Advances in the development of supramolecular polymeric biomaterials

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Introduction

Ideal biomaterials need to meet the trinity requirements, that is, tunability of mechanical properties, the ability to regulate degradability, and the incorporation of bioactivity and moreover need to mimic the natural environment of the site of implantation. In the 1960–1970s, first-generation biomaterials were designed to be used in the body. They were developed in a way that they comprised physical properties that match those of the replaced tissue and to induce a minimal toxic response. In the 1980–1990s, second-generation biomaterials were developed with a strong emphasis on bioactivation, bioinertness, and controlled action–reaction in the physiological environment. Although minor improvements were made, synthetic materials were still unable to respond to changes in the physiological environment. Therefore, third-generation biomaterials are designed to stimulate specific cellular responses at the molecular level. Molecular modifications of biodegradable polymers direct specific interactions with cells and tissues, that is, differentiation, extracellular matrix (ECM) production, and organization.

To date, biomaterials have found multiple applications in the fields of tissue engineering and regenerative medicine, ranging from dental implants to vascular grafts, stents, and contact lenses. In general, it is the material surface which dictates the biological reaction in vivo. A cascade of reactions takes place upon implantation, where first proteins from the blood adsorb to the surface, followed by cell interrogation. Subsequently, these cells release biochemical factors and upon tissue formation ECM is produced whereby the biomaterial is encapsulated and isolated, or degraded and resolved in case of a degradable material. Ideally, the biomaterial instructs the in vivo environment to induce regeneration and the material degrades in time without the formation of scar tissue or fibrous tissue. Although many materials have been developed in order to meet all the properties as they are present in the highly ordered, dynamic, and organized in vivo environment, no material is yet able to meet all of these characteristics.

Therefore, a challenge in the development of new generation biomaterials that find their application in the field of regenerative medicine is to introduce structural and functional properties into these materials that closely mimic the natural environment. In order to meet these requirements, supramolecular biomaterials are envisioned to be suitable.
Supramolecular chemistry, which is defined as the chemistry beyond the covalent bond, deals with molecular building blocks that are held together via non-covalent interactions, that is, hydrogen bonds, electrostatic interactions, van der Waals interactions, host–guest assemblies, and \( \pi-\pi \) interactions. Via these secondary interactions, a multitude of complex structures with varying functions can be assembled. Due to the reversibility of the supramolecular interactions, these systems are inherently dynamic and to some extent show similarity with living systems found in nature. Many natural systems are comprised of supramolecular components that via association and dissociation are engaged in a specific function and are able to respond to environmental changes (i.e., temperature and pH). Supramolecular polymers can form by an array of non-covalently interacting building blocks using highly directional interactions, which provides them with polymeric properties both in solution and in the solid state, yet with a dynamic character. These types of supramolecular polymers hold promise as a class of novel biomaterials that can be applied in the field of tissue engineering and regenerative medicine, especially due to the controllable material properties in a dynamic, tunable, and reversible way.

A multitude of materials have been developed with a varying degree of dynamics, ranging from soluble assemblies that are highly dynamic, to hydrogels with tunable yet less dynamic assembly kinetics and more robust solid-like materials that possess rather slow assembly kinetics. Structural parameters in the design and synthesis of functional supramolecular polymers for biomedical applications involve non-covalent interactions and topological structures. The non-covalent interactions greatly determine the secondary structure that is adapted by the supramolecular polymer. Moreover, as a result of the association constant and the concentration of the non-covalent interactions, the final structure and related function of the aggregates is determined. Topological structures depend on the degree of functionalization of the building blocks and thereby determine greatly the macroscopic performance of the supramolecular material. Although these classes of materials are highly promising and have shown applicability already in many areas, a major challenge in the formulation of supramolecular biomaterials is to provide both control over surface composition and surface functionality.

Ultimately, in regenerative medicine applications, biomaterials that have the ability to adapt themselves and help the body to regenerate itself are desired. In this account, we highlight recent advances in the field of supramolecular polymeric biomaterials, based on the self-assembly behavior and the introduction of functionality, that is, bioactivity. In the first part, we focus on pristine macromolecular assemblies that are inspired by nature or exhibit natural building blocks and show intrinsic functionality. The synthetic assemblies that are disclosed discuss materials that are inspired by proteins and growth factors, peptides and carbohydrates, nucleobases as well as hydrogen bonding motifs to direct the self-assembly behavior (Fig. 1BI). In the second part, materials that contain functionality as a result of host–guest assemblies based on cyclodextrins, cucurbit[n]urils, crown ethers, and calix[n]arenes are discussed. These systems are particularly interesting as their dynamic assembly behavior can be tuned by the choice of different building blocks (Fig. 1BII). In the third part, the introduction of bioactivity into supramolecular thermoplastic elastomers is described, where materials based on polyurethanes, benzene tricarboxamide, bis-urea motifs as well as ureido-pyrimidinone (UPy) are highlighted. Thermoplastic elastomeric materials exhibit mechanical properties that can easily be tuned as a function of the base polymer. The design of the supramolecular motifs facilitates a modular approach toward the introduction of functionality in these classes of materials. Moreover, clinical translation and in vivo applications of these materials are disclosed (Fig. 1BIII).

**Synthetic Supramolecular Polymeric Materials Inspired by Natural Building Blocks**

Multiple intermolecular interactions (i.e., hydrogen bonding, the hydrophobic effect, and \( \pi-\pi \) stacking) are employed in the controlled synthesis of supramolecular polymers that are designed to mimic the performance of native proteins. These interactions are highly directional, reversible, and dynamic, providing the supramolecular polymers with attractive properties such as processability, self-healing, and stimuli-responsiveness. Although many elegant synthetic systems have been described to fabricate...
bio-inspired polymeric architectures (i.e., polypeptides and DNAs), the direct assembly of proteins into well-ordered polymeric superstructures remains a major challenge. The field of supramolecular chemistry takes inspiration from these design principles, in order to develop new synthetic materials that mimic these complex molecular assemblies. The design principles can be engineered according to a specific requirement that is needed for the material, that is, bioactivity or biocompatibility. The hierarchical self-assembled order and the ensemble of material properties, that is, mechanical, structural, and bioactive properties, found in the ECM is the main source of inspiration in the development of new generation biomaterials. In the next paragraphs, we highlight synthetic supramolecular materials that are inspired by natural building blocks, that is, proteins, growth factors, carbohydrates, peptides, nucleobases, and hydrogen bonding motifs.

**Supramolecular Biomaterials Inspired by Proteins and Growth Factors**

In the field of tissue engineering and regenerative medicine, many materials need to fulfill multiple criteria, of which bioactivity is an important one. Many reports describe bioactivation of materials through the introduction of bioactive peptide sequences or the non-covalent and covalent conjugation of proteins onto the biomaterial. It is proposed that the natural protein interface is responsible for the stabilization of supramolecular protein structure. Proteins self-assemble into well-defined hierarchical structures, which has been a source of inspiration for many researchers over the past decades to develop and synthesize synthetic analogs that can mimic the dynamic and reversible self-assembly process of proteins. Biological biopolymers consist of repetitive sequences and domains that are stabilized by noncovalent interactions that contribute to mechanical properties of the final structure they form, which enables assembly in hierarchical aggregates that ultimately determines their function. These characteristics and principles are a source of inspiration in the design of functional self-assembled polymeric biomaterials.

Maynard et al. focus on the design and synthesis of polymer-protein conjugates and develop polymers that mimic natural proteins. Besides that, materials surfaces and structures are designed through nanopatterning. Many of these strategies rely on covalent modification strategies to introduce bioactivity and are thus beyond the scope of this account; however, there are a few beautiful examples which are disclosed here. Using photolithography, micron and submicron-scale features were fabricated in polymer films in order to develop a platform for protein immobilization and assembly. Aldehyde-functionalized patterns were generated by exposure of pH-responsive poly(3,3'-diethoxypropyl methacrylate) and photoacid generator films to 365 nm light through a mask to site-specifically hydrolyze acetal to aldehydes. Subsequently, acid functionalities at the surface were incubated with biotin-functionalized hydroxylamine, generating an oxime bond. Upon exposure to 365 nm light, remaining acetal were hydrolyzed to aldehydes. Next, incubation with aminooxy-terminated poly(ethylene glycol) yielded a protein-resistant surface and streptavidin was allowed to immobilize onto the biotin functionalities at the surface. In a subsequent final step, any biotinylated compound can be immobilized onto the streptavidin, giving rise to highly controlled surface functionalization with bioactive compounds.

As a special class of proteins, growth factors have increased interest in recent years, since they are involved in many processes. The therapeutic potential of growth factors holds great potential for applications in regenerative medicine. However, the translation into clinical treatments is rather limited which might be a result of the poor stability of these proteins, a short circulation half-life and rapid cell internalization rate of the growth factors. Growth factor proteins are essential factors in the regeneration process which are secreted by cells and upon secretion are able to directly interact with or are sequestered by the surrounding ECM for presentation to cell surface receptors.

In the field of biomaterials, there are a few strategies to present growth factors at the surface of the material, that is, through natural affinity binding and adsorption, binding to ECM upon the introduction of a specific domain in the growth factor (heparin-binding domain, collagen-binding domain, or other ECM-binding domains) or covalent attachment through a chemical or enzymatic cross-link. Due to the short lifetime of growth factors, the requirement of high and frequent use and the high costs, the biomaterials that have been developed either physically entrap growth factors in a polymer of supramolecular network or graft them onto supramolecular structures via non-covalent electrostatic interactions, whereby a sustained and controlled release could be realized. Peptide cues that mimic the active site of the growth factor could also be introduced into the supramolecular material, thereby eliminating the need to use full growth factors. Many reports and review articles cover biomaterials presenting or incorporating growth factors based on hydrogels, which is not covered in this account.

Hubbell and Maynard reported on the discovery of a sulfated tetrapeptide that binds to vascular endothelial growth factor. Molecules that mimic the sulfated glycosaminoglycan heparin and have the property to bind growth factors with a heparin-binding domain are important building blocks for synthetic biomaterials. Due to the ease of synthesis and modification, peptide-based heparin mimics are of interest and a sulfated tetrapeptide library that binds to vascular endothelial growth factor (VEGF) was synthesized using split-tool combinatorial chemistry. The library of sulfated tetrapeptides was tested toward VEGF165 binding, an isoform of VEGF that is able to bind heparin, via a fluorescence assay. Subsequently, SPR analysis was performed on the best binding couples in order to determine the binding affinity for VEGF165. Via this combinatorial approach they were able to design a small peptide with only two sulfate groups that binds with higher affinity to the VEGF165 than well-known heparin mimics. This concept may be applicable for other heparin-binding growth factors as well and might elucidate high binding affinity small sulfated peptides.

Lee et al. reported on the local delivery of insulin-like growth factor (IGF-1) delivery in the myocardium. To this end, they designed self-assembling peptides composed of alternating hydrophilic and hydrophobic amino acids that assemble into nanofibers upon exposure to physiological conditions. Biotinylated IGF-1 was complexed with streptavidin which in turn can bind to
biotinylated self-assembled peptides. This approach did not interfere with the peptide amphiphile (PA) self-assembly into nanofibers and yet displayed the growth factor at the nanofiber surface. After injection into rat myocardium, specific and controlled delivery of IGF-1 to local myocardial microenvironments was observed which lead to improved results of cell therapy.15 An interesting study by Chmielewski et al. reported on mimicking the ECM by the design of collagen-mimetic peptides that are able to assemble into a highly cross-linked 3-D matrix upon a metal ion stimulus (Fig. 2A). Three collagen-mimetic peptides were synthesized (HBN, HRGDSN, and HBRGDS; Fig. 2B). Moreover, these assemblies can be functionalized with His-tag cargoes, in this case green fluorescent protein (GFP-His₈) and human epidermal growth factor (hEGF-His₆). The hEGF-His₆ is released gradually from the matrix and induces cell proliferation in an EGF-dependent cell line. The incorporation of RGDS in the collagen-mimetic peptide facilitates encapsulation of the cells into the cross-linked 3-D matrix (Fig. 2C).16

Fig. 2 ECM mimic with functionalized metal-assembled collagen peptide scaffolds. (A) Chemical structures of the HBN, HRGDSN, and HBRGDS collagen-mimetic peptides with (in blue) His₂ ligand for metal binding, (in green) bipyridine (Byp) for metal binding, (in red) NTA for metal binding, and (in purple) the RGDS peptide sequence for cell attachment. (B) Strategy for functionalization of the collagen-mimetic peptide (CMP) scaffold with his-tagged biomolecules. Upon metal-ion-promoted assembly, metal-ligands are able to incorporate His-tagged biomolecules. (C) MCF 10A cell encapsulated in the CMP scaffold are viable and organize into spheroid structures in the HBN/HBRGDS scaffolds. Pictures were recorded after 6 days of encapsulation of soluble (top row) or bound (bottom row) hEGF-His₆, scale bars represent 100 μm. The stars in the triple-helix cartoons indicate positions of the RGDS sequences. Reprinted from Hernandez-Gordillo, V.; Chmielewski, J. Biomaterials 2014, 35 (26), 7363 with permission from Elsevier.
Inspiration taken from the assembly of proteins and higher ordered protein assemblies can be applied in the development of synthetic materials that are highly dynamic or functional. Proteins and growth factors are essential components that are abundant in the natural ECM. Natural materials based on these compounds are inherently biocompatible and bioactive, which makes them extremely suitable as biomaterials. However, due to rapid degradation rates, poor stability, and their high costs, it remains a challenge to use full-length proteins and growth factors in the design and synthesis of supramolecular polymeric materials. Synthetic materials that mimic the intrinsic structure or function of the protein or growth factors are interesting alternatives toward new generation biomaterials. Progress in this field has been made; however, there is much more to be done.

