groups were prepared by sonication in water and extrusion. These polymersomes were non-toxic and the different functional groups did not induce any negative effects in cellular response. The carboxyl functionalized polymersomes bound to HeLa cells more strongly than the hydroxyl functionalized polymersomes in PBS buffer, while this effect was not observed in Dulbecco's Modified Eagle's Medium (DMEM), which indicates that the binding behavior of polymersomes is strongly dependent on the environment. Novel water-soluble nanoparticle carriers are reported by Koshkina *et al.* [DOI: 10.1002/masy.201100041], who grafted PEG onto polyorganosiloxane nanocarriers. These grafted nanoparticles were then coated with oligonucleotides and DNA, which created water-soluble, biofunctionalized nanoparticles.

Shape-memory polymers possess the ability to change their shape when triggered by an external stimulus, such as heat, light, or an alternating magnetic field. Dual-shape polymers have been reported, which have a permanent shape that can be deformed by application of external stress and fixed in a second, temporary shape using a programming procedure. This temporary shape is retained until the application of an appropriate stimulus, which causes the original shape to recover. An investigation on the influence of programming conditions on the recovery behavior of triple-shape memory polymers, which are able to perform two consecutive shape changes upon the application of heat,[5] is reported by Zotzmann *et al.* [DOI: 10.1002/masy.201100039]. A thermo-reversible approach of preparing shape-memory polymers is reported by Defize *et al.* [DOI: 10.1002/masy.201100036], who used a [4 + 2] Diels-Alder cycloaddition reaction to form networks of PCL. The

networks showed excellent fixity and recovery rates (>99%), which quantify the ability of the materials to fix a temporary shape and recover the permanent shape, respectively, which could be reproduced following a recycling period *via* a thermally-induced retro-Diels-Alder reaction. Shape-memory networks may also be functionalized with specific groups, which add biofunctionality to the systems as reported by Xu *et al.* [DOI: 10.1002/masy.201100060]. Networks based on PCL diacrylates and acrylated PEG-Gly-Arg-Gly-Asp-Ser (GRGDS) were shown using tetrathiol as a crosslinker and 2,2-dimethoxy-2-phenylacetophenone (DMPA) as an initiator. The GRGDS molecules facilitated fibroblasts adhesion and spreading on the hydrogel surface. Moreover, the shape fixity and recovery ratios for the GRGDS-containing networks were nearly quantitative (>99%), and the melting temperatures of the networks were between 39–43 °C, which is relevant for applications in regenerative medicine.

