



Cite this: *Biomater. Sci.*, 2016, 4, 9

Poly(trimethylene carbonate)-based polymers engineered for biodegradable functional biomaterials

K. Fukushima

Aliphatic polycarbonates have drawn attention as biodegradable polymers that can be applied to a broad range of resorbable medical devices. In particular, poly(trimethylene carbonate) (PTMC), its copolymers, and its derivatives are currently studied due to their unique degradation characteristics that are different from those of aliphatic polyesters. Furthermore, their flexible and hydrophobic nature has driven the application of PTMC-based polymers to soft tissue regeneration and drug delivery. This review presents the diverse applications and functionalization strategies of PTMC-based materials in relation to recent advances in medical technologies and their subsequent needs in clinical settings.

Received 14th April 2015,
Accepted 16th August 2015

DOI: 10.1039/c5bm00123d

www.rsc.org/biomaterialsscience

1. Introduction

Synthetic biodegradable polymers are widely used and studied for their biomedical applications, ranging from drug delivery to tissue engineering.¹ Aliphatic polyesters such as polylactides (PLAs) and poly(ϵ -caprolactone) (PCL) have been used most widely for a long time due to their easy accessibility and

decent mechanical properties.² Recently, aliphatic polycarbonates have drawn more attention as another class of degradable and resorbable materials. They are biodegradable and some are derived from carbon dioxide and epoxides or anhydrides.^{3,4} Thus, like PLA, aliphatic polycarbonates are also recognized to be bio-based biodegradable polymers.

Poly(trimethylene carbonate) (PTMC), its copolymers, and its derivatives are extensively studied for their biomedical applications. PTMC can be prepared by a ring-opening polymerization (ROP) of trimethylene carbonate (TMC) using both conventional organometallic catalysts and emerging organocatalysts.^{5,6} Currently, TMC is also regarded as a bio-based monomer, since the starting material 1,3-propanediol can be derived from carbohydrates and some of the carbonylation reagents used to close the ring are potentially produced from carbon dioxide.^{7–9} PTMC is a hydrophobic non-crystalline polymer with a glass transition temperature (T_g) of around $-20\text{ }^\circ\text{C}$.^{10,11} Therefore, PTMC is usually used as a soft material in a scaffold application for soft tissue regeneration and as a hydrophobic segment of amphiphilic block copolymers for drug delivery. The unique degradation behavior of PTMC such as resistance to non-enzymatic hydrolysis, generation of non-acidic degradation products, and enzymatic degradation with a surface erosion mechanism¹² opens a new window for applications in biomedical devices that could never be achieved with aliphatic polyesters. For instance, slow degradation prolongs its lifetime, non-acidic degradation products reduce the risk of adverse reactions in *in vivo* applications, and the mechanical properties of the polymer tend to be maintained with surface erosion.¹²

However, progress in current medical technologies has led to the requirement for more complex and higher level functional materials. Thus, the integration of multiple functions

Department of Polymer Science and Engineering, Graduate School of Science and Engineering, Yamagata University, Yonezawa, Yamagata 992-8510, Japan.
E-mail: fukushima@yz.yamagata-u.ac.jp



K. Fukushima

Kazuki Fukushima received his Bachelor's and Master's degrees in Polymer Science and Engineering in 2002 and 2004 and his Doctorate in Applied Science for Functionality in 2007 from Kyoto Institute of Technology, Japan under the supervision of Prof. Yoshiharu Kimura. He subsequently conducted postdoctoral research at IBM Almaden Research Center with Dr James L. Hedrick in 2007–2011. In 2011, he was appointed as an

Assistant Professor of Yamagata University. He currently focuses on the synthesis and applications of functionalized biodegradable polymers. He has received the Award for Encouragement of Research in Polymer Science from the Society of Polymer Science, Japan in 2015.

has been explored for synthetic biodegradable polymers by various approaches, including polymer blends, composites, copolymerization, and functional pendant groups, in order to respond to a broad range of applications. Since most synthetic biodegradable polymers are prepared by ROP of the corresponding cyclic monomers, several efforts have been made to develop heterocyclic monomers with functional pendant groups such as analogues of lactide (LA),^{13,14} glycolide (GA),^{15–17} and ϵ -caprolactone (CL).^{18,19} TMC analogues can also be obtained from substituted 1,3-propanediols so as to yield PTMC derivatives with functional pendant groups *via* the subsequent ROP.²⁰ Generally, the TMC analogues are relatively stable under ambient conditions as compared to the substituted lactide and glycolide, which allows for easy handling and storage. Furthermore, recent advances in controlled polymerization techniques enable the construction of complex macromolecular architectures.²¹ Hence, the number of studies on PTMC-based polymers as biomaterials increases every year. This review presents recent studies on biomedical applications of PTMC, its copolymers, and its derivatives, focusing particularly on the progress in the last few years.

2. Aims of modifying TMC-based polymers

2.1. Alteration of mechanical properties

As mentioned above, PTMC is flexible and soft. Sometimes, the mechanical properties of PTMC do not meet a required range for the target materials, particularly in bulk applications. The simplest way of tuning the mechanical properties of PTMC is to change its molecular weight. A significant difference in PTMC bulk mechanical properties can be observed between PTMC materials with a molecular weight of a few kilodaltons (kDa) and those with a molecular weight of several hundreds of kDa.^{10,11} This difference is attributed to the molecular weight dependence of the glass transition. Nevertheless, there are few examples of the use of unmodified PTMC in biomaterial applications.

Cross-linking is commonly employed to provide elasticity to the PTMC-based polymers in most cases. The mechanical properties are controllable by the cross-linking density that can be regulated by the concentration of the cross-linker, geometry of the reactive points for cross-linking in the prepolymer structure, and the molecular weight between the cross-linking points.²² An interesting study showed that PTMC cross-linking affects the differentiation of adipose stem cells (ASCs) into smooth muscle cells (SMCs).²³ ASCs seeded on UV-cross-linked PTMC of low molecular weight (20 kDa) differentiated into SMCs more than those seeded on high molecular weight PTMC (250 kDa) cross-linked by gamma irradiation. Surface flexibility seems to influence cell attachment and differentiation (Young's moduli were 4.3 MPa and 6.6 MPa, respectively).^{24,25} Although the difference in the mechanical properties is not significant, the molecular mobility at the surface upon hydration may substantially differ from that in the dry state.

Therefore, the mechanical properties should be assessed at 37 °C in an aqueous environment to determine whether the materials can be utilized under *in vivo* conditions.

Copolymerization has also been adopted to improve the mechanical strength. In this case, random copolymers or segmented multi-block copolymers are included. Since PTMC is prepared through ROP of TMC, heterocyclic monomers such as LA, GA, and lactones are often used as comonomers. Similarly, the formation of segmented polyurethanes results in a soft segment elastomer, which is another option to improve the mechanical properties of PTMC. The target range of the mechanical properties varies depending on the targeted tissues. The copolymerization and cross-linking should be used in combination in order to provide the ideal properties to the materials.^{26,27}

2.2. Control of biodegradation

PTMC biodegradation only occurs from the surface and in the presence of enzymes, by hydrolysis into 1,3-propanediol and carbon dioxide.²⁸ Therefore, the PTMC degradation process is slower than that of poly(L-lactide) (PLLA) and other aliphatic polyesters that are degraded through bulk erosion by both enzymatic and non-enzymatic hydrolysis. Additionally, autocatalysis by carboxyl end groups is involved in the degradation of the polyesters. The copolymerization of TMC and the other cyclic esters can regulate the biodegradation with the comonomer ratio. Regarding aliphatic polyesters, the copolymerization with TMC is beneficial in decreasing acidic degradation products and in tuning the degradation period.

High molecular weight PTMC is known to degrade faster than low molecular weight PTMC *in vivo*¹² mainly *via* macrophage-mediated enzymatic and oxidative degradation.^{29,30} Vyner *et al.* recently proved that this difference is associated with the conformation of adsorbed enzymes on the surface rather than with macrophage behavior.³¹ The enzymes appear to recognize the surface stiffness that is relevant to the polymer chain mobility upon hydration. The surface hydration is known to control protein adsorption and conformation changes.³² Therefore, more flexible low molecular weight PTMC, possessing more hydroxyl termini, is liable to absorb water and, thereby, is less subjected to enzymatic degradation. This surface hydration dependence of the enzymes could extend to PTMC derivatives with hydrophilic side chains, resulting in slow biodegradation. In fact, the degradation needs to be estimated from the composition of carbonate bonds in the main chain and the extent of surface hydration and wettability.

2.3. Extension of chemical/biological properties

Typically, PTMC is recognized as a cell friendly material. High levels of cell viability and cell adhesion are observed on the PTMC surface. Thus, PTMC is considered to be biocompatible. Therefore, PTMC-coating is used to improve the biocompatibility of some inorganic biomaterials, including biometals and bioactive ceramics that have a good mechanical strength and high bioactivity, but a brittle surface in some cases.³³

Compared to coatings of polyesters, the PTMC-coating presents a better efficacy in terms of protecting the inorganic biomaterials against corrosion that usually occurs faster than desired under biological conditions. This property is attributed to the absence of acidic degradation products from PTMC.²⁸

As aforementioned, the biological response is affected by surface properties, including stiffness, topology, hydration, and charge as well as the primary chemical structure. Indeed, some modifications may unexpectedly weaken the other properties. Therefore, multiple modifications are required for practical application. PTMC is hydrophobic and thereby adsorbs proteins and cells non-specifically.³⁴ Conjugation of hydrophilic polymers such as poly(ethylene glycol) (PEG) increases hydration that suppresses the adhesion of proteins and cells at the interface.^{35,36}

Sometimes, PTMC-based polymers with amphiphilicity form micelles in water, which are mostly applied in drug delivery. Functionalization of end groups can significantly alter the biochemical properties and solubility of the PTMC-based polymers when the molecular weight is low because the effect of the functional groups depends on the density of the functional groups. Alternatively, the introduction of functional pendant groups into the PTMC backbone expands not only the solubility, but also the extent of interaction with (bio)molecules and cells at the interface more than the end functionalization. Although synthesis of TMC analogues with the functional pendant group is usually necessary, a broader range of applications can be potentially targeted. Regardless of the approaches, the composition and density of the functional groups relative to the PTMC framework roughly dictate the physicochemical properties of the PTMC-based polymers.

3. Strategies for the functionalization of PTMC-based polymers and for polymer architecture design

Functionalization approaches of the PTMC-based polymers are classified into two types: peripheral decoration and vertical decoration. The former includes end functionalization, cross-linking, and copolymerization that are mostly carried out for PTMC. The latter involves preparation of the PTMC derivatives with functional side chains and the post-modifications of the side chains, which will create a new class of biodegradable polycarbonate materials with a broad range of physicochemical properties.

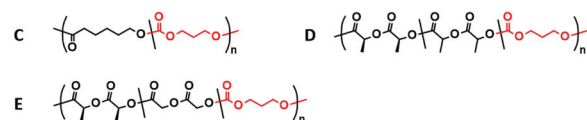
3.1. Cross-linking

Cross-linking of PTMC is performed through UV irradiation and gamma irradiation (Fig. 1A and B). UV irradiation needs a double bond moiety in the polymer structure, while strong gamma radiation generates free radicals for cross-linking by itself. Cross-linking density, which dictates the mechanical strength, is regulated only by irradiation time and beam strength for the gamma irradiation. UV cross-linking is more

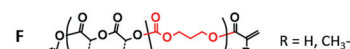
Cross-linking



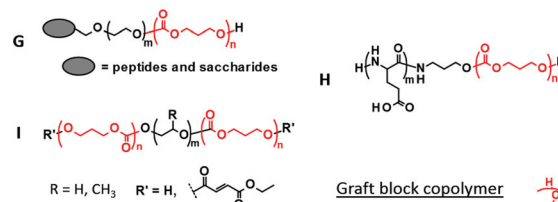
Copolymerization (random)



Cross-linked random copolymer



Amphiphilic block copolymer



Graft block copolymer

End functionalized amphiphilic PTMC

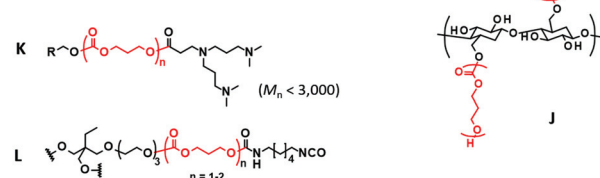


Fig. 1 Typical examples of PTMC-based polymers applied to various biomedical applications in this review. The TMC repeating units are shown in red.

controllable, in which the architecture and molecular weight of prepolymers regulate the cross-linking density. Both irradiations are useful for simultaneous sterilization of the polymers, which is one of the advantages of this type of cross-linking.³⁷

