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Review

Biodegradable dendrimers for drug delivery

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ABSTRACT

Dendrimers, as a type of artificial polymers with unique structural features, have been extensively explored for their applications in biomedical fields, especially in drug delivery. However, one important concern about the most commonly used dendrimers exists - the nondegradability, which may cause side effects induced by the accumulation of synthetic polymers in cells or tissues. Therefore, biodegradable dendrimers incorporating biodegradability with merits of dendrimers such as well-defined architectures, copious internal cavities and surface functionalities, are much more promising for developing novel nontoxic drug carriers. Herein, we review the recent advances in design and synthesis of biodegradable dendrimers, as well as their applications in fabricating drug delivery systems, with the aim to provide researchers in the related fields a good understanding of biodegradable dendrimers for drug delivery.

1. Introduction

Natural and artificial macromolecular structures have frequently been employed as vehicles for the delivery of drugs, especially hydrophobic drugs, since the vectors could improve the solubility of drugs along with protecting them from burst release and undesirable interactions with components of the biological milieu. In past decades, several kinds of carriers have been developed, including liposomes, micellar nanoparticles, vesicles, linear polymers, and dendritic structures (dendrimers and dendrons) [1–5]. Among them, dendrimers have attracted much more attention because of their unique structure and characteristics.

Dendrimers are a family of synthetic polymers with three-dimensional, highly branched and well-defined architectures. The term dendrimer was derived from the Greek words "*Dendron*" meaning "tree", which gave a vivid description of their distinctive "tree-like" branched structure [6–8]. The first dendrimer-like compound, polypropylenimine (PPI) with low generation, was reported by Voegtle and coworkers in 1978 [9]. Later on, Tomalia, Frechet, Newkome and colleagues synthesized dendrimers at higher generations with well-defined structures at mid-1980s [10–12], and ever since then, a variety of dendrimers with various structures and functions have been developed. A typical dendrimer consists of three parts: (a) a central core with two or more reactive groups; (b) interior layers composed of repeated branching units covalently attached to the core (each layer is called one "generation" (G)); (c) terminal functional groups on the outer surface (Fig.1). Generally, dendrimers can be synthesized *via* a step-by-step iterative coupling method either in a divergent or convergent manner [6,13].

With copious internal cavities and surface functionalities, dendrimers have been regarded as promising carriers for drug delivery since they were developed. Based on their structures and properties, drug molecules can either be physically encapsulated into the internal cavities of dendrimers or chemically conjugated to the terminal functional groups [3,14–16]. The first trial of using dendrimer for encapsulation of drug was demonstrated by Jansen et al. at mid-1990s, putting forward the concept of "dendritic box" [17]. Soon afterwards, multitude insoluble drugs have been entrapped into the interior of dendrimers to develop drug delivery systems. In addition, a large number of studies have demonstrated the conjugation of drugs to dendrimer surface. By now, several drug delivery systems based on some commercially available dendrimers such as poly(amido amine) (PAMAM) [10], poly(propylene imine) (PPI) [9] and poly(L-lysine) (PLL) [18], have already reached clinical trials. For example, DEP®, a PEGylated PLL dendrimer-docetaxel conjugate, which was originally developed by Starpharma Holdings Ltd. for treatment of a wide range of solid tumors including lung, breast and prostate, is currently undergoing phase I clinical trials. In addition, a sulfonated PLL dendrimer from the same company (VivaGel®) is in clinical evaluations as an antimicrobial agent for treatment/prevention of sexually transmitted diseases [5,19].

Despite the progress in this field, the use of dendrimers as drug carriers has not translated into the clinic at an appreciable level,

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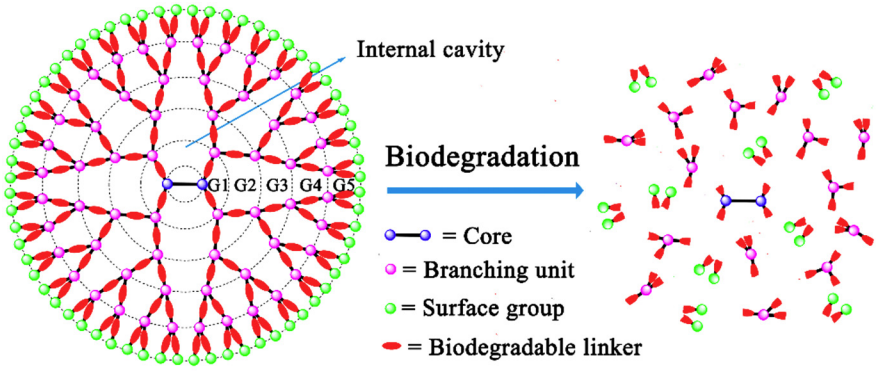

Fig. 1. Schematic illustration of biodegradation of biodegradable dendrimers.

compared to the enormous research effort and the accompanying funding [20]. One of the most important limits is that most of the commonly used dendrimers are nondegradable in physiological environment, which will result in serious side effects induced by the accumulation of nondegradable artificial macromolecules inside cells or in tissues [21–23]. For instance, dendrimers like PAMAM and PPI not only exert remarkable *in vitro* cytotoxicity due to their surface cationic groups, but also associate with cell membrane disruption and succedent necrosis/non-apoptotic cell death [24–31]. In recent years, researchers have tried some strategies to keep away from the toxicity of dendrimers, such as crosslinking low generation dendrimers with biodegradable linkers [32,33]. However, the biocompatibility of low generation dendrimers is still full of controversy. Some studies declared that PAMAM and PPI dendrimers at low generation are not as toxic as initially reported [34–38], while others reported toxicity profiles of the same dendrimers [39–41]. Therefore, more and more researchers turned their attentions to focus on the design and preparation of completely biodegradable dendrimers in recent years. As illustrated in Fig. 1, biodegradable dendrimers, generally composed by biodegradable repeat units, will degrade into small fragments under physical conditions, which can be excreted or eliminated through metabolic pathways.

