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Synthesis and therapeutic applications of biocompatible or biodegradable hyperbranched polymers

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Abstract: Biocompatible or biodegradable hyperbranched polymers (HBPs), an important subclass of hyperbranched macromolecules, have recently received an increasing attention due to their unique physical and chemical properties as well as their great advantages in therapeutic applications. This review highlights recent advances and future trends in the preparation and applications of biocompatible or biodegradable HBPs for therapeutic purpose. Various biocompatible or biodegradable hyperbranched structures can be obtained by means of step-growth polycondensation (SGP), self-condensing vinyl polymerization (SCVP), self-condensing ring-opening polymerization (SCROP), and so forth. The properties of biocompatible or biodegradable HBPs can be tailored for a specialized purpose through terminal modification, backbone modification, or hybrid modification. A particular emphasis is then placed on their diagnostic, therapeutic delivery and theranostic applications. Finally, future directions and perspectives in this emerging field are briefly discussed. These developments on synthesis and therapeutic applications of biocompatible or biodegradable HBPs promote the interdisciplinary research spanning polymer materials and biomedical sciences.

1. Introduction

It is well known that the molecular architecture of a polymer is one of the most important factors which determine its properties. Changing the architecture from conventional linear or cross-linked to partially or highly branched is therefore an effective way to tailor a polymer's properties. As early as 1952, Flory proposed that highly branched polymers could be prepared by utilizing multi-functional monomers without the occurrence of gelation.[1] Thereafter, in the

late 1980s, Kim and Webster first synthesized a highly branched polyphenylene from AB_2 monomers and named this type of polymers as hyperbranched polymers (HBPs),[2,3] HBPs are highly branched macromolecules with a three-dimensional dendritic architecture. They have three important characteristics: (1) their three-dimensional dendritic architecture can prevent the entanglement among polymer chains, thereby resulting in some completely different properties from linear polymers; (2) their good solubility and low viscosity can improve processability in comparison with linear polymers; (3) there are a large population of terminal functional groups in HBPs that are easy to be chemically modified.[4-8] Due to these unique topological structures and distinct physical/chemical properties, HBPs and their assemblies have exhibited great potential in various biomedical fields, especially for therapeutic applications.[9-12]

Advances of HBPs in biomedical applications have led to an accelerated discovery of HBPs with biocompatible or biodegradable backbones. Generally, HBPs with no or poor biocompatibility/biodegradability have issues of toxicity, immunogenicity and poor body clearance. It is also difficult to achieve a controlled release of therapeutic agents using these polymers. The development of biocompatible or biodegradable HBPs can overcome these challenges and therefore significantly expand the application fields of HBPs.[13-25] To date, many elegant reviews related to HBPs have been published.[26-34] However, a systematic review on synthesis and therapeutic applications of biocompatible or biodegradable HBPs has not yet been published. Herein, a variety of synthesis methodologies and modification manners of biocompatible or biodegradable HBPs are highlighted. Their diagnostic, therapeutic delivery and theranostic applications are also summarized.

2. Biocompatibility or biodegradability of HBPs

Biocompatibility or biodegradability is among major concerns in designing ideal biomedical polymeric materials. Biocompatible or biodegradable HBPs have become increasingly important in therapeutic applications owning to their low toxicity, non-immunogenicity as well as general ease of degradation and metabolization.[17-21] So far, biocompatible or biodegradable HBPs have shown great potential for delivering diagnostic/therapeutic agents and controlling their release. Biodegradable HBPs with excellent biocompatibility, defined structure, and controlled degradation profiles are highly demanded for use as *in vivo* diagnostic/therapeutic delivery systems. Up to now, a great number of biocompatible or biodegradable HBPs have been well designed and widely used in therapeutic applications. They can be divided into seven major types: (1) hyperbranched polyether, (2) hyperbranched polyester, (3) hyperbranched polyphosphate, (4) hyperbranched polysaccharide, (5) hyperbranched polypeptide, (6) hyperbranched polyamide, and (7) others. Structures of several representatives are shown in Fig.

1. As a typical example, hyperbranched polyglycerol (HPG) possesses good water solubility, excellent biocompatibility, and low/non-immunogenicity.[9,10,27] Therefore, HPG and its derivatives are widely regarded as promising biomaterials for a variety of therapeutic applications in both diagnosis and therapy through encapsulation or conjugation with diagnostic agents, drugs, genetic segments, proteins and peptides. Considering that synthesis and modification are always the basis of practical applications, we thereby summarize the synthesis methodologies and modification manners for biocompatible or biodegradable HBPs before discussing their therapeutic applications in various aspects.

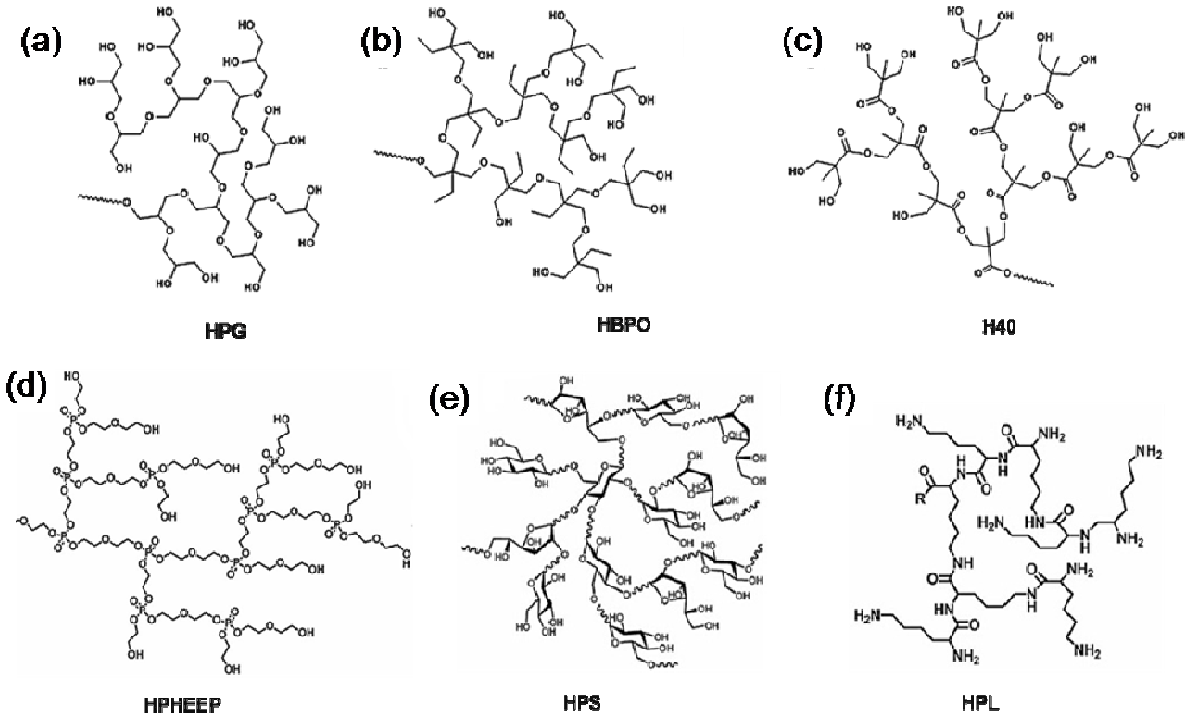

Fig. 1 Schematic structures of representative biocompatible or biodegradable HBPs: (a) hyperbranched polyglycerol (HPG), (b) hyperbranched poly(3-ethyl-3-oxetanemethanol) (HBPO), (c) hyperbranched polyester (Boltorn® H_{40}), (d) hyperbranched polyphosphate (HPHEEP), (e) hyperbranched polysaccharide (HPS), and (f) hyperbranched polylysine (HPL). Reproduced from ref. 10. Copyright 2014 Royal Society of Chemistry.

3. Synthesis and modification of biocompatible or biodegradable HBPs

3.1 Synthesis of biocompatible or biodegradable HBPs

Conventional polymer synthesis methodologies, such as step-growth polycondensation (SGP), self-condensing vinyl polymerization (SCVP), and self-condensing ring-opening polymerization (SCROP),[5,36-43] can be used to construct biocompatible or biodegradable HBPs.

SGP: Through SGP, the HBPs are generated by direct polymerization of one type of

monomers (AB_n, $n \geq 2$) or two types of monomers ($A_n + B_m$, $n \geq 2$; $m \geq 3$). As a typical example of SGP using one type of AB_2 monomers, branching units are generated when both B functionalities of one monomer react with A groups contained on others. It is possible that only one B functionality reacts, resulting in some linear units in the HBPs. The primary advantage of SGP is that normal step-growth polymerization characteristics are retained, for example, each polyfunctional oligomer present in the reaction mixture may couple with any other species in the absence of crosslinking; while the inherent drawback is potential undesirable side reactions. Unwanted side reactions that take place in early stages of the process may hinder the formation of polymers with high molecular weight, especially when the A functional group in the AB_n monomer is consumed by side reactions such as intramolecular cyclization to form cyclic oligomers. To date, this method has been successfully used to produce a large number of biocompatible or biodegradable HBPs. A good example is Boltorn® H_x (x = 20, 30, 40) reported by Hult and coworkers, as shown in Fig 1c. This is a hyperbranched polyester synthesized from 2,2-bis(hydroxymethyl)propionic acid as an AB_2 monomer.[44-46] The esterification procedure is performed in the bulk using an acid catalyst and requires no purification steps, facilitating large-scale production. Besides, Klok and coworkers have synthesized a hyperbranched polylysine (HPL) by means of SGP using *L*-lysine monomers (Fig. 2).[47,48] *In vitro* evaluations reveal that HPL exhibits higher solubility, lower toxicity and enhanced proteolytic stability as compared with linear peptide analogues, which offers a great potential in many biomedical applications.

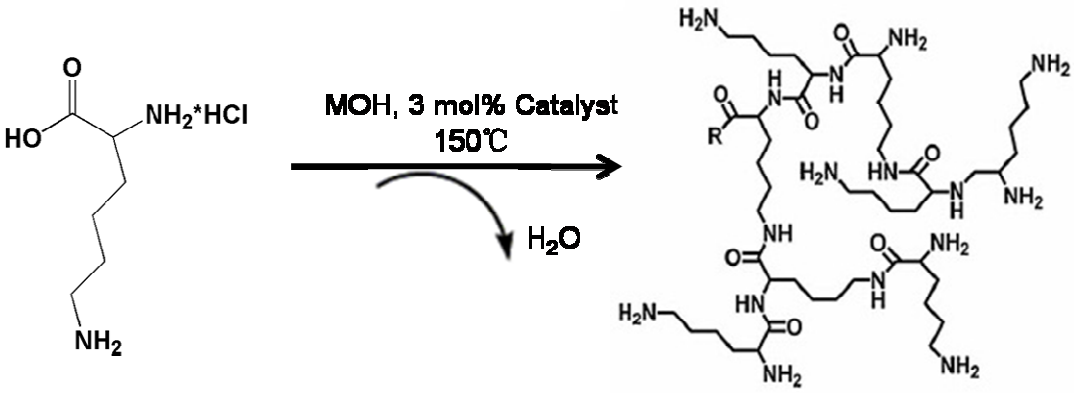

Fig. 2 A schematic illustration of hyperbranched polylysine constructed by the SGP of *L*-lysine monomers. Reproduced from ref. 48. Copyright 2007 Wiley-VCH.

On the other hand, HBPs can also be constructed by an "$A_n + B_m$" approach using two types of monomers. The success of "$A_n + B_m$" approach is dependent upon a number of factors, including the ratio of functionalities, solvent, reaction time and temperature. Kakimoto and coworkers[49] synthesized a hyperbranched polyamide from diamine (A_2) and trimesic acid (B_3)

via the "A_2 + B_3" approach. Fréchet and coworkers independently applied the "A_2 + B_3" approach to synthesize hyperbranched polyether employing 1,2,7,8-diepoxyoctane as the A_2 monomer and 1,1,1-tris(hydroxymethyl)ethane as the B_3 monomer.[50] Although the "A_2 + B_3" approach to HBPs holds some advantages over the conventional AB_2 polycondensation approach, such as facile preparation and commercial availability of monomers, it still exhibits the major problem of uncontrollable gelation, especially under conditions of relatively high monomer concentration and high reaction temperature. To avoid crosslinking, the reaction should be performed under a low monomer concentration or slow monomer addition, or the polymerization must be stopped prior to the critical point of gelation. This strongly hinders the wide application of the A_2 + B_3 approach in large-scale manufacture of HBPs. Therefore, a new strategy based on the non-equal reactivity of functional groups in specific monomer pairs was invented independently by Yan[51-52] and DSM Research.[53-54] In this case, choosing suitable monomer pairs is the most important step for the molecular design of HBPs. Unlike the conventional method, this approach enables the molecular weight and terminal functional groups of the resultant HBPs to be adjusted by the feed ratio of two monomers.[5] Currently, SGP using A_n + B_m monomers has been successfully utilized to synthesize varieties of biocompatible or biodegradable HBPs. For example, we know that saccharide units are the main components in the biology world, so the HBPs that are constructed from these units are inherently biocompatible and biodegradable.[55] A hyperbranched polysaccharide based on kanamycin and *N*,*N*′-methylene bisacrylamide has been recently reported by Zhu and Yan (Fig. 3), demonstrating excellent biocompatibility, biodegradability, and low cytotoxicity.[56] Besides, they have also prepared a biocompatible and biodegradable hyperbranched polyamidoamine (HPAMAM) from *N*,*N*′-methylene bisacrylamide and 1-(2-aminoethyl)piperazine to lower the cytotoxicity of polycationic vectors and improve the gene transfection efficiency.[57]

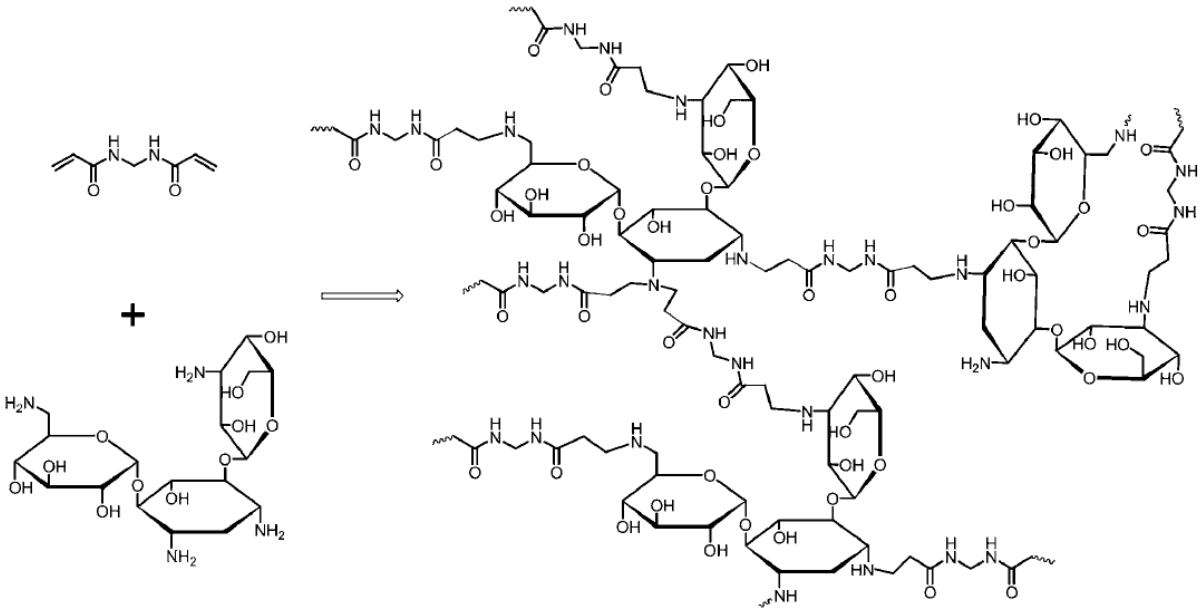

Fig. 3 A schematic illustration of hyperbranched polysaccharide constructed by SGP using *N*,*N*′-methylene bisacrylamide and kanamycin monomers. Reproduced from ref. 56. Copyright 2011 Royal Society of Chemistry.