The ROP of TMC initiated by an alcohol initiator brings a hydroxyl end group. UV reactive groups are then easily introduced by esterification with (meth)acryloyl chloride (or anhydride) as the most common approach.^{23,38,39} Cinnamoyl chloride is also employed as an alternative UV reactive moiety.⁴⁰⁻⁴² The radical addition reaction of the double bonds can be performed by UV irradiation, and photosensitizers such as benzophenone are sometimes added to prompt the reaction. Multi-arm alcohols serve as initiators to provide PTMC with multiple UV reactive terminals. The initiation terminal also plays a role of a cross-linking point when the number of hydroxyl groups in the initiator is more than three. There is another way of cross-linking where the reactive side chains are bridged with each other⁴¹ or through the multi-functional cross-linkers by UV irradiation and/or click reactions described later (see Fig. 4B).⁴³⁻⁴⁶ In combination with advancing 3D printing technology, the UV irradiation assisted cross-linking is applied for stereolithography where resin deposition is con-

comitantly conducted, producing tailor-made 3D scaffolds with a tunable mechanical strength.^{47–50}

3.2. Copolymerization

Since the ROP of TMC is performed through transesterification, copolymerization with other cyclic esters yields a random sequence (Fig. 1C–F), particularly when the ROP is performed using tin catalysts upon heating.^{51,52} The comonomers often used include LA, GA, and CL. Emerging organocatalytic ROP sometimes induces gradient or blocky sequences, resulting from different monomer reactivities to the catalysts.²¹

Amphiphilic block copolymers are mostly studied among PTMC-containing block copolymers for biomaterial applications (Fig. 1G–I). PEG has been the first choice as a hydrophilic block for a long time because PEG is non-ionic and compatible with the blood.⁵³ Due to difficulties in synthesis and hazard control, the preparation of heterofunctional mono-hydroxy PEG by ROP of ethylene oxide, leading to end-functionalized PEG-PTMC block copolymers (Fig. 1G), is rarely performed at the laboratory level. Instead, various heterofunctional PEGs are commercially available, although some are expensive. Currently, poly(L-glutamic acid) (PGlu), which has a carboxyl residue at the side chain, is also used as the hydrophilic segment. Recent progress in controlled polymerization of amino acid *N*-carboxyanhydride (NCA)⁵⁴ may facilitate the use of PGlu and allows for easy access to the end functionalization of PGlu-PTMC block copolymers (Fig. 1H).

For graft copolymers with degradable polymer branches, the “grafting-from” approach is the most popular, using polymers with hydroxyl side chains as an initiator of ROP. Poly(vinyl alcohol) (PVA) and poly(2-hydroxyethyl methacrylate) (PHEMA) are famous as hydroxy side-functionalized polymers for applications in biocompatible medical devices. Cellulose has also drawn attention as a macroinitiator⁵⁵ for the “grafting-from” ROP of TMC (Fig. 1J)⁵⁶ since homogeneous ROP using cellulose in ionic liquids was established.^{57,58}

3.3. End functionalization

Attaching functionality to the chain ends is a straightforward approach to modifying or adding chemical functions to PTMC. The typical end functionalities attached contain UV reactive terminal groups for cross-linking, multi-arm initiators for divergent architecture (Fig. 1B, F and L), multiple tertiary amine terminals for dissolution in water and binding DNA (Fig. 1K), and isocyanate terminals (Fig. 1L) for covalent conjugation with proteins (–NH₂). There are two ways for the end functionalization, the use of alcohols with a functional or reactive moiety and esterifying the terminal hydroxyl groups with acid halides presenting a functional or reactive moiety. In addition, further functionalization can sometimes be conducted *via* the reactive groups introduced at the chain end. Since the carbonate bonds are relatively more stable than ester bonds, several end modification approaches are available for PTMC.

3.4. Incorporation of functional side chains

Side chain functionalization of PTMC is usually performed through ROP of TMC analogues with a functional residue. The TMC analogues are derived from substituted 1,3-propanediols through ring-closing reactions (Fig. 2(I)) with carbonylation agents⁵⁹ such as phosgene derivatives,^{60–62} bis-carbonates,^{9,63} and *N,N'*-carbonyldiimidazole.⁶⁴ The synthesis and ROPs (Fig. 2(II)) of the TMC analogues have previously been reviewed in detail elsewhere.^{20,65,66}

3.4.1. Starting materials. Several starting materials are available to develop PTMC derivatives, incorporating protected and/or reactive functional side chains (Fig. 3). The difference between starting materials is mainly in the linker structure to conjugate the functional group to the PTMC backbone.

2,2-Bis(hydroxymethyl)propionate (bisMPA) has been used as a building block of biocompatible dendrimers,⁶⁷ which could support the potential safety of bisMPA as a constituent of biodegradable biomaterials. From the synthetic aspect, the carboxyl group of bisMPA is favorable for introducing functional groups.⁶¹ As with (meth)acrylate analogues, a wide variety of functional groups are reasonably installed through ester and amide linkers using commercially available alcohols and amines. For these reasons, the bisMPA-derived PTMC derivatives (Fig. 3A) have been predominantly studied as typical functionalized PTMC derivatives for applications in

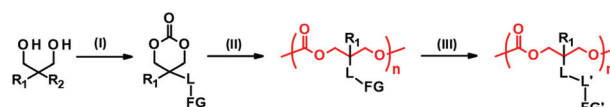


Fig. 2 A typical synthetic pathway to PTMC derivatives bearing a functional side chain. (I) Cyclization, (II) ring-opening polymerization, and (III) post-modification. R₁, R₂: substituents. L, L': linkers. FG, FG': functional groups.

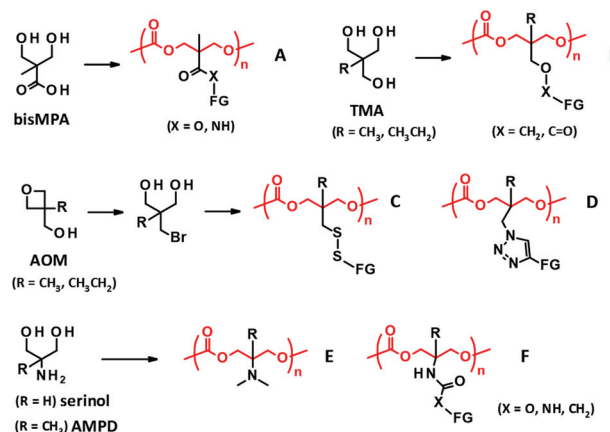


Fig. 3 PTMC derivatives bearing a functional side chain derived from bisMPA (A), TMA (B), AOM (C, D), and serinol and AMPD (E, F). FG denotes functional group.

biomaterials. Recent trends appear to shift to post-modification strategies to attach drugs and generate the desired functions indirectly, but with high efficiency (Fig. 2-(III)).

Trimethylol alkanes (TMA) provide PTMC derivatives, tagging functional groups through an ether linker⁴⁶ or a reverse ester (oxycarbonyl) linker^{42,68} (Fig. 3B). As compared to the bisMPA-derived TMC analogues, synthesis of the TMA-derived TMC analogues is somewhat tedious, because of a troublesome ether formation and equal reactivity of three methylol (hydroxymethyl) groups. Furthermore, a limited number of functional groups can be introduced. Hence, not many monomers and PTMC derivatives have been reported. The ether linker presents a low risk of being involved in transesterification during the ROP to result in scrambling chains and cross-linking, which could be an advantage of the TMA-derived TMC analogues. However, these side reactions would not occur by steric hindrance of the α -methyl group for the bisMPA-derived TMC analogues. Indeed, there are no reports on the side reactions, at least when using organocatalysts.⁵

Recently, new synthetic approaches to TMC analogues have been developed using 3-alkyl-3-oxetanemethanol (AOM), which is converted to 2-bromomethyl-2-alkyl-1,3-propanediol. The bromo group is then altered to thiol and azide groups to yield PTMC derivatives possessing disulfide⁶⁹ and triazole linkers⁷⁰ with functional groups (Fig. 3C and D).

Serinol (2-amino-1,3-propanediol) and 2-amino-2-methyl-1,3-propanediol (AMPD) have also proved useful as other starting materials towards functionalized PTMC derivatives. The primary amino group can be transformed to a tertiary amine and polymerized the cyclized monomer by an enzymatic ROP. The resultant polymer (Fig. 3E) is water soluble, with a molecular weight of around 5000 Da and minimal cytotoxicity.⁷¹ Furthermore, the amino groups of serinol and AMPD are effective in selective reactions with esters and bis-carbonates to form amides and carbamates without the protection of the hydroxyl groups.⁷² The synthesis of the corresponding TMC analogues is relatively straightforward compared to that of others, and thus exploring the applications of the PTMC derivatives (Fig. 3F) is very much expected. In addition to the reagents cited above, there are further commercially available substituted 1,3-diols. New platforms for the development of PTMC derivatives with functional side chains will emerge if the facile synthetic route is established and the versatility of the substituent is discovered.

3.4.2. Post-modifications. Some functional groups at the side chain can serve as a reactive moiety to further introduce a different functional group. A typical post-modification for the bisMPA-derived PTMC derivatives is the *N,N*-dicyclohexylcarbodiimide (DCC)-mediated coupling of alcohols and amines with a carboxyl group that arises from hydrogenolysis of the benzyl ester side chain (Fig. 4A).^{73–76} Efficient aminolysis of pentafluorophenyl ester side chains has also been proposed as an alternative route.⁷⁷ Recent progress of organic acid catalysis for ROP yielded PTMC derivatives with a pendant of pentafluorophenyl ester that is known as an activated ester.⁷⁸ These approaches are applied to directly conjugate

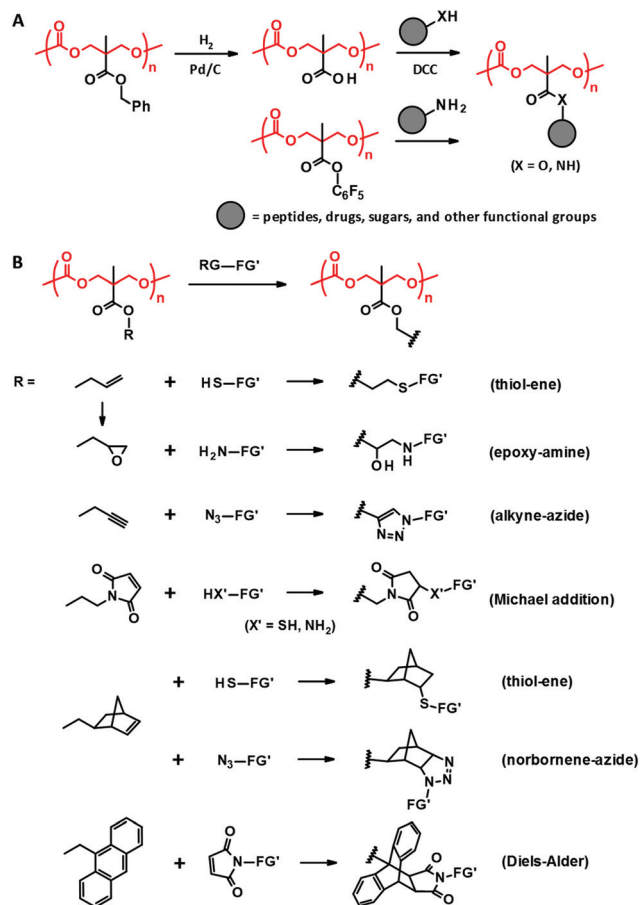


Fig. 4 Post-functionalization of PTMC derivatives derived from bisMPA through DCC coupling and amidation (A) and “click” reactions (B). RG: reactive group, FG: functional group.

drugs and (bio)molecules that contain sensitive moieties to the ROP conditions, when reactive groups interfere with the ROP, and when the synthesis of the drug-conjugated monomers is difficult. Indeed, the conjugation of paclitaxel,⁷⁵ gemcitabine,⁷⁴ vitamin E,⁷⁶ and heparin⁷³ to the PTMC backbone has been recently reported using the methods mentioned above. However, these approaches are substantially limited to drugs possessing hydroxyl and amino groups that are not associated with drug potency, and the drug release is dependent on the hydrolysis of the ester and amide linkers.