The development of biodegradable dendrimers not merely addressed the toxicity issue of dendrimers, but also met the demands of "smart" drug carriers, which means the vectors leak drugs as few as possible before arriving the target sites, then degrade and completely release their payloads in the specific environment of niduses. In this smart controlled manner, reduced side effects along with improved drug delivery efficiency can be achieved. Lately, several examples of using biodegradable dendrimers as smart drug delivery vehicles have been proposed [42–44].

Herein, we present the recent advances in developing biodegradable dendrimers for drug delivery. The design and synthesis of several categories of biodegradable dendrimers are demonstrated, as well as their applications in drug delivery.

2. Development of biodegradable dendrimers

According to the type of degradable units, previously reported biodegradable dendrimers can be classified into three categories: polyester dendrimers (Section 2.1), polyacetal dendrimers (Section 2.2) and other biodegradable dendrimers (Section 2.3). The design and synthesis of these dendrimers are presented in the following subsections. And then in Section 2.4, we will give a brief summarization of the development of synthetic approaches for biodegradable dendrimers. It is worthy of note that although peptides are generally claimed as biodegradable polymers for the peptide linkage can be hydrolyzed by proteases, peptide dendrimers such as PLL, poly(L-glutamic acid), poly (proline) and so forth, are found much more stable to proteolysis than their linear polymeric analogs, and no reliable data shows their proteolysis *in vivo* [45,46]. Besides, the synthesis and applications of peptide dendrimers have already been well summarized by several reviews [18,47–51]. Therefore, this type of dendrimer will not be discussed in the context of this review. In addition, there have been reported some other so-called biodegradable dendrimers which contains one or several biodegradable linkers in the core, and will degrade into two or several branches in biological environment. These types of dendrimers will not be considered in this review, because of the risk of side effects associated with the long term presence of high molecular weight compounds cannot be really avoided.

2.1. Polyester dendrimers

Polyester dendrimers, as a type of biodegradable dendrimers which were first synthesized, formed the majority of this family. Generally, polymers with degradable linkages mean rigorous synthetic conditions, since they are susceptible to cleavage under specific conditions. However, polyester dendrimers realize a compromise between the biodegradability characteristic and the possibility of synthetic manipulation, compared with other more hydrolytic susceptible polymers, such as polyanhydrides [53]. Incorporating with good biocompatibility, polyester dendrimers become a fascinating class of nanomaterials and enjoy a bomb since they were first developed by Hawker and Frechet in 1992 [54]. This first case of polyester dendrimers contained aromatic ester linkages with high hydrolytic stability, thus they can barely be considered as biodegradable dendrimers. Subsequently, Amrein et al. reported the first study mentioning biodegradable dendrimers (Fig. 2), where polyester dendrimers based on (*R*)-3-hydroxybutanoic acid and trimesic acid were synthesized and their enzymatic degradation was investigated [52]. Then in the following decades, a large number of polyester dendrimers have been developed, which can be grouped into three categories: polyester dendrimers based on 2,2-bis(hydroxymethyl)propanoic acid (bis-HMPA) monomers (Section 2.1.1), polyester dendrimers based on alternating monomers (Section 2.1.2) and other polyester dendrimers (Section 2.1.3).

2.1.1. Polyester dendrimers based on bis-HMPA monomers

Bis-HMPA (Fig. 3A), a commercially available monomer with low cost, has been the main choice in the preparation of polyester dendrimers or dendritic structures since its first use. The dendrimers built from bis-HMPA possess several merits such as nontoxicity, biodegradability and non-immunogenicity, which make them attractive candidates for biomedical applications [59].

In 1996, Söderlind et al. reported the first synthesis of polyester dendrimers based on bis-HMPA (Fig. 3B) [55]. A fourth generation dendrimer was synthesized in the convergent fashion, and the focal point of the dendrons was protected by a benzyl ester group and deprotected by catalytic hydrogenolysis. Since then, a large number of

