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Developing Advanced Functional Polymers for Biomedical Applications

The design, fabrication and clinical translation of biomaterial based medical devices and drug delivery systems represent one of the fast emerging fields of science. Several megatrends can be observed in this multidisciplinary field, from the molecular design and synthesis of biomacromolecules, structure/property/functions of biomaterials – correlation understanding, functional tailoring and interactions with living systems. Furthermore, one can say that recent achievements in medical imaging, digital 3D-design and additive manufacturing have opened up amazing opportunities for novel multifunctional biomaterials and customized implants. Insights gained in tissue regeneration, cell cultivation and stem cell technologies open up great prospects when combined with the knowledge of tailored polymeric biomaterials. Thus, multifunctional polymeric biomaterials play a key role to enable breakthroughs in regenerative medicine and surgery. Such breakthroughs have huge societal impact and we do not need to wait for that for too long, the first clinical applications are already there.

The precise synthesis of the biomacromolecules form the basis for biomaterial science and engineering. The properties and functions of the synthetized polymers need to meet strict demands. For example, they need to be absolutely non-toxic, they need to show appropriate structural characteristics, from bone-like load bearing hardness to soft hydrogels, depending on the intended application.

Aliphatic (co)polyesters are established in clinical application as degradable materials in sutures and surgical implants. Especially this class of materials illustrated that processing effects on the material properties need to be understood. This is relevant for injection molding, fiber spinning and modern additive manufacturing techniques. The area has been researched in depth at KTH in Sweden by professor Finne-Widstrand and her group[1]. Control of molecular architecture and block structural composition has enabled self-assembly functionality and micelle formation. Professor Nottelet's group has reported families of PCL/PEG copolymers with functional groups[2,3]. They have application potential in drug delivery systems, and tissue engineering.

Next generation hydrogels have recently prepared in professor Jérôme´s group including isocyanate free poly(hydroxyurethanes) based hydrogels[4]. Biodegradable and histocompatible polyphosphoesters are promising candidates to replace conventional aliphatic polyesters as well.

Poly(trimethylene carbonate) (PTMC) is a polymer with high potential that degrades in a relatively low rate through an enzymatic surface erosion mechanism. The degradation does not produce acidic components. The materials phase transition from liquids to solids need to be mastered during processing, whether it is thermoplastic melt's solidification or prepolymer

photocuring in stereolithography. The controlled degradation of the biopolymers or guarantee its long-term stability in the demanding biological conditions are important aspects to be considered. Professor Seppälä's group has previously reported on photocuring composite resins for stereolithography[5]. Here, PTMC-composites that have systematically been loaded with variable amounts of bioactive agents, in this case β-tricalcium phosphate (β-TCP) in a spherical powdery form. Concentrations of up to 60wt-% can be photocured to form a mechanically solid biomaterial. Interestingly, using stereolithography as the processing method results in materials where β-TCP is clearly visible and accessible on the surface.

Functionality in this context can be bioactivity, active agent release property or interaction with the biological system. Professor Pêgo's group has applied two main strategies in the research of targeted therapies and regeneration of the nervous system: The design of nucleic acid delivery to neurons by using chitosan[6] or specifically synthetized dendrimers as vectors[7]. In the article of this special issue, she reviews laminin-inspired cell instructive microenvironments for neural stem cells. Polymeric nanoparticles can be used as vehicles for administration of active agents. Professor Tirelli's group has pioneered the field of Reactive Oxygen Species[8]. Here, they report on the strong anti-inflammatory performance of polysulfide nanoparticles used as an extracellular reactive oxygen species.

The ability of the materials to show 'smart' or 'intelligent' behavior are of great interest. The true intelligence might lie in the side of the biological system that interacts with the designed biomaterial. Today's progress in electronics and cordless information and energy transfer may offer unique opportunities in developing intelligent materials. Professor Lendlein's group has reported various mechanisms to prepare responsive and smart biomaterials[9,10]. Activation performance has been reported based on physically cross-linked polylactone blends using polylactide stereo complexation. Another kind of smart and bio-mimetic materials have been researched in professor Kaltenbrunner's laboratory[11]. In his article, soft electronic and robotic systems based on biocompatible and degradable materials have been reported.

Novel manufacturing technologies bind together advanced and amazingly high resolution medical imaging, digital 3D-design and high precision voxel-by-voxel additive manufacturing enabling high resolutions, earlier impossible complicated geometry manufacturing and patient specific individual surgical implants. The materials selection can be tailored and implant designs optimized according to the individual needs. Professor Larsen's group has researched light guided chemical patterning to produce designed and complicated hydrogel 3D-structures for tissue engineering[12,13]. They report in the special issue about the stereolithographic 3D-printing of low protein-binding poly(ethylene glycol)-diacrylate hydrogels. They have potential in the generation of contractile tissues.

Various hydrogels have been investigated to offer matrices for cell cultivations, proliferation and tissue formation in cell seeded conditions. Three dimensional hydrogel printing, so called bio-printing, has enabled optimized specimen production for nutrient delivery and vascularization with the aim of forming fully integrated and functional tissues or even organs with the aid of functional biopolymers. Professor Vozzi's group has used GPTMS as crosslinking agent for the preparation of nature-derived biomaterials[14]. In this special issue, they report on the preparation of pectin-GPTMS based hydrogel biomaterials for bioprinting.

Gelatin based hydrogels have been successfully transformed into biocompatible aligned porous structures through a freeze thawing method by professor Kumar's group[15,16]. These kind of hydrogel derived scaffold materials have been shown to be exceptionally promising in nerve and bone regeneration both *in vitro* and *in vivo*. In this special issue, the group reports on the application of gelatin-based scaffolds for wound healing. Additionally, they report on the bone forming properties of a nanohydroxyapatite based ceramic carrier. Especially interesting is that the materials can be incorporated with active agents like growth factors to boost their performance.

The pathway from basic research of functional medical polymers up to approved clinical use requires determinant long-term translational research in multiple fields fulfilling strict regulatory aspects and in depth and committed end use proofing, convincing the end users. Thus, the forums where fundamental scientists in functional polymers meet biological and medical researchers are of outmost importance. In addition, the interface dialogue between the scientists and industrial companies in the field is of essence for the progress. With this we can guarantee societally significant results taking place soon. This reflects the profile of the conference series of Advanced Functional Polymers for Medicine (AFPM).

This Special Issue of Biomacromolecules is based on the excellent contributions presented at the ''Advanced Functional Polymers for Medicine'' (AFPM) conference held in Aalto University, Finland, in May 5th to 7th 2019. The conference series AFPM was established for the first time in 2011 by professors Andreas Lendlein and Dirk Grijpma. Since then it has been organized eight times in various interesting locations by distinguished biomaterial scientists. In the year 2019, the AFPM-conference was organized by prof. Jukka Seppälä.

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