The aforementioned coupling reactions based on esterification and amidation are less efficient in terms of completing the reaction than “click” reactions, including thiol-ene,^{45,79} alkyne-azide cycloaddition,^{43,79,80} Michael addition,^{81,82} Diels-Alder,^{79,83} and epoxide-amine reactions (Fig. 4B).⁴⁴ Indeed, these “click” post-modifications are completed in one step with high conversion for the bisMPA-derived PTMC derivatives bearing reactive side groups, e.g., allyl,^{44,45} propargyl,^{43,80} norbornene,⁷⁹ maleimide,^{81,82} anthracene,⁸³ and epoxy.⁴⁴ Since the polycarbonate backbone is subjected to decomposition under acidic or basic conditions, the post-modifications

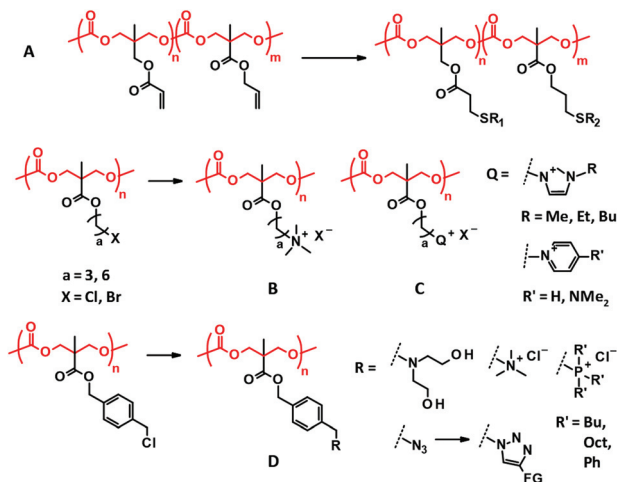


Fig. 5 Other selected examples of post-modifications of the PTMC derivatives. (A) Multi-functionalization of acrylate and allyl pendants of TMA and bisMPA-derived PTMC derivatives. (B, C) Quaternization of bisMPA-derived PTMC derivatives for antimicrobial applications. (D) Facile transformation of the benzyl chloride side chain.

should be performed under ambient and neutral conditions with no harsh catalysts. Thus, the “click” reactions have actually been preferred to load peptides,⁸¹ ferrocene,⁸² and spiro-pyran.⁸⁰ Furthermore, due to the reaction characteristics, these reactions are also exploited for *in situ* cross-linking to form hydrogels and 3D scaffolds using multi-functional reagents as cross-linkers such as dithiols and diamines.⁴³

TMA-derived PTMC derivatives can extend the range of functionality introduced at the side chain by post-modification of the acryloyl pendant through Michael reaction with thiols and amines.⁸⁴ The acryloyl group is added to a pendant hydroxyl group with acryloyl chloride. The acryloyl side chain is also applicable to photo cross-linking.⁶⁸ Combination with an allyl functionalized bisMPA-derived PTMC derivative enables multiple and selective post-functionalization by both thiol-ene and Michael reactions (Fig. 5A).⁸⁵

Quaternization reaction between tertiary amine and alkyl halides is known to be a relatively highly efficient reaction. Less bulky amines and alkyl bromides are favored for the high conversion of the reaction. In most cases, the quaternized side chains are used for antimicrobial purposes due to their cationic nature (Fig. 5B and C). The introduced additional pendant groups have not been considered important so far. Benzyl chloride side chains have recently been presented as a new versatile precursor for the facile and efficient post-modification of the bisMPA-derived PTMC derivatives.⁸⁶ Due to its higher reactivity compared to that of alkyl chloride, benzyl chloride can be readily converted to tertiary amines, quaternary ammonium and phosphonium, and azide followed by triazole under mild conditions in which the PTMC backbone remains intact (Fig. 5D).

The thiol-disulfide exchange reaction is also famous for a highly efficient reaction and is employed for post-modifications. The AOM-derived PTMC derivative with a pyridyl

disulfide side chain has been designed for post-modification with a thiol-functionalized PEG to introduce PEG branches.⁶⁹ In contrast, the thiol functionalized side chains of the bisMPA-derived PTMC derivative have also been effective in the exchange reaction with functionalized disulfides.⁸⁷ However, the direction of the reversible reactions, including thiol-disulfide exchange and Diels-Alder reaction, is determined by the equilibrium based on concentration and temperature, which may affect the stability of the products after the reaction. Some post-modifications form a bulky junction that may influence the side chain properties, including the added functionality. Hence, it would be better to consider the properties of the forming junction when the type of post-modification is selected.

4. Applications of the PTMC-based polymers for biomedical devices

4.1. Scaffold for tissue regeneration

Along with the advance in stem cell research, tissue regeneration using biodegradable scaffolds and hydrogels is now being boosted.⁸⁸ For tissue regeneration, the backing materials usually need to retain a certain level of mechanical properties for several months. PTMC could be suitable as scaffold materials because of its slow degradation profile and surface erosion mechanism that usually has only a little effect on the mechanical properties of the polymer during the healing. However, the mechanical strength of PTMC is mostly considered insufficient⁸⁹ even as a scaffold for soft tissue regeneration. Hence, cross-linking and copolymerization with LA and GA are often employed to meet the required mechanical strength.^{10,88,90–92}

Copolymerization also plays a significant role in regulating the degradation of PLLA and poly(glycolide) (PGA) that is rapidly degraded by non-enzymatic hydrolysis through bulk erosion, inducing a drastic decline in mechanical strength.⁹³ Furthermore, the surge of local acid concentration in the body caused by the degradation is not negligible, provoking various adverse reactions.^{91,94} Therefore, studies on PTMC-containing scaffold materials are increasingly expanding.

4.1.1. Bone regeneration. For bone regeneration, hydroxyapatite and bioglass particles are used as the “gold standard” scaffold materials.^{95,96} They are biodegradable, and favorable to biomineralization and compatible with osteoblast cells. However, their brittle nature is an issue for their mechanical strength that needs to be improved. Therefore, efforts have been made to explore composites with biodegradable polymers as scaffold materials for bone regeneration. However, in addition to the adverse reactions, acidic degradation products generated from aliphatic polyester-based scaffolds dissolve the regenerated bone during healing in the body.^{97–99}

A composite of the high molecular weight PTMC with 50 wt% (30 vol%) of biphasic calcium phosphate (BCP) and its laminate with poly(D,L-lactide) (PDLLA) were then tested for reconstruction of orbital floor defects with 2.5–3.0 cm² size in

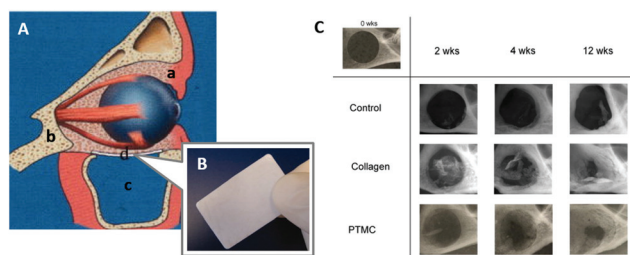


Fig. 6 Schematic representation of the reconstruction of the human orbital floor (A): soft tissue (a), bone tissue (b), the maxillary sinus (c), and an implant (d). An image of the fabricated PTMC/calcium phosphate composite (B). Microradiographic X-ray images of the mandibular defect of rats treated by membranes (C). (A, B) Reprinted with permission from ref. 101. Copyright (2012) Wiley Periodicals, Inc. (C) Reprinted with permission from ref. 107. Copyright (2011) Elsevier Ltd.

a sheep model (Fig. 6A and B).¹⁰⁰ BCP, which is a constituent of the human bone and consists of β -tricalcium phosphate and hydroxyapatite, enables not only toughness and rigidity with the increased flexural modulus of 6–17 MPa,¹⁰¹ but also provides osteoinductive properties to the PTMC membranes. As a consequence of the excellent bone formation and the retained mechanical stability 9 months after implantation, the PTMC–BCP composite and its laminate with PLLA were proven to be appropriate as osteoinductive materials for the orbital floor reconstruction.

Incorporating TMC units allows the formation of a PLA-based scaffold more compatible with osteoblast cells. A random copolymer composed of L-lactide (LLA), D,L-lactide (DLLA), and TMC (PLDLT, Fig. 1D) with a weight-average molecular weight (M_w) of more than 100 000 Da has been examined as a scaffold for culturing human osteoblast-like SaOS-2 cells *in vitro*.⁵¹ TMC units (30 mol%) were incorporated, which imparted sufficient softness to the scaffold. The viability of the osteoblast-like cells grown on the PLDLT scaffold was greater than that of cells grown on poly(LLA-co-DLLA) (PLDLA). Moreover, the alkaline phosphatase (ALP) activity level, which is known as a differentiation marker for bone tissues,¹⁰² was also greater for the cells grown on the PLDLT scaffold than for cells grown on the PLDLA. These results may be explained by both the increased softness of the scaffold and the decrease in acidic degradation products as a result of copolymerization with TMC.

Polymeric materials have been applied to guided bone regeneration (GBR), where bone regeneration is promoted in a space retained by a barrier membrane to prevent ingrowth of fibroblasts.^{103,104} For the GBR, the ideal barrier membrane entails resorbability, space retentivity for bone formation, prevention of ingrowth of fibroblasts, and retentive mechanical strength.^{105,106} Van Leeuwen *et al.* used PTMC with high molecular weight over 400 000 Da in M_w as a barrier membrane for the GBR *in vivo*.^{107,108} The PTMC was compression molded and subjected to gamma irradiation for sterilization and simultaneous cross-linking (Fig. 1A).¹⁰ By using the PTMC barrier membrane, a created mandibular defect (5 mm diameter) in

rats was covered by regenerated tissues after 12 weeks. This result is comparable to that obtained with a collagen membrane as the control (Fig. 6C). Furthermore, the PTMC membrane demonstrated almost two times greater space-maintaining properties than the collagen membrane at 2 and 4 weeks after implantation, resulting from the slow and surface erosive degradation of PTMC.

4.1.2. Cartilage repair. Articular (hyaline) cartilage tissue possesses shape-consistency and repetitive load bearing capacity together with three-dimensional shape.^{109,110} Thus, flexible and elastic three-dimensional porous scaffold materials are required for cartilage tissue regeneration.^{111,112} Although several hydrogel scaffolds have offered a three-dimensional environment for cell growth, including spaces to transport nutrients and metabolic wastes,^{88,113–115} the mechanical properties are insufficient for cartilage reconstruction in most cases.^{116,117} Photo cross-linked flexible polymers with a low molecular weight are now proposed as an alternative 3D scaffold for elastic tissue regeneration, including cartilage repair.^{118,119}

A porous scaffold (350 μ m diameter, 54% porosity) was fabricated by stereolithography of a three-armed methacrylated PTMC with a number-average molecular weight (M_n) of 3000 Da (Fig. 1B) and tested for the culture of bovine chondrocytes *in vitro*.³⁹ Favorable cell adhesion was observed after 3 weeks of incubation and the superficial pores of the scaffold were filled with the cells after 6 weeks. Moreover, sulfated glycosaminoglycans, which are major components of cartilage-specific proteoglycans,^{110,120,121} and fibrillar collagens, were formed on the scaffold after 6 weeks, suggesting that the cells recognize the scaffold as an appropriate growing environment.¹²² However, the compression modulus of the scaffold was not as high as that of natural cartilage tissue (450–800 kPa).¹¹⁰ The modulus was around 120 kPa at 21 °C in the dry state, and it was depressed to 47 kPa after immersion in water at 37 °C (47 kPa). Even after the chondrocytes adhered and proliferated, the modulus remained (68 kPa). This is mainly attributed to the plasticization of PTMC by water, which is often found in low molecular weight PTMC.³² Since 70–85% of the cartilage tissue is water,^{109,110} the mechanical properties of the scaffold should be targeted assuming its use in aqueous environment.

The PTMC porous scaffold has also been investigated for intervertebral disc repair, especially annulus fibrosus (AF) composed of fibrocartilage.¹²³ The compression modulus of the scaffold fabricated by the stereolithography of a three-armed PTMC of M_n of about 5000 Da was adjusted to 0.21–0.31 MPa, which is comparable to that of human AF.^{124,125} The scaffold demonstrated good cell adhesion and proliferation during 14 days of culturing of human AF cells. Furthermore, Pirvu *et al.* recently tested the implantation of the PTMC scaffold by seeding mesenchymal stromal cells¹²⁶ covered with a polyurethane (PU) membrane into a bovine annulotomy model. The hybrid device successfully restored the AF rupture with prevention of herniation of the nucleus pulposus (Fig. 7A and B).¹²⁷ This system is proposed

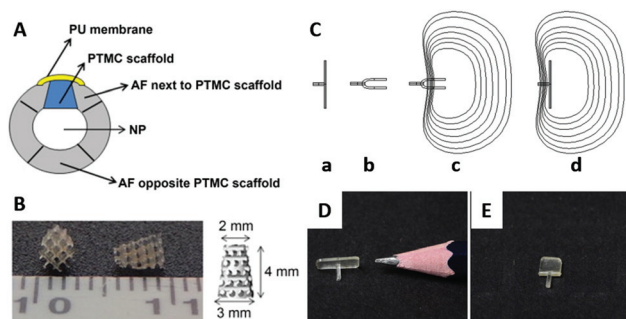


Fig. 7 A schematic view of the intervertebral disc implanted with the PTMC scaffold and covered by a PU membrane (A); PU: polyurethane, NP: nucleus pulposus. Photographical images of the PTMC scaffold (B). Working concept of a shape memory AF closure device (C): the permanent shape above the T_g (a), the folded temporary shape fixed below T_g (b), minimal invasive implantation of the device with the temporary shape (c), and self-deployment of the device at the body temperature (d). Images of the AF closure devices of permanent shape (D) and temporary shape at 0 °C (E). Reprinted with permission from ref. 127 and 130. Copyright (2014) Elsevier Ltd.

for the repair of AF rupture after herniotomy and partial discectomy.