SCVP: SCVP was first reported by Fréchet and coworkers in 1995.[58-60] In regard to SCVP utilizing AB* monomers, the B groups of the AB^* monomers are activated to generate the initiating B^* sites. B^* initiates the propagation of the vinyl group A in the monomer, forming a dimer with a vinyl group, a growth site, and an initiating site. The dimer can function as an AB_2 monomer, and undergo further polymerization to produce HBPs.[5] An important factor of SCVP that must be taken into consideration is the relative activities of chain propagation of the growth sites and the initiating sites, which may affect the degree of branching (DB). Moreover, side reactions may cause gelation, and the molecular weight distribution is often broad in SCVP method. In order to avoid these problems, living/controlled polymerizations such as atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT) polymerization and group transfer polymerization (GTP) are combined with SCVP.[61-66] Recently, Zhu and coworkers synthesized a hyperbranched poly((*S*-(4-vinyl) benzyl *S*′-propyltrithiocarbonate)-*co*-(poly(ethylene glycol) methacrylate)) (poly(VBPT-*co*-PEGMA)) with multiple thiol groups *via* SCVP-RAFT copolymerization (Fig. 4).[67,68] *In vitro* results revealed that this HBP exhibited high solubility, low toxicity, and excellent biocompatibility. Significantly, thiol-containing anti-cancer drugs could be conjugated to this biocompatible HBP *via* disulfide linkages after aminolysis reaction to realize a redox-triggered drug release.

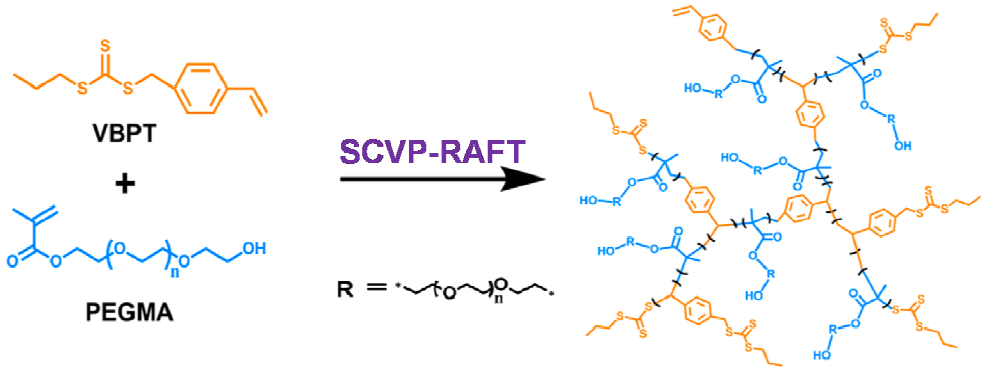

Fig. 4 A schematic illustration of hyperbranched poly(VBPT-*co*-PEGMA) constructed by SCVP-RAFT using VBPT and PEGMA monomers. Reproduced from ref. 68. Copyright 2014 American Chemical Society.

SCROP: A third pathway to HBPs is the SCROP of cyclic latent AB_2-type monomers. In 1992, Suzuki reported polymerization of a cyclic carbamate and referred to his concept as "multibranching ring-opening polymerization".[69,70] In this case, the terminal functional group of a polymer acts as a reactive centre on which other cyclic monomers bond to form a larger polymer chain. Generally, HBPs prepared by this synthetic method are often biocompatible or biodegradable such as hyperbranched polyethers, polyesters and polyamines. For example, biocompatible HPG was synthesized in a controlled manner by Frey and coworkers through an anionic SCROP from glycidol (a latent cyclic AB_2-type monomer) with trimethylolpropane as a trifunctional core-initiator (Fig. 5).[71] Fig. 1b shows the structure of HBPO synthesized *via* a cationic SCROP, which was first reported by Hult, Penczek and Yan independently.[72-76] These two kinds of hyperbranched polyethers and their derivatives offer enormous potential for a variety of biomedical applications due to their excellent biocompatibility and low/non-immunogenicity. HPHEEP, as shown in Fig. 1d, was recently reported by Yan and Huang through SCROP of cyclic phosphate monomers 2-(2-hydroxyethoxy)ethoxy-2-oxo-1,3,2-dioxaphospholane.[77-79] This polymer and its derivatives have demonstrated eminent biocompatibility, biodegradability, and flexibility in adjusting the pendant structures, and are promising candidates in various biomedical applications.

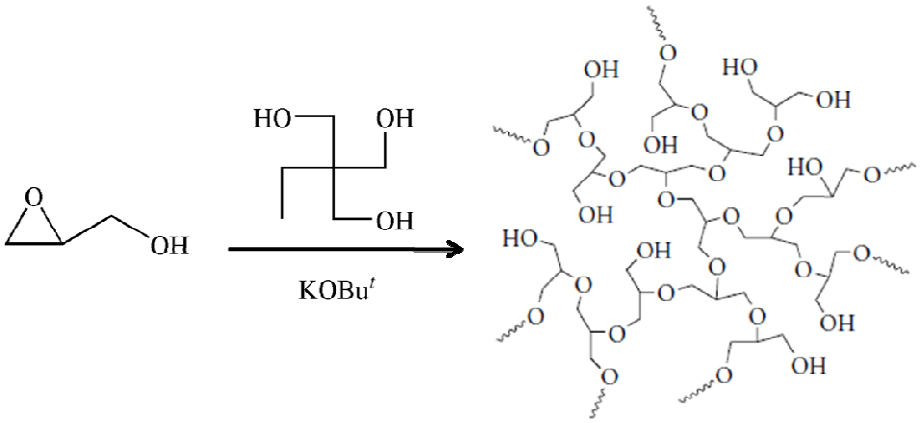

Fig. 5 A schematic illustration of HPG constructed by the SCROP of glycidol monomers. Reproduced from ref. 71. Copyright 1999 American Chemical Society.

Other synthesis methodologies: Biocompatible or biodegradable HBPs can also be synthesized *via* proton-transfer polymerization (PTP).[80-83] As an example, Fréchet and coworkers have described a synthesis of hyperbranched poly(hydroxyether) (HPHE) by means of PTP from a latent AB_2-type monomer featured two epoxide moieties and one hydroxy group.[84] Moreover, recently there is a growing tendency in academia to construct biocompatible or biodegradable HBPs through hybrid polymerization, in which two or more types of polymerization occur simultaneously. Glycidyl methacrylate (GMA) is a commercially available monomer bearing two different types of reactive groups: a vinyl group and an epoxy group.[85-94] Therefore, GMA is a useful hybrid monomer for synthesis of HBPs. Zhu, Yan and coworkers recently developed a hybrid polymerization of SCVP with SCROP using GMA and oligo(ethylene glycol)s as monomers and potassium hydride (KH) as a catalyst (Fig. 6).[95] The resultant hyperbranched poly(ether-ester) (HPEE) has excellent biocompatibility and biodegradability, and can be widely used as a promising carrier for therapeutic applications.

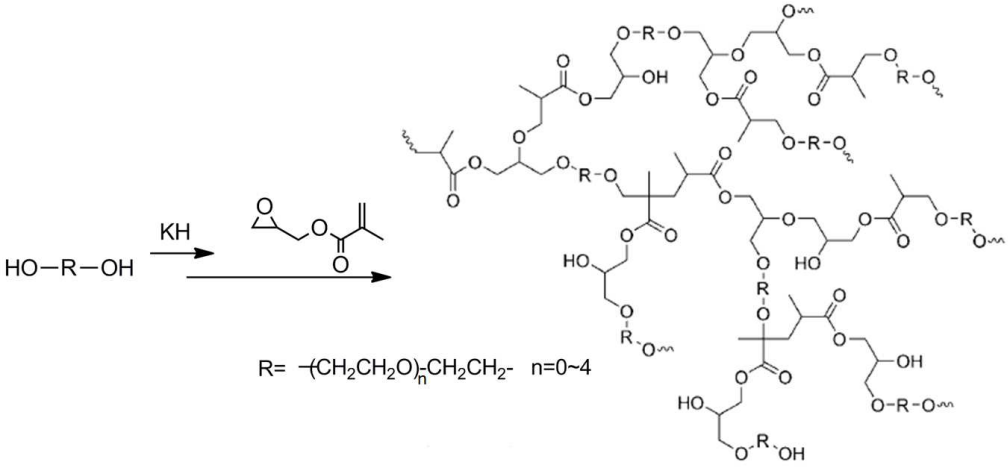

Fig. 6 A schematic illustration of the simultaneous vinyl polymerization and ring-opening

polymerization of GMA to synthesize biocompatible and biodegradable hyperbranched poly(ether-ester). Reproduced from ref. 95. Copyright 2009 Wiley-VCH.

In addition, biocompatible or biodegradable HBPs can be prepared by introducing biocompatible, biodegradable and/or bio-responsive groups into polymer backbones. These HBPs, such as hyperbranched polyketals, polyacetals, polyorthoesters, polyanhydrides, polyurethanes, and disulfide-containing polymers, can undergo degradation to various extents *in vitro* and/or *in vivo* through hydrolysis, enzymatic degradation, pH changes and/or redox reactions.[96-100] The existence of multiple reactive functionalities in the HBPs along with their defined biodegradation profiles, water solubility, and biocompatibility are critical for developing them as therapeutic devices. For example, in order to improve biodegradability of the HBPs prepared by SGP, SCVP or SCROP, various degradable linkages (*e.g.* ester linkage, amido linkage, oxime linkage, acylhydrazone and disulfide) are commonly introduced into monomers to construct biodegradable HBPs. Generally speaking, it is very difficult to prepare biodegradable HPG *via* conventional SCROP method.[11,29,101,102] Interestingly, Zhu and coworkers reported an oxyanionic initiating hybrid polymerization of glycerol and GMA to introduce lots of ester linkages into the HPG backbone for obtaining an excellent biodegradability.[103] Kizhakkedathu and coworkers also incorporated ketal groups into the backbone of hyperbranched polyether to tune its biodegradability (Fig. 7a).[97] A range of poly(ketal hydroxyether)s (PKHEs) were prepared by anionic SCROP of structurally different ketal monomers bearing cyclic and/or acyclic groups. Owing to the differences in ketal group structures, the pH-dependent degradability of PKHEs could be well-controlled at mild acidic pH, with the hydrolysis half-lives ranging from a few hundred days (Fig. 7b).

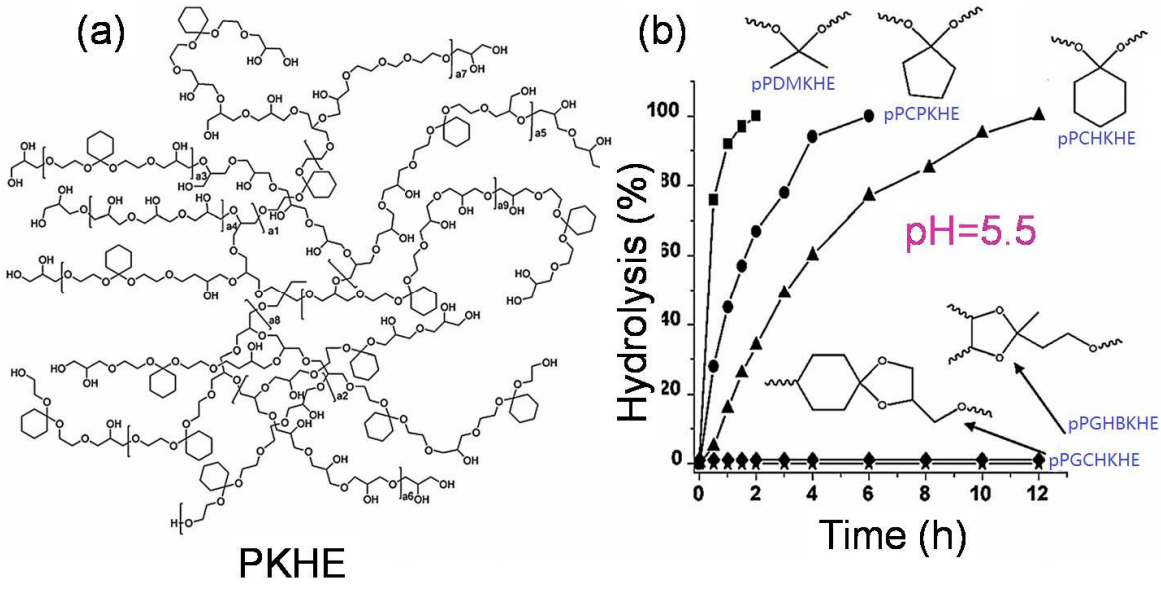

Fig. 7 Schematic structures of hyperbranched PKHEs and comparison of hydrolysis kinetics plots of different PKHEs at pH 5.5. Reproduced from ref. 104. Copyright 2012 American Chemical Society.

As discussed above, biocompatible or biodegradable HBPs are typically constructed by means of different polymerization techniques. Table 1 summarizes some typical examples of biocompatible or biodegradable HBPs and their synthesis methodologies.

Table 1 Typical examples of biocompatible or biodegradable HBPs and their synthesis methodologies

HBPs	Examples	Biocompatible(-)/ biodegradable(+)	Synthesis methodology	References
Hyperbranched polyether	HPG	-	SCROP	11,29,101-103
	HBPO	-	SCROP	9,27,71-76,105
Hyperbranched polyester	Boltorn H_x	±	SGP	5,35,44-46
Hyperbranched polyphosphate	HPHEEP	±	SCROP	9,10,77-79
Hyperbranched polysaccharide	HPS	±	SGP	10,56,106,107
Hyperbranched polypeptide	HPL	±	SGP	47,48,108,109
Hyperbranched polyamide	HPAMAM	±	SGP	10,5,35,57,110
	HPHE	-	PTP	5,35,80-84
Others	HPEE	±	SCVP-SCROP	5,35,85-95
	PKHE	±	SCROP	10,96-104

3.2 Modification of biocompatible or biodegradable HBPs

The properties of polymer are often affected by the functional chain-end groups and the nature of backbone. As mentioned above, biocompatible or biodegradable HBPs are characterized by a high density of functional groups in combination with three-dimensional dendritic architecture, which establishes a good foundation for their functionalization. It is particularly worth mentioning here that modification of biocompatible or biodegradable HBPs is essential to tailor their properties for specialized purposes, such as improving solubility, tuning biocompatibility/biodegradability, as well as obtaining stimuli-responsive behaviors. Benefiting from the highly branched architecture and the large number of terminal functional groups of these HBPs, at least three modification manners have been developed, such as terminal modification, backbone modification, and hybrid modification (Fig. 8).