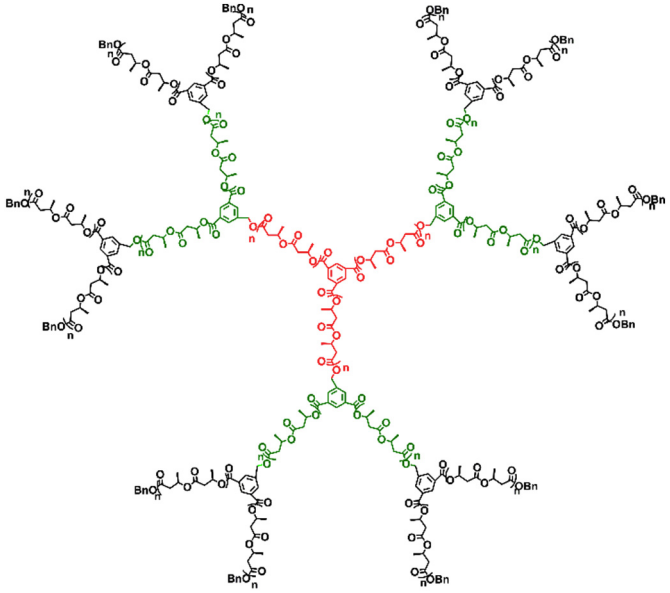

Fig. 2. The first published biodegradable dendrimers [52].

research papers proposed several alternative synthetic routs using different protecting groups, for the sake of simplifying the synthesis of this class of polyester dendrimers and improving the yields [59–64]. Besides, a series of different core and/or different surface functional groups were employed to produce this type of dendrimers for different use [65–68].

Since their first report of a "bow-tie" dendrimer consisting of two bis-HMPA dendrons in 2002 (Fig. 3C), Gillies and Frechet prepared a series of "bow-tie" dendrimer with different structures, aiming at water-soluble drug carriers [56,69,70]. The biological evaluation of these dendrimers were conducted, and the results indicated that the polymers were nontoxic to cells and were degraded to small species at pH 7.4 and pH 5.0 [70].

Employing different functional cores will endow the resulted dendrimers with various structures and functionalities. In 2004, Malmstrom et al. reported the synthesis of bis-HMPA dendrimers using porphyrins as core [65]. Porphyrins were selected for their potential applications in many areas, including catalyst, electroluminescent materials, nanosensors, photodynamic therapy and so on [71–73]. In 2007, Hawkers et al. reported the preparation of bis-HMPA dendron functional initiators capable of initiating polymerization by atom transfer radical polymerization [74]. Subsequently, dendron functionalized core cross-linked star polymers were synthesized *via* an "arm-first" synthetic strategy. In 2009, Cheng et al. demonstrated a series of well-defined dumbbell-shaped tri-block copolymers composing of *comb*-shaped poly(L-lactide) (PLLA) terminal arms and linear poly(ethylene glycol) (PEG) with narrow molecular weight distributions, in which bis-HMPA dendrons were used as linkages (Fig. 3D) [57]. By varying the generation of the dendrons and the length of central PEG block and PLLA end arms, controllable material structure and properties as well as cell response were achieved, indicating great potential of these polymers in biomedical fields. Soon afterwards, presented by the same