Photo cross-linked copolymers of DLLA and TMC (Fig. 1F) exhibit shape memory properties with switching temperatures at 0 and 40 °C,¹²⁸ in addition to a tunable degradation speed.¹²⁹ Using the poly(DLLA-co-TMC), the AF closure device consisting of a defect-covering membrane and holding grip has been fabricated and applied to the AF defect in a canine spine model. The device showed successful temperature-responsive sealing of the AF defect *in vivo*, supporting a minimal invasive treatment of the AF tear by the shape memory polymer (Fig. 7C–E).¹³⁰

4.1.3 Nerve system reconstruction. Nerve conduits, consisting of biodegradable polymers, have been studied as peripheral nerve repair devices to facilitate bridging axons in the channel without infiltration of adjacent scarred tissues.¹³¹ The nerve conduits should mechanically match the adjacent tissues and actively guide axonal growth inside the tubular space.¹³² A few synthetic materials are now clinically used only for peripheral nerve repairs in limited cases.¹³³ For the peripheral nerve system, the injured axons are able to regenerate. In contrast, central nerve reconstruction toward spinal cord regeneration is much more challenging because the glial scar disturbs the regeneration of the injured axons in the micro-environment.^{134,135} Therefore, at the *in vitro* experimental levels, many efforts have been made to understand how much the polymer surfaces are favorable for axonal growth and can control the glial inflammatory reaction, which then promotes spinal cord regeneration.

Rocha *et al.* determined that a copolymer of TMC and CL (11 : 89 mol%) (P(TMC-CL), Fig. 1C) significantly stimulates higher neuronal polarization and axonal elongation on the surface than PCL and PTMC alone.¹³⁶ This polymer-specific cell response is explained by nanomechanical properties of the

copolymer surface rather than surface topology that is generally known to play a key role in controlling axonal growth for other polymers.^{137,138} For instance, stiffness and hardness values for P(TMC-CL) measured by nanoindentation were $312 \pm 56.4 \text{ N m}^{-1}$ and $3.32 \pm 0.373 \times 10^6 \text{ N m}^{-2}$, respectively, while those for PCL were $435 \pm 40.4 \text{ N m}^{-1}$ and $6.60 \pm 2.11 \times 10^6 \text{ N m}^{-2}$, respectively. Another study¹³⁹ revealed that microglia,¹⁴⁰ immune cells in the central nervous system (CNS), seeded on the P(TMC-CL) is guided toward a pro-regenerative profile and engaged in phagocytosis of myelin that forms glial scar to inhibit CNS regeneration.¹³⁹ It turns out that the nano-mechanical properties of P(TMC-CL) also influence the microglia function. Consequently, the surface properties of P(TMC-CL) are involved in CNS regeneration both directly and indirectly.

4.1.4 Blood vessels. Most vascular diseases involve the occlusion of blood vessels. Stenting is applied mainly to treat coronary arteries, while artificial blood vessels are employed for the treatment of an aortic aneurysm. Many challenges remain in developing polymeric devices for repairing blood vessels because they require flexibility, elasticity, and robustness,¹⁴¹ at least to be mechanically compatible with the neighboring vascular tissue. Therefore, not much success has been reported for artificial blood vessels prepared using synthetic biodegradable polymers. Porous scaffolds fabricated by the simultaneous electro-spinning and gamma-irradiated cross-linking of poly(LLA-co-TMC) with a molecular weight of around 10 000 Da (Fig. 1F) exhibited moderate Young's moduli that are similar to those of human arteries (0.4–0.8 MPa),¹⁴² and the favorable adhesion and proliferation of human mesenchymal stem cells were confirmed by using *in vitro* tests.³⁸ This porous scaffold could be a breakthrough in developing synthetic degradable vascular grafts. However, how blood compatibility, particularly the antithrombotic property, should be achieved will be the next hurdle to be overcome for the application of small-diameter vascular grafts of less than 3 mm that have been longed for in the coronary bypass surgery and treatment in child patients.^{143,144}

Biodegradable polymers have often been used in drug-eluting stents (DES) where the polymer is coated on metal stents incorporating drugs to prevent coagulation and abnormal proliferation of smooth muscle cells.¹⁴⁵ The surface-eroding and slow-degrading properties of PTMC should be ideal for DES to manage slow and prolonged drug release. Moreover, since no acidic degradation products are generated, the corrosion of the base metal is less affected. Magnesium-based stents are known to be biodegradable, mechanically strong, and non-toxic.¹⁴⁶ However, the corrosion-based degradation is fast *in vivo*, which incites rapid hydrogen formation, hemolysis due to a high pH, and loss of the required mechanical strength at the early stage of the detainment.¹⁴⁷ The PTMC-coating has effectively suppressed the corrosion of the Mg-based stents, exhibiting significantly better performance than the coating by bulk-eroding PLA, PCL, and PGA that generate acidic degradation products.¹⁴⁸

Fully polymer-based resorbable cardiovascular stents have been recently studied for a low risk vascular therapy where no

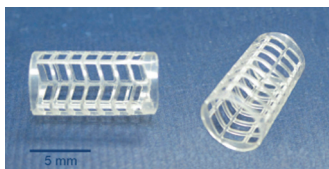


Fig. 8 A prototype stent fabricated from a high molecular weight poly(LLA-co-GA-co-TMC) (LLA/GA/TMC = 95/5/5). Reprinted with permission from ref. 151. Copyright (2013) Society of Plastics Engineers.

materials remain after healing.¹⁴⁹ The required mechanical properties become more complex than those for artificial vascular grafts. The stents need to expand and maintain the shape of the occluded part of the blood vessel. For this reason, shape-memory polymers have drawn attention as promising candidates for polymeric stents. Linear terpolymers of LLA, TMC, and GA (Fig. 1E) were then designed to demonstrate the shape-memory property around 40 °C with the high LLA composition.¹⁵⁰ The shape-memory property was not affected by incorporation of drugs. This fully polymeric shape memory stent has been proven to be useful as DES.⁵² Due to its decent processability, industrial fabrication of the terpolymer-based stent appears feasible (Fig. 8).¹⁵¹

4.1.5. Tissue adhesive. Tissue adhesives represent a large market next to sutures worldwide. Fibrin glue and cyanoacrylates are the only tissue adhesives allowed for clinical use.¹⁵² They are applied to wound healing and experimentally used as an alternative tool to sutures and staples. For instance, suturing for nerve repair might induce a tissue reaction and local formation of scar tissues that disturb elongation of axial fibers.¹³⁵ Thus, there is a certain need for suture alternatives. However, fibrin glue degrades too fast and the bonding strength is not sufficient.¹⁵³ Cyanoacrylates are also not suited because of the formation of toxic formaldehyde by degradation,¹⁵⁴ although the mechanical properties are much better than those of fibrin glue.¹⁵⁵ Hence, the development of a new class of biodegradable tissue adhesives, which has good mechanical properties and generates non-toxic degradation products, is needed. Low molecular weight ($M_n < 1000$ Da) block copolymers (oligomers) of oligo(ethylene glycol) (M_n of about 400 Da) and oligoTMC ($M_n < 300$ Da) with isocyanate terminal groups have been developed for application as tissue adhesives (Fig. 1L).^{156,157} The oligomers presented a low T_g so as to retain the fluid state at room temperature for good handling as adhesives. The isocyanate is designed to react with amino groups in the tissue (protein) to form covalent bridges with the tissue. In both linear and multi-armed architectures, the oligomer adhesives manifested no adverse reactions and high bonding strength up to 0.6 MPa, which value is comparable with that of a clinically used adhesive Dermabond®.

4.2. Drug delivery and theranostics

Drug delivery and therapeutics are two of the largest areas in which biodegradable polymers are studied due to their bio-

medical applications at the experimental level. Recent efforts entail active drug release upon stimuli,^{76,80,158} integration of imaging agents,¹⁵⁹ and targeting properties.^{160,161} The last two are relevant to theranostics that allows for therapy and diagnostics at the same time using one delivery vehicle.^{162,163} PTMC is used as a hydrophobic part of amphiphilic block copolymers to form spherical carriers, including micelles and vesicles, as well as other hydrophobic biodegradable polymers such as PLLA and PCL. In most cases, PEG and PGlu are used in the hydrophilic segment.¹⁶⁴ PEGylated block copolymers forming micelles show extremely low cytotoxicity both *in vitro* and *in vivo*.^{165–167} Moreover, due to their stealth property, PEGylated drug carriers tend to circulate longer in the bloodstream, avoiding phagocytosis, although recent reports revealed that multiple doses induce anti-PEG IgM production, resulting in an accelerated blood clearance (ABC) phenomenon of the PEGylated carriers.^{168,169} PGlu-*b*-PTMC (Fig. 1H), which generally forms vesicles, exhibits no cytotoxicity, but provokes oxidative stress against hepatocellular carcinoma cells (HepG2) and human lymphoblast cells (TK6) and slightly high cytokine production in lung epithelial cells (A549).¹⁷⁰ These findings indicate that the negative charge could be somewhat immunogenic and triggers an inflammatory response.^{170,171} However, the negative charge of the carboxylate is useful to enhance drug loading of doxorubicin (Dox) and pH-responsive release of drugs upon protonation.¹⁷²

Since the functions of targeting and cell recognition are applied to the surface of the carriers, the chemistry is not directly associated with PTMC that resides inside the carrier. Decoration of the terminal of PEG or PGlu by conjugating peptides^{173–175} and sugars^{176,177} (Fig. 1G) has been recently reported as new approaches for surface functionalization of PTMC-based drug carriers (Fig. 9). When the molecular weight of PTMC is quite small, hydrophilic terminal modification almost equates surface functionalization of micelle-like aggregates of PTMC to disperse in the aqueous system. Short PTMC ($M_n < 3000$ Da) with positively charged end groups (Fig. 1K) has been proposed as a new candidate for non-viral gene vectors¹⁷⁸ in which entirely charged cationic polymers are often used.^{179–181} The hydrophobic PTMC segment functions as a part of the DNA-binding moiety in combination with the peripheral charged end groups. Consequently, the low charge density likely contributes to the high transfection efficacy.

Due to the availability and a wide range of variation, PEG is predominantly used as the hydrophilic domain of the carriers and PEGylated block copolymers form micelles. The loading of the hydrophobic drug in the micelle core depends on the hydrophobic interaction between the drug and the hydrophobic segment when covalent conjugation of drugs is not exerted,^{182–184} while the drug release is susceptible to degradation of the hydrophobic core composed of biodegradable polymers. The advantage of PTMC-based drug carriers is the slow and moderate degradation of the hydrophobic core,^{185,186} promising constant and prolonged release of the drugs loaded. In contrast, PLA-based drug carriers often show an “initial burst” type release profile.

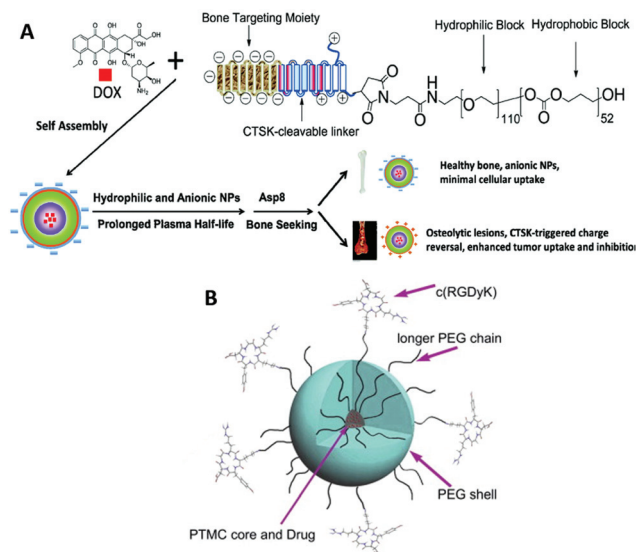


Fig. 9 Illustration of peptide-decorated PEG-*b*-PTMC for bone metastasis chemotherapy (A). Paclitaxel delivery to target integrin-rich malignant glioma cells (B). Reprinted with permission from ref. 173. Copyright (2013) Elsevier Ltd.