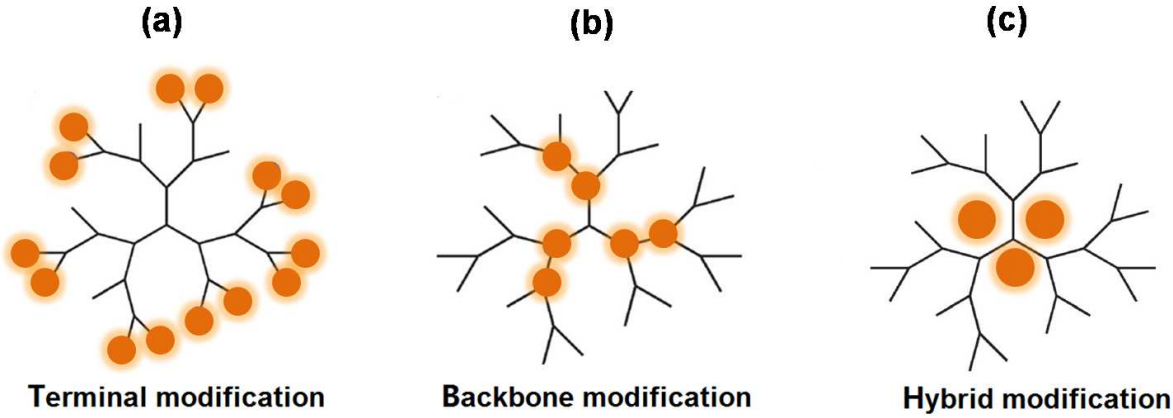

Fig. 8 Three types of modification of biocompatible or biodegradable HBPs including terminal modification, backbone modification and hybrid modification.

Terminal modification: An apparent characteristic of these HBPs is that they hold abundant functional groups in the periphery, which are easy to be chemically modified *via* multiple derivatization reactions. The terminal groups commonly include carboxyl, hydroxyl, and amine, through which a lot of biocompatible/biodegradable and functional components can be introduced onto the periphery of biocompatible or biodegradable HBPs, such as poly(ethylene glycol) (PEG), poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL), stimuli-responsive segments and other functional components.[111-115] For example, Sideratou and coworkers introduced a number of biocompatible PEG arms onto the hydrophobic hyperbranched polyester Boltorn® H_{40} to tailor its hydrophilicity and self-assembly.[116] Paleos and coworkers grafted folated PEG arms onto HPG to form unimolecular micelles as an excellent drug carrier with a targeting ability.[117] The terminal modification by PEG chains, in addition to their well-established function as protective coating, enhanced the encapsulation efficiency and controlled the release of drugs. Furthermore, terminal modification can also offer stimuli-responsive behaviors to biocompatible or biodegradable HBPs. Recently, Ji and coworkers have modified the biocompatible and biodegradable HPHEEP with a photo-responsive segment (Fig. 9), hydrophobic 2-diazo-1,2-naphthoquinone-5-sulfonyl chloride (DNQ).[118] The resultant terminal-modified HPHEEP can self-assemble into micelles in water. The *in vitro* cytotoxicity assay shows that the micelles have excellent biocompatibility. The photochemical reaction of DNQ moieties under UV irradiation results in destabilization of the micelles to realize triggered drug release.

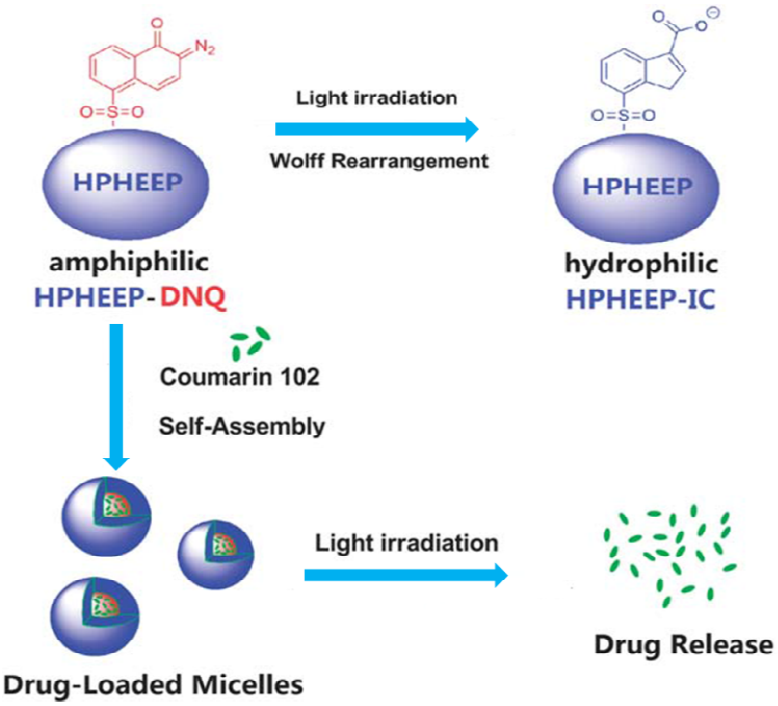

Fig. 9 Photo-responsive behavior of HPHEEP-DNQ and schematic illustration of the self-assembly and light-triggered drug release behavior of HPHEEP-DNQ micelles. Reproduced from ref. 118. Copyright 2011 Royal Society of Chemistry.

Backbone modification: The backbone modification focuses on changing the innate properties of polymer backbone by choosing appropriate functional monomers.[119,120] Different functional groups, including acylhydrazone, ketals, acetals, and disulfide, can undergo cleavage to various extents under the condition of hydrolysis, enzymatic degradation, pH change, or redox reaction.[96-100,103,104] Therefore, increasing functional groups have been widely introduced into the monomers to incorporate functionalities into the backbone of biocompatible or biodegradable HBPs. As an example, Zhu and coworkers prepared a novel, pH-triggered, backbone-degradable, hyperbranched polyacylhydrazone using an "A_2 + B_3" approach by introducing acylhydrazone bonds into the monomers (Fig. 10).[121] The resultant acylhydrazone-modified HBP could self-assemble into polymeric micelles in an aqueous solution that result from its amphiphilicity. *In vitro* evaluations revealed that the micelles had excellent biocompatibility. Importantly, the micelles remained stable at physiological pH 7.4, while readily biodegraded into small molecules at endosomal pH range of 5~6. These backbone-modified HBPs could be used to construct a promising intelligent therapeutic delivery system due to their excellent biocompatibility, biodegradability, and stimuli-responsive behaviors.

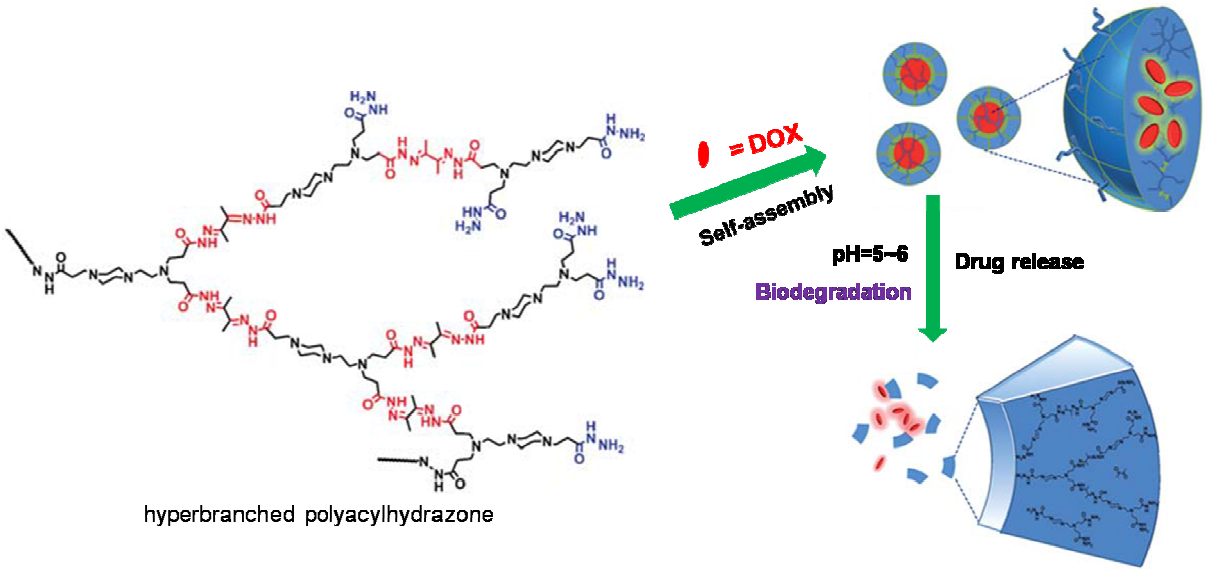

Fig. 10 A schematic illustration for self-assembly of hyperbranched polyacylhydrazone and subsequent drug delivery for efficient, pH-triggered, intracellular release of doxorubicin (DOX). Reproduced from ref. 121. Copyright 2011 Royal Society of Chemistry.

Hybrid modification: Hybrid modification refers specifically to introducing exterior components (*e.g.* metal nanoparticles, carbon nanotubes, and quantum dots) into biocompatible or biodegradable HBPs.[122-127] Biocompatible or biodegradable HBPs with specialized properties can be developed through weak interactions (*e.g.* complexation, electrostatic interaction, and hydrogen bonding) or covalent conjugation with exterior components. This modification is particularly highlighted in the biomedical fields of diagnosis and therapy. As an example, a double-hydrophilic multiarm HBPs with a HPAMAM core and many PEG arms connected by pH-sensitive acylhydrazone bonds was successfully prepared by Zhu and coworkers.[128] Due to the cationic dendritic core and PEGylation shell, CdS quantum dots with high stability were easily synthesized and composited inside the nanocavity of the HBP nanoreactor. The acylhydrazone linkages were readily cleaved under acidic conditions. These pH-responsive CdS/HPAMAM-*star*-PEG nanocomposites could be used as a novel fluorescent diagnosis in acidic lysosomes. Kono and coworkers recently reported a smart therapy platform based on a biocompatible and biodegradable PAMAM-hybridized gold nanorod (Fig. 11).[129] PEG-DOX-PAMAM-AuNR particles were constructed through covalent conjugation of PEG-attached PAMAM onto the surface of a mercaptohexadecanoic acid-functionalized gold nanorod (MHA-AuNR). The anti-cancer drug DOX was conjugated onto the PAMAM layer by use of hydrazone linkage. *In vitro* evaluations demonstrated that these particles had excellent biocompatibility and exhibited high cancer treatment efficiency using the combined photothermal therapy and chemotherapy.

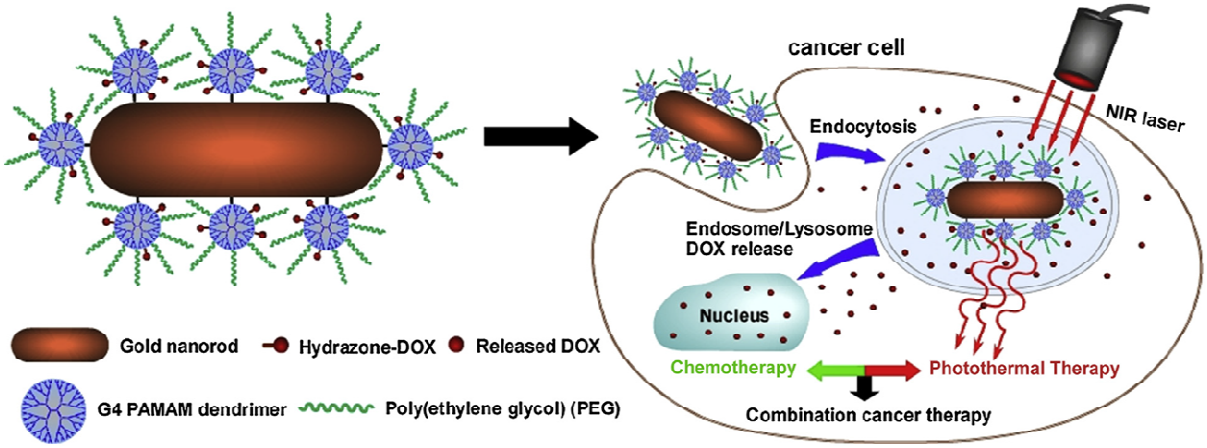

Fig. 11 A schematic illustration of PEG-DOX-PAMAM-AuNR particles for combined photothermal chemotherapy. Reproduced from ref. 129. Copyright 2014 Elsevier.

4. Therapeutic applications of biocompatible or biodegradable HBPs

Benefiting from the unique topological structures and controllable multi-functionality, biocompatible or biodegradable HBPs and their assemblies have exhibited great potential for therapeutic applications in three areas: (1) diagnostic applications, (2) therapeutic delivery, and (3) theranostic applications.

4.1 Diagnostic applications

Diagnosing is an emerging research field aiming at extending or developing novel methods to image specific molecular pathways *in vitro* and/or *in vivo*, particularly those that play important roles in disease processes.[130] During the past few decades, a wide range of diagnostic agents have been exploited in order to increase the sensitivity, selectivity and stability of diagnosis.[131-133] Compared with small molecular agents, polymer-based diagnostic agents are attracting a steady and growing interest in diagnostic applications due to their enhanced stability, reduced cytotoxicity, prolonged plasma half-lives, and improved targeting ability. Especially, diagnostic agents based on biocompatible or biodegradable HBPs have exhibited unique advantages in the diagnostic applications owing to their highly branched architectures, excellent biocompatibility/biodegradability, and versatile functionalities. To date, the combination of biocompatible or biodegradable HBPs and various diagnostic agents has been used in different varieties of diagnostic modalities including fluorescence diagnosis, magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and ultrasound diagnosis.

The unique topological structures, abundant functional groups, excellent biocompatibility and biodegradability of biocompatible or biodegradable HBPs enable various fluorescent probes to

be encapsulated or covalently conjugated for fluorescence diagnosis.[134-143] Recently, Zhou, Zhu and coworkers modified biocompatible HBPO-*star*-PEG with aptamer as a targeting ligand and with carboxyfluorescein as fluorescent probe respectively, and then co-assembled them into nanoparticles (Fig. 12).[144] *In vitro* results demonstrated that the nanoparticles had low cytotoxicity and excellent biocompatibility against MCF-7 cells. These functional nanoparticles exhibited excellent cancer imaging efficiency and cancer-specific targeting capability.

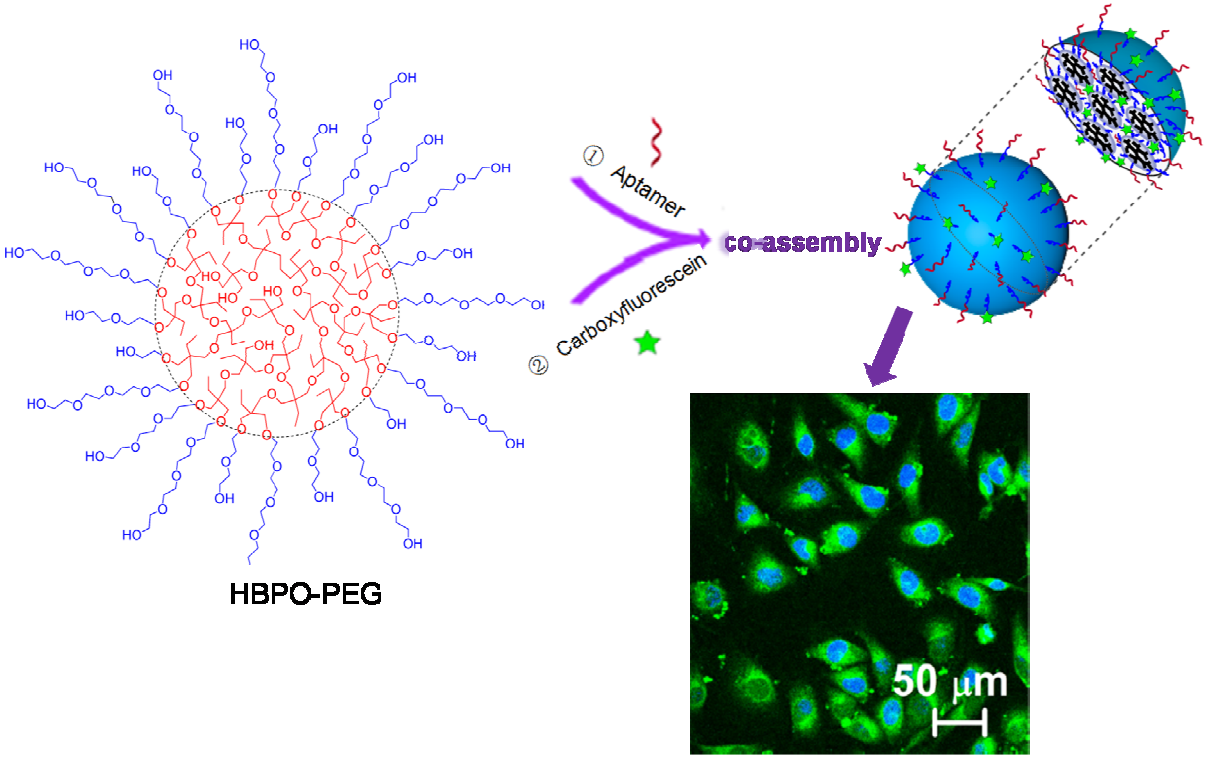

Fig. 12 A schematic illustration of co-assembly and cancer fluorescence imaging of the functional nanoparticles made from aptamer-functionalized and fluorescent probe-functionalized HBPO-PEG. Reproduced from ref. 144. Copyright 2014 American Chemical Society.