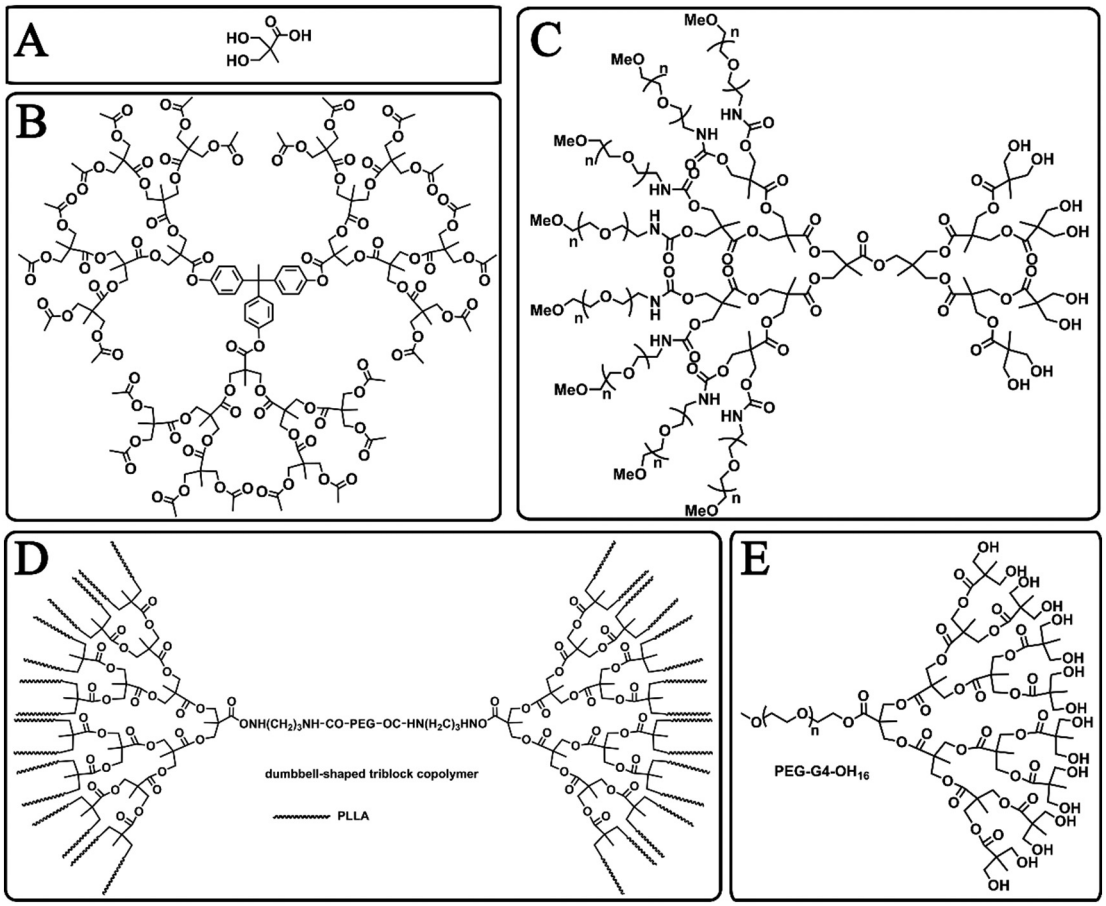

Fig. 3. (A) Bis-HMPA. (B) First reported polyester dendrimers (Readapted with permission from Ref. [55] Copyright © 1996, American Chemical Society.), (C) "bow-tie" dendrimers (Readapted with permission from Ref. [56] Copyright © 2002, American Chemical Society.), (D) dumbbell-shaped triblock copolymers (Readapted with permission from Ref. [57] Copyright © 2009, Elsevier Ltd.) and (E) linear-dendritic copolymers (Readapted with permission from Ref. [58] Copyright © 2008, Elsevier Ltd.) based on bis-HMPA monomers.

group, a series of amphiphilic dumbbell-shaped triblock copolymers consisting of linear PEG connected to the focal point of bis-HMPA dendrons and poly(ε-caprolactone) (PCL) linked to the terminal groups were synthesized, and microspheres were prepared using these polymers *via* a double emulsion method [75].

Linear-dendritic block copolymers (LDBCs) composed of a linear polymer linked to a bis-HMPA dendron were reported by several groups. In 2008, Chen et al. presented a series of carboxylic acid functionalized hybrid LDBCs derived from PEG and variant generation dendrons from bis-HMPA, which could be employed as $CaCO_3$ crystallization growth modifiers (Fig. 3E) [58]. In 2013, Hoogenboom et al. reported the synthesis of a bis-HMPA dendron-functionalized poly(2-ethyl-2-oxazoline) (PEtOx) [76]. The aqueous solution behavior and pH-responsivity of the PEtOx-dendron are investigated at neutral pH as well as acidic pH. In the same year, Hong et al. reported the synthesis and self-assembly of PEGylated bis-HMPA dendron based copolymers with different end-group functionalities, which displayed low levels of nonspecific cellular interactions, indicating great potential in drug delivery [77]. Very recently, non-ionic self-assembling amphiphilic LDBCs based on bis-HMPA dendrons were prepared by Govender et al. and expected to be used as new drug delivery excipients [78]. In addition, polyester dendronized polymers which refer to linear polymers having polyester dendrons at each repeating units were also presented by Frechet et al. [79,80]. Polymers with very high molecular weight and multivalency were obtained, and their degradation half-life were 2.5 days at pH = 9 and 16 days at pH = 7.7 respectively, while no significant degradation was observed at acidic conditions, in line with a degradation mechanism involving random ester hydrolysis along the polyester backbone.

In 2001, Wheeler et al. reported the conjugation of identical dendrons to build symmetrical dendrimers *via* Diels-Alder reaction [81]. Since then, the Diels-Alder cycloaddition was frequently employed to furnish LDBCs or asymmetrical dendrimers, due to their high efficiency, mild conditions and nonuse of toxic metals. In 2008, Sanyal et al. demonstrated the synthesis of segment block dendrimers (Janus dendrimers) consisting of polyaryl ether and bis-HMPA dendrons using the Diels-Alder cycloaddition [82].

The biodegradation behaviors of polyester dendrimers based on bis-HMPA are closely associated with their generations and surface groups. In 2012, Fadeel et al. carried out a systematic evaluation of the *in vitro* biocompatibility and biodegradability of a library of polyester dendrimers based on bis-HMPA with different generations and terminal groups [83]. The degradation experiments revealed that the 4th generation hydroxyl functional bis-HMPA dendrimers degraded faster at physiological pH (7.5) when compared to acidic pH (4.5) (no degradation after 40 days). However, for some applications such as anticancer drug delivery, polymers that can remain stable in the neutral environment of blood circulation are preferred [4]. Therefore, in spite of the widely use of these polyester dendrimers based on bis-HMPA, there are still some issues such as undesirable degradation need to be addressed. It was reported that developing dendrimers by incorporating bis-HMPA with other robust monomers would improve their stability in physiological environment. Frechet et al. prepared a robust and biodegradable dendrimer which combined the biocompatibility of bis-HMPA dendrimers with the robustness of polyamide dendrimers in 2010 [84]. The degradation half-time of these dendrimers was 10 days, which was long enough for drug delivery.

2.1.2. Polyester dendrimers based on alternating monomers

The synthesis of bis-HMPA-based dendrimers generally requires tedious protection/deprotection reactions, which makes the process inefficient and increases the risk of producing defects caused by incomplete reactions [85–87]. Although an efficient and sustainable esterification approach with 1,1′-carbonyldiimidazole as the coupling reagent and cesium fluoride as an essential catalyst, which proposed by Malkoch et al. in 2015 [88], significantly improved the synthesis of bis-HMPA-based dendrimers, researchers never stopped exploring new synthetic methods for building polyester dendrimers with novel structures and properties. In recent years, several efficient reactions including thiol-ene/yne, copper(I)-catalyzed azide–alkyne cycloaddition (CUAAC) and thiol/azo-Michael Addition reactions as well as orthogonal coupling strategies were employed to prepare polyester dendrimers based on alternating monomers, called by some scientist “alternating dendrimers”, in which the ester linkages alternate with other types of linkages.

