Advanced Functional Polymers for Medicine

When addressing biomedical applications, requirements for materials will comprise specific bulk properties, such as elasticity and thermal transitions; functions of the material, such as the rate of degradation; as well as the design of the biointerface enabling, for example, tissue integration.[1] Inspiration for biomaterial research can also be found in the structures and properties of materials in nature, representing a kind of default. Therefore, biomaterial research has to be seen between the poles of envisioned application and biological principles. In the course of designing polymers for biomedical applications, researchers may encounter limitations, such as the insurmountable complexity of structures when trying to analyze and emulate natural structures such as the extracellular matrix. This special issue was inspired by the sixth *Advanced Functional Polymers for Medicine* conference, held on 15–17 June 2016 at the University of Twente. The meeting was dedicated to bringing together scientists from chemistry, biology, pharmacy, and engineering, thereby progressing the field of polymeric biomaterials. Discussions included advancing syntheses of polymeric biomaterials, tailoring (bio)interfaces, and exploring the processing, highlighting the key fields of biomaterial research today.

The functionalization of linear (co)polymers on the molecular level often requires accessible chemical side groups. Some of the most commonly applied polymeric implant materials such as (co)polyesters do not contain such groups and their introduction is challenging.[2] In two review articles, alternative degradable polymers with easily transformable functional groups are presented. Yılmaz and Jerome discuss the trends in the synthesis and drug delivery applications of polyphosphoesters. The precursor enables the introduction of different side chains with functional groups such as alkenes and alkynes, which can be converted further after polymerization by, for example, thiol–ene reactions or alkyne–azide cycloadditions. In this way, a large variety of further functional groups can be introduced. The post-polymerization functionalization can be beneficially performed without impairing the molecular weight of the polymer. Thomas and Dove review the polymer-analogous modifications of alkene-functional polycarbonates, which, for example, can be utilized in thiol–ene reactions or in radical polymerizations for the formation of graft polymers and polymer networks.

Polymer networks are of interest for biomedical applications as their degradation profile leads to increasing elasticity over time rather than a spontaneous loss of material integrity as is often observed for linear polymers. Rupnik et al. show the formation of elastic polymer networks based on block copolymers, which have been cross-linked with segments containing disulfide bonds and which therefore can be degraded by reduction. Such materials may be employed for applications requiring on-demand degradation, or could be exploited in situations requiring intracellular degradation.

Block copolymers may show interesting phase segregation and organization behavior, especially when the different blocks are non-miscible, for example, because of contrasting hydrophilicity. The tendency of block-copolymers to self-assemble is on the one hand a function of the lengths of the hydrophilic and hydrophobic blocks, but is on the other hand furthermore subject to external conditions such as pH and temperature, giving rise to stimuli-sensitive materials. Khorshid et al. show that in thermosensitive hydrogels based on PLGA-PEG-PLGA block copolymers not only the transition temperature but also the type of superstructures formed depend on the length of the hydrophilic block. The self-assembly of amphiphilic block copolymers to nanoparticles is exploited by Palao-Suay et al. Here, it is demonstrated that the introduction of a small amount of a hydrophilic comonomer in the hydrophobic part of an amphiphilic block copolymer can be used to tune the disassembly of polymeric particles and release of cargo, putatively because of a higher water uptake into the hydrophobic phase than in the case of purely hydrophobic blocks. Particulate structures are widely explored as drug carriers. Different concepts are being evaluated to improve targeting and cellular uptake. Montanari et al. demonstrate the transitory covalent stabilization of nanoparticles through boronic esters, in this case in systems based on hyaluronan and tannic acid. The hyaluronan part of the particles was incorporated to increase the cellular uptake, as it is recognized by specific receptors. The boronic esters are hydrolyzed under acidic conditions as present in the endosome. In this way particles were received, which were efficiently internalized and degraded intracellularly. Ionic interactions stabilizing particles have been investigated by Goycoolea et al. It is shown that for chitosan-tripolyphosphate, the degree of acetylation as well as the molar mass are ruling the physical cross-linking and particle formation. Such fundamental studies are of relevance for the biological evaluation of the particles.

The cellular uptake of particles is an example illustrating the importance of the biointerface between materials and cells, tissues and body

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fluids. Venturato et al. demonstrate that for random and block copolymers from dimethylaminoethylacrylate and ethylacrylate (EA), increasing the EA content corresponded to an increased attachment of HeLa and HEK cells. More specific interactions on surfaces based on biological recognition approaches can be obtained by equipping interfaces with bioactive molecules, for example, integrin receptor ligands. Schulz et al. report on aptamers forming strong physical interactions with, for example, polyetherimide surfaces. Such aptamers serve as anchor groups for biomacromolecules. As aptamers with specific binding affinity to polymers are identified by an evolutionary selection and enrichment technique, the presented strategy can be transferred to other polymer surfaces not displaying chemical groups for covalent functionalization.

Progress in biomaterial science is closely related to the biomedical application. The fabrication of such products requires suitable processing techniques. This aspect is covered by Houben et al., who investigated processing of urethane-PEG gels by indirect solid freeform fabrication into porous scaffolds. In this way, the porous structure as well as the mechanical behavior of the scaffolds could be tailored. Complementing, van Bochove et al. showed the formation of precision meniscus implants based on CT data from poly(trimethylene carbonate) by stereolithography.

In summary, the articles in this special issue of Macromolecular Bioscience cover several promising approaches to tailor and control the properties and functions of polymers for medical applications. The chemical structure of the macromolecules forming the bulk material as well as the chemistry of the material surface influences various properties and functions of biomaterials. Processing techniques are of similar importance as biomaterial morphologies and surface topology largely influences, for example, biofunctionality. This toolbox can be used to create implants with tailorable multifunctionality.

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