Recently, PET diagnosis has become increasingly popular in both preclinical and clinical settings as it offers excellent tissue penetration, higher detection efficiency, non-invasiveness, and superb quantitative accuracy.[145-147] To prepare a radioactive diagnostic agent based on biocompatible or biodegradable HBPs, most of radioisotopes are bound by coordination to these HBPs with good stability and long circulation time. Häfeli and coworkers modified biocompatible HPG with hexadentate ligand NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), and then ^{68}Ga-radiolabeling was performed by coordinating radioactive gallium (Fig. 13).[148] The resultant radiopharmaceutical in kit form was stable and non-toxic under physiological conditions. A pharmacokinetic biodistribution study demonstrated that its biological half-life (50.7 h) in blood was longer than that of the currently used radiolabeled red

blood cells (29 h). Therefore, the ^{68}Ga-HPG radiopharmaceutical had the potential to be a blood pool diagnostic agent.

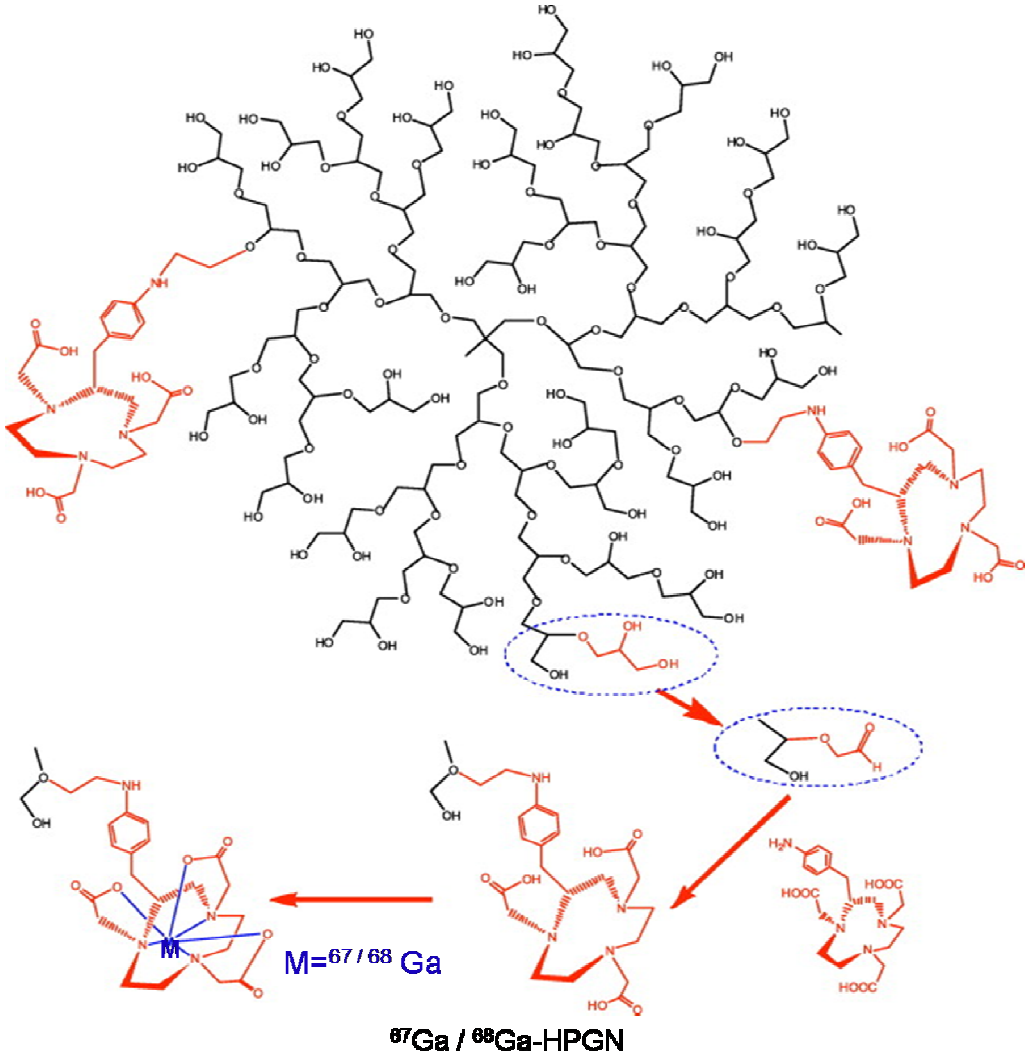

Fig. 13 Synthesis and radiolabelling scheme for Ga-HPG derivatization. Reproduced from ref. 148. Copyright 2012 Elsevier.

One of the major issues of current diagnosis is that there is no single diagnostic modality that possesses high resolution, high sensitivity and high throughput of data access. A method to overcome these problems is to develop multimodal devices which combine the advantages of numerous diagnostic modalities into a single platform.[149-152] Biocompatible or biodegradable HBPs have a distinct advantage in this regard, due to their high end-group functionality, which allows for the attachment of an array of diagnostic ligands. In particular, their excellent biocompatibility and biodegradability have the capability for reducing toxicity and prolonging circulation time of the diagnostic agents. A trimodal long-circulating diagnosing agent labeled with radioactive, magnetic resonance, and fluorescence markers is able to combine the high sensitivity of SPECT with the high resolution of MRI over hours or days. The fluorescence

marker helps to confirm the *in vivo* diagnosing information at the microscopic level, in the context of the tumor microenvironment. To obtain such trimodal long-circulating diagnostic agent for SPECT, MRI, and fluorescent diagnosis, Häfeli and coworkers developed a biocompatible HPG that was functionalized with a suitable ligand for ^{111}In radiolabelling and Gd coordination, and additionally tagged with a fluorescent dye (Fig. 14a).[153] They found that *in vivo* MRI of the Gd-labeled HPG could provide physiologically relevant data regarding the vascular function, whilst the ^{111}In-labeling was able to quantitatively analyze the probe's biodistribution over time. The micro-regional location of the probe within the tumor microenvironment, including how long the probe stayed in intravascular, could be evaluated at the microscopic level using the HPG labeled with the fluorescent dye imaged using a fluorescence microscope (Fig. 14b). HPG derivatized with radioactivity, gadolinium, and fluorescence possesses great potential in preclinical investigations to provide highly specific and quantitative data with respect to the physiological function of healthy and leaky blood vessels.

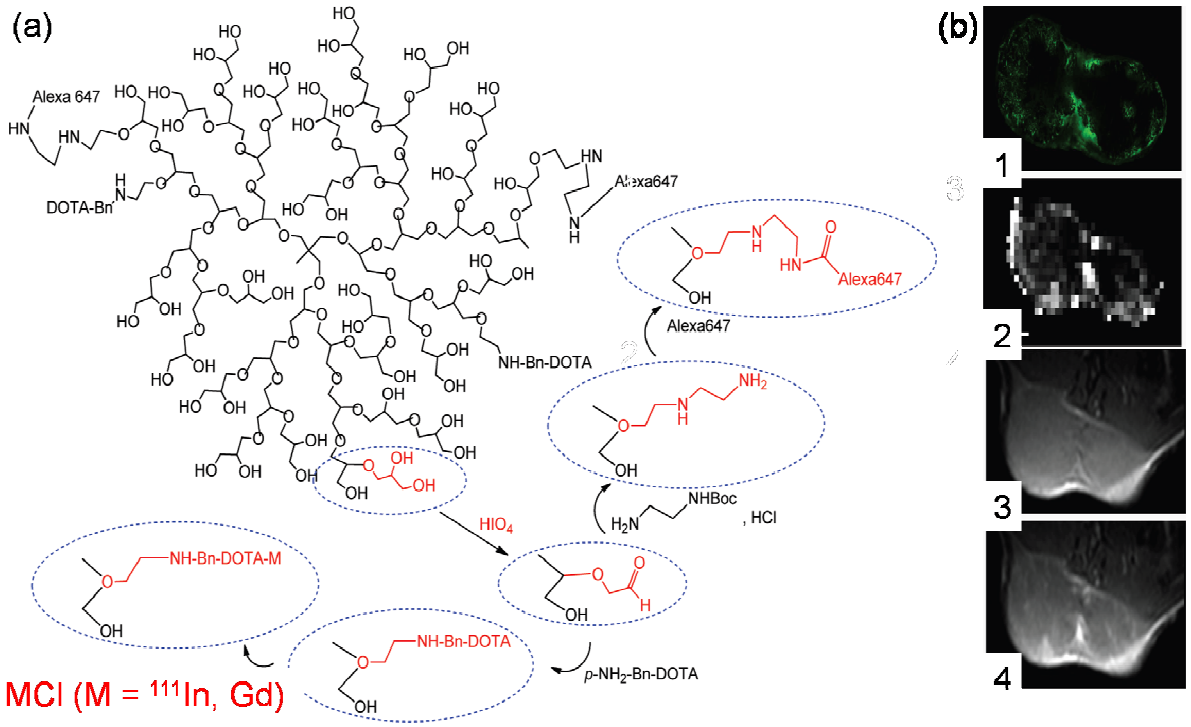

Fig. 14 (a) A schematic illustration of HPG derivatization. (b) (1) Image of HPG derivative fluorescence of a tumor cryosection. (2) HPG derivative concentration from the calibrated change in the R1 relaxation rate (ranging from 0 to 1 s^{-1}) of the same slice and orientation *in vivo*. Corresponding T_1-weighted RARE MR images are shown (3) prior to and (4) 40 min post-injection of 600 mg/kg of the HPG derivative. Scale bar indicates 1 mm. Reproduced from ref. 153. Copyright 2012 American Chemical Society.

4.2 Therapeutic delivery

Recent developments in biotechnology and biomaterial science have seen the growing use of novel small molecular and macromolecular therapeutic agents, including small molecular drugs, peptides, proteins and genes, for treatment of a variety of diseases. However, their use is partly limited by their rapid destruction in both digestive and circulatory system, resulting in the easy removal by various enzymes digestion and renal excretion. On the other hand, their transport across biological barriers is poor because of their poor diffusivity and lower partition coefficients. Therefore, the success of these therapeutic agents for treatment greatly depends on development of technologies to improve and control delivery of these agents. Among the numerous classes of materials employed for this purpose, biocompatible or biodegradable HBPs have attracted an increasing attention owing to their unique topological structures, abundant functional groups, low toxicity, non-immunogenicity, as well as easy degradation for controlled release of therapeutic agents. This section provides an overview of therapeutic delivery systems based on biocompatible or biodegradable HBPs for use in drug delivery, protein delivery, and gene transfection.

Drug delivery: An ideal drug carrier is required to offer excellent biocompatibility and biodegradability, form a stable drug complex or conjugate, transport the drug to its target site specifically, and then efficiently release the drug in a controlled manner without disturbing its pharmacological properties. In recent years, numerous biocompatible or biodegradable HBPs, including HPG, HBPO, H_{40} and HPHEEP, and their assemblies have been widely exploited as promising drug delivery vehicles.[154-164] For example, Yan and coworkers have reported a biocompatible and biodegradable, HPHEEP-based, phospholipid-mimicking material.[77-79] Through SCROP of hydroxyl functionalized cyclic phosphates and subsequent terminal modification with palmitoyl chloride, phospholipid-mimicking amphiphilic polymers with a polar HPHEEP headgroup and many hydrophobic aliphatic tails (HPHEEP-alkyls) have been constructed (Fig. 15). The amphiphilic HPHEEP-alkyls can self-assemble into nanomicelles in aqueous media, which have excellent biocompatibility and can be easily internalized by living cells. An *in vitro* investigation shows that the micelles loaded with a hydrophobic anticancer drug, chlorambucil, can inhibit the proliferation of MCF-7 breast cancer cells.

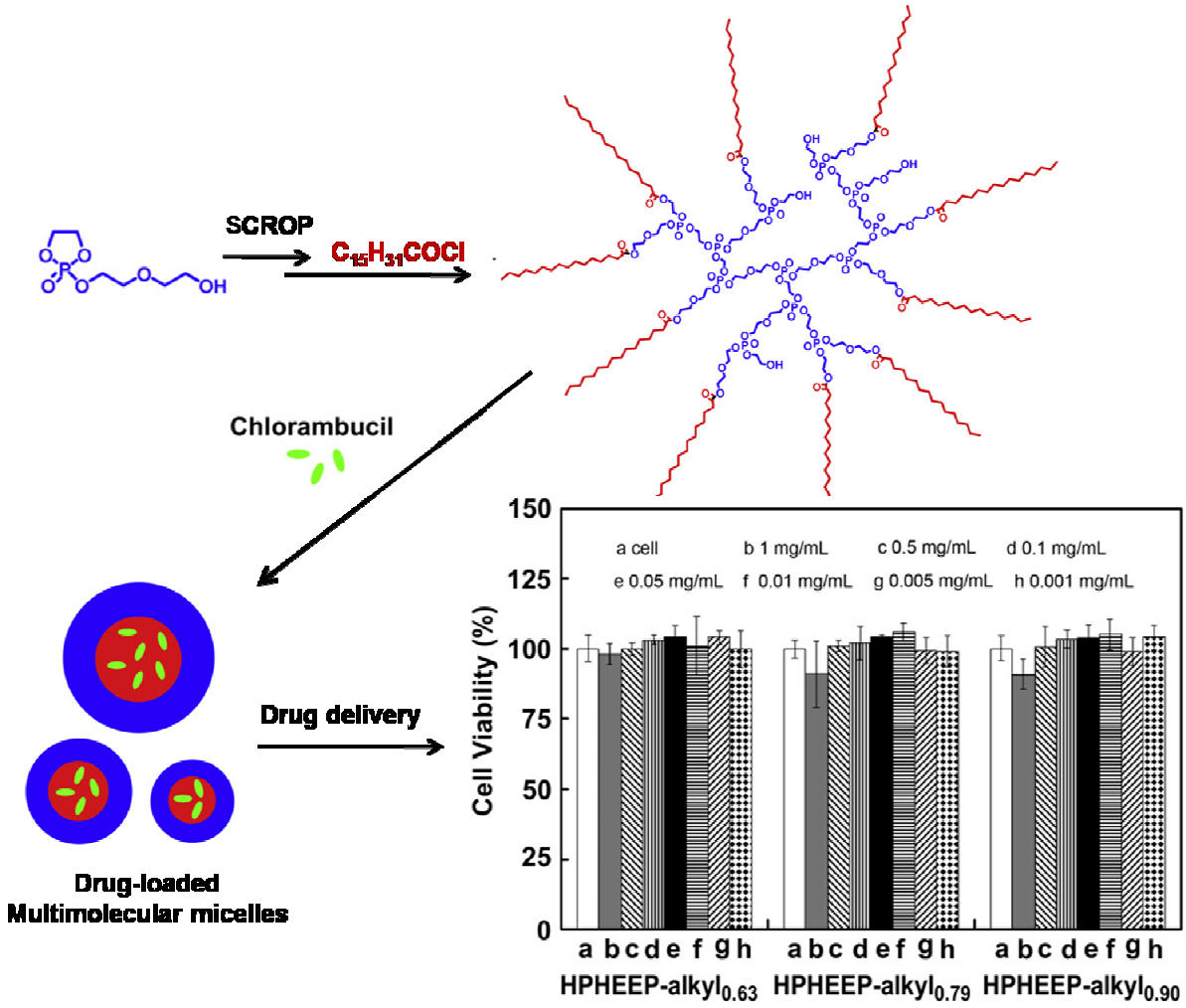

Fig. 15 A schematic illustration of synthesis and self-assembly of phospholipid mimicking HPHEEP-alkyls. Reproduced from ref. 79. Copyright 2010 Elsevier.