The first case of alternating polyester dendrimers was demonstrated by Malkoch et al. in 2007 [89]. They obtained a fourth generation dendrimers in five steps by alternate orthogonal coupling of two different AB_2 monomers. In 2010, by utilizing two AB_2 monomers with orthogonal, “clickable” groups, Hawker et al. pushed the limits for thiol-ene and CUAAC reactions: yield a sixth generation dendrimer in a single day [90]. Like several other examples [44,91], one or two monomers used in these synthetic process were derived from bis-HMPA, thus these dendrimers can also be categorized into polyester dendrimers based on bis-HMPA.

In 2009, Shen et al. reported facile synthesis of alternating polyester dendrimers from sequential click coupling of asymmetrical monomers (2-[(methacryloyl)oxy]ethyl acrylate (MAEA) and cysteamine) (Fig. 4) [92]. By utilizing another two monomers (2-isocyanatoethyl methacrylate (IEMA) and 1-thioglycerol), another alternating dendrimer could be obtained, indicating universality of this synthetic strategy. Subsequently, they simplified the synthesis by using a β-cyclodextrin core, from which asymmetric alternating polyester dendrimers with high molecular weight were facilely yield without complicated purifications [43]. Then in 2014, they further developed Jellyfish-shaped amphiphilic dendrimers composed of 7 PEG arms and 14 hydrophobic alternating polyester dendrons with β-cyclodextrin as the core [93]. Lately, a novel alternating polyester dendrimer was synthesized by them using orthogonal monomer pairs: 2,2-bis(methacryloyloxymethyl)propionyl isothiocyanate (BMATIC)/cysteamine [94]. And more notably, they carried out comprehensive evaluations of the potentials of these polyester dendrimers in drug delivery, which will be further discussed in Section 3.

1-Thioglycerol contains a thiol group which can react with alkenes *via* thiol-ene “Click” reactions, and two hydroxyls which can undergo esterification, thus it's a popular candidate for synthesis of alternating polyester dendrimers [95]. In 2008, Hawker et al. presented robust, efficient, and orthogonal synthesis of polyester dendrimers *via* thiol-ene “Click” chemistry using 1-thioglycerol and 4-pentenoic anhydride as alternating monomers [96]. The obtained dendrimers had pendant hydroxyls or alkenes which could be easily used for conjugation of bioactive molecules. Percec et al. provided an iterative two-step divergent growth approach to the synthesis of a new class of alternating polyester dendrimers based on a novel nucleophilic thiol-bromine “Click” reaction [97]. The same strategy was combined with atom transfer nitroxide radical coupling (ATNRC) by Wang et al. to develop polyester dendrimers with good properties of biocompatibility and biodegradability [98]. The combination of mercaptoethanol/mercaptopropionic acid and an alkyne functionalized monomer was also frequently used for preparing alternating polyester dendrimers. In 2013, Li et al. report a highly efficient approach to prepare polyester dendrimers using a mercaptoethanol and but-3-ynyl acrylate monomer pair [99]. By taking advantage of the orthogonal characteristic of azo-Michael addition and thiol-yne reaction, a fifth generation dendrimer was synthesized within five steps without protection/deprotection procedures. Very recently, arginyl-glycyl-aspartic acid (RGD)-conjugated core-shell amphiphilic copolymers consisting of a polyester dendrimer core and hydrophilic PEG shells were demonstrated by Li et al., in which the polyester dendrimers were synthesized by alternative reaction of a pair of two commercial available monomers: propargyl alcohol and mercaptopropionic acid [100]. Micelles formed from the copolymers showed considerable potential as tumor-targeted drug delivery