**Supramolecular Biomaterials Inspired by Carbohydrates**

Carbohydrates are involved in many biological processes and due to the ability to form hydrogen bonds they are interesting components in supramolecular chemistry. Carbohydrate-carbohydrate interactions and carbohydrate-protein interactions regulate biochemical processes in the human body, ranging from cell differentiation and proliferation to the immune response. The ensemble of multiple carbohydrates in a multivalent complex ensures strength of the relatively weak noncovalent interactions of the single components. Glycosylated surfaces have been developed and used to study multivalent glycol interfaces. Many reports focus on the immobilization of host–guest-responsive systems on gold or glass substrates, as well as the use of supramolecular polysaccharide moieties in hydrogel development has grown interest in recent years, which is not covered in this account. In this section, we highlight a few literature examples in the development of supramolecular biomaterials that take inspiration from carbohydrate chemistry and their intriguing properties.

Seeberger et al. reported on the decoration of graphene sheet surfaces with multivalent sugar ligands in order to prepare a supramolecular carbohydrate-functionalized 2-D surface. In the interest of investigating carbohydrate-protein interactions, adamantyl-functionalized graphene was supramolecularly assembled with mannose-β-CD. These self-assembled sensors can reversibly bind bacteria as a result of an interaction between the mannose and E. coli bacteria. Subsequent IR-laser irradiation results in killing of the bacteria and yields these types of materials feasible for disinfection applications.

Tran et al. reported on the development of a one-step recyclable method to synthesize a supramolecular polysaccharide composite material comprising cellulose, chitosan, and crown ether (B15C5). The composite material demonstrated supramolecular properties, mechanical properties in the range of cellulose mechanical properties and adsorption capability of heavy metal ions and organic pollutants. The superior adsorption properties of the material are attributed to the presence of the crown ether. In order to develop protein-resistant materials, Guan et al. studied the structure-property relationship of a carbohydrate-derived side-chain ether polymer. It was shown by surface plasmon resonance that side-chain permethoxylated polyesters demonstrate excellent protein resistance toward nonspecific protein adsorption. Moreover, the introduction of amide bonds in the polymer backbone leads to increased protein resistance. The results show that the molecular design of polymers can be tailored in order to aim for the desired material properties, which can be applied as various biomaterials. A similar study based on polyethers was published a few years earlier where protein resistance behavior upon the introduction of a carbohydrate-derived side-chain polyether was also demonstrated.

More recently, Sun et al. reported on a layer-by-layer assembly approach to create healable antifouling films. They assemble the material by exponential layer-by-layer assembly of PEGylated branched poly(ethyleneimine) (bPEI) and hyaluronic acid (HA) followed by cross-linking via PEG diacid. The surface of these material films shows protein-resistant behavior as well as inhibited cell attachment under physiological conditions. The antifouling properties of the surface are assigned to the synergic effect of the PEG-rich surface and the soft mechanical nature of the films. As a result of high mobility of the bPEI-PEG and HA polyelectrolytes and the noncovalent hydrogen bonding and electrostatic interactions, the material exhibits healing behavior.

Materials inspired by or composed of carbohydrates are inherently biocompatible and bioactive as well as antifouling. These materials display interesting material properties that on the one hand facilitate engagement into the human body while on the other hand prevent nonspecific adsorption of undesired compounds. Upon the introduction of additional, specific bioactivity it is hypothesized that these carbohydrate-based materials can exhibit a specific function.

**Supramolecular Biomaterials Inspired by Peptides and Peptide Amphiphiles**

In recent years, the use of peptides as building blocks in supramolecular architectures has been demonstrated. Oligopeptide-based self-assembled structures have been used to synthesize hybrid conjugates that are composed of peptides in combination with polymers, alkyl chains, or phospholipids. Peptides can serve to bring specific bioactivity into the material as well as due to electrostatic interactions dictate the self-assembly of the moieties into desired secondary structures, which makes them highly suitable to be applied in the field of tissue engineering and regenerative medicine. Due to their biocompatible properties they can be applied in an aqueous environment directly or can act at the supramolecular polymer-water interface. Here we discuss the use of functional peptides in conjunction with polymer materials to develop highly structured biomaterials as well as their application as synthetically accessible peptide amphiphiles (PA) that self-assemble as a result of electrostatic interactions and the hydrophobic effect.

Collagen-mimetic peptides containing the triad amino acid sequence Gly-Hyp-X and Gly-X-Hyp, X frequently being Pro, have extensively been studied in order to reveal the triple-helix formation as well as the influence of different amino acids on the assembly process. Self-assembling peptides have been synthesized that form collagen-like triple helices and are able to assemble eventually into hydrogels, based on hierarchical assembly of natural collagen. Another example of ordered supramolecular
polymers are the formation of β-sheet-like structures, based on electrostatic interactions as a result of an alternating cationic-hydrophobic-anionic-hydrophobic peptide sequence. These structures are proposed to entangle and form hydrogels under physiological conditions, which provides them with useful properties for regenerative medicine applications and is widely explored by Zhang et al. Moreover, β-sheet peptides have been widely applied as functional building blocks in the preparation of bioactive supramolecular materials due to the inherent biocompatibility as well as the structural feature to adopt a secondary structure as a result of the specific amino acid sequence. The development of nanoﬁber scaffolds, inspired by nature and of which the design is based on supramolecular self-assembling β-sheet forming peptides, is performed by Zhang et al. Guan et al. focus on the synthesis of a polymeric β-sheet mimics that are able to assemble into hierarchical nanofibrils. Copper (I)-catalyzed azide-alkyne cycloaddition was employed for the polymerization of a peptide monomer in order to induce high-order structure formation in the synthetic polymers. The self-assembled nanostructures were visualized with transmission electron microscopy (TEM) and atomic force microscopy (AFM) and demonstrated the formation of nanofibrils composed of stacks of molecular fibrils from the β-sheet polymer. Moreover, these polymers further self-assemble intermolecularly into amyloid-like nanofibrils. The cycloaddition not only served as a polymerization method, but also induced the folding and self-assembly of the resultant polymer. The polymerization thus leads to intramolecular folding to form a β-sheet (secondary structure) and further intermolecular organization into hierarchical nanostructures. These results pave the way for development of more advanced and functional materials. In a mini review, Guan describes the current understanding of the molecular mechanisms that contribute to the exceptional mechanical properties of two biopolymers. Spider dragline silk which uses intermolecular weak forces between the β-sheets to gain strength and toughness, and sarcomere muscle titin which uses intramolecular modular design for achieving mechanical strength, toughness, and elasticity. It is proposed that supramolecular chemistry plays a critical role in the design of synthetic polymers that have a combination of advanced mechanical and other functional properties that can be used in the advancement of biomaterials. Another class of biomaterials described by Guan et al. is derived from natural saccharide and amino acid building blocks. Based on the abundance of the natural monomers, the likelihood to generate biocompatible and biodegradable polymers, the convenient modification of these materials toward desired applications and the modularity of synthesis, these saccharide-peptide hybrid copolymers are designed as a new class of biomaterials. The materials were shown to be nontoxic, biodegradable, and nonimmunogenic and were tested for possible gene delivery applications and tissue engineering.

Inspired by the intriguing properties of elastin, as an important ECM protein, a bioinspired modular synthesis approach to synthesize elastin-mimic polymers (EMPs) to probe the mechanism of elastin elasticity was reported. Three EMPs were synthesized, all based on the abundant sequence of elastin hydrophobic domain (VPGVG)n, that shares identical chemical composition, with differences in peptide sequence. Polymerization was performed using Cu-catalyzed azide-alkyne cyclization, and pentapeptides were end functionalized with an azide and an alkyn. It was shown that the polymer conformation is not essential for the elasticity of EMPs. However, the hydrophobic hydration, as opposed to an organized secondary structure, turned out to play an important role for the elasticity. Moreover, the bioinspired EMPs show similarities with natural elastin in elasticity in bulk as well as LCST behavior. It is proposed that the relatively easy modular platform for elastin mimicking polymers provide great potential for biomedical applications. In an effort to mimic the highly nonlinear elastic properties of human skin, a similar strategy via a bioinspired design of nanostructured elastomers with cross-linked soft-matrix-grafted rigid nanofibers was used. The synthetic material consists of cellulose and polyisoprene (PI), which differ in mechanical performance, semirigid, and strong versus highly elastic, respectively, to mimic stiff collagen and elastin in the skin. The polymers are connected in order to allow for large deformation. Moreover, microphase separation into nanocomposite occurs which results in the nonlinear mechanical properties of skin. The materials were characterized using dynamic mechanical analysis, TEM, SAXS, and mechanical tensile testing and the results showed microstructures as well as mechanical properties that mimic the properties of skin. These materials might have high potential as skin mimics for robotics and prosthetics when this strategy is applied to more biocompatible material components. More results and examples can be found in an interesting review by Guan about the structure and molecular mechanisms of natural polymeric materials and the progress toward synthetic mimics of these remarkable systems that was published in 2011. The reader is referred to this article for a detailed explanation about these natural peptide-based materials and how mimicking nature's approach leads to a new generation of advanced materials bearing useful properties that exceed those available by current methods.

Hubbell et al. reported on the development of a coating of surface-active copolymers that are RGD grafted to induce specific cell attachment and spreading and contained poly(ethylene glycol) (PEG) in order to prevent nonspecific protein adsorption. A poly-(L-lysine) (PLL) backbone from which PEG was grafted with short and long chains was synthesized. Moreover, the long chains of the PEG grafts were specifically conjugated with the RGD-containing peptide motif via the thiol of a cysteine in the peptide and a vinylsulfone terminus in the PEG chain, in order to facilitate cell binding. Due to the positive charge, the copolymers adsorb onto negatively charged surfaces. Protein adsorption assay revealed efficient blocking of serum proteins, while human dermal fibroblasts specifically adhered to Nb2O3 and tissue culture polysulfone surfaces. Another report on the use of poly(ethylene glycol) (PEG) brushes in order to introduce non-fouling behavior into materials, was published by Klok and Hubbell et al. A non-biofouling coating is introduced following a two-step strategy that involves photobromination of a low-density polyethylene (LDPE) substrate followed by surface-initiated atom transfer radical polymerization (SI-ATRP) of PEG-methacrylate (PEGMA) resulting in poly(poly(ethylene glycol)methacrylate) (PPEGMA) brushes. The surfaces were characterized using XPS and ATR-FTIR. It was shown that these coatings prevent nonspecific adhesion of cells and hence could be functionalized with ECM-derived peptides (GGGRGDS) to allow integrin-specific cell adhesion. In the abovementioned examples, we highlighted the use of peptides in the design of self-assembled ordered nanostructured materials. As a result of electrostatic and hydrogen bonding interactions a
secondary structure, that is, β-sheet formation, could be predicted. Moreover, the introduction of peptides into polymeric materials can also facilitate function, that is, bioactivity.

An elegant supramolecular system that is widely applied in the field of tissue engineering is based on peptide-based amphiphilic molecules that form three-dimensional nanofibers, which has been developed by Stupp et al. (Fig. 3B). These peptide amphiphiles (PA) are able to reversibly self-assemble into three-dimensional nanofibers and this nanofiber self-assembly process can be modulated either via pH, concentration, and ionic composition (Fig. 3C). Furthermore, PA is composed of three regions, a long aliphatic tail, a flexible peptide linker region, and a bioactive region, which acts as specific bioactive cue (Fig. 3A).