Cheng and coworkers developed a biocompatible and biodegradable hyperbranched copolymer, H_{40}-*star*-(PCL-*b*-PEG), with folate moieties as the targeting ligands.[165] Two antineoplastic drugs, 5-fluorouracil and paclitaxel, were encapsulated into the hydrophobic core of the core-shell nanostructure self-assembled from H_{40}-*star*-(PCL-*b*-PEG). The *in vitro* results showed that the drug-loaded multimolecular micelles exhibited excellent biocompatibility and enhanced cell inhibition against folate receptor overexpressing tumor cells. Kannan and coworkers covalently grafted ibuprofen onto the surface of biocompatible HPG with high drug payload.[166] *In vitro* evaluations illustrated that these HPG-ibuprofen conjugates were more stable than their polymer-drug complexes, which prolonged drug circulation and enhanced cellular uptake. Furthermore, biocompatible and biodegradable HBPs are frequently functionalized to respond to stimuli in the target environment for controlled drug release. For example, Gong and coworkers constructed a biocompatible and biodegradable hyperbranched

copolymer, H_{40}-*star*-(PLA-*b*-PEG), as a carrier for tumor-targeting drug delivery (Fig. 16a).[167] The anticancer drug DOX was covalently conjugated onto the hydrophobic PLA blocks by pH-sensitive hydrazone linkages. The rate of DOX release significantly increased in the acidic medium as result of the cleavage of hydrazone linkages (Fig. 16b).

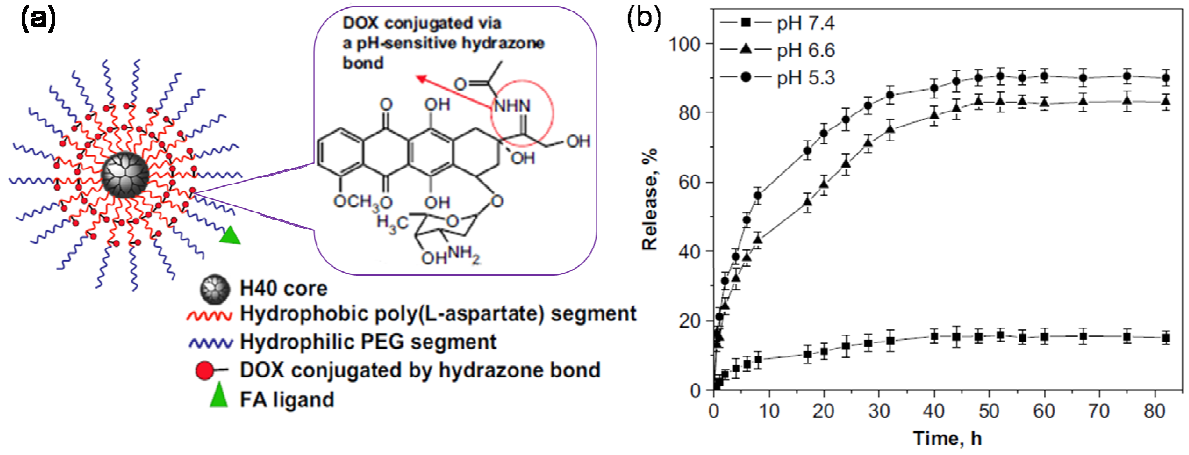

Fig. 16 (a) Schematic structure of the H_{40}-*star*-(PLA-DOX)-*b*-PEG-OH/FA copolymer. (b) Release profiles of DOX from the H_{40}-*star*-(PLA-DOX)-*b*-PEG-OH/FA micelles at 37 ^{o}C. Reproduced from ref. 167. Copyright 2009 Elsevier.

Protein delivery: Therapeutic proteins and peptides have exciting potential in disease therapy, but their clinical use is greatly limited by their fast destruction in both digestive and circulatory systems, leading to an easy removal through proteolytic digestion and renal excretion.[168,169] Therefore, there is an increasing need to develop protein delivery systems to improve protein stability, prolong circulation time, and reduce immunogenicity. In addition to the abovementioned delivery of diagnostic agents and small molecular drugs, biocompatible or biodegradable HBPs have been proved to be excellent delivery systems for proteins. Zhang and coworkers constructed the biocompatible HPG-*star*-PLA micelles for the encapsulation and delivery of bovine serum albumin (BSA).[170] The results revealed that the loading capacity and association efficiency of HPG-*star*-PLA were up to 23% and 86%, respectively, and the protein release was well-controlled by accurately adjusting the characteristics of HBPs. Significantly, the released BSA from the nanoparticles was well preserved in its original structure over a period of 4 days. In addition, the biocompatible or biodegradable HBPs can be chemically or physically conjugated with proteins under physiological conditions to generate supramolecular nanocomposites with suitable physicochemical and biopharmaceutical properties. Biocompatible HPG is an outstanding choice for preparing protein-HBPs conjugates due to its excellent solubility and stability, good biocompatibility and low toxicity. For instance, Frey and coworkers reported hyperbranched-*b*-linear (HPG-*b*-PEG) heterotelechelics consisting of a

linear PEG block, a HPG block and biotin for noncovalent bioconjugation with avidin.[168] HBPs exhibited a great potential for introduction of a variety of functional groups and could also be covalently conjugated with other proteins and peptides. As an example, Klok and coworkers attached BSA and lysozyme into the HPG and hyperbranched-linear polymer HPG-PEG with the squaric acid mediated coupling strategy, and subsequently used for protein delivery.[171]

Gene transfection: Gene therapy has gained a significant attention as a potential method to treat a wide variety of previously intractable diseases with genetic disorders. It is widely regarded to be superior to traditional chemotherapy.[172-174] Current research in this area is focused on designing effective carrier vectors that compact and protect oligonucleotides for gene therapy since genetic materials (*e.g.* oligonucleotides, DNA and RNA) are easily degraded by serum nucleases in the blood when injected intravenously.[175-178] Hyperbranched polyethylenimine (HPEI), often considered as the gold standard of gene transfection, is one of the most prominent examples of synthetic cationic HBPs capable of gene transfection.[179-184] Unfortunately, the fundamental problems associated with HPEI, including high cytotoxicity and non-biodegradability, hinder its clinical application in gene therapy. To obtain safe and effective gene delivery, various gene vectors based on biocompatible or biodegradable HBPs have been designed and synthesized. As an example, hyperbranched poly(amidoamines) (HPAMAMs) have been demonstrated to be a versatile class of HBPs for gene delivery owning to their low toxicity, excellent biocompatibility/biodegradability. Recently, through SGP of *N*,*N*′-methylene bisacrylamide and 1-(2-aminoethyl)piperazine monomers, Zhu and coworkers prepared a series of cationic HPAMAMs with similar compositions and molecular weights but different DB (from 0.04 to 0.44) for gene delivery (Fig. 17a).[57] It was found that the DNA condensation capability of HPAMAM could be readily adjusted by only altering the branched architecture of polycations (Fig. 17b). With the increase of the DB, the cytotoxicity of HPAMAM was reduced, whereas the DNA condensation capability of HPAMAM was enhanced greatly, which could be attributed to the more compact structure and the increased amount of primary and tertiary amino groups. Consequently, the efficiency of gene transfection was improved by more than three orders of magnitude.

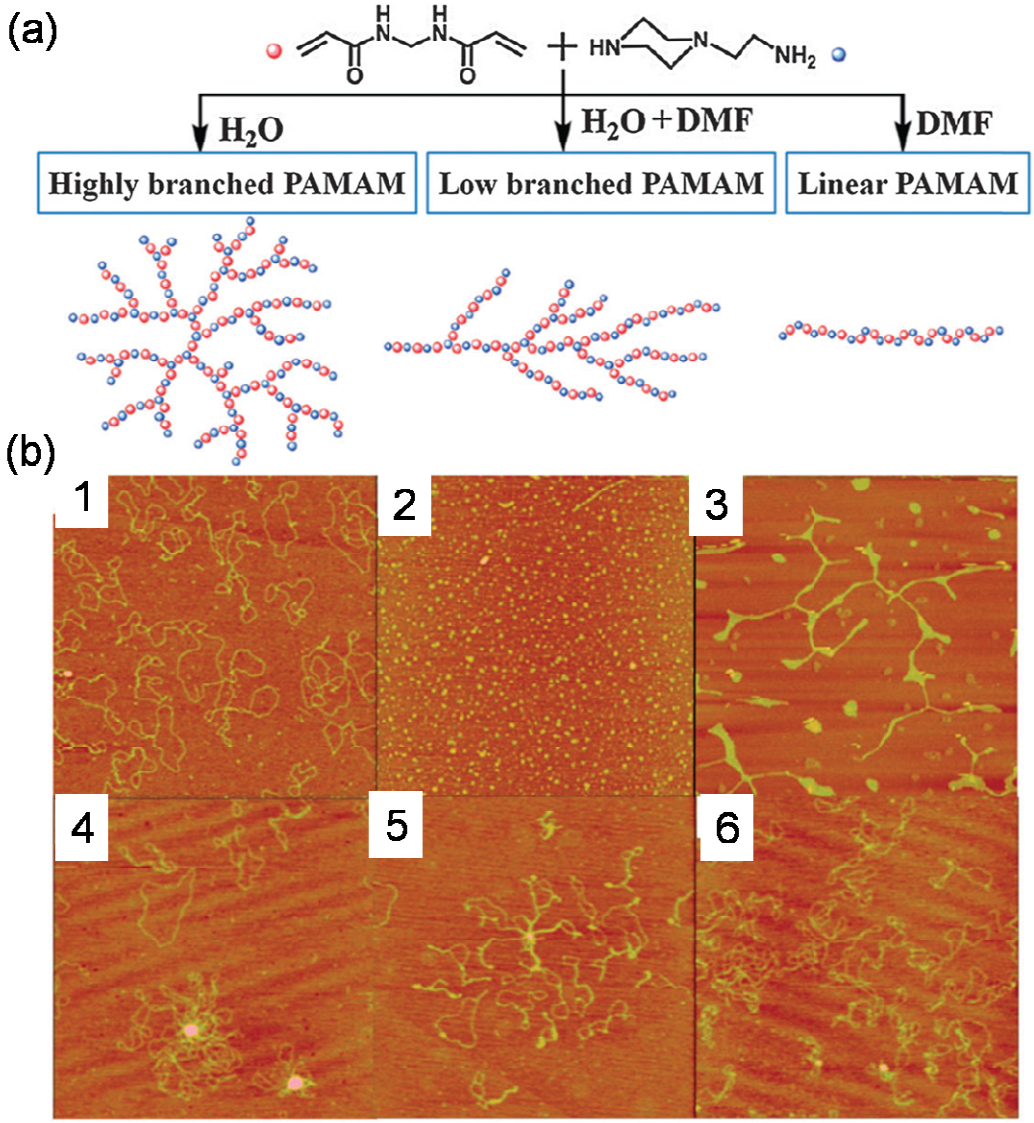

Fig. 17 (a) Synthesis routes of different branched PAMAMs. Highly branched PAMAM was obtained in pure water, low branched PAMAM was obtained in a binary solvent mixture of water and DMF and linear PAMAM was obtained in pure DMF. (b) AFM images of DNA condensation by various branched PAMAMs. DNA binding by polymers at N/P = 2. Each image represents a 2×2 μm scan. (1) Pure plasmid DNA in Hepes buffer. (2-6) DNA binding by various PAMAMs with a degree of branching of 0.44, 0.31, 0.21, 0.11, and 0.04, respectively. Reproduced from ref. 57. Copyright 2010 American Chemical Society.

Furthermore, biocompatible HPGs were also chosen to construct safe and effective gene vectors. Recently, Zhu and coworkers developed a facile supramolecular approach for the preparation of charge-tunable dendritic polycations *via* host-guest interactions between primary or tertiary amine-modified β-CD derivatives (per-6-amino-β-CD with seven primary amines and per-6-dimethylaminoethyl-β-CD with seven tertiary amines) and an adamantane (AD)-modified

biocompatible HPG (Fig. 18a).[185] Through tuning of the molar ratios of the AD-modified HPG to the cationic β-CD derivatives, the surface charge of the resultant polycations could be optimized, leading to the controlled plasmid DNA-condensing ability and enhanced *in vitro* transfection efficiency (Fig. 18b). *In vitro* transfection showed that these polycations had the comparable transfection efficiency but lower cytotoxicity in contrast to 25 kDa HPEI.

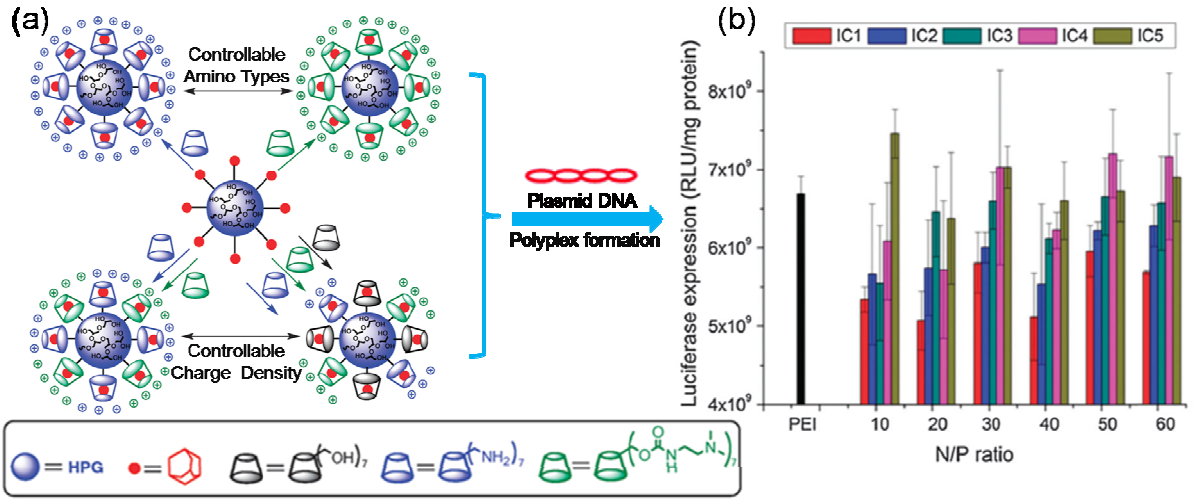

Fig. 18 (a) Preparation of charge-tunable supramolecular polycations based on HPG *via* host-guest interactions. (b) Luciferase expression of these supramolecular poly(ether-amine)s in COS-7 cells. Reproduced from ref. 185. Copyright 2011 Royal Society of Chemistry.