4.2.1. Functionalized micelles. The abovementioned side chain functionalized PTMC derivatives (Fig. 3 and 4) are used in PEGylated block copolymers to enhance drug loading and stimuli responsive ‘on-off’ switching of drug release. Hydrogen bonding has been previously exploited to enhance the drug loading in the micelle core.^{187,188} A urea and carboxyl functionalized PTMC derivative¹⁸⁹ derived from bisMPA (Fig. 3A) manifested high loadings of doxorubicin and thioridazine and also contributed to the sustained drug release.^{190,191} The use of photochromism imparts a photo-responsive shape transformation property to micelles.¹⁹² A spiropyran was conjugated to a PTMC derivative derived from bisMPA, exhibiting a light-triggered release and encapsulation of coumarin as a hydrophobic model drug by switching UV/vis irradiation because the light alters the molecular structure and hydrophilicity of spiropyran.⁸⁰ As another chemically responsive gimmick for the micelle core, the phenylboronic acid side chain can be used for the reversible binding of 1,2- and 1,3-diols, including glucose, catechol, and their derivatives.¹⁹³ A bisMPA-derived PTMC derivative with the phenylboronic acid side chain has been recently developed as a hydrophobic segment of the PEGylated block copolymer forming micelles with a diameter of less than 100 nm.¹⁵⁸ This polymer is promising as a glucose-responsive drug carrier for insulin delivery in the future.¹⁹⁴

Conjugation of fluorophores in the micelle core helps to monitor the stability of the micelle. A quinine-functionalized PTMC derivative in the form of the amphiphilic random copolymer indicated minimal fluorescence in water because of self-quenching of the quinine pendants in the micelle core, whereas higher fluorescence emission was observed for the much shorter oligomer (dimer) and free quinine.¹⁵⁹ This result

suggests that the collapse of the micelle based on the polymer degradation can be traced in real time by the fluorescence emission level of the quinine pendants.

The disulfide bridge is often employed as a reduction responsive cleavable linkage.⁸⁷ An AOM-derived PTMC derivative (Fig. 3C) with cleavable PEG side chains in the form of a block copolymer with PCL has demonstrated drug release by 1,4-dithiothreitol (DTT), a model reductive agent, resulting from the detachment of PEG and the subsequent dissociation of the micelle.⁶⁹ In another case, a bisMPA-derived PTMC derivative with attached PLLA grafts through the disulfide bridge showed reductive removal of the PLLA grafts by DTT.⁸⁷

4.2.2. Hydrogels. Besides micelles and nanoparticles, hydrogels are another option for drug delivery, in particular for topical administration of drugs on specific diseased or damaged tissues.^{195–197} Chemically cross-linked PEG is the most popular hydrogel.¹⁹⁸ Cross-linked PEGylated block copolymers with biodegradable polyesters offer degradability and hydrophobic domains for encapsulation of hydrophobic drugs and as a function of physical cross-linking points. Photo cross-linked PEG-*b*-PTMC hydrogels are recognized as slowly degrading hydrogels. According to a recent report, the protein release from the cross-linked PEG-*b*-PTMC hydrogels can be controlled only by diffusion from the meshes rather than by degradation when the mesh size is optimized for the loaded proteins and when no initial burst occurs. The optimized radical photo cross-linking contributes to the prevention of protein denaturation.¹⁹⁹

Recently, thermoresponsive biodegradable hydrogels have drawn more attention as an alternative to non-degradable poly-(*N*-isopropylacrylamide) (PNIPAAm)²⁰⁰ for its application as an injectable hydrogel-type drug carrier. Typically, they are handled as solution at room temperature outside the body and form hydrogels upon injection in the body, responding to the body temperature. A PTMC-containing triblock copolymer with a clinically used thermoresponsive hydrophilic polymer Pluronic F127® (PTMC-F127-PTMC, Fig. 11), showing a sol-gel transition at 37 °C, locally accumulated at the injected position, presenting a stable drug release profile over 25 days and no adverse reactions during the *in vivo* test using a rabbit glaucoma model.²⁰¹ Kim *et al.* first reported the thermoresponsive hydrogel system based on the PEG-tagged PTMC derivatives derived from bisMPA, displaying a lower critical solution temperature (LCST) around the body temperature, which is tuned by copolymerization of the TMC analogues with a long alkyl pendant.²⁰² Ajiro *et al.* also reported that a TMA-derived PTMC derivative (Fig. 3B) bearing a methoxy terminated triethylene glycol unit at the side chain showed an LCST around the body temperature at a particular molecular weight range.^{203,204} This is the first example of the LCST-type polymer obtained by using PTMC derivatives comprising a single monomer unit.

4.3. Antimicrobial

One of the growing areas in biomaterials is polymeric antimicrobials, corresponding to the urgent demand in medical settings where emerging multi-drug resistant bacteria threaten

patients worldwide.²⁰⁵ Quaternary ammonium tagged PTMC derivatives (Fig. 5B) have now been extensively studied as degradable polymeric antimicrobials since the first report in 2011.²⁰⁶ The first polymer demonstrated minimal hemolytic property and high antimicrobial activities against Gram-positive bacteria, including drug-resistant species such as methicillin-resistant *Staphylococcus aureus* (MRSA). As with other cationic polymers with methacrylate^{207–209} and vinyl ether²¹⁰ backbones, recent challenges converge on improving the antimicrobial activities and broadening the antimicrobial spectrum without increasing the hemolytic properties. According to recent comprehensive reviews,^{211,212} amphiphilicity, which is defined as a hydrophilic–hydrophobic balance of the polymer, plays a crucial role in the selectivity of membranes between bacteria and mammalian cells. The amphiphilicity is tuned by copolymerization with hydrophobic monomers with an alkyl pendant (segregated monomer approach)^{209,210,213} and variation of the length of an alkyl spacer between the cationic charge center and the backbone^{208,214–216} or of peripheral alkyl arms extending from the charge center²¹⁷ (the same center approach, Fig. 5B and C). Although no report has been published yet, some of the serinol-derived PTMC derivatives (Fig. 3E and F) can be potentially used as polymeric antimicrobials through quaternization and acidolysis of *tert*-butoxycarbonyl (Boc)-protected side chain affording ammonium salts.⁷²

Besides the modulation of the primary architecture of the cationic moiety, the introduction of biocompatible biomolecules,^{216,218} supramolecular approach,²¹⁹ and hydrogelation²²⁰ has also been surveyed to increase and broaden the antimicrobial properties with a low level of hemolytic properties (Fig. 10). In particular, the supramolecular approach raised the importance of the shape of antimicrobials on the efficacy against some fungi.^{219,221} According to a recent study by Stupp *et al.*, the cytotoxicity of cationic supramolecular aggregates depends on the strength of the interaction in the internal domain.²²² The strong “internal binding affinity” maintains the stable cationic supramolecular structure that could rip out the cell membrane, while the weak affinity augments the dynamic nature of the cationic aggregates to release unimers by stronger interaction with cell membranes. When the cells are of human origin, the former is regarded as cytotoxic and the latter leads to no damage to the cells. Thus, this

study suggests that various structural factors from the backbone structure to higher-order structures should be considered to comprehensively elucidate the hemocompatibility and biocidal activity of the polymeric antimicrobials. Otherwise, relatively long-life aliphatic polycarbonates may be regarded as unsuitable platforms as alternatives and/or supplements to conventional antibiotics. One of the preliminary results indicated a distinguished hydration behavior only for the carbonate linkage in the backbone, different from ester linkages, which may contribute to the high biocompatibility of PTMC.^{32,223}

5. Conclusions and outlook

This review focuses on PTMC and its derivatives with peripheral and/or vertical decorations developed in response to the diversifying demand for degradable biomedical devices. The modifications of the PTMC-based polymers affect the primary architecture, which alters the mechanical strength, degradation behavior, chemical properties, and affinity for cells and tissues. The peripheral decorations include block and random copolymerization, cross-linking, and terminal functionalization that often maintain the inherent characteristics of PTMC. Therefore, the peripheral decorations are valuable for the improvement and amendment of PTMC and for the addition of supplemental functions. Additionally, the modified PTMC materials are still easy to use for *in vivo* evaluation and the subsequent clinical testing. In contrast, the vertical decoration involves the introduction of side chains with some functionality onto the backbone of PTMC, providing polymers with a different physicochemical nature from that of PTMC. This means that any advantages of PTMC, including softness, compatibility with cells/tissues, and even biodegradability, are not technically guaranteed for the PTMC derivatives, although no generation of the acidic degradation products could be promised. As aforementioned, this is because the biological response highly depends on the surface chemistry of the materials, significantly involving side chain functionality. Thus, each PTMC derivative should be thoroughly examined *in vitro* to estimate the *in vivo* behavior. Nevertheless, PTMC derivatives have great potential to solve issues and technical limitations of the peripheral decorations. The next-generation biodegradable biomaterials can be created by integrating the knowledge obtained from the *in vivo* experiments designed to test the peripheral decorations and the synthetic solutions in the vertical decorations.

In addition, when we consider the application of PTMC or design the PTMC derivatives, we should understand and take full advantage of the specific characteristics of the main chain such as flexibility, resistance to hydrolysis, hydration properties, biocompatibility, and non-generation of acidic degradation products. Otherwise, the aforementioned PTMC derivatives would become temporary once another platform is proven to be more valuable. It is also important to determine new characteristics observed only in the PTMC derivatives in

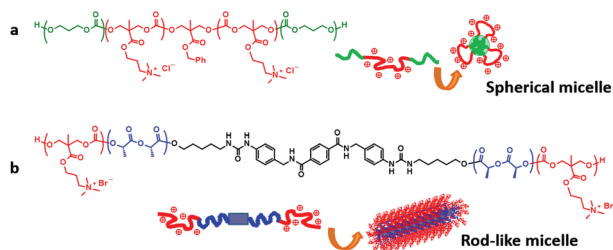


Fig. 10 PTMC derivatives for antimicrobials in different active forms. (a) Spherical micelles and (b) rod-like micelles. Reprinted with permission from ref. 223. Copyright (2015) The Society of Polymer Science, Japan.

order for PTMC derivatives to remain attractive as a biodegradable functional biomaterial compared to other polymer platforms with the same side chain architecture.

Acknowledgements

This study was supported by a JSPS Grant-in-Aid for Young Scientists (B) #25870078, the Takeda Science Foundation, and the Ito Science Foundation. The author would like to thank Editage (<http://www.editage.jp>) for English language editing of the manuscript.