Biopolymer-based materials show advantageous properties in regenerative medicine because they can mimic functions of the natural extracellular matrix (ECM). Gelatin has been explored as a basis for tailorable biopolymer systems.[6–8] A hybrid biopolymer containing gelatin as well as chondroitin sulfate was created by functionalizing the two biopolymers with methacrylamide and then crosslinking a mixture of the two functionalized biopolymers using photoirradiation (Van Vlierberghe *et al.* [DOI: 10.1002/masy.201100030]). The storage modulus of the resulting crosslinked biopolymer hybrids was tailorable and varied according to the composition amounts and degrees of methacrylamide substitution ($G' = 0.1$–20 kPa). Gelatin can be functionalized with desaminotyrosine (DAT) or desaminotyrosyl tyrosine (DATT) to create supramolecular gels with mechanical properties that are ruled by such the interactions of such moieties.[7,8] These materials have been previously shown to show tailored swelling degrees ($Q \sim 300$–3000 vol%), which were dictated by the aromatic interactions between the tyrosine-derived side groups and the presence of triple helices. An important feature of these novel biomaterials is how they affect the cellular response of distinct immune relevant cells, which is reported by Roch *et al.* [DOI: 10.1002/masy.201100048]. The prepared materials had a low endotoxin content and the production of interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) of an immune relevant macrophage cell line were significantly reduced for the materials. Gelatin can also be used as a coating for metal implants, as presented by Vanderleyen *et al.* [DOI: 10.1002/masy.201100040]. Type A gelatin, which possesses an isoelectric point of 7 to 9, and Type B gelatin, which possesses an isoelectric point of 5 to 6, were immobilized to titanium surfaces using e-beam irradiation (25 kGy). The gelatin-treated surfaces were investigated using x-ray photoelectron spectroscopy (XPS), and the same synthetic techniques were also used to immobilize collagen to the titanium surfaces. Gelatin is prepared from collagen and may be further degraded to obtain fragments that may be useful as telechelic oligomers, which is reported by Piluso *et al.* [DOI: 10.1002/masy.201100054]. Hydroxylamine cleavage of gelatin resulted in controlled degradation and production of a mixture of fragments with molecular weights of 15, 25, 37, and 50 kDa as measured by SDS-Page. A directed cleavage by hydroxylamine at the asparyginyl glycyl bond is discussed in detail as a site-specific point of degradation. Proteins and peptides have attracted interest from the biomaterial community due to their specific interactive capabilities. The synthesis and characterization of a peptide, which shows propensity to adopt a beta-sheet conformation and potential as a building block for supramolecular biomaterials is reported by Federico *et al.* [DOI: 10.1002/masy.201100055]. The telechelic peptide precursor, LSELRLHNN, was synthesized using an Fmoc protocol and a solid-state peptide synthesizer. The purified peptide was characterized using matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS),

fourier transform infrared spectroscopy (FTIR), and 2D-NMR.

Polysaccharides also comprise a major portion of the ECM biomacromolecular milieu and thus can be used to create novel biomimicking systems. Injectable hydrogels based on dextran-tyramine and hyaluronic acid-tyramine networks were crosslinked using horseradish peroxidase (Wennink *et al.* [DOI: 10.1002/masy.201100032]). The hydrogels required gelling times of less than one minute and exhibited positive cytocompatibility in the presence of chondrocytes, which also maintained their round shape, indicating their potential for cartilage regenerative applications. A hybrid gel composed of hyaluronic aldehyde and alginate is discussed by Möller *et al.* [DOI: 10.1002/masy.201100045]. The *in vivo* degradation of the hydrogels was monitored by tracking the signal intensity of Lucifer Yellow, which was incorporated in the hydrogel and estimated the degradation time of the material to occur within 125 d. Moreover, histological analyses showed that inflammatory reactions and fibrous capsule formation were avoided. Neffe *et al.* [DOI: 10.1002/masy.201100049] shows that hyaluronic acid also serves as an excellent basis for local application to the retina, which can detach when the sensory retina is separated from the retinal pigment epithelium. HA was crosslinked using diepoxybutane under basic conditions and loaded with triamcinolone, which is used in the treatment of inflammatory processes. The hydrogels allowed this drug to diffuse and equilibrate after 120 h and showed hydrolytic degradation times starting after 3 weeks. The HA gels were tested in rabbit models and showed minimal inflammatory reactions, no scar tissue, and allowed tissue regeneration to occur. Biopolymers are also of interest in directing the differentiation pathway of stem cells. Collagen type IV can direct differentiation of mouse embryonic fibroblasts to vascular progenitor cells (Flk-1), but only to a limited degree. A small molecule, QS11, is shown by Poels *et al.* [DOI: 10.1002/masy.201100043] to substantially enhance this differentiation because of its synergistic effects on canonical Wnt signaling.

Creating and implementing multifunctional polymeric materials for medical purposes is complex and demands materials that address the multitude of challenges present *via* their multiple functions. In this issue of *Macromolecular Symposia*, several approaches of designing such polymeric materials are discussed. We thank all authors for their interesting and insightful contributions to this special issue of *Macromolecular Symposia* as well as Sibylle Meyer from Wiley-VCH, Dr. Karolin Schmälzlin and Sabine Benner, both from the HZG, for their valuable editorial and administrative support.

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