The most well-known PA was synthesized to be applied in the mineralization of hydroxyapatite and consists of five structural regions. In addition to the aliphatic tail, the peptide linker region, and the bioactive cell adhesion cue (RGD), four cysteine residues were built in between the alkyl tail and the peptide linker, in order to facilitate oxidation to form disulfide bonds which can facilitate the polymerization of the nanofibrous structure. In addition to the bioactive cell adhesive RGD sequence, a phosphoserine residue was introduced to facilitate strong interaction with calcium ions. Lowering the pH below 4 induced the PA self-assembly and the disulfide bond formation ensures fiber cross-linking resulting in a chemically robust fiber, which could be reversed by the reduction of the disulfide bonds. Moreover, the fibers are able to direct the mineralization of hydroxyapatite to create a composite material of which the c-axis is aligned along the long axis of the supramolecular nanofibers, in a similar way as is observed in bone between collagen fibrils and hydroxyapatite crystals, yielding this system highly promising for bone tissue engineering applications.

The co-assembly of two bioactive PA by electrostatic interactions at different pH has also been shown. At low pH, negatively charged PA self-assemble, while at high pH positively charged PA self-assemble and pairs of positively and negatively charged PA co-assemble at neutral pH. PA has a modular character, making them extremely valuable for a variety of applications, among which the mineralization of hydroxyapatite crystals on cross-linked PA as mentioned above is one. Among others, the ability to bind oligonucleotides was also explored via the synthesis of peptide nucleic acid/peptide amphiphile conjugates (PNA-PA) that self-assemble into fiber-like nanostructures and are able to bind nucleotides with high affinity as well as specificity. This would make these supramolecular hybrid materials suitable for RNA interference and gene silencing applications.
In the development of nanomaterials for new blood vessel formation in regenerative medicine, heparin chemistry in combination with PA self-assembly was applied. The PA was equipped with the peptide sequence LRKKLGKA, which is known to have a strong binding affinity for heparin that in turn strongly binds angiogenic growth factors. Heparin was used to nucleate the self-assembly of the PA, yielding rigid nanofibers that display heparin to orient proteins for cell signaling. The heparin-decorated PA nanostructures stimulated new blood vessel formation in vivo in rat cornea.56 PA nanofibers with the neurite-promoting laminin-derived IKVAV peptide sequence were studied for the application of tissue engineering of nerves. The IKVAV sequences were present at high density and it was shown that the artificial nanofiber scaffold-induced selective differentiation of neuron progenitor cells, as compared to the soluble peptide. Moreover, the development of astrocytes was discouraged upon PA presentation. The epitope density is thought to be the key factor for the rapid and selective differentiation into neurons.57 The supramolecular structure in the natural ECM is related to the bioactive epitope density and dynamics and plays important roles in cell-matrix interactions as well as signaling. Stupp et al. probed the interactions of cells with supramolecular PA fibers that display cell adhesion RGD epitopes in various extremely high densities, that is, branched and linear, in order to demonstrate the possibility of signaling cells using these supramolecular nanofibers. They have shown that branched architectures in the PA forming the nanofibers provide greater epitope accessibility to cells, due to the lower packing efficiency and thus additional space for epitope motion. Moreover, when the supramolecular nanostructures display mobile epitopes at high density, improved signaling for cell adhesion, spreading, and migration is observed.57 This concept was explored for bladder tissue engineering, where traditional PGA scaffolds were coated with both linear and branched RGD-terminated PA in order to influence cell attachment and phenotype expression. The PA was reproducibly coated onto the poly(glycolic acid) (PGA) fiber scaffolds and showed surface retention upon cell culture conditions and moreover, self-assembled into nanofibers. In terms of cell response they showed that bladder smooth muscle cells preferably attach to scaffolds that were coated with the PA, demonstrating the power of this approach.58

More recently, the order of PA was investigated and it was shown that the anisotropic interactions of the peptide linker domain of PA consisting of amino acids with a high β-sheet forming tendency directly connected to the hydrophobic tail ensure self-assembly into supramolecular nanofibers.59 The attachment of VEGF-mimetic peptide sequences to the PA have shown to improve the survival, proliferation, and migration of human umbilical vein endothelial cells, compared to nonfunctionalized PA. The VEGF-mimetic PA was investigated for the use as a therapy for ischemic disease and were evaluated using a mouse hind limb ischemia model showing increased tissue perfusion, functional recovery, limb salvage, and treadmill endurance compared to controls that only included the VEGF-mimetic peptide.60 Multiple length scale signaling of materials to cells is important in regenerative medicine applications, in particular when functional recovery is related to spatial control in the field of nerve tissue regeneration. The use of IKVAV-PA to examine the ability of Schwann cells to attach and proliferate within the material was reported. The results show that Schwann cells adhere and proliferate better on IKVAV-PA as compared to non-modified PA.61 Stupp et al. continue their work on the development of stimuli-responsive dynamic materials. The ability of materials to respond to changes in physical structure and chemical composition would greatly improve the development of synthetic materials that ultimately mimic the dynamic features of the ECM.62

The introduction of bioactive functionality in supramolecular polymeric materials by the introduction of peptide sequences has been widely applied in tissue engineering and regenerative medicine. The easy accessibility of peptides and their ability to mimic the properties of full-length proteins makes them suitable candidates for various applications. The processing conditions of peptide sequences are compatible with polymer processing conditions which allows for multiple material bioactivation approaches, that is, surface functionalization, incorporation of peptide sequences in a polymer chain or via PA self-assembly. Moreover, inspired by nature, the use of peptides as building blocks to guide the self-assembly of aggregates into well-defined structures acknowledges the wide applicability of these moieties.

**Supramolecular Biomaterials Inspired by Nucleobase Self-Assembly**

Inspired by the defined and selective self-assembly of nucleobases as found in nature, nucleobase supramolecular polymeric materials have gained attention in recent years. The use of nucleobases as recognition motifs to functionalize polymeric materials has been investigated by various research groups.

In the area of nucleobase supramolecular polymeric materials, Long et al. have investigated the nucleobase self-assembly in supramolecular adhesives based on molecular recognition, with adenine and thymine. A flexible alkyl chain spacer for recognition sites was constructed, that was compared with a styrene analog in order to investigate the structural modifications on the nucleobase self-assembly, both by AFM and SAXS. These novel acrylic nucleobases were synthesized using an aza-Michael addition combined with copolymerization with n-butyl acrylate. AFM images, SAXS and WAXS measurements revealed that 7 mol% adenine-containing polymers self-assembled into needle-like microstructures within the polymer matrix, whereas thymine-containing polymers did not aggregate into distinct morphologies up to 32 mol%. Upon mixing, the thymine and adenine physically base pair together, resulting in thermodynamically stable complex formation. Moreover, these nucleobase-functionalized polyacrylates exhibit tunable adhesive and cohesive strength, whereby the molar fractions of each nucleobase, their stacking interactions as well as the complementary hydrogen bonding are of influence on the self-assembly of these materials.63 An approach to synthesize triblock copolymers with nucleobase, adenine, and thymine, functionalized outer blocks was reported. These thermoplastic elastomeric block copolymers were synthesized following nitroxide-mediated radical polymerization with n-butyl acrylate rubber middle blocks that were varied in size. In blends of the complementary polymers, hydrogen bonding interactions resulted in increased viscosity which can be attributed to association of the nucleobases in solution. Increased solution viscosity scaled with
concentration, demonstrating the influence of the hydrogen bonding equilibrium of the nucleobases. Moreover, in solid state, hydrogen bonding resulted in compatibilization of the blends through the formation of associated adenosine-thymine hard phase upon annealing. Morphology of the solid films was investigated using AFM, revealing intermediate domain spacing and surface textures for the blends of the complementary block copolymers. Introducing complementary guest molecules resulted in selective uptake into the nucleobase-containing domains, which may potentially extrapolate toward use in drug delivery and biological applications.

An interesting feature article on the incorporation of nucleobases and other complementary hydrogen bonding functionalities into well-defined block copolymers was reported. The design of synthetic macromolecules based on multiple noncovalent interactions is inspired by the way nature’s biopolymers (nucleic acids and proteins) assemble into complex structures to achieve function. The incorporation of noncovalent interactions into a range of macromolecular structures generates complex tertiary and quaternary structures, which enables the supramolecular assembly and modification to adapt new properties. Orthogonal functionalization through electrostatic interactions and complementary hydrogen bonding allows modification of polymer properties significantly and the design of materials with properties that are required for biomedical applications.

Another elegant example reports on the use of RAFT polymerization to create self-complementary nucleobase-functionalized ABC triblock copolymers with fully acrylic backbones that self-assemble into well-defined lamellar microphase-separated morphologies. Moreover, complementary hydrogen bonding within the hard phase resulted in further enhanced mechanical performance of these materials. This class of thermoplastic elastomers is considered perfectly suitable for a wide variety of applications. A feature article by Long and Anderson covers the use of imidazole derivatives and imidazolium-containing polymers in materials science and their potential use in biomedical applications. Another material based on nucleobase-grafted polycaprolactones as reversible networks was reported by Chang et al. Aliphatic polyesters with pendant chloride moieties were synthesized by controlled ring-opening polymerization and subsequently these were used for adenine or uracil or both nucleobase grafting by Cu(I)-catalyzed azide-alkyne click reaction. The grafting resulted in retarded crystallization due to the supramolecular polymer formation. Molecular recognition experiments showed interactions between the adenine and uracil through strong cooperative hydrogen bonding. AFM and TEM were performed to study the morphology and revealed discrete nanoscale spherical aggregates upon self-assembly. In vitro cytotoxicity revealed biocompatibility of these materials, suggesting they are suitable for biomedical engineering applications.

The ability of nucleobases to self-assemble via molecular recognition into higher ordered structures has inspired many research groups in the development of supramolecular polymeric materials. Due to the intrinsic biological nature of the nucleobases, they form an interesting class of building blocks in the design and synthesis of complex nanostructured materials.

**Supramolecular Biomaterials Inspired by Synthetic Hydrogen Bonding Motifs**

Supramolecular polymers that gain structure as a result of hydrogen bonding motifs form an interesting class of synthetic modules that show great applicability in materials science. Due to the reversible nature of hydrogen bonds, a dynamic character of the materials is ensured. Simultaneously, applying an array of hydrogen bonds facilitates the formation of strongly interacting aggregates. Hydrogen-bonded systems are eminently suitable for tissue engineering and regenerative medicine applications not only due to the dynamic behavior of the hydrogen bonds, but also as a result of convenient synthesis methods via self-assembly and the ability to meet biocompatibility requirements.

Guan et al. reported on the design of a biomimetic modular polymer that consists of high modulus, toughness, and resilience, and moreover possesses adaptive mechanical properties. The concept is based on the skeletal muscle protein titin, with a modular...
domain forming part that is composed of a 2-ureido-4H-pyrimidinone (UPy) motif and a cyclic modular polymer using a peptidomimetic β-sheet dimer. These modular polymers exhibit unusual stress–strain behavior and unique shape-memory properties, giving rise to a material with a combination of mechanical properties, alike found in titin, including high modulus, toughness, large extensibility as well as intriguing adaptive behavior. The proposed mechanism for these properties is explained by the fact that upon stretching, the polymer modules gradually unfold which result in a large extension and energy absorption. Upon cooling and stress removal, the unfolded UPy-moieties are in mutual proximity to other UPy-moieties of neighboring chains, resulting in the dimerization into another network, and another material shape. Upon temperature increase, in time the newly formed interchain formed UPy dimers become dynamic again and return to the original stable dimerized state. These materials give rise to the development of novel biomimetic polymeric materials with advanced properties. Another beautiful example by Guan et al. described the design of supramolecular block copolymers for new multiphase self-healing materials in bulk solid state. The soft block in the block copolymer consisted of poly(n-butyl acrylate) (PBA) and polystyrene (PS) as the hard block (PBA-b-PS), which exhibit microphase separation morphology as well as thermoplastic elastomer properties. In order to equip the polymers with self-healing behavior, the PBA-b-PS diblock copolymers were end functionalized with UPy-motifs, resulting in the formation of an ABA triblock supramolecular polymer. The incorporation of UPy-moieties resulted in thermoplastic elastomers with dynamic and self-healing properties. Moreover, modularity of this system can facilitate the incorporation of bioactive motifs in order to develop functional biomaterials. Another self-healing material was developed based on a multiphase design strategy to program dynamic healing motifs based on hydrogen bonds in the soft phase of a hard-soft multiphase system (Fig. 5A). Thereby, the unique properties of hybrid polymers (stiffness and toughness) are merged with those of dynamic supramolecular assemblies (autonomic healing). Here, a hydrogen bonding brush polymer (HBP) that self-assembles into a two-phase morphology and behaves like a TPE, with a high Young’s modulus and extensibility, was synthesized (Fig. 5B). These materials showed tunable mechanical properties via the molecular design (Fig. 5C). Moreover, the creep recovery behavior of these self-healing supramolecular thermoplastic elastomers showed creep recovery behavior at different stress levels similar to that of covalently linked elastomers (Fig. 5D). Microphase-separated behavior of these materials was revealed by TEM (Fig. 5E).