Notes and references

- H. Tian, Z. Tang, X. Zhuang, X. Chen and X. Jing, *Prog. Polym. Sci.*, 2012, **37**, 237–280.
- A. L. Sisson, M. Schroeter and A. Lendlein, in *Handbook of Biodegradable Polymers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2011, pp. 1–21.
- D. J. Darensbourg and F.-T. Tsai, *Macromolecules*, 2014, **47**, 3806–3813.
- Y. Liu, K. Deng, S. Wang, M. Xiao, D. Han and Y. Meng, *Polym. Chem.*, 2015, **6**, 2076–2083.
- A. P. Dove, *ACS Macro Lett.*, 2012, **1**, 1409–1412.
- F. Nederberg, B. G. G. Lohmeijer, F. Leibfarth, R. C. Pratt, J. Choi, A. P. Dove, R. M. Waymouth and J. L. Hedrick, *Biomacromolecules*, 2007, **8**, 153–160.
- D. J. Darensbourg, A. Horn Jr. and A. I. Moncada, *Green Chem.*, 2010, **12**, 1376–1379.
- C. J. Whiteoak, N. Kielland, V. Laserna, E. C. Escudero-Adán, E. Martin and A. W. Kleij, *J. Am. Chem. Soc.*, 2013, **135**, 1228–1231.
- K. Koga, A. Sudo and T. Endo, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 4351–4355.
- A. P. Pêgo, D. W. Grijpma and J. Feijen, *Polymer*, 2003, **44**, 6495–6504.
- K. J. Zhu, R. W. Hendren, K. Jensen and C. G. Pitt, *Macromolecules*, 1991, **24**, 1736–1740.
- Z. Zhang, R. Kuijter, S. K. Bulstra, D. W. Grijpma and J. Feijen, *Biomaterials*, 2006, **27**, 1741–1748.
- J. Zou, C. C. Hew, E. Themistou, Y. Li, C.-K. Chen, P. Alexandridis and C. Cheng, *Adv. Mater.*, 2011, **23**, 4274–4277.
- R. J. Pounder and A. P. Dove, *Biomacromolecules*, 2010, **11**, 1930–1939.
- Y. Yu, J. Zou and C. Cheng, *Polym. Chem.*, 2014, **5**, 5854–5872.
- O. T. du Boullay, N. Saffon, J.-P. Diehl, B. Martin-Vaca and D. Bourissou, *Biomacromolecules*, 2010, **11**, 1921–1929.
- F. Coumes, V. Darcos, D. Domurado, S. Li and J. Coudane, *Polym. Chem.*, 2013, **4**, 3705–3713.
- J. Hao, Y. Cheng, R. J. K. U. Ranatunga, S. Senevirathne, M. C. Biewer, S. O. Nielsen, Q. Wang and M. C. Stefan, *Macromolecules*, 2013, **46**, 4829–4838.
- F. Ercole, A. E. Rodda, L. Meagher, J. S. Forsythe and A. P. Dove, *Polym. Chem.*, 2014, **5**, 2809–2815.
- S. Tempelaar, L. Mespouille, O. Coulembier, P. Dubois and A. P. Dove, *Chem. Soc. Rev.*, 2013, **42**, 1312–1336.
- M. K. Kiesewetter, E. J. Shin, J. L. Hedrick and R. M. Waymouth, *Macromolecules*, 2010, **43**, 2093–2107.
- S. Schüller-Ravoo, J. Feijen and D. W. Grijpma, *Acta Biomater.*, 2012, **8**, 3576–3585.
- S. J. German, M. Behbahani, S. Miettinen, D. W. Grijpma and S. P. Haimi, *Macromol. Symp.*, 2013, **334**, 133–142.
- N. D. Evans, C. Minelli, E. Gentleman, V. LaPointe, S. N. Patankar, M. Kallivretaki, X. Chen, C. J. Roberts and M. M. Stevens, *Eur. Cells Mater.*, 2009, **18**, 1–13.
- X. Li, Y. Huang, L. Zheng, H. Liu, X. Niu, J. Huang, F. Zhao and Y. Fan, *J. Biomed. Mater. Res., Part A*, 2014, **102**, 1092–1101.
- F. Wang, Z. Li, J. L. Lannutti, W. R. Wagner and J. Guan, *Acta Biomater.*, 2009, **5**, 2901–2912.
- X. J. Loh, W. Guerin and S. M. Guillaume, *J. Mater. Chem.*, 2012, **22**, 21249–21256.
- J. Yang, W. Tian, Q. Li, Y. Li and A. Cao, *Biomacromolecules*, 2004, **5**, 2258–2268.
- R. Chapanian, M. Y. Tse, S. C. Pang and B. G. Amsden, *Biomaterials*, 2009, **30**, 295–306.
- E. Bat, T. G. van Kooten, J. Feijen and D. W. Grijpma, *Biomaterials*, 2009, **30**, 3652–3661.
- M. C. Vyner, A. Li and B. G. Amsden, *Biomaterials*, 2014, **35**, 9041–9048.
- K. Fukushima, M.-Y. Tsai, T. Ota, Y. Haga, K. Matsuzaki, Y. Inoue and M. Tanaka, *Polym. J.*, 2015, **47**, 469–473.
- E. Pirhonen and P. Törmälä, *J. Mater. Sci.*, 2006, **41**, 2031–2036.
- F. Nederberg, J. Watanabe, K. Ishihara, J. Hilborn and T. Bowden, *J. Biomater. Sci., Polym. Ed.*, 2006, **17**, 605–614.
- R. Michel, S. Pasche, M. Textor and D. G. Castner, *Langmuir*, 2005, **21**, 12327–12332.
- P. Charles, V. Stubbs, C. Soto, B. Martin, B. White and C. Taitt, *Sensors*, 2009, **9**, 645.
- N. Zeng, A. van Leeuwen, R. R. M. Bos, D. W. Grijpma and R. Kuijter, *Macromol. Symp.*, 2013, **334**, 68–74.
- B. L. Dargaville, C. Vaquette, F. Rasoul, J. J. Cooper-White, J. H. Campbell and A. K. Whittaker, *Acta Biomater.*, 2013, **9**, 6885–6897.
- S. Schüller-Ravoo, S. M. Teixeira, J. Feijen, D. W. Grijpma and A. A. Poot, *Macromol. Biosci.*, 2013, **13**, 1711–1719.
- D. Tunc, C. Le Coz, M. Alexandre, P. Desbois, P. Lecomte and S. Carlotti, *Macromolecules*, 2014, **47**, 8247–8254.
- A. Garle, S. Kong, U. Ojha and B. M. Budhlall, *ACS Appl. Mater. Interfaces*, 2012, **4**, 645–657.
- X. Hu, X. Chen, H. Cheng and X. Jing, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 161–169.
- V. Truong, I. Blakey and A. K. Whittaker, *Biomacromolecules*, 2012, **13**, 4012–4021.
- D. M. Stevens, S. Tempelaar, A. P. Dove and E. Harth, *ACS Macro Lett.*, 2012, **1**, 915–918.

- 45 D. M. Stevens, A. Rahalkar, B. Spears, K. Gilmore, E. Douglas, M. Muthukumar and E. Harth, *Polym. Chem.*, 2015, **6**, 1096–1102.
- 46 P. Olsén, K. Odelius and A.-C. Albertsson, *Macromolecules*, 2014, **47**, 6189–6195.
- 47 S. Skoog, P. Goering and R. Narayan, *J. Mater. Sci.: Mater. Med.*, 2014, **25**, 845–856.
- 48 J. L. Ifkovits and J. A. Burdick, *Tissue Eng.*, 2007, **13**, 2369–2385.
- 49 E. Sachlos and J. T. Czernuszka, *Eur. Cells Mater.*, 2003, **5**, 29–39; discussion 39–40.
- 50 S. M. Peltola, F. P. W. Melchels, D. W. Grijpma and M. Kellomäki, *Ann. Med.*, 2008, **40**, 268–280.
- 51 A. D. Messias, K. F. Martins, A. C. Motta and E. A. d. R. Duek, *Int. J. Biomater.*, 2014, **2014**, 7.
- 52 J. Jaworska, K. Jelonek, M. Sobota, J. Kasperczyk, P. Dobrzynski, M. Musial-Kulik, A. Smola-Dmochowska, H. Janeczko and B. Jarzabek, *J. Appl. Polym. Sci.*, 2015, **132**, 41902.
- 53 C.-J. Pan, Y.-H. Hou, B.-B. Zhang, Y.-X. Dong and H.-Y. Ding, *J. Mater. Chem. B*, 2014, **2**, 892–902.
- 54 H. Lu and J. Cheng, *J. Am. Chem. Soc.*, 2008, **130**, 12562–12563.
- 55 D. Roy, M. Semsarilar, J. T. Guthrie and S. Perrier, *Chem. Soc. Rev.*, 2009, **38**, 2046–2064.
- 56 S. A. Pendergraph, G. Klein, M. K. G. Johansson and A. Carlmark, *RSC Adv.*, 2014, **4**, 20737–20743.
- 57 Y. Luan, J. Wu, M. Zhan, J. Zhang, J. Zhang and J. He, *Cellulose*, 2013, **20**, 327–337.
- 58 C. Yan, J. Zhang, Y. Lv, J. Yu, J. Wu, J. Zhang and J. He, *Biomacromolecules*, 2009, **10**, 2013–2018.
- 59 W. Guerin, M. Helou, M. Slawinski, J.-M. Brusson, J.-F. Carpentier and S. M. Guillaume, *Polym. Chem.*, 2014, **5**, 1229–1240.
- 60 L. Pasquato, G. Modena, L. Cotarca, P. Delogu and S. Mantovani, *J. Org. Chem.*, 2000, **65**, 8224–8228.
- 61 R. C. Pratt, F. Nederberg, R. M. Waymouth and J. L. Hedrick, *Chem. Commun.*, 2008, 114–116.
- 62 S. Venkataraman, J. L. Hedrick and Y. Y. Yang, *Polym. Chem.*, 2014, **5**, 2035–2040.
- 63 D. P. Sanders, K. Fukushima, D. J. Coady, A. Nelson, M. Fujiwara, M. Yasumoto and J. L. Hedrick, *J. Am. Chem. Soc.*, 2010, **132**, 14724–14726.
- 64 J. V. Olsson, D. Hult, Y. Cai, S. Garcia-Gallego and M. Malkoch, *Polym. Chem.*, 2014, **5**, 6651–6655.
- 65 J. Xu, E. Feng and J. Song, *J. Appl. Polym. Sci.*, 2014, **131**, 39822.
- 66 W. Chen, F. Meng, R. Cheng, C. Deng, J. Feijen and Z. Zhong, *J. Controlled Release*, 2014, **190**, 398–414.
- 67 H. Ihre, A. Hult and E. Söderlind, *J. Am. Chem. Soc.*, 1996, **118**, 6388–6395.
- 68 F. Chen, J. W. S. Hayami and B. G. Amsden, *Biomacromolecules*, 2014, **15**, 1593–1601.
- 69 W. Chen, Y. Zou, J. Jia, F. Meng, R. Cheng, C. Deng, J. Feijen and Z. Zhong, *Macromolecules*, 2013, **46**, 699–707.
- 70 J. Mindemark and T. Bowden, *Polym. Chem.*, 2012, **3**, 1399–1401.
- 71 X. Zhang, M. Cai, Z. Zhong and R. Zhuo, *Macromol. Rapid Commun.*, 2012, **33**, 693–697.
- 72 S. Venkataraman, N. Veronica, Z. X. Voo, J. L. Hedrick and Y. Y. Yang, *Polym. Chem.*, 2013, **4**, 2945–2948.
- 73 L. Shen, Z. Li, F. Gong, F. Zhang, Q. Qin, S. Cheng and J. Ge, *Polym. Degrad. Stab.*, 2013, **98**, 1015–1021.
- 74 D. Chitkara, A. Mittal, S. W. Behrman, N. Kumar and R. I. Mahato, *Bioconjugate Chem.*, 2013, **24**, 1161–1173.
- 75 H. Xiao, H. Song, Q. Yang, H. Cai, R. Qi, L. Yan, S. Liu, Y. Zheng, Y. Huang, T. Liu and X. Jing, *Biomaterials*, 2012, **33**, 6507–6519.
- 76 M. Wang, J. Sun, Y. Zhai, H. Lian, C. Luo, L. Li, Y. Du, D. Zhang, W. Ding, S. Qiu, Y. Liu, L. Kou, X. Han, R. Xiang, Y. Wang and Z. He, *Biomacromolecules*, 2015, **16**, 1179–1190.
- 77 A. C. Engler, X. Ke, S. Gao, J. M. W. Chan, D. J. Coady, R. J. Ono, R. Lubbers, A. Nelson, Y. Y. Yang and J. L. Hedrick, *Macromolecules*, 2015, **48**, 1673–1678.
- 78 A. C. Engler, J. M. W. Chan, D. J. Coady, J. M. O'Brien, H. Sardon, A. Nelson, D. P. Sanders, Y. Y. Yang and J. L. Hedrick, *Macromolecules*, 2013, **46**, 1283–1290.
- 79 R. J. Williams, I. A. Barker, R. K. O'Reilly and A. P. Dove, *ACS Macro Lett.*, 2012, **1**, 1285–1290.
- 80 D. Hu, H. Peng, Y. Niu, Y. Li, Y. Xia, L. Li, J. He, X. Liu, X. Xia, Y. Lu and W. Xu, *J. Polym. Sci., Part A: Polym. Chem.*, 2015, **53**, 750–760.
- 81 D. Xing, L. Ma and C. Gao, *Macromol. Biosci.*, 2014, **14**, 1429–1436.
- 82 S. Onbulak, S. Tempelaar, R. J. Pounder, O. Gok, R. Sanyal, A. P. Dove and A. Sanyal, *Macromolecules*, 2012, **45**, 1715–1722.
- 83 A. Dag, M. Aydin, H. Durmaz, G. Hizal and U. Tunca, *J. Polym. Sci., Part A: Polym. Chem.*, 2012, **50**, 4476–4483.
- 84 S. Li, F. Meng, Z. Wang, Y. Zhong, M. Zheng, H. Liu and Z. Zhong, *Eur. J. Pharm. Biopharm.*, 2012, **82**, 103–111.
- 85 B. B. Uysal, U. S. Gunay, G. Hizal and U. Tunca, *J. Polym. Sci., Part A: Polym. Chem.*, 2014, **52**, 1581–1587.
- 86 R. J. Ono, S. Q. Liu, S. Venkataraman, W. Chin, Y. Y. Yang and J. L. Hedrick, *Macromolecules*, 2014, **47**, 7725–7731.
- 87 A. C. Engler, J. M. W. Chan, K. Fukushima, D. J. Coady, Y. Y. Yang and J. L. Hedrick, *ACS Macro Lett.*, 2013, **2**, 332–336.
- 88 R. Jin, L. S. Moreira Teixeira, P. J. Dijkstra, C. A. van Blitterswijk, M. Karperien and J. Feijen, *Biomaterials*, 2010, **31**, 3103–3113.
- 89 L.-Q. Yang, B. He, S. Meng, J.-Z. Zhang, M. Li, J. Guo, Y.-M. Guan, J.-X. Li and Z.-W. Gu, *Polymer*, 2013, **54**, 2668–2675.
- 90 E. H. Busaina Dhariwala and T. Boland, *Tissue Eng.*, 2004, **10**, 1316–1322.
- 91 E. Bat, B. H. M. Kothman, G. A. Higuera, C. A. van Blitterswijk, J. Feijen and D. W. Grijpma, *Biomaterials*, 2010, **31**, 8696–8705.