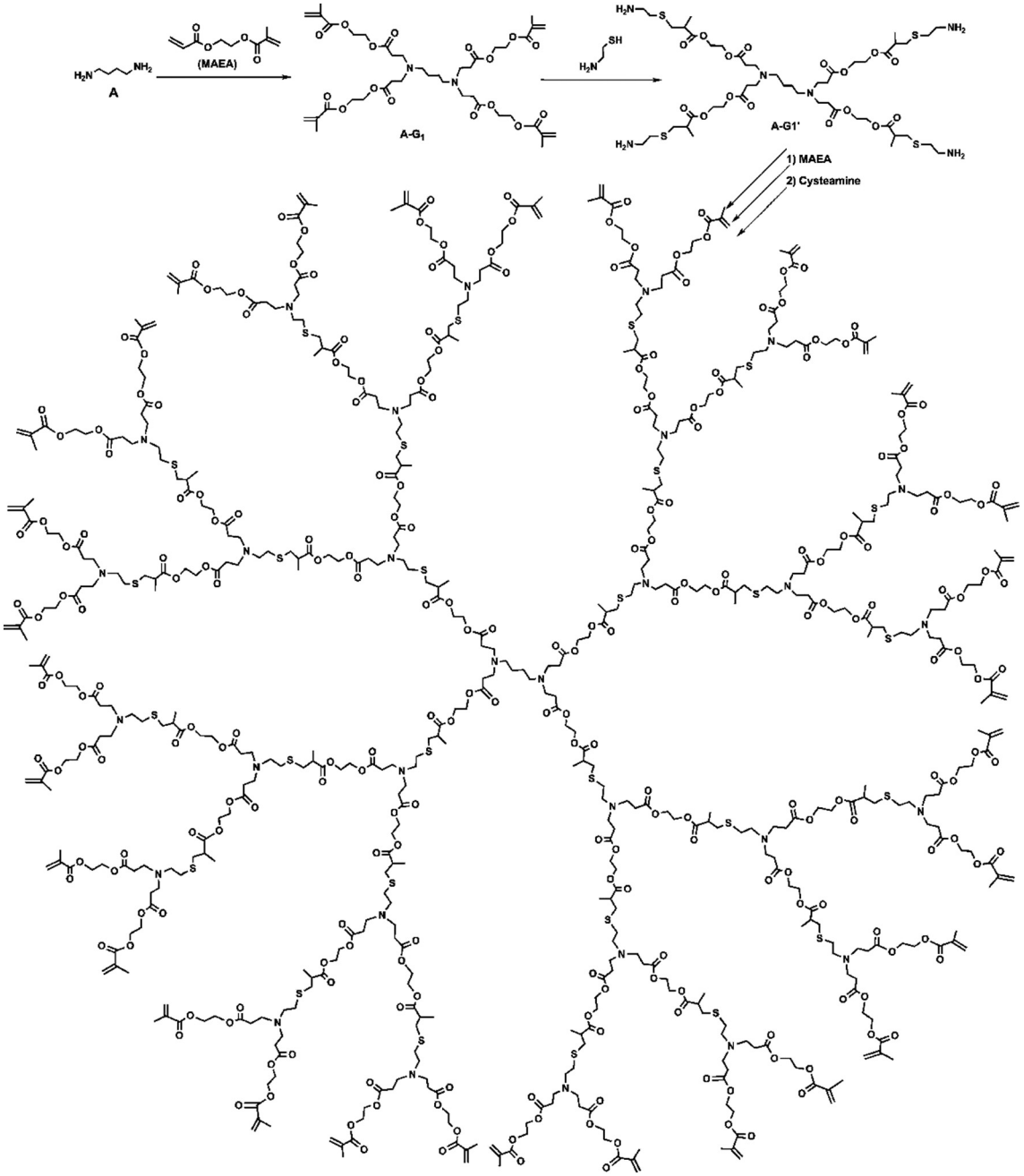

Fig. 4. Alternating polyester dendrimers from sequential click coupling of asymmetrical monomers. Readapted with permission from Ref. [92]. Copyright © 2009, American Chemical Society.

nanocarriers.

In 2013, linear-dendritic-linear copolymers composed of poly (amino ester) dendrons, PCL and PEG as well as their self-assembly around oleic acid-stabilized Fe_3O_4 nanoparticles *via* the ligand exchange method were reported by Hemati et al. [101]. The poly(amino ester) dendrons were prepared by sequential acrylation and Michael addition reactions, using acryloyl chloride and diethanolamine as alternating monomers. Then in 2015, they published the preparation of a similar system and the effect of the dendrons' surface groups on viability of human prostate carcinoma cell lines DU145 was investigated [102].

2.1.3. Other polyester dendrimers

Apart from bis-HMPA monomer, other aliphatic ester monomers such as succinic acid and lactic acid have also been utilized to prepare polyester dendrimers. For instances, Grinstaff et al. synthesized poly (ether ester) dendrimers from glycerol and lactic acid *via* an efficient divergent procedure, which expanded the repertoire of dendrimers available for study [103]. In addition, several kinds of novel polyester dendrimers based on glycerol and succinic acid or adipic acid were also prepared by them. Subsequently, applications of these dendrimers in biomedical fields including corneal adhesives and cartilage regeneration have been explored [104–108].

In 2006, Hildgen et al. reported novel poly(ether ester) dendrimers consisting of a hydrophilic core by combination of convergent and divergent methods [109]. The core was constructed from biocompatible moieties, butanetetracarboxylic acid and aspartic acid, and the dendrons were fabricated from poly(ethylene oxide) (PEO), dihydroxybenzoic acid or gallic acid, and PEG monomethacrylate. A series of this type of dendrimers with different architectures were synthesized and

methotrexate was used as a model drug to investigate the influence of molecular architecture on the encapsulation and release of drugs.

Several authors reported polyester dendrimers based on Michaele addition of acrylates, in which internal tertiary amines were formed [110,111]. A tertiary amines contained polyester dendrimer was also synthesized by Park et al. using bis(2-hydroxy-ethyl)-amino]-acetic acid tert-butyl ester as the growing unit [112]. The amine groups can serve as buffers to neutralize the acidic byproducts from degradation of ester groups, avoiding potential inflammation caused by these acidic metabolites, thus these poly(amine ester) dendrimers are promising candidates for fabricating drug carriers.