A series of ABA block copolymers that are composed of a rigid poly(methyl methacrylate) (PMMA) middle block and two dynamic poly(acrylate amide) (PA-amide) terminal blocks that have hydrogen bonding capacity were synthesized in order to synthesize a multivalent hydrogen bonding block copolymer that can self-assemble into a strong and tough self-healing material. By adjusting the chain length of the blocks, the mechanical properties of the material could be tuned. Moreover, the block copolymers self-assemble into spherical microphase-separated morphologies. As compared to other systems reported by Guan et al., these hydrogen bonding block copolymers exhibit improved mechanical properties as well as self-healing capability.

A single-component sticky polymer-grafted nanoparticle approach has been developed by the introduction of strong molecular interactions to the graft in order to increase the cohesive attraction in the self-assembled nanocomposites. Multivalent hydrogen bonding motifs were introduced onto the polymer grafts in order to facilitate self-assembly into 3-D superlattice nanocomposites. The method provides a scalable approach and the materials possess both high structural order and robust and dynamic mechanical properties. The dynamic hydrogen bonding facilitates the formation of dynamic, self-healing materials and mechanochromic nanocomposite materials in bulk, which can be tuned upon changing the length of the grafted polymer chains. These types of materials hold great promise for the development of functional nanocomposite materials which are robust and dynamic. Along these lines, self-healing multiphase polymers were developed based on dynamic metal-ligand interactions. In this case, a polystyrene (PS) was used as the backbone from which multiple imidazole-containing brushes were grown. Imidazole is able to complex with Zn²⁺ thereby inducing the formation of a microphase-separated material with a PS hard phase and a Zn²⁺-imidazole soft phase. Materials were characterized using small angle X-ray scattering (SAXS) and transmission electron microscopy (TEM), and mechanical and self-healing properties were investigated. The mechanical properties could easily be tuned by varying several molecular parameters. Self-healing behavior was excellent under ambient conditions. The metal-ligand interactions offer advantages over hydrogen-bonded systems as they are less sensitive to moisture and have a broad range of tunability both in terms of kinetics and thermodynamics. A thermoplastic elastomer brush copolymer which is self-healing was synthesized. Via a two-step polymerization, a copolymer with a PMMA backbone and a flexible polycrylate-amide (PA-amide) brush that exhibits thermoplastic elastomer properties in bulk was generated. The dynamic hydrogen bonds in the soft PA-amide matrix enable spontaneous self-healing properties after mechanical damage. The materials were characterized by AFM, TEM, and DSC and mechanical as well as self-healing studies were performed. Inspired by the nucleobase complementary hydrogen bonding capacity, Long et al. designed another class of materials, in which star-shaped poly(ethylene-co-propylene) (MW 12–90 KDa) was end functionalized with the fourfold self-complementary hydrogen bonding UPy motif and analyzed using both AFM and SAXS, as a function of architecture, molecular weight, and degree of functionalization. It was found that UPy end-functionalized poly(ethylene-co-propylene) forms microphase-separated morphologies.

Supramolecular polymers based on dynamic and reversible hydrogen bonding give rise to the formation of materials that exhibit interesting properties. Moreover, an array of hydrogen bonds enables use of macromolecules, that via self-assembly form supramolecular polymeric structures with properties that are similar to conventional polymers. The ECM is a large supramolecular complex in which the interplay of dynamic and constantly remodeling components are able to adapt to environmental changes. Supramolecular polymeric materials that obtain their properties as a result of hydrogen bonding arrays have great potential in the development of functional biomaterials that ultimately serve as a synthetic analog of the natural ECM.

In conclusion, in the development of supramolecular polymeric biomaterials, nature and natural building blocks are a main source of inspiration. In particular, mimicking the natural ECM, which is composed of multiple supramolecular assemblies of both
structural and functional compounds, with completely synthetic materials is a challenge. In the previous sections, we highlighted recent developments where either the supramolecular polymer assemblies consist of natural building blocks to introduce specific function and guide the self-assembly or the development of supramolecular polymers that are based on hydrogen bonding motifs. Although beautiful contributions are reported in the field, much work still needs to be done toward the development of a fully synthetic ECM analog.
Host–Guest Complexation

Biomaterials that are surface functionalized show great potential in a variety of different applications, among which are biosensors for biomarker detection, drug discovery, and materials that promote cell growth and thereby tissue formation. In particular, the immobilization of functional proteins for tissue engineering applications and the development of medical devices have grown interest in recent years. The main challenge in the protein immobilization is to find a suitable chemical immobilization strategy in order to control the orientation and to ensure both functionality and activity of the protein. Many elegant immobilization strategies have been employed in recent years to covalently attach proteins at the surface of solid supports, including chemoselective covalent attachment of proteins via the amine functionality of lysines of proteins to N-hydroxysuccinimide (NHS) or aldehydes to form peptide or imine bonds which are the most commonly used method. Moreover, native chemical ligation, split-intein-mediated protein trans-splicing, or enzyme-mediated ligations are among others also explored in this field. In order to maintain protein stability and allow for site-specific reversible immobilization using mild reaction conditions, supramolecular ligation strategies prove to be excellent candidates. Well-studied supramolecular ligation strategies include hexahistidine tag (His6 tag) and nickel nitritriacetic (NTA) surfaces and biotinylated proteins with avidin-modified surfaces. Although the His6 tag can easily be genetically encoded in the protein without further chemical modification, there is a need for metal ions which could influence protein function. Moreover, genetic encoding complex protein structures remain a challenge. The interaction between biotin and avidin has an extremely high association constant \(K_a = 10^{13} - 10^{15} \text{ M}^{-1}\), which is comparable in strength to covalent bonds. Avidin is equipped with four biotin binding sites which allows for sequential interactions and has proven successful in the immobilization of proteins and vesicles. This method has proven to be successful in a variety of applications, a major drawback is the need for biotinylated proteins which may result in protein instability and inactivity.

In order to overcome the limitations of the abovementioned methods, supramolecular complexation based on host–guest interactions have grown interest in biomaterials science. One-dimensional linear supramolecular polymers can be formed through the engagement of complementary host and guest unimers, which can be associated via host–guest heteroditopic monomers or via two-component equimolar mixtures of hosts and guests heterocomplementary complexes. Polya ssociation of host–guest monomers yields supramolecular homopolymers, in which association and growth occur immediately after host–guest recognition. Regularly alternating supramolecular heteropolymers form upon mixing stoichiometric ratios of hosts and guests. Both approaches compete with the formation of cyclic oligomers. Synthetic macrocyclic molecules such as cyclodextrin and cucurbit[n]urils can host different guest compounds. The ring sizes of these macrocycles differ, which results in the ability to incorporate multiple guest molecules in the cavity with different affinity. The incorporation of these synthetic receptors on a solid surface facilitates the immobilization of proteins that contain the corresponding ligand. Host–guest complexes involve a cooperative effect of non-covalent interactions, that is, hydrophobic interactions, hydrogen bonding, and electrostatic interactions, and guest molecules are able to incorporate into the cavity of the host. The complexation of host and guest relies on complementarity in size and shape. Many reports in the literature report on stimuli-responsive supramolecular polymers based on host–guest assemblies, in aqueous solution, which is beyond the scope of this account.

Supramolecular polymers based on host–guest interaction exhibit interesting properties and, therefore, are perfectly suitable for various applications. Host–guest supramolecular polymers are able to form well-defined macromolecular architectures, and can be used to prepare responsive materials with properties that can be tuned upon changing environmental conditions. Complementarity in both shape and interaction with a host is a typical phenomenon of the guest, that is, molecular recognition including hydrogen bonding, electrostatic interactions, van der Waals interactions, and the hydrophobic effect. The dynamic behavior in complex biological systems can elegantly be mimicked by host–guest systems that rely on supramolecular complexation. Moreover, the introduction of surface functionality through this approach has grown interest toward multifunctional biointerfaces that are stimuli-responsive, biocompatible, and adaptable. Commonly studied host–guest complexes include cyclodextrins (CD), cucurbit[n]urils (CB[n]s), crown ethers, and calix[n]arenes, which are discussed in the following sections.

Host–Guest Complexes Based on Cyclodextrin

Cyclodextrin (CD) is composed of a hydrophilic exterior surface and a hydrophobic interior cavity, which is able to host multiple guest ligands. They are cyclic oligosaccharides composed of five or more \(\alpha\)-D-glucopyranoside units in a ring linked through \(\alpha\)-1,4-glycosidic bonds. Frequently used CD is composed of six (\(\alpha\)-CD), seven (\(\beta\)-CD), or eight (\(\gamma\)-CD) glucopyranoside monomers. A widely used approach is the grafting of polymers with CD to provide a cationic surface charge which may reduce polymer toxicity as well as facilitate molecular stabilization. Polyethyleneimine (PEI) is a cationic polymer which is widely used in delivery applications for its internalization properties. Most examples of successful application of CD host–guest assemblies report on their hydrogel formation capabilities. It has been shown that macroscopic self-assembly can take place based on the molecular recognition of the CD with the corresponding ligands.

CD host–guest inclusion has also proven to be an efficient approach to functionalize surfaces of solid material films. Li et al. report on a strategy where first \(\beta\)-CD were covalently grafted onto a cellulose fiber surface and subsequently adamantane end-capped oligomers were immobilized onto the fiber surface, thereby changing the properties of the cellulose materials as desired. PCL on both ends capped with adamantane (AD-PCL) was synthesized and supramolecularly assembled onto the
CD-containing cellulose fibers. Surface functionalization was characterized by ATR-FTIR spectroscopy and XPS and both techniques confirmed successful PCL-AD assembly at the cellulose-CD surface. Moreover, a significant change in water contact angle was observed toward more hydrophobic character after conjugation of the AD-PCL, indicating the assembly was successful. As a next step toward bioactive supramolecular biomaterials, the introduction of adamantane-conjugated biomolecules can be assembled in order to introduce surface functionality.

In the development of functional supramolecular solid materials, Zhao et al. have developed a method to selectively functionalize poly(e-caprolactone) (PCL) surfaces with both an antifouling coating as well as the introduction of a peptide to specifically bind endothelial progenitor cells (EPC) (Fig. 6A). Via the host-guest assembly of β-CD and adamantane they realized surface functionalization of the PCL materials. The PCL films were surface grafted with β-CD and subsequently adamantane-functionalized PEG and EPC-binding peptides were immobilized on the PCL-CD surface (Fig. 6B). The materials were characterized by XPS, water contact angle, and by means of a fluorescence assay with a FITC-labeled EPC peptide. XPS revealed a difference in surface composition after assembly of the adamantane compounds (Fig. 6C). Water contact angle measurements revealed a slight decrease in angle, indicative of surface functionalization. Moreover, PEG functionalization of the surface resulted in antifouling behavior, fibrinogen adhesion as well as platelet adhesion was reduced. Inclusion of the EPC-binding peptide resulted in enhanced attachment of EPCs (Fig. 6D and E). The results indicate that the dual functionalization approach was applied successfully and is promising in the development of vascular grafts to induce in situ endothelialization.

Ohya et al. reported on the synthesis of an amphiphilic biodegradable poly(l-lactide)-grafted α-CD copolymer (CD-g-PLLA) and determined thermal, mechanical, degradation, and microphase separation properties of the materials. These materials could find possible applications as an implantable drug-encapsulating depot which is based on the CD-AD interactions. AD-functionalized drugs could be specifically assembled onto the materials surface. Another elegant illustration in the design of dynamic biomaterial surfaces is reported by Yui et al. They synthesized a triblock copolymer-containing hydrophilic polyrotaxane and hydrophobic poly(iso-butylnmethacrylate) (PibMA) segments via atom transfer radical polymerization (ATRP). Due to the rotational motion potential of the polyrotaxanes, these moieties are considered beneficial in the design of dynamic material interfaces. In order to prepare the polyrotaxane triblock copolymer, the hydrophobic monomer iso-butylnmethacrylate was synthesized using a pseudopolyrotaxane with a 2-bromoisobutyryl end-capped PEG and α-CD as a macro-initiator. Hydrophilicity was introduced via the methylation of α-CD. Surfaces were subsequently subjected to dynamic wettability as well as molecular mobility studies by both dynamic contact angle measurements as well as QCM-D. Protein adsorption on the polyrotaxane triblock copolymer surfaces was investigated with a bicinchonic acid (BCA) assay. Dynamic contact angle and QCM-D measurements revealed a loop-like structure of the polyrotaxane at the surface as well as high mobility at the surface. Interestingly, the micro-BCA assay showed that the hydrophilicity and molecular mobility of the surface has no influence on the amount of human serum albumin (HSA) that was...
The grafting of multiwalled carbon nanotubes (MWNTs) with biodegradable supramolecular polypseudorotaxane has been reported by Xie et al. They have successfully functionalized MWNTs with biodegradable supramolecular polypseudorotaxanes by combining ring-opening polymerization and supramolecular inclusion complexation between guest-grafted PCL and host β-CD. The surfaces of the MWNTs were characterized with FTIR, NMR, and XPS, showing the covalent attachment of PCL to the MWNTs which provided a platform to form a core-shell nanostructure, as a result of supramolecular polypseudorotaxane complexation.