- 92 Q. Hou, D. W. Grijpma and J. Feijen, *Acta Biomater.*, 2009, **5**, 1543–1551.
- 93 A. P. Pêgo, M. J. A. Van Luyn, L. A. Brouwer, P. B. van Wachem, A. A. Poot, D. W. Grijpma and J. Feijen, *J. Biomed. Mater. Res., Part A*, 2003, **67A**, 1044–1054.
- 94 X.-H. Qu, Q. Wu, K.-Y. Zhang and G. Q. Chen, *Biomaterials*, 2006, **27**, 3540–3548.
- 95 S. Talebian, M. Mehrali, S. Mohan, H. r. Balaji Raghavendran, M. Mehrali, H. M. Khanlou, T. Kamarul, A. M. Afifi and A. A. Abass, *RSC Adv.*, 2014, **4**, 49144–49152.
- 96 T. Pyhälä, M. Lapinsuo, H. Päätilä, M. Peltö, P. Törmälä and P. Rokkanen, *Biomaterials*, 2005, **26**, 645–654.
- 97 L. Wu and J. Ding, *Biomaterials*, 2004, **25**, 5821–5830.
- 98 J. E. Bergsma, W. C. de Bruijn, F. R. Rozema, R. R. M. Bos and G. Boering, *Biomaterials*, 1995, **16**, 25–31.
- 99 M. S. Taylor, A. U. Daniels, K. P. Andriano and J. Heller, *J. Appl. Biomater.*, 1994, **5**, 151–157.
- 100 A. C. van Leeuwen, H. Yuan, G. Passanisi, J. W. van der Meer, J. D. de Bruijn, T. G. van Kooten, D. W. Grijpma and R. R. Bos, *Eur. Cells Mater.*, 2014, **27**, 81–96; discussion 96–87.
- 101 A. C. van Leeuwen, R. R. M. Bos and D. W. Grijpma, *J. Biomed. Mater. Res., Part B*, 2012, **100B**, 1610–1620.
- 102 A. Polini, D. Pisignano, M. Parodi, R. Quarto and S. Scaglione, *PLoS One*, 2011, **6**, e26211.
- 103 S. A. Kay, L. Wisner-Lynch, M. Marxer and S. E. Lynch, *Practical Periodontics and Aesthetic Dentistry: PPAD*, 1997, **9**, 185–194; quiz 196.
- 104 T. von Arx, D. L. Cochran, R. K. Schenk and D. Buser, *Int. J. Oral Maxillofac. Surg.*, 2002, **31**, 190–199.
- 105 H.-L. Wang and L. Boyapati, *Implant Dent.*, 2006, **15**, 8–17.
- 106 P. Gentile, V. Chiono, C. Tonda-Turo, A. M. Ferreira and G. Ciardelli, *Biotechnol. J.*, 2011, **6**, 1187–1197.
- 107 A. C. van Leeuwen, J. J. R. Huddleston Slater, P. F. M. Gielkens, J. R. de Jong, D. W. Grijpma and R. R. M. Bos, *Acta Biomater.*, 2012, **8**, 1422–1429.
- 108 A. C. Van Leeuwen, T. G. Van Kooten, D. W. Grijpma and R. R. M. Bos, *J. Mater. Sci.: Mater. Med.*, 2012, **23**, 1951–1959.
- 109 S. Park, C. T. Hung and G. A. Ateshian, *Osteoarthritis Cartilage*, 2004, **12**, 65–73.
- 110 J. M. Mansour, *Biomechanics of Cartilage*, Lippincott Williams & Wilkins, Philadelphia, PA, 2003.
- 111 J. A. Stella, A. D'Amore, W. R. Wagner and M. S. Sacks, *Acta Biomater.*, 2010, **6**, 2365–2381.
- 112 L. Kock, C. van Donkelaar and K. Ito, *Cell Tissue Res.*, 2012, **347**, 613–627.
- 113 S. P. Zustiak, Y. Wei and J. B. Leach, *Tissue Eng., Part B*, 2013, **19**, 160–171.
- 114 L. Calderon, E. Collin, D. Velasco-Bayon, M. Murphy, D. O'Halloran and A. Pandit, *Eur. Cells Mater.*, 2010, **20**, 134–148.
- 115 G. D. Nicodemus and S. J. Bryant, *Tissue Eng., Part B*, 2008, **14**, 149–165.
- 116 C. Scotti, L. Mangiavini, F. Boschetti, F. Vitari, C. Domeneghini, G. Frascini and G. Peretti, *Knee Surgery, Sports Traumatology, Arthroscopy*, 2010, **18**, 1400–1406.
- 117 B. G. Amsden, A. Sukarto, D. K. Knight and S. N. Shapka, *Biomacromolecules*, 2007, **8**, 3758–3766.
- 118 S. J. Hollister, *Nat. Mater.*, 2005, **4**, 518–524.
- 119 Y.-J. Seol, T.-Y. Kang and D.-W. Cho, *Soft Matter*, 2012, **8**, 1730–1735.
- 120 C. D. Hoemann, J. Sun, V. Chrzanowski and M. D. Buschmann, *Anal. Biochem.*, 2002, **300**, 1–10.
- 121 P. Roughley, C. Hoemann, E. DesRosiers, F. Mwale, J. Antoniou and M. Alini, *Biomaterials*, 2006, **27**, 388–396.
- 122 R. Jin, L. S. Moreira Teixeira, A. Krouwels, P. J. Dijkstra, C. A. van Blitterswijk, M. Karperien and J. Feijen, *Acta Biomater.*, 2010, **6**, 1968–1977.
- 123 H. J. Wilke, P. Neef, M. Caimi, T. Hoogland and L. E. Claes, *Spine*, 1999, **24**, 755–762.
- 124 S. B. G. Blanquer, S. P. Haimi, A. A. Poot and D. W. Grijpma, *Macromol. Symp.*, 2013, **334**, 75–81.
- 125 D. Périé, D. Korda and J. C. Iatridis, *J. Biomech.*, 2005, **38**, 2164–2171.
- 126 M. E. Bernardo and W. E. Fibbe, *Cell Stem Cell*, 2013, **13**, 392–402.
- 127 T. Pirvu, S. B. G. Blanquer, L. M. Benneker, D. W. Grijpma, R. G. Richards, M. Alini, D. Eglin, S. Grad and Z. Li, *Biomaterials*, 2015, **42**, 11–19.
- 128 M. Bao, X. Lou, Q. Zhou, W. Dong, H. Yuan and Y. Zhang, *ACS Appl. Mater. Interfaces*, 2014, **6**, 2611–2621.
- 129 A. P. Pêgo, A. A. Poot, D. W. Grijpma and J. Feijen, *J. Controlled Release*, 2003, **87**, 69–79.
- 130 S. Sharifi, T. G. van Kooten, H.-J. C. Kranenburg, B. P. Meij, M. Behl, A. Lendlein and D. W. Grijpma, *Biomaterials*, 2013, **34**, 8105–8113.
- 131 R. Deumens, A. Bozkurt, M. F. Meek, M. A. E. Marcus, E. A. J. Joosten, J. Weis and G. A. Brook, *Prog. Neurobiol.*, 2010, **92**, 245–276.
- 132 R. Li, Z. Liu, Y. Pan, L. Chen, Z. Zhang and L. Lu, *Cell Biochem. Biophys.*, 2014, **68**, 449–454.
- 133 R. A. Wach, A. Adamus, A. K. Olejnik, J. Dzierzawska and J. M. Rosiak, *J. Appl. Polym. Sci.*, 2013, **127**, 2259–2268.
- 134 P. Prang, R. Müller, A. Eljaouhari, K. Heckmann, W. Kunz, T. Weber, C. Faber, M. Vroemen, U. Bogdahn and N. Weidner, *Biomaterials*, 2006, **27**, 3560–3569.
- 135 J. Silver and J. H. Miller, *Nat. Rev. Neurosci.*, 2004, **5**, 146–156.
- 136 D. N. Rocha, P. Brites, C. Fonseca and A. P. Pêgo, *PLoS ONE*, 2014, **9**, e88593.
- 137 E. Martínez, E. Engel, J. A. Planell and J. Samitier, *Ann. Anat. – Anat. Anz.*, 2009, **191**, 126–135.
- 138 M. S. Lord, M. Foss and F. Besenbacher, *Nano Today*, 2010, **5**, 66–78.
- 139 L. R. Pires, D. N. Rocha, L. Ambrosio and A. P. Pêgo, *J. R. Soc., Interface*, 2014, **12**.
- 140 A. Aguzzi, B. A. Barres and M. L. Bennett, *Science*, 2013, **339**, 156–161.