Recently, Shen et al. demonstrated a rare example of polyester dendrimers with a natural product - protocatechuic acid (PCA) as repeating units [113]. The PCA was well-known for its antioxidative effect and potential antitumor function. Therefore the PCA dendrimers could serve as potential anticancer drugs and also as nanocarriers for anticancer drug delivery.

Along with the exploration of new strategies for dendrimer synthesis, some polyester dendrimers with novel structures emerged. In 2012, Morin et al. synthesized third and fourth generation ethylene oxide-containing polyester dendrimers containing triazole units through metal-free Huisgen 1,3-dipolar cycloaddition ("Click") reaction between activated disubstituted alkyne and terminal azido groups [116]. Without using toxic metal or excess of reagents, the dendrimers were obtained in high yield with minimal purification effort. In 2014, Li et al. proposed efficient divergent synthesis of polyester dendrimers with structural diversity by combination of orthogonal ABB and ABC multicomponent reactions (Fig. 5A) [114]. The dendrimers possessed internal functional groups and two kinds of terminal groups, which could be used for simultaneous conjugation of different functional molecule such as drugs, target ligands and fluorescent molecules. Our group demonstrated the first known approach to create polyester dendrimers using polyhedral oligomeric silsequioxanes (POSS) as building blocks (Fig. 5B) [115]. By employing a 1–7 branching monomer, polyester dendrimers with 392 terminal vinyl groups were obtained in only three steps, significantly enhanced the efficiency of preparing dendrimers with high molecular weight and abundant peripheral groups.

2.2. Polyacetal dendrimers

Polyacetals/polyketals were a class of acid-labile polymers composed of acetal/ketal monomers. Due to their great pH sensitivity and non-acidic metabolites, polyacetals/polyketals were deemed to have a great potential in developing smart drug carriers for cancer or inflammation therapy, since it has been reported the pH in tumor and inflammatory tissues is often 0.5–1.0 pH units lower than that in normal tissues [117–120]. However, despite the extensive report of synthesis and applications of linear and hyperbranched polyacetals/polyketals [121–123], the polyacetals/polyketals dendrimers incorporated acid-responsive degradability and unique structural features have rarely been reported.

The first mention of polyacetal dendrimers were reported by Fuchs in 2002 [124]. Novel polyacetal dendrimers with 2,4,8,10-tetraoxaspiro[5,5]undecane dendrons from pentaerythritol and polyaldehydes were synthesized using sequential transacetalation and protection/deprotection techniques. In spite of that only a second generation dendrimer was obtained, this study showed the possibility of developing novel family of biodegradable dendrimers.

Unfortunately, in the following years, no novel polyacetal dendrimers were reported, probably due to the tough synthetic conditions. It is not until 2011, polyketal dendrimers with short PEO chain as repeating units were synthesized using an original ABC-type branching agent featuring a cleavable ketal group [125]. A seventh generation dendrimer carrying 192 peripheral hydroxyls was obtained, and benefiting from the abundant embedded PEO segments, the dendrimer was water soluble. Besides, the degradation of this polymer at acidic conditions produced linear PEO chains with low molecular weight. The good solubility in water, copious peripheral hydroxyls and acid-responsive degradation made this dendrimer a promising candidate for developing dendrimer-drug conjugates.

It is worth to be mentioned that Taton et al. proposed one pot synthesis of hyperbranched polyacetals with a degree of branching of 100%, namely dendrimer-like polyacetals, using a commercially available AB_2-type monomer in 2014 [126]. Although they were not really polyacetal dendrimers, they possessed several merits of polyacetals and dendrimers such as multivalency and acid-liable degradability.

In 2016, our group proposed the facile synthesis of a class of well-defined acid-labile polyacetal dendrimers by alternating reaction of an asymmetry acetal monomer and cysteamine *via* highly efficient azo-Michael addition and thiol-ene "Click" reaction (Fig. 6) [127]. By using a POSS core, the purification was simplified and quickly increase of terminal functionalities and molecular weight were achieved. Notably, the resulted polyacetal dendrimers were easily functionalized by PEG or zwitterions and self-assembled into pH-responsive degradable micelles or nanofibers. The dendrimers and self-assembled nanoaggregates were stable at neutral condition but quickly degrade into small fragments at