TEM revealed a uniform morphology of the nanostructures with a PCL-grafted thickness of 5–7 nm. Upon the inclusion of β-CD, more bundles and entanglements of MWNTs were identified, indicative for the supramolecular β-CD host–guest assembly at the surface of the MWNTs.86 Another interesting study was performed by Amiel et al., where they developed a supramolecular host–guest strategy based on β-CD to decorate polymer interfaces with PEG grafts. By copper(I)-catalyzed azide-alkyne cycloaddition a series of bifunctional adamantyl bearing different PEG-chains-grafted CD chains were synthesized. Both ITC and SPR measurements in solution and at the interface revealed stable layer formation onto the neutral and positively charged β-CD polymer films, as a result of the multivalent interpolymer host–guest interactions. It was shown that the ability to form inclusion complexes with monomeric β-Cd, neutral poly-β-CD, and cationic poly-β-CD is strongly dependent on the degree of substitution by the adamantyl functions, indicative for a cooperative binding effect. These PEG-adamantyl-grafted β-CDs can form an interesting new class of materials in biomedical applications where reversible PEGylation is desired.99 Recently, Chen et al. reported on the regulation of protein binding capability of surfaces via β-CD host–guest interactions by varying the localized and average ligand density. It is long known that the ligand presentation at interfaces has a significant influence on their interaction with biomolecules and subsequent biological responses. Therefore, modulation of the ligand density of biomaterials is of great importance. Lysine-plasminogen (Lys-Ptg) was chosen as a model to investigate specific protein binding capability of ligand-modified surfaces. Via surface-initiated atom transfer radical polymerization (SI-ATRP) a bioinert surface was generated by poly[2-hydroxyethyl methacrylate-co-(adamantan-1-yl)-methyl methacrylate] on a silicon wafer. Lysine-monomosubstituted β-CD containing one lysine per β-CD moiety and lysine-persubstituted β-CD containing seven lysines per β-CD moiety were integrated onto the surfaces via host–guest interactions between β-CD and adamantane. The average lysine density of the surface could be modulated by changing the lysine valency on the β-CD scaffold as well as by using pure β-CD to dilute the per-6-lysine-β-CD. Surfaces were characterized with water contact angle, XPS, and ellipsometry, which showed an increase in hydrophilicity and a nitrogen increase at the surface, indicative for successful complexation at the surface. Anti fouling behavior was studied and revealed hardly any difference between the different surfaces. Plasminogen adsorption on the different surfaces could elegantly be linearly modulated by diluting the β-CD containing seven lysines into β-CD. This method of host–guest post-modification showed to be facile, mild, and adjustable.100 The biocompatible nature and the self-assembling properties with multiple guest molecules in a variety of different applications yield CD perfectly suitable for the use in biomedical applications.

Host–Guest Complexes Based on Cucurbit[n]uril

Another host–guest system is based on cucurbit[n]uril (CB) hosts that have the ability to complex various guests in their cavity, depending on the corresponding ring size. Although CBs were first synthesized in the early 1900s, the structure was not revealed until 1981. CB[n]s can be obtained by the condensation of glycoluril and formaldehyde giving rise to macrocyclic structures of glycoluril repeating units (typically n = 5–8) linked via methylene groups. The rigid hydrophobic cavity of CBs give rise to supramolecular complexation with various ligands, depending on the size of the cavity.101 In this way, CBs have been explored in a multitude of applications, ranging from drug delivery, molecular recognition, and self-assembly and have also been explored as multivalent scaffold.102–104 Recent studies propose that the electrostatic positive outer surface of CB[n]s provides a balance in the various supramolecular driving forces for CB[n] assembly, including other CB[n]s, aromatic moieties, inorganic molecules based on hydrogen bonding between methine or methylene groups on the outer surface of CB[n]s.105 Due to the larger cavity volume, CB [8] is able to host two guests in its cavity to form a 1:1:1 ternary complex affording high selectivity and molecular recognition. The guest pairs are composed of an electron-deficient guest, that is, viologen derivatives, and an electron-rich guest, that is, naphtol.105

CB[5] has the ability to bind gases and small solvents (i.e., Ar, N2, CO2, CH3OH, and CH3CN), investigated both in solution state and in solid state. CB[6] can bind ω-αmino acids, ω-amino alcohols, aliphatic alcohols, acids and nitriles, bipyridine derivatives, aromatic compounds, non-ionic surfactants and poly(ethylene glycols), cycloextrinsics, diamides, and γ-amino acids and dipeptides. CB[7]s have a somewhat larger cavity and are therefore able to bind a wider range of guests, among which positively charged aromatic compounds including adamantanes and bicyclooctanes, naphthalenes, stilbenes, viologens, ω-carborane, ferrocene and cobaltocene derivatives, and metal complexes. CB[8]s have a similar cavity size as γ-CD, with less conformational flexibility. CB[8] prefers to bind positively charged guests by ion-dipole interactions, where the guests either fill partly or completely fill the cavity. Moreover, CB[8] is able to host two aromatic rings, leading to the formation of termolecular complexes in a cooperative fashion. In biomedical applications, the aromatic amino acid phenylalanine is mostly used through homogeneous termolecular complex formation. Hetero-termolecular complexes with CB[8] have also been reported, that is, methylviologen and tryptophan or naphthalene.106
Urbach et al. described the selective recognition and noncovalent dimerization of N-terminal aromatic peptides in aqueous solution by CB[8]. It turned out this binding goes in a cooperative fashion with high affinity, $K = 10^{11} \text{ M}^{-2}$ for the ternary complex in aqueous medium at neutral pH. Moreover, Urbach reported on the charge-mediated recognition of N-terminal tryptophan and methylviologen in aqueous medium by CB[8], for which affinities in the range of $K_a = 1.3 \times 10^5 \text{ M}^{-1}$ were reported. These findings yield CB[8] homogeneous and heterogeneous complexation as interesting candidates for application in biomedical surface functionalization.

Various examples have been reported where these strategies have been applied either on silicon, gold, or glass substrates. Jonkheijm et al. reported on highly ordered monolayers of β-CD on gold and glass surfaces to immobilize glycoconjugates via photoresponsive azobenzene moieties. Azobenzene are able to bind in the CD and CB cavity in the stable trans form and can be released upon UV irradiation and subsequent isomerization into the cis-azobenzene. By QCM-D measurements, they were able to determine the binding affinity of glycoconjugates on β-CD SAMS. Besides this, they were able to immobilize azobenzene-functionalized dyes and carbohydrates and proved this by fluorescence microscopy. Upon an external light stimulus, azobenzene moieties could be released from the surface. Moreover, nanostructured materials based on cucurbituril supramolecular chemistry approaches have grown interest in recent years.

In order to introduce surface functionality at polymer surfaces, chemical surface modifications of the polymers are required, that is, plasma oxidation of poly(dimethylsiloxane) (PDMS) in order to create activated PDMS surfaces which can be further functionalized. Poly(methyl methacrylate) (PMMA) can be treated with 1,6-hexanediamine in order to yield an aminated surface that can subsequently be biofunctionalized. Polycarbonates (PCs) surfaces have successfully been sulfonated with sulfate groups. These strategies are beyond the scope of this account.

Scherman et al. also applied the CB[8] host–guest chemistry extensively in order to develop supramolecular hydrogel formulations with many potential applications. The reader is referred to references about this topic since it is out of scope of this account.

Due to the applications in biological and materials sciences, bilayer lipid membranes have received significant attention in recent years. Bilayer lipid membranes are of interest in the design of biofunctional coatings, controlled release technologies, and biosensors, but optimization toward more stable systems is required. The covalent stabilization of the supramolecular polymericizable lipids is highlighted as well as the emerging applications of mechanically robust self-assembled lipid architectures. Recently, Brunsveld et al. reported on the controlled immobilization of proteins on DOPC lipid bilayers using supramolecular noncovalent interactions based on CB[8] (Fig. 7C). They relied on the formation of the ternary complex in two steps where first the methylviologen binds, followed by the binding of an indole. Both binding events have individual binding constants in the range of $K_a = 10^5 \text{ M}^{-1}$. A YFP model protein with an N-terminal tryptophan-glycine-glycine (WGG-YFP) motif was expressed and methylviologen guests anchored with a cholesterol moiety to enable incorporation into the lipid bilayer (Fig. 7A and B). The supramolecular complex formation in solution was studied using isothermal titration calorimetry (ITC) revealing an enthalpy-driven process. Subsequent study of supramolecular protein immobilization was studied with quartz crystal microbalance with dissipation monitoring (QCM-D). They showed subsequently the immobilization of the lipid bilayer, the incorporation of the cholesterol-methylviologen anchor into the bilayer, and the WGG-YFP assembly upon CB[8] administration (Fig. 7C). Moreover, the protein immobilization proved to be reversible by subsequently assembly and disassembly steps up to three times (Fig. 7D). The system provides a method for site-selective reversible protein immobilization on supramolecular material surfaces.

The association constants and, therefore, the stability of the supramolecular complexes formed by CBs as well as solubility concerns at high concentrations are a drawback for these systems in the development of new generation biomaterials. However, the high selectivity in host–guest interactions and the tunable ring sizes of CBs, affords this class of materials with high potential for future developments.

Crown-Ether-Based Host–Guest Systems

Crown-ether-based molecular recognition motifs have been widely explored to fabricate supramolecular polymers with interesting properties due to their good selectivity and convenient environmental responsiveness. Moreover, the host–guest complex can be applied to afford rotaxanes, mechanically interlocked structures. Mechanical bonds can be an integral part of the polymer backbone and thereby can introduce mobility elements such as rotation and elongation mobility into the main chain, resulting in viscoelastic material properties. Crown ethers are known as the first generation of supramolecular host moieties, explored by Stoddart et al. Typically, crown-ether-based host–guest assemblies are a class of self-assembled structures in which cyclic species are associated onto rod-like molecules and are locked by two bulky moieties at the ends, preventing dissociation. Crown ether hosts, such as bis(p-phenylene)-34-crown-10, bis(m-phenylene)-32-crown-10 and dibenzo-24-crown-8 are involved to afford host–guest complexes and create rotaxanes. The guest moiety is able to interlock into the crown ether, creating a pseudorotaxane in case there are no bulky stoppers present and upon the addition of a bulky moiety at the end of the guest a rotaxane is formed.

Stang et al. reported on the development of functionalizable supramolecular polymer networks based on hierarchical unification of coordination-driven self-assembly, hydrogen bonding, and crown-ether-based host–guest interactions. A Pt(II)-pyridine motif was used to assemble a metallohexagon bearing two different functional moieties, a UPy group and a benzo-21-crown-7 (B21C7) motif. The complementary hydrogen bonding interactions of the UPy-groups result in the formation of a hexagon-cored supramolecular polymer network with free B21C7 moieties. Orthogonal functionalization is obtained by crown
ether-dialkylammonium salt-based host–guest interactions, which does not interfere with the structure of the supramolecular network. The combination of metal-ligand coordination, hydrogen bonding, and host–guest interactions in a hierarchical fashion has proven to be an elegant approach to develop functionalizable supramolecular polymers. These findings can pave the way toward the formation of gels or soft materials for biomedical applications.

It was shown by Huang et al. that supramolecular nanofibers and nanogels exhibit unique mechanical properties, which led to the development of a host–guest monomer containing a B21C7 group and a second ammonium salt moiety connected via a long alkyl chain. Upon self-assembly, linear high-molecular-weight supramolecular fibers form in solution, with a high viscosity. Via electrospinning, these polymers can form smooth nanofibers, which were characterized by SEM, TEM, and AFM. This approach is unique considering the low-molecular-weight monomers and paves the way to post-functionalize these materials in order to introduce surface bioactivity.