4.3 Theranostic application

Diagnosis-guided therapy has been recently introduced as a new paradigm of treatment of diseases including cancer, and has shown promise in the optimization of therapeutic efficiency. Diagnosis is of great significance in therapy for at least three reasons: firstly, diagnosis can provide useful information such as size and location of the tumor, as well as the relationship of the tumor with surrounding tissues; secondly, diagnosis can offer an optimal time window for therapy when therapeutic agents reach a peak level in the targeted lesion; lastly, diagnosis is important to monitor the proceeding of diseases after therapy.[186-191] Therefore, designing and engineering a theranostic system, which integrates diagnosis and therapy into a single platform for diagnosis-guided therapy, is eagerly anticipated. Due to their unique topological structures, abundant functional groups, prominent biocompatibility/biodegradability, low toxicity, and low/non-immunogenicity, biocompatible or biodegradable HBPs and their derivatives are widely regarded as promising biomaterials for theranostic applications through encapsulation or conjugation with diagnostic agents (*e.g.* fluorescence probes, gadolinium and radioisotopes) and therapeutic agents (*e.g.* small molecular drugs, genetic segments, proteins and peptides). For example, Haag and coworkers prepared a multiarm biocompatible HPG-*star*-PEG with a HPG

core and many PEG arms (Fig. 19a).[192] The near infrared (NIR) fluorescence probe, indotricarbocyanine, and the anticancer drug, DOX, were encapsulated into the interior cavities of HPG-*star*-PEG. At 6 h post intravenous injection of the probe-loaded HPG-*star*-PEG, a preferential uptake with a maximum of tumor-to-normal tissue contrast was observed for tumor-bearing mice. Compared with the results using the fluorescence probe alone, the tissue fluorescence of HPG-*star*-PEG was improved greatly (Fig. 19b), suggesting the improved biodistribution by HPG-*star*-PEG nanocarriers.

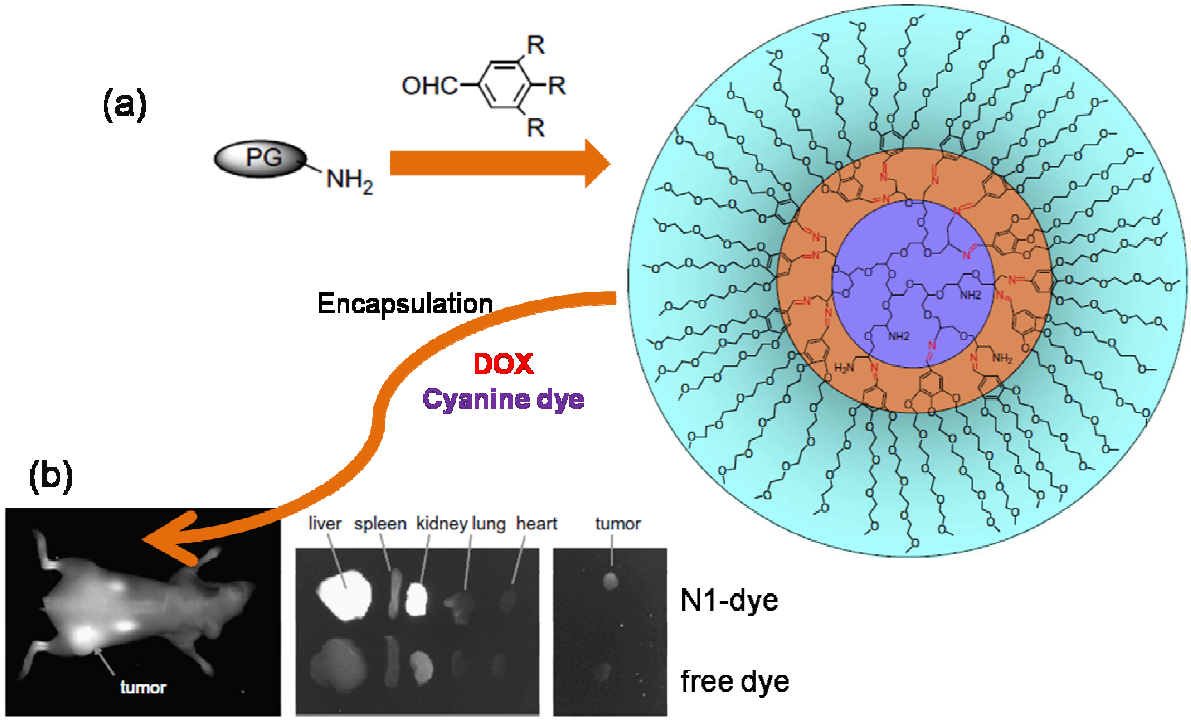

Fig. 19 (a) Synthesis of multiarm HPG-*star*-PEG. (b) Fluorescence images of a tumor-bearing mouse (F9 teratocarcinoma) at 6 h after injection of nanocarrier N1/dye (1:5) at a dye dose of 2.5 μmol/kg, and organ preparations of animals injected with free dye and nanocarrier N1/dye (6 h), laser excitation at 740 nm, image acquisition with CCD-camera above 780 nm. Reproduced from ref. 192. Copyright 2009 Elsevier.

Recently, Gong and coworkers developed a multifunctional unimolecular micelle as a nanocarrier for targeted cancer theranostics. The unimolecular micelle was self-assembled by a biocompatible and biodegradable hyperbranched copolymer, H_{40}-*star*-poly(*L*-glutamate-hydrazone-DOX)-*b*-PEG (H_{40}-*star*-P(LG-Hyd-DOX)-*b*-PEG) that was conjugated with *cyclo(Arg-Gly-Asp-D-Phe-Cys)* peptides (cRGD) for integrin $\alpha_v\beta_3$ targeting) and macrocyclic chelators NOTA for ^{64}Cu-labeling and PET imaging (referred to as H_{40}-DOX-cRGD) (Fig. 20).[193] As a model anticancer drug, DOX was conjugated onto the nanocarriers *via* a pH-sensitive hydrazone bond to realize pH-controlled release. *In vitro*

evaluations demonstrated that H_{40}-DOX-cRGD exhibited a much higher cellular uptake in U87-MG human glioblastoma cells thanks tothe integrin-mediated endocytosis than that of H_{40}-DOX without cRGD (Fig. 20b). In tumor-bearing mice, H_{40}-DOX-cRGD-^{64}Cu also offered a much higher level of tumor accumulation than H_{40}-DOX-^{64}Cu, as revealed by the non-invasive PET imaging (Fig. 20c), which was further testified by the biodistribution studies and *ex vivo* fluorescence imaging. All in all, these H40-based multifunctional unimolecular micelles possess tumor-targeting abilities, pH-controlled drug release, and PET diagnosing capabilities, suggesting a great potential in theranostic application.

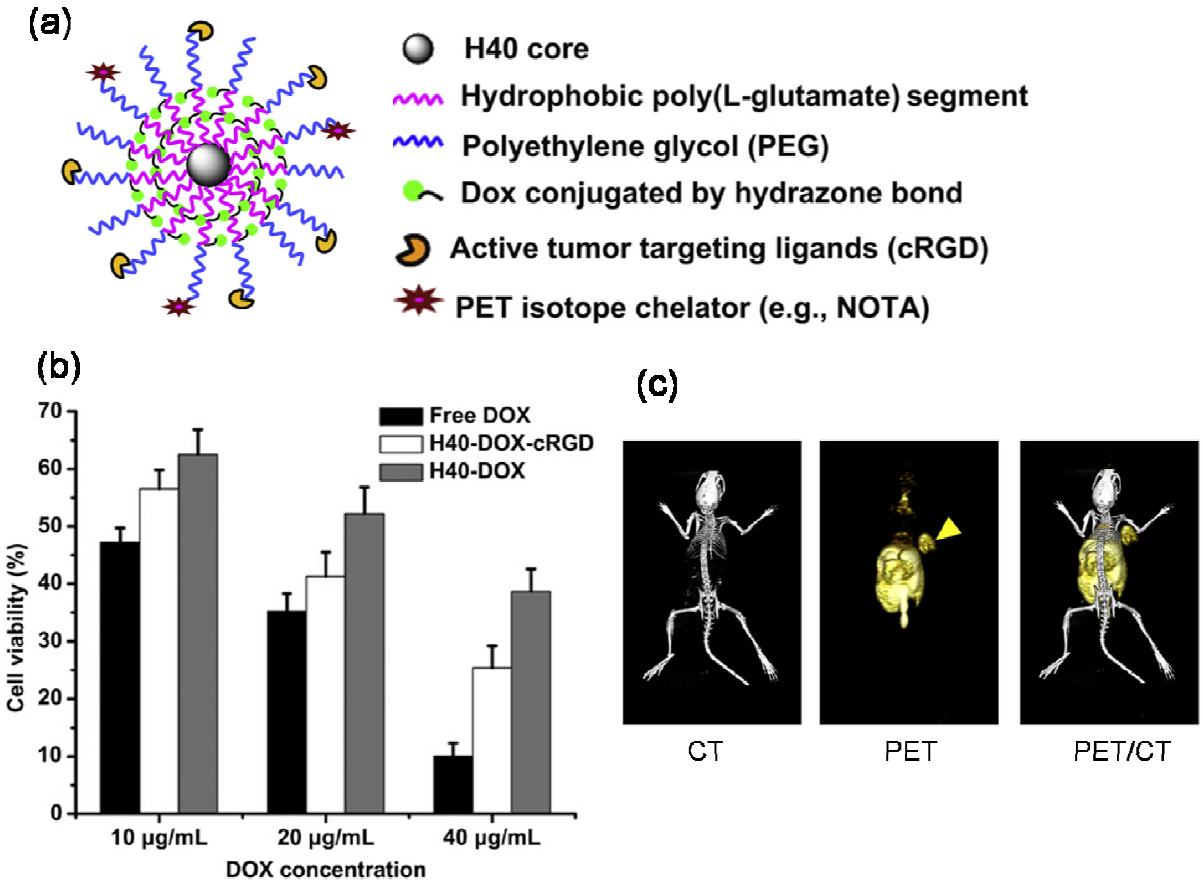

Fig. 20 (a) A schematic illustration of the multifunctional H_{40}-DOX-cRGD nanocarrier for tumor-targeted drug delivery and PET imaging; (b) cytotoxicity of free DOX, H_{40}-DOX, and H_{40}-DOX-cRGD towards U87-MG cells at various DOX concentrations; (c) representative PET/CT images of a U87-MG tumor-bearing mouse at 4 h post injection of H_{40}-DOX-cRGD-^{64}Cu. Reproduced from ref. 193. Copyright 2012 Elsevier.

5. Conclusions and perspectives

Recent years have witnessed significant progress in the field of biocompatible or biodegradable HBPs, an important subclass of hyperbranched macromolecules. A number of polymer synthesis methodologies, such as SGP, SCVP and SCROP, can be used to prepare biocompatible or

biodegradable HBPs. They can be modified and functionalized by terminal modification, backbone modification, or hybrid modification, achieving tailor-made properties for specialized purposes. Benefiting from their unique topological structures, abundant functional groups, low toxicity, non-immunogenicity, as well as easy degradation for controlled release of therapeutic agents, biocompatible or biodegradable HBPs and their assemblies have exhibited great potential for diagnostic, therapeutic delivery, and theranostic applications.

Nevertheless, we should recognize that the research of biocompatible or biodegradable HBPs, particularly their functionalization and bioapplication, is still in its infancy. Although a wide variety of biocompatible or biodegradable HBPs have been synthesized and investigated for the delivery of diagnostic (*e.g.* fluorescence probes, gadolinium and radioisotopes) and therapeutic agents (*e.g.* drugs, genetic segments, proteins and peptides), there is still no reported success of their use in the clinic. One of the major future challenges is to transfer the existing biocompatible or biodegradable HBPs to *in vivo* investigations and further to clinic applications.

The following directions and perspectives deserve an attention in future work: (1) new, controlled, cost-effective synthetic strategies need to be explored to develop the optimal structure of biocompatible or biodegradable HBPs for potential bioapplications. (2) Great offers continue to be required to better understand the structure-property relationship and therefore to better modify and tailor polymer properties to meet the future demands of bioapplications. (3) Promising translational opportunities of biocompatible or biodegradable HBPs should be explored through interdisciplinary collaborations between supramolecular chemistry, nanotechnology, biology and medicine.

Acknowledgements

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References

1 P. J. Flory, *J. Am. Chem. Soc.*, 1952, **74**, 2718-2723.
2 Y. H. Kim and O. W. Webster, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, 1988, **29**, 310-311.
3 Y. H. Kim and O. W. Webster, *J. Am. Chem. Soc.*, 1990, **112**, 4592-4593.
4 D. A. Tomalia and J. M. J. Fréchet, *J. Polym. Sci., Part A: Polym. Chem.*, 2002, **40**, 2719-2728.
5 C. Gao and D. Y. Yan, *Prog. Polym. Sci.*, 2004, **29**, 183-275.
6 A. Carlmark, C. Hawker, A. Hult and M. Malkoch, *Chem. Soc. Rev.*, 2009, **38**, 352-362.
7 B. I. Voit and A. Lederer, *Chem. Rev.*, 2009, **109**, 5924-5973.
8 S. Peleshanko and V. V. Tsukruk, *Prog. Polym. Sci.*, 2008, **33**, 523-580.
9 H. B. Jin, W. Huang, X. Y. Zhu, Y. F. Zhou and D. Y. Yan, *Chem. Soc. Rev.*, 2012, **41**, 5986-5997.
10 D. L. Wang, T. Zhao, X. Y. Zhu, D. Y. Yan and W. X. Wang, *Chem. Soc. Rev.*, 2015, DOI:

10.1039/C4CS00229F.
11 M. Calderón, M. A. Quadir, S. K. Sharma and R. Haag, *Adv. Mater.*, 2010, **22**, 190-218.
12 Q. Zhu, F. Qiu, B. S. Zhu and X. Y. Zhu, *RSC Adv.*, 2013, **3**, 2071-2083.
13 H. Zhang, L. Bre, T. Zhao, B. Newland, M. Da Costa and W. Wang, *J. Mater. Chem. B*, 2014, **2**, 4067-4071.
14 Y. Dong, W. U. Hassan, R. Kennedy, U. Greiser, A. Pandit, Y. Garcia and W. Wang, *Acta Biomaterialia*, 2014, **10**, 2076-2085.
15 R. Kennedy, W. Ul Hassan, A. Tochwin, T. Zhao, Y. Dong, Q. Wang, H. Tai and W. Wang, *Polym. Chem.*, 2014, **5**, 1838-1842.
16 H. Zhang, L. P. Bré, T. Zhao, Y. Zheng, B. Newland and W. Wang, *Biomaterials*, 2014, **35**, 711-719.
17 J. Nicolas, S. Mura, D. Brambilla, N. Mackiewicz and P. Couvreur, *Chem. Soc. Rev.*, 2013, **42**, 1147-1235.
18 I. Omeis, J. A. Neil, R. Murali and J. M. Abrahams, *Neurosurgery*, 2008, **63**, 1011-1021.
19 S. Gupta and S. P. Moulik, *J. Pharm. Sci.*, 2008, **97**, 22-45.
20 J. Nicolas, S. Mura, D. Brambilla, N. Mackiewicz and P. Couvreur, *Chem. Soc. Rev.*, 2013, **42**, 1147-1235.
21 G.-Y. Liu, C.-J. Chen and J. Ji, *Soft Matter*, 2012, **8**, 8811-8821.
22 C. Y. Ang, S. Y. Tan and Y. Zhao, *Org. Biomol. Chem.*, 2014, **12**, 4776-4806.
23 T. Zhao, H. Zhang, B. Newland, A. Aied, D. Zhou and W. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 6095-6100.
24 B. Newland, A. Aied, A. V. Pinoncely, Y. Zheng, T. Zhao, H. Zhang, R. Niemeier, E. Dowd, A. Pandit and W. Wang, *Nanoscale*, 2014, **6**, 7526-7533.
25 A. Aied, Y. Zheng, B. Newland and W. Wang, *Biomacromolecules*, 2014, **15**, 4520-4527.
26 Y. F. Zhou and D. Y. Yan, *Chem. Commun.*, 2009, 1172-1188.
27 Y. F. Zhou, W. Huang, J. Y. Liu, X. Y. Zhu and D. Y. Yan, *Adv. Mater.*, 2010, **22**, 4567-4590.
28 E. Žagar and M. Žigon, *Prog. Polym. Sci.*, 2011, **36**, 53-88.
29 D. Wilms, S.-E. Stiriba and H. Frey, *Acc. Chem. Res.*, 2010, **43**, 129-141.
30 X. Y. Zhu, Y. F. Zhou and D. Y. Yan, *J. Polym. Sci., Part B:Polym. Phys.*, 2011, **49**, 1277-1286.
31R. J. Dong, Y. F. Zhou and X. Y. Zhu, *Acc. Chem. Res.*, 2014, **47**, 2006-2016.
32 J. Khandare, M. Calderon, N. M. Dagia and R. Haag, *Chem. Soc. Rev.*, 2012, **41**, 2824-2848.
33 M. Irfan and M. Seiler, *Ind. Eng. Chem. Res.*, 2010, **49**, 1169-1196.
34 C. M. Paleos, D. Tsiourvas, Z. Sideratou and L.-A. Tziveleka, *Expert Opin. Drug Deliv.*, 2010, **7**, 1387-1398.
35 C. R. Yates and W. Hayes, *Eur. Polym. J.*, 2004, **40**, 1257-1281.
36 D. Astruc, E. Boisselier and C. Ornelas, *Chem. Rev.*, 2010, **110**, 1857-1959.
37 L. M. Bronstein and Z. B. Shifrina, *Chem. Rev.*, 2011, **111**, 5301-5344.
38 A. M. Caminade, A. Ouali, M. Keller and J. P. Majoral, *Chem. Soc. Rev.*, 2012, **41**, 4113-4125.
39 M. V. Walter and M. Malkoch, *Chem. Soc. Rev.*, 2012, **41**, 4593-4609.
40 Y. Segawa, T. Higashihara and M. Ueda, *Polym. Chem.*, 2013, **4**, 1746-1759.
41 T. Satoh, *Int. J. Polym. Sci.*, 2012, 816163-816168.
42 M. Jikei and M. A. Kakimoto, *Prog. Polym. Sci.*, 2001, **26**, 1233-1285.
43 L. J. Hobson and R. M. Harrison, *Curr. Opin. Solid State Mater. Sci.*,1997, **2**, 683-692.
44 E. Malmstroem and A. Hult, *Macromolecules*, 1996, **29**, 1222-1228.
45 E. Malmstroem, M. Johansson, and A. Hult, *Macromolecules*, 1995, **28**, 1698-1703.
46 H. Ihre, A. Hult and E. Söderlind, *J. Am. Chem. Soc.*, 1996, **118**, 6388-6395.
47 Z. Kadlecova, L. Baldi, D. Hacker, F. M. Wurm and H.-A. Klok, *Biomacromolecules*, 2012, **13**,

3127-3137.
48 M. Scholl, T. Q. Nguyen, B. Bruchmann and H.-A. Klok, *J. Polym. Sci., Part A: Polym. Chem.*, 2007, **45**, 5494-5508.
49 M. Jikei, S.-H. Chon, M.-a. Kakimoto, S. Kawauchi, T. Imase and J. Watanebe, *Macromolecules*, 1999, **32**, 2061-2064.
50 T. Emrick, H.-T. Chang and J. M. J. Fréchet, *Macromolecules*, 1999, **32**, 6380-6382.
51 D. Y. Yan and C. Gao, *Macromolecules*, 2000, **33**, 7693-7699.
52 C. Gao and D. Y. Yan, *Chem. Commun.*, 2001, 107-108.
53 P. Froehling and J. Brackman, *Macromol. Symp.*, 2000, **151**, 581-589.
54 R. A. T. M. van Benthem, N. Meijerink, E. Geladé, C. G. de Koster, D. Muscat, P. E. Froehling, P. H. M. Hendriks, C. J. A. A. Vermeulen and T. J. G. Zwartkruis, *Macromolecules*, 2001, **34**, 3559-3566.
55 T. Satoh and T. Kakuchi, *Macromol. Biosci.*, 2007, **7**, 999-1009.
56 M. S. Chen, J. L. Wu, L. Z. Zhou, C. Y. Jin, C. L. Tu, B. S. Zhu, F. Wu, Q. Zhu, X. Y. Zhu and D. Y. Yan, *Polym. Chem.*, 2011, **2**, 2674-2682.
57 R. B. Wang, L. Z. Zhou, Y. F. Zhou, G. L. Li, X. Y. Zhu, H. C. Gu, X. L. Jiang, H. Q. Li, J. L. Wu, L. He, X. Q. Guo, B. S. Zhu and D. Y. Yan, *Biomacromolecules*, 2010, **11**, 489-495.
58 J. M. J. Fréchet, I. Gitsov, R. B. Grubbs, C. J. Hawker, M. Henmi, M. Leduc, E. Sanford and K. Yui, *Polym. Mater. Sci. Eng.*, 1995, **73**, 271-272.
59 M. W. Weimer, J. M. Fréchet and I. Gitsov, *J. Polym. Sci., Part A: Polym. Chem.*, 1998, **36**, 955-970.
60 C. J. Hawker, J. M. J. Fréchet, R. B. Grubbs and J. Dao, *J. Am. Chem. Soc.*, 1995, **117**, 10763-10764.
61 P. F. W. Simon and A. H. E. Müller, *Macromol. Rapid Commun.*, 1997, **18**, 865-873.
62 P. F. W. Simon and A. H. E. Müller, *Macromolecules*, 2001, **34**, 6206-6213.
63 K. Sakamoto, T. Aimiya and M. Kira, *Chem. Lett.*, 1997, 1245-1246.
64 H. Liu and C.-E. Wilén, *Macromolecules*, 2001, **34**, 5067-5070.
65 V. Coessens, T. Pintauer and K. Matyjaszewski, *Prog. Polym. Sci.*, 2001, **26**, 337-377.
66 T. E. Patten and K. Matyjaszewski, *Adv. Mater.*, 1998, **10**, 901-915.
67 Y. Y. Zhuang, Q. Zhu, C. L. Tu, D. L. Wang, J. L. Wu, Y. M. Xia, G. S. Tong, L. He, B. S. Zhu, D. Y. Yan and X. Y. Zhu, *J. Mater. Chem.*, 2012, **22**, 23852.
68 Y. Y. Zhuang, Y. Su, Y. Peng, D. L. Wang, H. P. Deng, X. D. Xi, X. Y. Zhu and Y. F. Lu, *Biomacromolecules*, 2014, **15**, 1408-1418.
69 M. Suzuki, A. Ii and T. Saegusa, *Macromolecules*, 1992, **25**, 7071-7072.
70 M. Liu, N. Vladimirov and J. M. J. Fréchet, *Macromolecules*, 1999, **32**, 6881-6884.
71 A. Sunder, R. Hanselmann, H. Frey and R. Mülhaupt, *Macromolecules*, 1999, **32**, 4240-4246.
72 M. Bednarek, T. Biedron, J. Helinski, K. Kaluzynski, P. Kubisa and S. Penczek, *Macromol. Rapid Commun.*, 1999, **20**, 369-372.
73 H. Magnusson, E. Malmstroem and A. Hult, *Macromol. Rapid Commun.*, 1999, **20**, 453-457.
74 J. Hou, D. Y. Yan, X. Y. Zhu and Y. P. Fang, *Chem. J. Chinese U.*, 1999, 11, 1815-1816.
75 D. Y. Yan, J. Hou, X. Y. Zhu, J. J. Kosman and H.-S. Wu, *Macromol. Rapid Commun.*, 2000, **21**, 557-561.
76 D. Y. Yan, Y. F. Zhou and J. Hou, *Science*, 2004, **303**, 65-67.
77 J. Y. Liu, W. Huang, Y. F. Zhou and D. Y. Yan, *Macromolecules*, 2009, **42**, 4394-4399.
78 J. Y. Liu, W. Huang, Y. Pang, X. Y. Zhu, Y. F. Zhou and D. Y. Yan, *Biomaterials*, 2010, **31**, 5643-5651.
79 J. Y. Liu, Y. Pang, W. Huang, X. Y. Zhu, Y. F. Zhou and D. Y. Yan, *Biomaterials*, 2010, **31**, 1334-1341.
80 C. G. Gong and J. M. J. Fréchet, *Macromolecules*, 2000, **33**, 4997-4999.
81 J. Kadokawa, Y. Kaneko, S. Yamada, K. Ikuma, H. Tagaya and K. Chiba, *Macromol. Rapid Commun.*,

2000, **21**, 362-368.
82 J. K. Paulasaari and W. P. Weber, Macromolecules, 2000, **33**, 2005-2010.
83 Z. F. Jia, H. Chen, X. Y. Zhu and D. Y. Yan, *J. Am. Chem. Soc.*, 2006, **128**, 8144-8145.
84 H. T. Chang and J. M. J. Fréchet, *J. Am. Chem. Soc.*,1999,**121**, 2313-2314.
85 S. K. Rajaraman, W. A. Mowers and J. V. Crivello, *Macromolecules*, 1999, **32**, 36-47.
86 J. V. Crivello and S. Y. Song, *Chem. Mater.*, 2000, **12**, 3674-3680.
87 W. Huang, Y. F. Zhou and D. Y. Yan, *J. Polym. Sci. Polym. Chem. Ed.*, 2005, **43**, 2038-2047.
88 A. D. Asandei and G. Saha, *Polym. Prepr. Am. Chem. Soc. Div. Polym. Chem.*, 2004, **45**, 999 -1000.
89 L. Z. Kong and C. Y. Pan, *Macromol. Chem. Phys.*, 2007, **208**, 2686 –2697.
90 Y. Pang, Q. Zhu, J. Y. Liu, J. L. Wu, R. B. Wang, S. Y. Chen, X. Y. Zhu, D. Y. Yan, W. Huang and B. S. Zhu, *Biomacromolecules*, 2010, **11**, 575-582.
91 Y. Pang, J. Y. Liu, Y. Su, J. L. Wu, L. J. Zhu, X. Y. Zhu, D. Y. Yan and B. S. Zhu, *Polym. Chem.*, 2011, **2**, 1661-1670.
92 L. Chen, X. Y. Zhu, D. Y. Yan, Y. Chen, Q. Chen and Y. F. Yao, *Angew. Chem., Int. Ed.*, 2006, **45**, 87-90.
93 X. Y. Zhu, L. Chen, Y. Chen, D. Y. Yan, *Sci. China, Ser. B*, 2008, **51**, 1057-1065.
94 H. S. Wan, Y. Chen, L. Chen, X. Y. Zhu, D. Y. Yan, B. Li, T. Liu, L. Zhao, X. L. Jiang and G. Z. Zhang, *Macromolecules*, 2008, **41**, 465-470.
95 Z. F. Jia, G. L. Li, Q. Zhu, D. Y. Yan, X. Y. Zhu, H. Chen, J. L. Wu, C. L. Tu and J. Sun, *Chem. −Eur. J.*, 2009, **15**, 7593-7600.
96 J. Y. Liu, Y. Pang, J. Chen, P. Huang, W. Huang, X. Y. Zhu and D. Y. Yan, *Biomaterials*, 2012, **33**, 7765-7774.
97 Y. Jin, L. Song, Y. Su, L. J. Zhu, Y. Pang, F. Qiu, G. S. Tong, D. Y. Yan, B. S. Zhu and X. Y. Zhu, *Biomacromolecules*, 2011, **12**, 3460-3468.
98 D. Steinhilber, A. L. Sisson, D. Mangoldt, P. Welker, K. Licha and R. Haag, *Adv. Funct. Mater.*, 2010, **20**, 4133-4138.
99 C. Tonhauser, C. Schull, C. Dingels and H. Frey, *ACS Macro Lett.*, 2012, **1**, 1094-1097.
100 Y. Pang, J. Y. Liu, J. L. Wu, G. L. Li, R. B. Wang, Y. Su, P. He, X. Y. Zhu, D. Y. Yan and B. S. Zhu, *Bioconjugate Chem.*, 2010, **21**, 2093-2102.
101 R. Haag, *Angew. Chem. Int. Ed.*, 2004, **43**, 278-282.
102 R. K. Kainthan, S. R. Hester, E. Levin, D. V. Devine and D. E Brooks, Biomaterials, 2007, **28**, 4581-4590.
103 M. Hu, M. S. Chen, G. L. Li, Y. Pang, D. L. Wang, J. L. Wu, F. Qiu, X. Y. Zhu and J. Sun, *Biomacromolecules*, 2012, **13**, 3552-3561.
104 R. A. Shenoi, J. K. Narayanannair, J. L. Hamilton, B. F. Lai, S. Horte, R. K. Kainthan, J. P. Varghese, K. G. Rajeev, M. Manoharan and J. N. Kizhakkedathu, *J. Am. Chem. Soc.*, 2012, **134**, 14945-14957.
105 D. Wilms, S.-E. Stiriba and H. Frey, *Acc. Chem. Res.*, 2010, **43**, 129-141.
106 M. Ahmed, B. F. Lai, J. N. Kizhakkedathu and R. Narain, *Bioconjugate Chem.*, 2012, **23**, 1050-1058.
107 Y. Tao, L. Zhang, F. Yan and X. Wu, *Biomacromolecules*, 2007, **8**, 2321-2328.
108 X. Chang and C. M. Dong, *Biomacromolecules*, 2013, **14**, 3329-3337.
109 T. L. Menz and T. M Chapman, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, 2003, **44**, 842-843.
110 X. Wang, Y. He, J. Wu, C. Gao and Y. Xu, *Biomacromolecules*, 2010, **11**, 245-251.
111 X. Meng, Q. G. He, H. M. Cao and J. G. Cheng, *Chin. Chem. Lett.*, 2011, **22**, 725-728.
112 C. Kojima, K. Yoshimura, A. Harada, Y. Sakanishi and K. Kono, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 4047-4054.