- 141 T. Courtney, M. S. Sacks, J. Stankus, J. Guan and W. R. Wagner, *Biomaterials*, 2006, **27**, 3631–3638.
- 142 W. A. Riley, R. W. Barnes, G. W. Evans and G. L. Burke, *Stroke*, 1992, **23**, 952–956.
- 143 D. Aytemiz, W. Sakiyama, Y. Suzuki, N. Nakaizumi, R. Tanaka, Y. Ogawa, Y. Takagi, Y. Nakazawa and T. Asakura, *Adv. Healthcare Mater.*, 2013, **2**, 361–368.
- 144 N. Kasoju and U. Bora, *Adv. Healthcare Mater.*, 2012, **1**, 393–412.
- 145 W. H. Maisel and W. K. Laskey, *Circulation*, 2007, **115**, e426–e427.
- 146 M. P. Staiger, A. M. Pietak, J. Huadmai and G. Dias, *Biomaterials*, 2006, **27**, 1728–1734.
- 147 A. Atrens, M. Liu and N. I. Zainal Abidin, *J. Mater. Sci. Eng. B*, 2011, **176**, 1609–1636.
- 148 J. Wang, Y. He, M. F. Maitz, B. Collins, K. Xiong, L. Guo, Y. Yun, G. Wan and N. Huang, *Acta Biomater.*, 2013, **9**, 8678–8689.
- 149 S. Nishio, K. Kosuga, K. Igaki, M. Okada, E. Kyo, T. Tsuji, E. Takeuchi, Y. Inuzuka, S. Takeda, T. Hata, Y. Takeuchi, Y. Kawada, T. Harita, J. Seki, S. Akamatsu, S. Hasegawa, N. Bruining, S. Brugaletta, S. de Winter, T. Muramatsu, Y. Onuma, P. W. Serruys and S. Ikeguchi, *Circulation*, 2012, **125**, 2343–2353.
- 150 E. Zini, M. Scandola, P. Dobrzynski, J. Kasperczyk and M. Bero, *Biomacromolecules*, 2007, **8**, 3661–3667.
- 151 J. Dong, L. Liao, L. Shi, Z. Tan, Z. Fan, S. Li and Z. Lu, *Polym. Eng. Sci.*, 2014, **54**, 1418–1426.
- 152 A. Lauto, D. Mawad and L. J. R. Foster, *J. Chem. Technol. Biotechnol.*, 2008, **83**, 464–472.
- 153 W. D. Spotnitz, *Am. J. Surg.*, 2001, **182**, S8–S14.
- 154 D. M. Toriumi, W. F. Raslan, M. Friedman and M. Tardy, *Arch. Otolaryngol., Head Neck Surg.*, 1990, **116**, 546–550.
- 155 T. B. Bruns and J. M. Worthington, *Am. Fam. Physician*, 2000, **61**, 1383–1388.
- 156 A. I. Bochyńska, S. Sharifi, T. G. van Tienen, P. Buma and D. W. Grijpma, *Macromol. Symp.*, 2013, **334**, 40–48.
- 157 S. B. Blanquer, S. Sharifi and D. W. Grijpma, *J. Appl. Biomater. Funct. Mater.*, 2012, **10**, 177–184.
- 158 Y. E. Aguirre-Chagala, J. L. Santos, B. A. Aguilar-Castillo and M. Herrera-Alonso, *ACS Macro Lett.*, 2014, **3**, 353–358.
- 159 J. A. Edward, M. K. Kiesewetter, H. Kim, J. C. A. Flanagan, J. L. Hedrick and R. M. Waymouth, *Biomacromolecules*, 2012, **13**, 2483–2489.
- 160 W. Cheng, C. Yang, J. L. Hedrick, D. F. Williams, Y. Y. Yang and P. G. Ashton-Rickardt, *Biomaterials*, 2013, **34**, 3697–3705.
- 161 Z. Y. Ong, C. Yang, S. J. Gao, X.-Y. Ke, J. L. Hedrick and Y. Yan Yang, *Macromol. Rapid Commun.*, 2013, **34**, 1714–1720.
- 162 I. Peták, R. Schwab, L. Órfi, L. Kopper and G. Kéri, *Nat. Rev. Drug Discovery*, 2010, **9**, 523–535.
- 163 S. S. Kelkar and T. M. Reineke, *Bioconjugate Chem.*, 2011, **22**, 1879–1903.
- 164 C. Sanson, C. Schatz, J.-F. Le Meins, A. Brûlet, A. Soum and S. Lecommandoux, *Langmuir*, 2010, **26**, 2751–2760.
- 165 R. Langer and N. A. Peppas, *AIChE J.*, 2003, **49**, 2990–3006.
- 166 C. Gong, S. Shi, P. Dong, B. Kan, M. Gou, X. Wang, X. Li, F. Luo, X. Zhao, Y. Wei and Z. Qian, *Int. J. Pharm.*, 2009, **365**, 89–99.
- 167 X. Yang, D. Cao, N. Wang, L. Sun, L. Li, S. Nie, Q. Wu, X. Liu, C. Yi and C. Gong, *J. Pharm. Sci.*, 2014, **103**, 305–313.
- 168 T. Ishida and H. Kiwada, *Int. J. Pharm.*, 2008, **354**, 56–62.
- 169 E. Hara, A. Makino, K. Kurihara, F. Yamamoto, E. Ozeki and S. Kimura, *Int. Immunopharmacol.*, 2012, **14**, 261–266.
- 170 F. Goñi-de-Cerio, V. Mariani, D. Cohen, L. Madi, J. Thevenot, H. Oliveira, C. Ubaldi, G. Giudetti, R. Coradeghini, E. Garanger, F. Rossi, M. Portugal-Cohen, M. Oron, R. Korenstein, S. Lecommandoux, J. Ponti, B. Suárez-Merino and P. Heredia, *J. Nanopart. Res.*, 2013, **15**, 1–17.
- 171 H. Oliveira, J. Thevenot, E. Garanger, E. Ibarboure, P. Calvo, P. Aviles, M. Guillen and S. Lecommandoux, *Pharm. Res.*, 2014, **31**, 983–991.
- 172 D. Bacinello, E. Garanger, D. Taton, K. C. Tam and S. Lecommandoux, *Eur. Polym. J.*, 2015, **62**, 363–373.
- 173 X. Jiang, X. Sha, H. Xin, X. Xu, J. Gu, W. Xia, S. Chen, Y. Xie, L. Chen, Y. Chen and X. Fang, *Biomaterials*, 2013, **34**, 2969–2979.
- 174 X. Jiang, H. Xin, J. Gu, X. Xu, W. Xia, S. Chen, Y. Xie, L. Chen, Y. Chen, X. Sha and X. Fang, *Biomaterials*, 2013, **34**, 1739–1746.
- 175 X. Wang, Y. Yang, H. Jia, W. Jia, S. Miller, B. Bowman, J. Feng and F. Zhan, *Biomater. Sci.*, 2014, **2**, 961–971.
- 176 X. Jiang, H. Xin, J. Gu, F. Du, C. Feng, Y. Xie and X. Fang, *J. Pharm. Sci.*, 2014, **103**, 1487–1496.
- 177 X. Jiang, H. Xin, Q. Ren, J. Gu, L. Zhu, F. Du, C. Feng, Y. Xie, X. Sha and X. Fang, *Biomaterials*, 2014, **35**, 518–529.
- 178 J. Mindemark, Y. Tabata and T. Bowden, *Macromol. Biosci.*, 2012, **12**, 840–848.
- 179 M. Yamagata, T. Kawano, K. Shiba, T. Mori, Y. Katayama and T. Niidome, *Bioorg. Med. Chem.*, 2007, **15**, 526–532.
- 180 M. Bertschinger, G. Backliwal, A. Schertenleib, M. Jordan, D. L. Hacker and F. M. Wurm, *J. Controlled Release*, 2006, **116**, 96–104.
- 181 Z. Y. Ong, K. Fukushima, D. J. Coady, Y.-Y. Yang, P. L. R. Ee and J. L. Hedrick, *J. Controlled Release*, 2011, **152**, 120–126.
- 182 J. P. K. Tan, S. H. Kim, F. Nederberg, E. A. Appel, R. M. Waymouth, Y. Zhang, J. L. Hedrick and Y. Y. Yang, *Small*, 2009, **5**, 1504–1507.
- 183 K. Fukushima, R. C. Pratt, F. Nederberg, J. P. K. Tan, Y. Y. Yang, R. M. Waymouth and J. L. Hedrick, *Biomacromolecules*, 2008, **9**, 3051–3056.
- 184 F. Nederberg, E. Appel, J. P. K. Tan, S. H. Kim, K. Fukushima, J. Sly, R. D. Miller, R. M. Waymouth, Y. Y. Yang and J. L. Hedrick, *Biomacromolecules*, 2009, **10**, 1460–1468.

- 185 C. Zhang, D. Liu, X. Zhang, P. Wang, Z. Zhen, J. Li, D. Yi, Y. Jin and D. Yang, *J. Appl. Polym. Sci.*, 2015, **132**, 41815.
- 186 L. Yang, J. Li, S. Meng, Y. Jin, J. Zhang, M. Li, J. Guo and Z. Gu, *Polymer*, 2014, **55**, 5111–5124.
- 187 J. P. K. Tan, S. H. Kim, F. Nederberg, K. Fukushima, D. J. Coady, A. Nelson, Y. Y. Yang and J. L. Hedrick, *Macromol. Rapid Commun.*, 2010, **31**, 1187–1192.
- 188 S. H. Kim, J. P. K. Tan, F. Nederberg, K. Fukushima, J. Colson, C. Yang, A. Nelson, Y.-Y. Yang and J. L. Hedrick, *Biomaterials*, 2010, **31**, 8063–8071.
- 189 X.-Y. Ke, V. W. Lin Ng, S.-J. Gao, Y. W. Tong, J. L. Hedrick and Y. Y. Yang, *Biomaterials*, 2014, **35**, 1096–1108.
- 190 A. B. Ebrahim Attia, C. Yang, J. P. K. Tan, S. Gao, D. F. Williams, J. L. Hedrick and Y.-Y. Yang, *Biomaterials*, 2013, **34**, 3132–3140.
- 191 C. Yang, A. B. Ebrahim Attia, J. P. K. Tan, X. Ke, S. Gao, J. L. Hedrick and Y.-Y. Yang, *Biomaterials*, 2012, **33**, 2971–2979.
- 192 Y. Zhao, *Macromolecules*, 2012, **45**, 3647–3657.
- 193 A. Matsumoto, K. Yamamoto, R. Yoshida, K. Kataoka, T. Aoyagi and Y. Miyahara, *Chem. Commun.*, 2010, **46**, 2203–2205.
- 194 I. Dasgupta, E. A. Tanifum, M. Srivastava, S. S. Phatak, C. N. Cavasotto, M. Analoui and A. Annapragada, *PLoS One*, 2012, **7**, e29585.
- 195 L. Yu and J. Ding, *Chem. Soc. Rev.*, 2008, **37**, 1473–1481.
- 196 C. Hiemstra, W. Zhou, Z. Zhong, M. Wouters and J. Feijen, *J. Am. Chem. Soc.*, 2007, **129**, 9918–9926.
- 197 M. K. Joo, M. H. Park, B. G. Choi and B. Jeong, *J. Mater. Chem.*, 2009, **19**, 5891–5905.
- 198 S. Q. Liu, C. Yang, Y. Huang, X. Ding, Y. Li, W. M. Fan, J. L. Hedrick and Y.-Y. Yang, *Adv. Mater.*, 2012, **24**, 6484–6489.
- 199 J. Jansen, G. Mihov, J. Feijen and D. W. Grijpma, *Macromol. Biosci.*, 2012, **12**, 692–702.
- 200 H. J. Moon, D. Y. Ko, M. H. Park, M. K. Joo and B. Jeong, *Chem. Soc. Rev.*, 2012, **41**, 4860–4883.
- 201 L. Xi, T. Wang, F. Zhao, Q. Zheng, X. Li, J. Luo, J. Liu, D. Quan and J. Ge, *PLoS One*, 2014, **9**, e100632.
- 202 S. H. Kim, J. P. K. Tan, K. Fukushima, F. Nederberg, Y. Y. Yang, R. M. Waymouth and J. L. Hedrick, *Biomaterials*, 2011, **32**, 5505–5514.
- 203 H. Ajiro, Y. Takahashi and M. Akashi, *Macromolecules*, 2012, **45**, 2668–2674.
- 204 H. Ajiro, Y. Takahashi, M. Akashi and T. Fujiwara, *Macromol. Biosci.*, 2012, **12**, 1315–1320.
- 205 H. Nikaido, *Annu. Rev. Biochem.*, 2009, **78**, 119–146.
- 206 F. Nederberg, Y. Zhang, J. P. K. Tan, K. Xu, H. Wang, C. Yang, S. Gao, X. D. Guo, K. Fukushima, L. Li, J. L. Hedrick and Y.-Y. Yang, *Nat. Chem.*, 2011, **3**, 409–414.
- 207 E. F. Palermo and K. Kuroda, *Biomacromolecules*, 2009, **10**, 1416–1428.
- 208 E. F. Palermo, S. Vemparala and K. Kuroda, *Biomacromolecules*, 2012, **13**, 1632–1641.
- 209 K. Kuroda and W. F. DeGrado, *J. Am. Chem. Soc.*, 2005, **127**, 4128–4129.
- 210 Y. Oda, S. Kanaoka, T. Sato, S. Aoshima and K. Kuroda, *Biomacromolecules*, 2011, **12**, 3581–3591.
- 211 E. Palermo and K. Kuroda, *Appl. Microbiol. Biotechnol.*, 2010, **87**, 1605–1615.
- 212 A. C. Engler, N. Wiradharma, Z. Y. Ong, D. J. Coady, J. L. Hedrick and Y.-Y. Yang, *Nano Today*, 2012, **7**, 201–222.
- 213 Y. Qiao, C. Yang, D. J. Coady, Z. Y. Ong, J. L. Hedrick and Y.-Y. Yang, *Biomaterials*, 2012, **33**, 1146–1153.
- 214 V. W. L. Ng, J. P. K. Tan, J. Leong, Z. X. Voo, J. L. Hedrick and Y. Y. Yang, *Macromolecules*, 2014, **47**, 1285–1291.
- 215 A. C. Engler, J. P. K. Tan, Z. Y. Ong, D. J. Coady, V. W. L. Ng, Y. Y. Yang and J. L. Hedrick, *Biomacromolecules*, 2013, **14**, 4331–4339.
- 216 V. W. L. Ng, X. Ke, A. L. Z. Lee, J. L. Hedrick and Y. Y. Yang, *Adv. Mater.*, 2013, **25**, 6730–6736.
- 217 W. Chin, C. Yang, V. W. L. Ng, Y. Huang, J. Cheng, Y. W. Tong, D. J. Coady, W. Fan, J. L. Hedrick and Y. Y. Yang, *Macromolecules*, 2013, **46**, 8797–8807.
- 218 S. Venkataraman, A. L. Lee, H. T. Maune, J. L. Hedrick, V. M. Prabhu and Y. Y. Yang, *Macromolecules*, 2013, **46**, 4839–4846.
- 219 K. Fukushima, J. P. K. Tan, P. A. Korevaar, Y. Y. Yang, J. Pitera, A. Nelson, H. Maune, D. J. Coady, J. E. Frommer, A. C. Engler, Y. Huang, K. Xu, Z. Ji, Y. Qiao, W. Fan, L. Li, N. Wiradharma, E. W. Meijer and J. L. Hedrick, *ACS Nano*, 2012, **6**, 9191–9199.
- 220 Y. Li, K. Fukushima, D. J. Coady, A. C. Engler, S. Liu, Y. Huang, J. S. Cho, Y. Guo, L. S. Miller, J. P. K. Tan, P. L. R. Ee, W. Fan, Y. Y. Yang and J. L. Hedrick, *Angew. Chem., Int. Ed.*, 2013, **52**, 674–678.
- 221 K. Fukushima, S. Liu, H. Wu, A. C. Engler, D. J. Coady, H. Maune, J. Pitera, A. Nelson, N. Wiradharma, S. Venkataraman, Y. Huang, W. Fan, J. Y. Ying, Y. Y. Yang and J. L. Hedrick, *Nat. Commun.*, 2013, **4**.
- 222 C. J. Newcomb, S. Sur, J. H. Ortony, O.-S. Lee, J. B. Matson, J. Boekhoven, J. M. Yu, G. C. Schatz and S. I. Stupp, *Nat. Commun.*, 2014, **5**.
- 223 M. Tanaka, K. Sato, E. Kitakami, S. Kobayashi, T. Hoshiba and K. Fukushima, *Polym. J.*, 2015, **47**, 114–121.