Randomly adsorbed proteins can have detrimental effects in their ability to promote bacterial colonization on implant surfaces which can accumulate in the formation of biofilms. In order to prevent protein adhesion, nonadhesive surfaces can be developed as well as slow releasing agents can be incorporated into the material. Ratner et al. developed a surface treatment to prevent nonspecific protein adhesion and reduce or eliminate subsequent bacterial adhesion and biofilm formation by plasma polymerization.
deposition. Material surface properties were characterized by XPS, TOF-SIMS, and dynamic contact angle goniometry. Moreover, they investigated the resistance to proteins and initial bacterial attachment in plasma-deposited crown ether thin films. In the interest of reduced bacterial biofilm deposition, Denes et al. report on the deposition of PEG-like structures onto stainless steel surfaces via a cold-plasma-enhanced process. Via the plasma treatment, a macromolecular network is deposited onto the stainless steel. Surfaces were characterized using electron spectroscopy for chemical analysis (ESCA), water contact angle, and AFM. ESCA showed a deposition of PEG-like structures after plasma treatment of the stainless steel. Moreover, the plasma-treated surfaces were more hydrophilic and showed reduced surface roughness as compared to the untreated materials. It was shown that this surface modification significantly reduced bacterial attachment and biofilm formation, yielding potential applications in the deposition of antifouling layers on a multitude of materials.

Crown ethers, which were first described as supramolecular host–guest systems, have received considerable interest in materials science research. Their specific ligand binding and ion-specific interactions can be incorporated into material networks to confer specific design criteria.

Calix[n]arenes Host–Guest Assemblies
Calix[n]arenes, a generic nomenclature for a class of macrocyclic compounds, are composed of phenolic units which are connected via methylene bridges. Baeyer et al. proposed the synthesis of these moieties via reaction of phenols and aldehydes under strong acidic conditions. The n in the nomenclature of the calixarenes denotes the number of phenolic units that are linked via methylene bridges, providing the cavity of the molecule. Among many applications of calixarenes, to date, the immobilization of calixarenes on a solid support is a prominent applied process to construct various calixarene-based materials. Moreover, calixarene-based supramolecular polymeric materials are equipped with interesting properties such as self-healing ability. Calixarene-based supramolecular polymers are electrochemically responsive systems. The structure enables calixarenes to feature “molecular basket” properties for neutral and ionic guests.

Ertul et al. reported on a novel approach where calixamide nanofibers were produced by electrospinning and subsequently demonstrated toxic anion binding to the fiber structures. To this end, polyacrylonitrile (PAN) nanofiber-based calixarene derivatives were electrospun in order to develop functional nanofibers. The fiber diameter of PAN electrospun fibers increased upon the addition of calixarenes. ATR-FTIR measurements revealed the presence of calixarene moieties at the surface of the fibers. Subsequently, toxic anion extraction of chromium (Cr(IV)) was studied from aqueous medium and revealed successful adsorption of the toxins on the nanofiber-based calixamide material. This system contributes to the development of functional nanofibers for a variety of applications, among which include controlled drug delivery, catalysis, and filtration.

As described in this section, calixarenes are an interesting class of supramolecular host–guest assemblies, owing to their ease of modification with respect to shape and size. These properties give rise to an expanding array of guest molecules that can assess different biomedical applications, due to the ability to either expand or shrink depending on the flexibility in the upper- or lower-rim components of the calixarenes.

To conclude, supramolecular polymeric materials that are equipped with host–guest assemblies form an interesting class of materials, as due to the specificity of the host–guest interactions, functionality can easily be introduced. Host–guest assemblies can improve the selectivity of biomolecule-ligand binding as a result of the recognition-directed interactions. Moreover, the high selectivity, strong yet dynamic interactions, and the reversible nature of these assemblies can be exploited in the field of tissue engineering and regenerative medicine. In order to mimic complex molecular recognition systems as they appear in nature that are able to adapt to changes in the environment, exploring host–guest chemistry as well as the development of functional bio-interfaces can contribute to future developments in this field.

Modification Strategies to Introduce Bioactivity Into Supramolecular Self-Assembled Materials
An elegant approach to introduce functionality at materials surfaces is via the modular incorporation of additives that can easily be mixed and matched with the bulk supramolecular polymer material. The supramolecular motif, which is the driving force for self-assembly is introduced in the bioactive moiety as well, to facilitate modular incorporation.

Toward the Bioactivation of Supramolecular Elastomers
Structural biomaterials that exhibit extraordinary properties that are specifically designed for a certain application, often require hierarchical structure formation on different length scales. Supramolecular polymers and networks based on molecular recognition units that guide the self-assembly give rise to elastomeric materials with tailorable mechanical properties. Moreover, this class of materials show excellent processing and self-healing properties and in particular show a modular tunable nature. Incorporation of structuring as well as the prevention of nonspecific surface reactions and the introduction of bioactivity can easily be achieved, while mechanical properties of the bulk remain unchanged. In the next sections, we highlight supramolecular elastomeric materials based on different supramolecular motifs, that is, polyurethanes, benzene tricarboxamides, bis-urea, and UPy-moieties. We end this section with recent results and advancement in the development of these materials toward supramolecular polymeric biomaterials.
**Supramolecular elastomers based on polyurethanes**

Due to the large number of cross-links through cooperative hydrogen bonds, supramolecular rubbers display self-healing properties. However, solvent resistance and creep resistance is limited due to a lack of chemical cross-links. Michaud et al. investigated a strategy to increase the number of chemical cross-links in self-healing materials by combining supramolecular chemistry and epoxides. The aim of the study was to generate an insoluble hybrid network that contains a fixed amount of terminal hydrogen bonding groups and a tunable number of chemical cross-links. The average functionality was modified through the combination of bifunctional and tetrafunctional epoxy resins in the compositions. Tetrafunctional epoxy resins resulted in the formation of insoluble, partially chemically bonded materials, characterized by rheology measurements and solubility tests. Moreover, the tetrafunctional epoxide after curing gave rise to gelled materials, which showed self-healing behavior. By this strategy it was shown that they can control network formation, both in terms of kinetics as well as final structure. In the development of supramolecular materials for adhesion applications, Leibler et al. demonstrated that the flexibility of polycondensation reactions could be employed in order to fix the molecular architecture and obtain semicrystalline structures. The materials have polymer-like properties at room temperature but are able to show liquid flow properties upon heating. The polycondensation reactions were designed in order to obtain a supramolecular polymeric material with a stress at break larger than 10 MPa and melt viscosity below 1 Pa s. Synthesis and rheological as well as mechanical properties were reported demonstrating that molecular size distribution, the strength of hydrogen bonds, and the crystallization of the different molecular building blocks could be controlled in order to achieve desired material properties. A report based on scaling theory of a self-healing material was disclosed by Leibler and Rubinstein. They studied the reaction kinetics of reversible bonds with a model and analyzed the different stages in the self-repair process based on fixed chains in space at one end and with reversible pairwise association at the other end. Soulić-Ziakovic et al. reported on the synthesis of thermoplastic elastomers composed of di- and triblock copolymers based on polyethylene and polyisobutene blocks. These block copolymers were constructed via an efficient click reaction (azide-alkyne) using relatively low-molar-mass polyethylene and polyisobutene. Spectroscopic characterization, as well as thermal, optical, X-ray scattering, and mechanical analyses were performed to investigate the thermoplastic elastomer properties.

In development toward more functional materials for biomedical applications, Wagner et al. explored thermoplastic elastomers exhibiting bioactive components. In order to improve thromboresistance in respiratory assist devices, Wagner et al. developed a hollow fiber membrane which was modified with functional zwitterionic macromolecules. These devices aim for optimized performance in terms of gas transfer efficiency and thromboresistance. In order to facilitate the exchange of gas with blood, the surface of hollow fiber membranes is used. Here they report on three zwitterionic macromolecules that were attached to the hollow fiber membrane surface in order to improve thromboresistance; carboxyl-functionalized zwitterionic phosphorylcholine (PC), sulfobetaine macromolecules through thiol-ene radical polymerization, and low-molecular-weight sulfobetaine—co-methacrylic acid block copolymer prepared via reversible addition-fragmentation chain transfer (RAFT) polymerization, respectively. Each zwitterionic macromolecule was covalently immobilized onto the hollow fiber membrane, and surfaces were characterized using XPS. Ovine blood was used to test thrombotic deposition in vitro as well as the gas exchange capacity. The zwitterionic surfaces showed an increase in phosphor and sulfur surface content and a significantly lower platelet deposition as compared to unmodified and heparin-coated control surfaces. Also the CO₂ removal rate of the zwitterionic surfaces was increased as compared to the control surfaces. Zwitterionic coatings display a promising approach in the performance of artificial lung devices.

In another study, Wagner et al. reported on a biodegradable, elastomeric polyurethane material containing a coating with anti-proliferative agent released in a controlled fashion for cardiovascular stent applications. The degradation behavior, hemocompatibility, and drug release were investigated for poly(carbonate urethane) urea (PCUU) and poly(ester urethane) urea (PEUU)-coated magnesium alloy stents, with poly(lactic-co-glycolic acid) (PLGA) coated and bare stents as controls. PCUU showed significantly decreased magnesium alloy erosion as compared to the PEUU and PLGA coated and bare magnesium alloy stents, confirmed by TEM, energy-dispersive X-ray spectroscopy, and magnesium ion release experiments. The PCUU coatings also showed reduced platelet adhesion and inhibited proliferation was observed upon paclitaxel loading in the PCUU coatings. PCUU coatings were thus shown to be promising candidates in biodegradable metallic cardiovascular stents. In order to apply multilayer coatings of biodegradable PEUIU embedded with anti-proliferation drug paclitaxel surface-modified metallic biomaterials, a direct-inkjet technique was employed, which provides selective patterning capability to deposit multimaterial coatings on three-dimensional implant devices, such as cardiovascular stents. To study the influence of drug loading and coating thickness, drug release profiles were studied in order to obtain tunable release kinetics. Paclitaxel-loaded coatings showed a significant reduction in platelet adhesion as well as decreased cell proliferation when compared to the unloaded control coatings. The method for direct writing of bio-functional coating was shown to be promising. Another elegant study reports on the prolonged effect of surface modification by the incorporation of pendant reactive groups in the bulk. Bio-degradable PEUIU polymers with variable amino content were developed, which could be functionalized with carboxylated phosphorylcholine in order to generate PEUIU-phosphorylcholine polymers. Surfaces were characterized using XPS and FTIR in order to study the different functionalization steps. Moreover, mechanical, thermal, and degradation properties were determined for the amine incorporation and the subsequent phosphorylcholine modifications. Upon amine incorporation, the water absorption increased and further increased after phosphorylcholine conjugation. In wet conditions, the tensile strength and initial modulus decreased with increasing hydrophilicity, but remained in the range of 5–10 MPa and 10–20 MPa, respectively, (Fig. 8C). As expected, phosphorylcholine conjugation resulted in reduced platelet adhesion and reduced cell proliferation (Fig. 8D).
Fig. 8  Prolonged effect of surface modifications is achieved by the incorporation of pendant reactive groups in the bulk. (A) Synthesis of carboxylated phosphorylcholine (PC-COOH) that can be conjugated to the poly(ester urethane) urea (PEUU) elastomers for subsequent bulk modifications. (B) Schematic representation of the bulk functionalization to generate PEUU-PC polymers. (C) Stress–strain curves of cast polyurethane films under dry conditions: (I) PEUU-NH₂, (II) PEUU-PC and wet conditions, (III) PEUU-NH₂-Wet, (IV) PEUU-PC-Wet, immersed in water (37°C) for 24 h. (D) Platelet adhesion after 3 h contact with ovine blood on cast films of PEUU, PEUU-N₅, PEUU-PC₁, PEUU-PC₃, PEUU-PC₅, scale bar = 50 μm top row, 10 μm bottom row. Reprinted from Fang, J.; Ye, S.-H.; Shankarraman, V.; Huang, Y.; Mo, X.; Wagner, W. R. Acta Biomater. 2014, 10 (11), 4639 with permission from Elsevier.
A nonthrombogenic biodegradable elastomeric polyurethane with variable sulfobetaine content was synthesized from a mixture containing PCL-diol and sulfobetaine-diol in various combinations, reacted with diisocyanatobutane and chain extended with putrescine. Characterization of the materials was done by chemical structure analysis, tensile mechanical testing, thermal testing, hydrophilicity properties, biodegradable testing, fibrinogen adsorption, and thrombogenicity testing. At higher sulfobetaine content, the wet tensile strength increased as well as breaking strain and moreover, thrombotic deposition was reduced. Via electrospinning these materials could be processed into vascular conduit formats.135 In another study, synthetic poly(ester urethane)urea (PEUU) electrospun (diameter 100–900 nm depending on the polymer concentration) scaffolds were prepared as an ECM mimic. Collagen was introduced into the PEEU by blending in order to increase cell adhesion and mechanical properties of the material. The results demonstrate an approach to mimic elastic ECM properties by relying on synthetic components that provide mechanical properties and function comparable to native matrix and proteins can provide the desired bioactivity.136 In order to stimulate wound healing, the hollow fiber membrane could be administered at the wound in order to provide local and externally regulated controlled release of regenerative factors and after sufficient healing, these materials desirably degrade themselves. Therefore, an enzymatically biodegradable thermoplastic elastomer was synthesized consisting of polyurethane urea (PUUU) based on polycaprolactone (PCL) as mechanically strong polymers and polyethylene glycol (PEG) as soft segments and a collagenase-sensitive peptide (GGGLGPAGGK) as a chain stopper. Electrospun fibers exhibited appropriate mechanical properties as a result of the PCL, showed sustained release of a model protein as a result of the PEG incorporation and were susceptible to collagenase degradation as a result of the incorporation of the peptide.137 In conclusion, biomaterials exhibiting elastomeric material properties are very suitable candidates for a multitude of different biomedical applications due to the robust mechanical properties and the relatively easy modification strategies in order to either incorporate bioactivity or delivery capability.