113 Z. Guo, Y. W. Zhang, W. Huang, Y. F. Zhou and D. Y. Yan, *Macromol. Rapid Commun.*, 2008, **29**, 1746-1751.
114 Y. M. Xia, Y. M. Wang, Y. P. Wang, C. L. Tu, F. Qiu, L. J. Zhu, Y. Su, D. Y. Yan, B. S. Zhu and X. Y. Zhu, *Colloids Surf.*, B, 2011, **88**, 674-681.
115 Y. Huang, R. J. Dong, X. Y. Zhu, and D. Y. Yan, *Soft Matter*, 2014, **10**, 6121-6138.
116 C. Kontoyianni, Z. Sideratou, T. Theodossiou, L. Tziveleka, D. Tsiourvas and C. M. Paleos, *Macromol. Biosci.*, 2008, **8**, 871-881.
117 L. Tziveleka, C. Kontoyianni, Z. Sideratou, D. Tsiourvas and C. M. Paleos , *Macromol. Biosci.*, 2006, **6**, 161-169.
118 C. Chen, G. Liu, X. Liu, S. Pang, C. Zhu, L. Lv and J. Ji, *Polym. Chem.*, 2011, **2**, 1389-1397.
119 J. Y. Liu, Y. Pang, Z. Zhu, D. L. Wang, C. T. Li, W.Huang, X. Y. Zhu and D. Y. Yan, *Biomacromolecules*, 2013, **14**, 1627-1636.
120 R. Barbey and S. Perrier, *ACS Macro Lett.*, 2013, **2**, 366-370.
121 L. J. Zhu, C. L. Tu, B. S. Zhu, Y. Su, Y. Pang, D. Y. Yan, J. L. Wu and X. Y. Zhu, *Polym. Chem.*, 2011, **2**, 1761-1768.
122 C. Schull and H. Frey, *Polymer*, 2013, **54**, 5443-5455.
123 G. S. Tong, T. Liu, S. M. Zhu, B. S. Zhu, D. Y. Yan, X. Y. Zhu and L. Zhao, *J. Mater. Chem.*, 2011, **21**, 12369-12374.
124 J.-Y. Yin, H.-J. Liu, S. Jiang, Y. Chen and Y. Yao, *ACS Macro Lett.*, 2013, **2**, 1033-1037.
125 H. W. Duan and S. M. Nie, *J. Am. Chem. Soc.*, 2007, **129**, 3333-3338.
126 Y. F. Shi, C. L. Tu, R. B. Wang, J. Y. Wu, X. Y. Zhu and D. Y. Yan, *Langmuir*, 2008, **24**, 11955-11958.
127 Y. F. Shi, L. B. Liu, C. L. Tu, L. J. Zhu, D. Y. Yan, G. L. Li, F. L. Guo and X. Y. Zhu, *J. Appl. Polym. Sci.*, 2011, **122**, 1077-1083.
128 L. J. Zhu, Y. F. Shi, C. L. Tu, R. B. Wang, Y. Pang, F. Qiu, X. Y. Zhu, D. Y. Yan, L. He, C. Y. Jin and B. S. Zhu, *Langmuir*, 2010, **26**, 8875-8881.
129 X. Li, M. Takashima, E. Yuba, A. Harada and K. Kono, *Biomaterials*, 2014, **35**, 6576-6584.
130 J. H. Kim, K. Park, H. Y. Nam, S. Lee, K. Kim and I. C. Kwon, *Prog. Polym. Sci.*, 2007, **32**, 1031-1053.
131 O. Gheysens and S. S.Gambhir, *Prog. Drug Res.*, 2005, **62**, 117-150.
132 R. Weissleder, *Science*, 2006, **312**, 1168-1171.
133 C. J. Sigurdson, K. Peter, R. Nilsson, S. Hornemann, G. Manco, M. Polymenidou, P. Schwarz, M. Leclerc, P. Hammarstrom, K. Wuthrich and A. Aguzzi, *Nat. Methods*, 2007, **4**, 1023-1030.
134 J. W. Lichtman and J. A. Conchello, *Nat. Methods*, 2005, **2**, 910-919.
135 S. Y. Chen, Z. H. Tan, N. Li, R. B. Wang, L. He, Y. F. Shi, L. Jiang, P. Y. Li and X. Y. Zhu, *Macromol. Biosci.*, 2011, **11**, 828-838.
136 S. J. Xu, Y. Luo, R. Graeser, A. Warnecke, F. Kratz, P. Hauff, K. Licha and R. Haag, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1030-1034.
137 H. Y. Chen, G. L. Li, H. R. Chi, D. L. Wang, C. L. Tu, L. J. Pan, L. J. Zhu, F. Qiu, F. L. Guo and X. Y. Zhu, *Bioconjugate Chem.*, 2012, **23**, 1915-1924.
138 G. L. Li, J. Y. Liu, Y. Pang, R. B. Wang, L. M. Mao, D. Y. Yan, X. Y. Zhu and J. Sun, *Biomacromolecules*, 2011, **12**, 2016-2026.
139 M. A. Quadir, M. R. Radowski, F. Kratz, K. Licha, P. Hauff and R. Haag, *J. Control. Release*, 2008, **132**, 289-294.
140 Q. Wang, L. J. Zhu, G. L. Li, C. L. Tu, Y. Pang, C. Y. Jin, B. S. Zhu, X. Y. Zhu and Y. Q. Liu, *Macromol. Biosci.*, 2011, **11**, 1553-1562.

141 C. L. Tu, L. J. Zhu, P. P. Li, Y. Chen, Y. Su, D. Y. Yan, X. Y. Zhu and G. Y. Zhou, *Chem. Commun.*, 2011, **47**, 6063-6065.
142 D. L. Wang, H. Y. Chen, Y. Su, F. Qiu, L. J. Zhu, X. Y. Huan, B. S. Zhu, D. Y. Yan, F. L. Guo and X. Y. Zhu, *Polym. Chem.*, 2013, **4**, 85-94.
143 W. Yang, C. Y. Pan, X. Q. Liu and J. Wang, *Biomacromolecules*, 2011, **12**, 1523-1531.
144 S. R. Yu, R. J. Dong, J. J. Chen, F. Chen, W. Jiang, Y. F. Zhou, X. Y. Zhu and D. Y. Yan, *Biomacromolecules*, 2014, **15**, 1828-1836.
145 N. R. B. Boase, I. Blakey and K. J. Thurecht, *Polym. Chem.*, 2012, **3**, 1384-1389.
146 H. Wang, S. T. Wang, H. Su, K. J. Chen, A. L. Armijo, W. Y. Lin, Y. J. Wang, J. Sun, K. Kamei, J. Czernin, C. G. Radu and H. R. Tseng, *Angew. Chem., Int. Ed.*, 2009, **48**, 4344-4348.
147 A. K. Boal, F. Ilhan, J. E. DeRouchey, T. Thurn-Albrecht, T. P. Russell and V. M. Rotello, *Nature*, 2000, **404**, 746-748.
148 K. Saatchi, N. Gelder, P. Gershkovich, O. Sivak, K. M. Wasan, R. K. Kainthan, D. E. Brooks and U. O. Häfeli, *Int. J. Pharm.*, 2012, **422**, 418-427.
149 K. J. Thurecht, *Macromol. Chem. Phys.*, 2012, **213**, 2567-2572.
150 D. Ding, G. Wang, J. Liu, K. Li, K. Y. Pu, Y. Hu, J. C. Ng, B. Z. Tang and B. Liu, *Small*, 2012, **8**, 3523-3530.
151 B. E. Rolfe, I. Blakey, O. Squires, H. Peng, N. R. Boase, C. Alexander, P. G. Parsons, G. M. Boyle, A. K. Whittaker and K. J. Thurecht, *J. Am. Chem. Soc.*, 2014, **136**, 2413-2419.
152 N. R. B. Boase, I. Blakey, B. E. Rolfe, K. Mardon and K. J. Thurecht, *Polym. Chem.*, 2014, **5**, 4450-4458.
153 K. Saatchi, P. Soema, N. Gelder, R. Misri, K. McPhee, J. H. Baker, S. A. Reinsberg, D. E. Brooks and U. O. Häfeli, *Bioconjugate Chem.*, 2012, **23**, 372-381.
154 R. K. Kainthan and D. E. Brooks, *Bioconjugate Chem.*, 2008, **19**, 2231-2238.
155 R. K. Kainthan, C. Mugabe, H. M. Burt and D. E. Brooks, *Biomacromolecules*, 2008, **9**, 886-895.
156 P. Kolhe, E. Misra, R. M. Kannan, S. Kannan and M. Lieh-Lai, *Int. J. Pharm.*, 2003, **259**, 143-160.
157 S. Kannan, P. Kolhe, V. Raykova, M. Glibatec, R. M. Kannan, M. Lieh-Lai and D. Bassett, *J. Biomater. Sci. Polym. Ed.*, 2004, **15**, 311-330.
158 Y. Y. Zhou, Z. Guo, Y. W. Zhang, W. Huang, Y. F. Zhou and D. Y. Yan, *Macromol. Biosci.*, 2009, **9**, 1090.
159 J. Zou, W. Shi, J. Wang and J. Bo, *Macromol. Biosci.*, 2005, **5**, 662-668.
160 S. Aryal, M. Prabaharan, S. Pilla and S. Gong, *Int. J. Biol. Macromol.*, 2009, **44**, 346-352.
161 M. R. Radowski, A. Shukla, H. von Berlepsch, C. Böttcher, G. Pickaert, H. Rehage and R. Haag, *Angew. Chem., Int. Ed.*, 2007, **46**, 1265-1269.
162 W. Saiyin, D. L. Wang, L. Li, L. J. Zhu, B. Liu, L. Sheng, Y. Li, B. S. Zhu, L. M. Mao, G. L. Li and X. Y. Zhu, *Mol. Pharmaceutics*, 2014, **11**, 1662-1675.
163 X. Y. Sun, Y. F. Zhou and D. Y. Yan, *Sci. China Ser. B Chem.*, 2009, **52**, 1703-1710.
164 H. Y. Hong, Y. Y. Mai, Y. F. Zhou, D. Y. Yan and Y. Chen, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 668-681.
165 S. Chen, X.-Z. Zhang, S.-X. Cheng, R.-X. Zhuo and Z.-W. Gu, *Biomacromolecules*, 2008, **9**, 2578-2585.
166 P. Kolhe, J. Khandare, O. Pillai, S. Kannan, M. Lieh-Lai and R. Kannan, *Pharm. Res.*, 2004, **21**, 2185-2195.
167 M. Prabaharan, J. J. Grailer, S. Pilla, D. A. Steeber and S. Gong, *Biomaterials*, 2009, **30**, 5757-5766.
168 F. Wurm, J. Klos, H. J. Räder, H. Frey, *J. Am. Chem. Soc.*, 2009, **131**, 7954-7955.
169 M. A. Gauthier and H.-A. Klok, *Chem. Commun.*, 2008, 2591-2611.
170 X. Gao, X. Zhang, X. Z. Wu, X. Zhang, Z. Wang and C. Li, *J. Control. Release*, 2009, **140**, 141-147.

171 F. Wurm, C. Dingels, H. Frey and H.-A. Klok, *Biomacromolecules*, 2012, **13**, 1161-1171.
172 I. M. Verma and N. Somia, *Nature*, 1997, **389**, 239-242.
173 W. F. Anderson, *Nature*, 1998, **392**, 25-30.
174 R. Duncan, *Nat. Rev. Drug Discov.*, 2003, **2**, 347-260.
175 M. E. Fox, F. C. Szoka and J. M. J. Fréchet, *Acc. Chem. Res.*, 2009, **42**, 1141-1151.
176 J. J. Green, R. Langer and D. G. Anderson, *Acc. Chem. Res.*, 2008, **41**, 749-759.
177 S.-D. Li and L. Huang, *J. Control. Release*, 2007, **123**, 181-183.
178 D. J. Gary, N. Puri and Y.-Y. Won, *J. Control. Release*, 2007, **121**, 64-73.
179 J. Suh, H.-J. Paik and B. K. Hwang, *Bioorg. Chem.*, 1994, **22**, 318-327.
180 O. Boussif, F. Lezoualc'h, M. A. Zanta, M. D. Mergny, D. Scherman, B. Demeneix and J.-P. Behr, *Proc. Natl. Acad. Sci.* USA, 1995, **92**, 7297-7301.
181 Z. Kadlecova, Y. Rajendra, M. Matasci, L. Baldi, D. L. Hacker, F. M. Wurm and H.-A. Klok, *J. Control. Release*, 2013, **169**, 276-288.
182 D. Dey, M. Inayathullah, A. S. Lee, M. C. LeMieux, X. Zhang, Y. Wu, D. Nag, P. E. De Almeida, L. Han, J. Rajadas and J. C. Wu, *Biomaterials*, 2011, **32**, 4647-4658.
183 W. Xia, P. Wang, C. Lin, Z. Li, X. Gao, G. Wang and X. Zhao, *J. Control. Release*, 2012, **157**, 427-436.
184 S. Sajeesh, T. Y. Lee, S. W. Hong, P. Dua, J. Y. Choe, A. Kang, W. S. Yun, C. Song, S. H. Park, S. Kim, C. Li and D. K. Lee, *Mol. Pharmaceutics*, 2014, **11**, 872-884.
185 R. J. Dong, L. Z. Zhou, J. L. Wu, C. L. Tu, Y. Su, B. S. Zhu, H. C. Gu, D. Y. Yan and X. Y. Zhu, *Chem. Commun.*, 2011, **47**, 5473-5475.
186 T. J. Vogl, K. Eichler, R. Straub, K. Engelmann, S. Zangos, D. Woitaschek, M. Böttger and M. G. Mack, *Eur. J. Ultrasound*, 2001, **13**,117-127.
187 Q. Tian, J. Hu, Y. Zhu, R. Zou, Z. Chen, S. Yang, R. Li, Q. Su, Y. Han and X. Liu, *J. Am. Chem. Soc.*, 2013, **135**, 8571-8577.
188 H. Gong, Z. Dong, Y. Liu, S. Yin, L. Cheng, W. Xi, J. Xiang, K. Liu, Y. Li and Z. Liu, *Adv. Funct. Mater.*, 2014, **24**, 6492-6502.
189 S. M. Janib, A. S. Moses and J. A. MacKay, *Adv. Drug Deliv. Rev.*, 2010, **62**, 1052-1063.
190 K. Yang, L. Hu, X. Ma, S. Ye, L. Cheng, X. Shi, C. Li, Y. Li and Z. Liu, *Adv. Mater.*, 2012, **24**, 1868-1872.
191 X. Li, Y. Qian, T. Liu, X. Hu, G. Zhang, Y. You and S. Liu, *Biomaterials*, 2011, **32**, 6595-6605.
192 S. Xu, Y. Luo, R. Graeser, A. Warnecke, F. Kratz, P. Hauff, K. Licha and R. Haag, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1030-1034.
193 Y. L. Xiao, H. Hong, A. Javadi, J. W. Engle, W. J. Xu, Y. A. Yang, Y. Zhang, T. E. Barnhart, W. B. Cai and S. Q. Gong, *Biomaterials*, 2012, **33**, 3071-3082.

Curriculum Vitae

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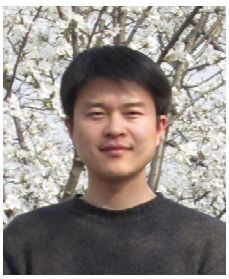

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Table of Contents Entry

Synthesis and therapeutic applications of biocompatible or biodegradable hyperbranched polymers

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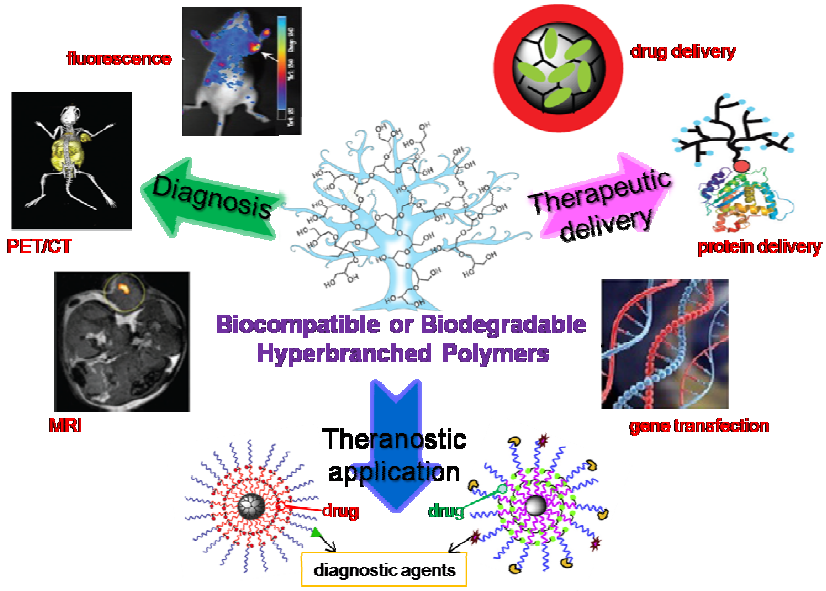
Keywords: Biocompatibility; Biodegradability; Hyperbranched polymers; Synthesis; Modification; Therapeutic applications



The recent progress in synthesis, modifications and therapeutic applications of biocompatible or biodegradable hyperbranched polymers have been reviewed.