**Supramolecular polymers based on benzene-1,3,5-tricarboxamide nanorods**

Supramolecular materials based on the triple-hydrogen bonding motif benzene-1,3,5-tricarboxamide (BTA) have been extensively studied. This motif forms 1-D columnar structures in solution as well as in the solid state as a result of a threefold intermolecular hydrogen bonding in a helical type of arrangement.138-140 However, the amount of publications where they are applied as solid supramolecular materials is limited. Mes et al. reported on the use of BTA motif for a supramolecular material based on phase-segregated nanorods in a polymer poly(ethylene butylene) (PEB) matrix. Telechelic polymers end capped or copolymerized with BTAs both result in the formation of supramolecular material. As a result of the intrinsic phase segregation behavior of the BTA nanorods with the amorphous PEB, thermoplastic elastomeric behavior is obtained. The phase segregation results in strong multiple cross-linking anchoring points with dimensional order within the soft PEB polymer matrix, which in turn leads to materials exhibiting thermoplastic elastomeric properties.141 This new class of supramolecular thermoplastic elastomer can find potential applications in the biomedicine engineering field. However, processing as well as bioactivation and surface enhancement still remains unexplored.

**Supramolecular thermoplastic elastomers based on a bis-urea hydrogen bonding motif**

Upon the introduction of polyurethanes and polyamides as polymeric materials, a new class of elastomeric materials that can be processed at elevated temperatures have been established. Noncovalent cross-links of the supramolecular hydrogen bonding motifs between the polymer chains are formed, which are able to crystallize. The thermoplastic elastomeric behavior of the materials is a result of breaking of the cross-links upon heating and thereby a decrease in viscosity. Due to the noncovalent cross-links, these materials are referred to as supramolecular polymers. The exceptional mechanical properties of these materials led researchers to develop new classes of supramolecular polymers based on urea moieties, which are able to form stronger and bifurcated hydrogen bonds. Functionalization of poly(e-caprolactone) (PCL) oligomers with urea motifs showed nanofiber morphology by AFM.142 Due to synergistic aggregation of a second urea in the bis-urea motif, these moieties aggregate in a cooperative fashion. Moreover, the bis-urea motif is able to bundle together and crystallize into long nanofibers that can act as supramolecular cross-links. The mechanical properties of these materials are perfectly suitable to be used in soft tissue engineering applications. Since there are only two urea groups involved in the hydrogen bonding, these segments stack exactly on top of each other, forming long nanofibers. Guest molecules can be highly selectively incorporated into these supramolecular polymers if they fit the supramolecular motif. The design of thermoplastic elastomers with monodisperse bis-urea hard blocks allows for the incorporation of guest molecules if they are equipped with an exactly matching bis-urea moiety facilitating molecular recognition and thereby selective modulation of mechanical properties.143 This selective incorporation reinforces the material and facilitates good mechanical properties. It was shown that the supramolecular reinforcement fillers can be successfully incorporated into the bis-urea polymers and thereby strengthen the materials from 12 to 20 MPa.144,145 Along these lines, the concept of self-sorting in elastomeric matrices with bis-urea polymers with only small differences in structure (i.e., variations of one or a few methylene units) between the urea groups was demonstrated.146 Thermoplastic elastomers are proposed to have great potential to be used as biomaterials, as a result of their elasticity, toughness properties, and modular character with regard to introducing specific bioactive functionality, that is, peptides or growth factors. Biodegradable polyurethane(urea)s based on poly(e-caprolactone) and 1,4-diisocyanatobutane have been shown to be biocompatible and fulfill mechanical requirements.147,148 Bis-urea-based supramolecular polymeric materials form an interesting class of materials that display a modular character as a result of the hydrogen bonding motif. Upon the introduction of a bis-urea motif, supramolecular additives can be introduced to provide the materials with a desired function, that is, bioactivity or anti-fouling behavior. Moreover, the mechanical properties of the materials can easily be tuned by the choice of polymer backbone in order to meet the requirements of the designated environment.
Ureido-pyrimidinone-based supramolecular polymers

A range of supramolecular polymers have been developed based on a synthetically very accessible quadruple hydrogen bonding unit with a high association constant, the UPy moiety. The UPy-moieties can either be applied as end groups of polymers, yielding bifunctional supramolecular macromolecules or can be incorporated in the polymer main chain, forming a supramolecular chain extended UPy-polymer (CE-UPy). Via a quadruple hydrogen bonding motif, the UPy-moieties are able to dimerize with an association constant exceeding $10^8 \text{ M}^{-1}$ ($K_{\text{dim}} = 6 \times 10^7 \text{ M}^{-1}$) in chloroform, $1 \times 10^7 \text{ M}^{-1}$ in chloroform saturated with water, and $6 \times 10^6 \text{ M}^{-1}$ in toluene. The UPy-motif is present as a mixture of different tautomers, two keto tautomers that display an AADD hydrogen bonding array and an enol form that forms a DADA hydrogen bonding array. It was shown that the keto tautomer bears less repulsive secondary interactions and concomitant higher dimerization constant than the enol tautomer.

Supramolecular polymers can be formed when these UPy-moieties are applied as associating end groups of bifunctional molecules. In order to obtain a high degree of polymerization and thereby real polymer-like behavior, the association constants need to be sufficiently high. The ease of UPy-moiety synthesis facilitates large-scale production of supramolecular polymers, with interesting material properties. Many examples have been published, including telechelically UPy-functionalized polydimethylsilanes (PDMS), poly(ethylenebutylenes) (PEB), polyethers, polycarbonates, polystyrenes (PS), and polyesters. Upon UPy-functionalization, the material properties change dramatically. Highly viscous amorphous PEB becomes a strong and flexible rubber-like material when UPy-moieties are introduced via a urethane linker. Moreover, UPy-functionalization of poly(caprolactone) (PCL) has proven to be an excellent supramolecular material for various tissue engineering applications. In addition to the effect of the UPy-moiety on the material properties of the supramolecular polymers, the influence of additional ordering was also investigated by the introduction of urethane and urea functionalities in the UPy-synthon that result in hydrogen bonding in the lateral direction. These additional hydrogen bonds result in stacking of the UPy-dimers in a lateral direction, forming one-dimensional rod-like nanofibers, as were clearly observed by AFM. Combining both the supramolecular polymerization and phase segregation behavior results in mechanically improved materials with thermoplastic elastomeric properties, which can be suitable for a wide variety of applications.

Supramolecular biomaterials developed in our group are based on the quadruple hydrogen bonding UPy motif, which strongly dimerizes in organic solvents and gives rise to interesting material properties, as described in section 2.3.1. The reversible nature of the supramolecular interactions in the UPy-polymer materials allows for a modular approach, thereby creating responsive materials. Regardless of the reversible nature, these materials show mechanical properties similar to conventional polymers. By using the UPy-UPy interactions in a modular approach, it has already been shown that these materials can be bioactivated by the incorporation of UPy-biomolecules, thereby creating supramolecular thermoplastic elastomeric biomaterials. The incorporation of UPy-modified peptides into a UPy-polymer scaffold has been reported, via a multistep noncovalent synthesis method, whereby the UPy-peptides were simply mixed with the UPy-polymer and then processed into material films exhibiting bioactive properties. This modular approach holds great promise in the development of biomaterials for a variety of applications, since the bioactive modules (i.e., peptides, proteins, and growth factors) can be synthesized and coupled to a UPy-moiety prior to incorporation into the UPy-polymer materials. Moreover, the material formulations of the scaffold can be tuned into different morphologies, that is, spin-coated films, drop cast films, and electrospun meshes, depending on the processing method.

The modular concept was demonstrated by the mixing of UPy-functionalized oligocaprolactones (UPy-PCL) with UPy-modified cell adhesion promotion Gly-Arg-Gly-Asp-Ser (UPy-GRGDS) and synergistic Pro-His-Ser-Arg-Asn (UPy-PHSRN) peptide sequences. In vitro results showed strong and specific cell binding of fibroblasts to the bioactivated supramolecular materials, containing both the UPy-GRGDS and UPy-PHSRN. Strikingly, the bioactive materials containing the UPy-peptides demonstrated in vivo the formation of single giant cells at the interface between the bioactive material and tissue. In the advance of the supramolecular materials based on the modular approach, applications in renal regenerative medicine, cardiovascular tissue engineering field, and drug delivery applications are being explored. Fig. 9 shows the development of a supramolecular bilayered scaffold with tailored properties (Fig. 8B). By a mix-and-match approach, UPy-PCL and UPy-modified poly(ethylene glycol) (UPy-PEG) polymers could be mixed and processed into electrospun fibers (Fig. 9A, C). The introduction of the UPy-PEG results in anti-fouling behavior of the materials, thereby preventing cell attachment and spreading (Fig. 9D). Upon the introduction of 4 mol% UPy-RGD bioactive peptide (Fig. 9A), surfaces that were initially anti-fouling could be reactivated and cell attachment as well as cell spreading could be observed (Fig. 9D).

Remarkably, in almost all of these materials, the exact distribution of the UPy-additive (i.e., peptide or anti-fouling agent) as well as the specific surface enhancement cannot be fully controlled, whereas in many of these applications solely surface functionality is required. Moreover, in the development of complex supramolecular biomaterials, the surface functionality that is required is frequently provided by complex bioactive modules, which in general are highly incompatible with the material processing conditions. It would, therefore, be of great interest to investigate decoupling of the material processing strategies on the one hand and functionalization strategies of the surface on the other hand. This would offer flexibility in the choice of processing method and at the same time allows for exclusive surface modification.

To this end more recently, a new strategy to functionalize supramolecular material surfaces we have developed. Both in in vitro and in vivo studies show the surface of the material is in contact with either cells or tissue and, therefore, functionality of the materials is mainly required at the surface. In order to selectively functionalize the material surface, a method to post-modify the surface of supramolecular thermoplastic elastomers was developed. Via the modular approach, UPy-functionalized tetrazine moieties are incorporated into the UPy-PCL. To date, inverse electron demanding Diels-Alder cycloaddition reaction between
Fig. 9  Supramolecular bilayered scaffolds with tailorable properties. (A) Chemical structures of the building blocks in this study, UPy-PCL ($M_n = 2$ kg/mol), UPy-PEG ($M_n = 2$ kg/mol), and UPy-RGD bioactive peptide. (B) Schematic representation of the bilayered scaffolds S1 and S2 that are electrospun using the different building blocks, where top layer A should facilitate cell adhesion and bottom layer B should prevent cell adhesion. (C) SEM micrographs of the electrospun bilayered scaffolds S1 and S2, in the cross section of the scaffolds the layer transition is indicated by the arrows (scale bars represent 200 μm). Top and bottom views show fiber diameters and pore sizes of the scaffolds (scale bars represent 5 μm, average fiber diameters ± standard deviation: S1-A: 576 ± 215 nm, S1-B: 636 ± 359 nm, S2-A: 428 ± 226 nm, S2-B: 283 ± 139 nm. (D) Fluorescent microscopy images of HK-2 cells on the different scaffolds 14 h after seeding, scale bars represent 200 μm, in the enlarged views (right) scale bars represent 25 μm, the morphological differences between the cells on the different scaffolds are clearly present. In the absence of UPy-PEG (S1-A) cells adhere and spread, in the presence of UPy-PEG (S1-B, S2-B) cells do not adhere. Upon UPy-RGS (S2-A) addition, cells adhere and spread even in the presence of UPy-PEG. Adapted and reprinted from Mollet, B. B.; Comellas-Aragones, M.; Spiering, A. J. H.; Sontjens, S. H. M.; Meijer, E. W.; Dankers, P. Y. W. J. Mater. Chem. B 2014, 2 (17), 2483, published by the Royal Society for Chemistry.
tetrazine and trans-cyclooctene is reported as the fastest bioorthogonal ligation strategy, with a $k_f$ of $10^3$–$10^6$ M$^{-1}$s$^{-1}$.\textsuperscript{173–175} It is proposed that solely surface functionalization occurs, upon the incorporation of UPy-tetrazine additives into the supramolecular material and a selective reaction at the surface between the tetrazine and trans-cyclooctene-modified bioactives. Not only is functionality at the surface of the material introduced via this strategy, but the scope of biomolecules that can be functionalized at the surface is also greatly expanded. Since the material processing conditions (i.e., organic solvents) and the functionalization approach (in aqueous environment) are decoupled, this paves the way for functionalization of the material surfaces with more complex biomolecules such as full-length proteins and growth factors. Via a multitude of different physical-chemical analysis techniques, including AFM, XPS, ToF-SIMS depth profiling, and MALDI-ToF MS, the molecular composition of the surface as well as the bulk can be revealed. In conclusion, with this new post-modification strategy it was shown that it is possible to selectively modify supramolecular surfaces via the incorporation of supramolecular additives.\textsuperscript{176} The molecular design and synthesis of the additive enables control on the assembly process within the material. Importantly, decoupling of the material processing and material functionalization conditions broadens the horizon for the moieties that can be functionalized at the surface. Along these lines, a variety of material preparation methods (i.e., 3-D printing, electrospinning, and melt spinning) can be realized. This functionalization and characterization strategy holds great promise in the field of regenerative medicine, in which design and detailed analysis of bioactive, functional biomaterials is important for the ultimate interaction with cells and tissues, and the ultimate performance.

As a result of the excellent mechanical properties, the modular character to introduce functionality and the broad scope of processing possibilities, supramolecular thermoplastic elastomers define a class of biomaterials with high potential. Depending on the application, the material characteristics and behavior can be tuned based on the molecular building blocks. In future biomaterials, the modular combination of different supramolecular building blocks might result in the introduction of specific bioactivity, while at the same time anti-fouling properties at the surface can be guaranteed and bulk material properties are retained.

**Supramolecular Biomaterials Toward in vivo Applications**

Supramolecular biomaterials that consist of functionalized surfaces and that can be processed into a desirable format, have already found a few applications in vivo.\textsuperscript{177,178} Here we list a few examples that have shown potential in recent reports. Tirrell et al. reported on an approach to promote a protective immune response in vivo based on self-assembled PA micelles that contained a cytotoxic epitope. They synthesized PA with two C$_{16}$ aliphatic tails conjugated to a peptide derived from a cytotoxic T-cell epitope from the model tumor antigen ovalbumin that self-assembled into cylindrical PA displaying a high density of the peptide. Both AFM and TEM measurements revealed the formation of cylindrical micelles upon self-assembly in PBS. These constructs induced an immune response in vivo in mice, tumors showed a significantly slower growth which resulted in longer survival times. The PA system acts as an antigen depot, thereby concentrating the antigen peptides and protecting them from degradation which as a result prolongs antigen exposure to the immune system. Characterization of the PA and understanding of the physical properties and their resulting in vivo efficacy is crucial in the development of these materials in immunotherapeutic applications.\textsuperscript{179}

In another study, Hess et al. developed a coating for polymer stents in order to prevent neointimal hyperplasia. Based on the assumption that platelet and inflammatory cellular recruitment can induce neointimal proliferation, this coating was developed in order to reduce cell-stent interactions. The copolymer coating is composed of a poly(L-lysine) backbone, grafted with poly(ethylene glycol) (PEG), developed by Hubbell et al., that can nonspecifically adsorb to the stainless steel stent surface. In vivo studies were performed in which the coated and uncoated stents were implanted in an epicardial coronary artery and after 6 weeks the animals were sacrificed. Histological examination revealed that the coated stents developed significantly less neointimal hyperplasia as compared to the uncoated controls. Thus, the coating improved biocompatibility of the stents without inflammatory or prothrombotic effects.\textsuperscript{180}

Wippermann et al. work on the investigation of bacterial cellulose (BC) as a potential scaffold for application as small-diameter vascular grafts. BC has been characterized as a biomaterial with high mechanical strength and high water retention values. In this study, they investigated the in vivo performance of BC small-diameter grafts with regard to technical feasibility, functional performance, the ability to provide a scaffold for neoformation of a vascular wall as well as the proinflammatory potential in sheep. The study showed that BC grafts provide a scaffold for cell ingrowth and support tissue engineering performed by the organism itself. This yields BC grafts as a promising material for small-diameter vascular grafts due to the mechanical as well as biological properties. However, these materials cannot proceed into clinical trials as they showed a disappointing patency and thus should first be further optimized in order to achieve a higher patency rate.\textsuperscript{181}

Hollinger et al. reported on the synthesis, biodegradability, and biocompatibility of lysine diisocyanate- (LDI) and glucose-based polymer. The materials are synthesized via polymerization of highly purified LDI with glucose and after subsequent hydration, a spongy matrix is spontaneously formed. In aqueous solution, these materials degraded and yielded lysine and glucose degradation products. In vivo examination for 8 weeks revealed that subcutaneous implantation of hydrated matrix degraded three times faster than in vitro. No immunogenic response was observed, nor was an antibody response induced in the host. Moreover, histological analysis of the implanted polymer showed that a minimal foreign body response had occurred and the formation of a capsule around the degrading polymer. Although these materials need to be optimized, the biodegradability as well as the biocompatibility provide them with interesting properties for optimization and further use in biomedical applications.\textsuperscript{182}
Both chemical and biological properties of supramolecular UPy-polymers based on oligocaprolactones were investigated in our group. In this study, we reported on the development of materials with different ratios of oligocaprolactones that were end functionalized with UPy-moieties or chain extended with UPy-moieties in the main chain. Due to the high crystallinity of the end-functionalized UPy-polymers, these polymers are more stiff and brittle, and subcutaneously implanted discs fractured. A low inflammatory response was observed, as well as fibrous capsule formation, demonstrating inertness of the material. On the other hand, the chain-extended UPy-polymers show less crystalline domains and bear more flexible properties. After in vivo implantation, deformation of the material was observed as well as cell infiltration. A mixture of the two different polymers (20% end-functionalized UPy-polymer and 80% chain-extended UPy-material) showed flexible material properties without visible deformation after in vivo implantation. Moreover, a mild foreign body response observed upon implantation of the pristine polymer mixture. This study demonstrates the tunability of material properties based on a modular approach, which opens up possibilities to develop scaffolds which meet material property requirements as well as contain biological cues based on UPy-functionalized bioactive peptides that are necessary to target specific biomedical applications. Recently, an in situ approach for early cellularization of supramolecular vascular grafts substituted with supramolecular stromal cell-derived factor 1α-derived peptides was presented. SDF1α is a powerful chemoattractant of lymphocytes, monocytes, and progenitor cells, and, plays an important role in cellular signaling and tissue repair. The SDF1α-derived peptides were functionalized with a supramolecular UPy motif in order to facilitate modular incorporation into UPy-modified polymer scaffolds and hence facilitate bioactivation of the materials. As a proof of concept in vivo, the bioactivated electrospun scaffolds were implanted as rat abdominal aorta interposition grafts. After 7 days an increased cellularity by CD68\(^{+}\) cells was observed, indicating that a synthetic, bioactivated, cell-free supramolecular biomaterial can attract and stimulate leukocyte populations upon SDF1α incorporation. This is a first step toward in situ cardiovascular tissue engineering using electrospun supramolecular bioactive scaffolds. In a similar way, a noncell adhesive vascular graft based on a modular supramolecular approach was developed. Here UPy-modified polycaprolactone (UPy-PCL) and UPy-modified poly(ethylene glycol) (UPy-PEG) or chain-extended PCL (CE-UPy-PCL) were used (Fig. 10A).

![Fig. 10](image)

**Fig. 10** Development of a noncell adhesive vascular graft. (A) Chemical structures of the molecules in this report, UPy-PCL, chain-extended UPy-PCL (CE-UPy-PCL), and UPy-PEG. (B) SEM images of the morphology of both the inside (lumen) and the outside of the electrospun vascular grafts of CE-UPy-PCL (top) and CE-UPy-PCL/UPy-PEG (90:10) (bottom) and an insert of the final construct (top left), scale bars represent 50 μm. (C) Cross sectional slices of the grafts both 4 and 48 h after implantation, scale bars represent 500 μm. (D) Quantitative analysis of histological data showing reduced cellularity in CE-UPy-PCL/UPy-PEG vascular grafts (left), MPO-positive granulocytes (middle) and CD68\(^{+}\) macrophages (right) relative to tissue area. Bar graphs represent infiltrating cell numbers from four representative high power fields (hpf) per tissue section analyzed at 400 × magnification. The data is represented as mean ± S.E.M. Reprinted with permission from van Almen, G. C.; Talacua, H.; Ippel, B. D.; Mollet, B. B.; Ramaekers, M.; Simonet, M.; Smits, A. I. P. M.; Bouting, C. V. C.; Kluin, J.; Dankers, P. Y. W. Macromol. Biosci. 2015, 16 (3), 350, copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.
Electrospun CE-UPy-PCL and CE-UPy-PCL/UPy-PEG (90:10) were evaluated as vascular grafts in vivo in a rat model and the noncell adhesive grafts showed hardly any cell infiltration after 48 h, demonstrating the non-fouling character of these materials (Fig. 10B, C, D). In current studies, these noncell adhesive materials are reactivated upon the incorporation of a small fraction of UPy-modified bioactive peptides.168

Although we have highlighted a few examples where supramolecular materials have been applied in in vivo evaluations, the number of clinical implementations of supramolecular biomaterials are very limited, which implies material design and performance still require considerable optimization. In future biomaterial design, the introduction of specific bioactivity on the one hand while addressing appropriate fouling behavior on the other hand, in conjunction with suitable mechanical properties for a specific application should be taken into account.

Perspective

This account demonstrates the strength and importance of bringing functionality into supramolecular biomaterials which ultimately find their application in the fields of tissue engineering and regenerative medicine. Upon implantation in an in vivo environment, the surface of any material inevitably is exposed to the environment, which emphasizes the importance of proper surface functionalization. We have disclosed here strategies to functionalize material surfaces in order to generate desired material properties, that is, bioactivity and nonfouling behavior. Typically, surface functionality can be introduced upon changes in or adaptation of the different building blocks that formulate the biomaterial. Although we have described a few materials that have been applied in in vivo studies, supramolecular materials have not yet made their way into many clinical applications. Although much progress has been made in the development of new biomaterials in order to meet nature’s complexity in recent years, there is still a large gap between synthetic (supra)molecular materials and those found in nature.183

In order to be able to regenerate damaged tissues or organs, the challenges that are faced in biomaterials and medicine are immense.184 We envision that multidisciplinary research, ranging from cell biology to materials science and physics, is necessary in order to advance the field to translation of biomedical advances from bench to bedside. Moreover, the use of supramolecular biomaterials in this area plays an important role, due to the intrinsic dynamic character of these materials, the modularity in their formulation and the ease of material property tunability. The development of supramolecular biomaterials has established highly functional materials that can be easily controlled and, therefore, find broad utility in a multitude of biomedical applications.

There are a few examples of supramolecular biomaterials that face early stages toward clinical translation, which include the first-in-man clinical application of a supramolecular bioabsorbable cardiovascular graft that was used to correct congenital cardiac malformation in children.185 The supramolecular polymers have been developed in our group, and it is the first ever in man study of a supramolecular bioabsorbable cardiovascular device. Moreover, here the pristine materials have been implanted, without any biological cues, nor with any additional surface functionality. We envision the further development of these types of materials in order to meet patient-specific needs.

In order for supramolecular biomaterials to find their way into the clinic, we envision the production of hybrid materials that provide good mechanical properties that show a relatively slow degradation behavior. In conjunction with appropriate bioactive cues to target a specific application and faster degrading materials [i.e., soft materials or hydrogels] that can be loaded with drugs or growth factors in order to trigger the regenerative capacity of the human body. These materials would combine all the desired mechanical and degradation properties and allow for the incorporation of complex functional bioactives that are required and can be found in natural ECM as well, en route to meet nature’s complexity.

References