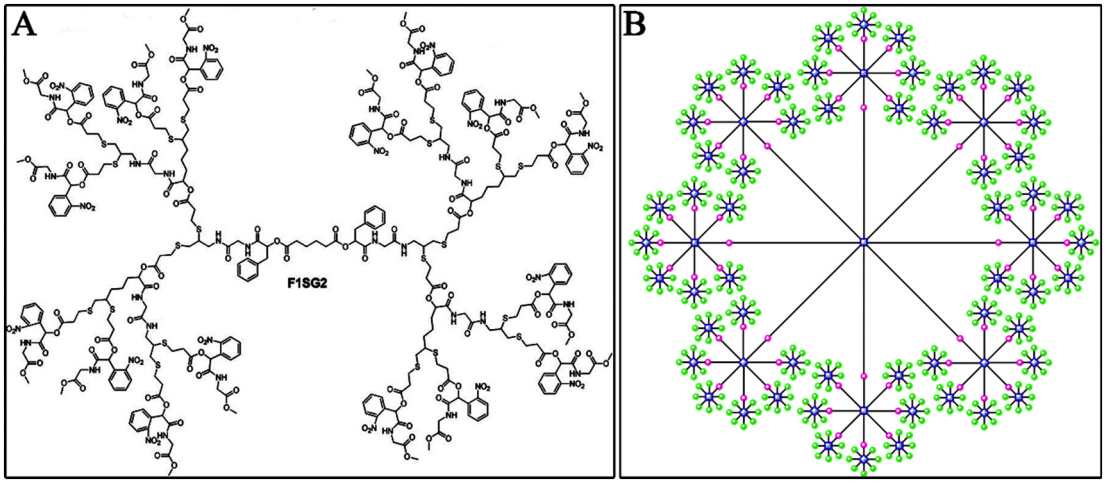

Fig. 5. (A) Polyester dendrimers from orthogonal ABB and ABC multicomponent reactions. Readapted with permission from Ref. [114]. Copyright © 2014, American Chemical Society. (B) Schematic illustration of polyester dendrimer using POSS as branching units. Readapted with permission from Ref. [115]. Copyright © 2014, Royal Society of Chemistry.

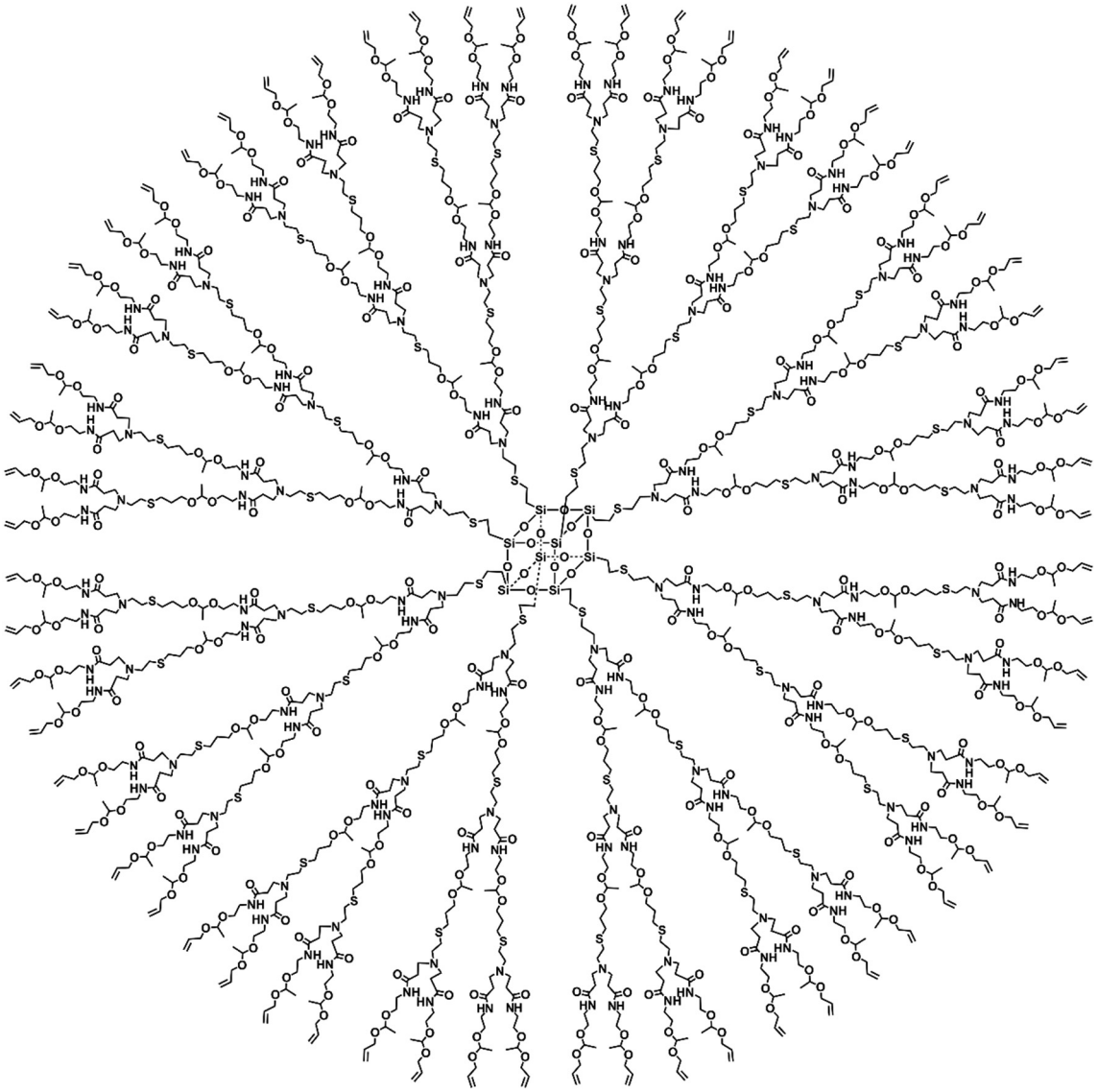

Fig. 6. Polyacetal dendrimers with a POSS core. Readapted with permission from Ref. [127]. Copyright © 2016, Royal Society of Chemistry.

pH = 5.8, indicating a considerable potential in fabricating smart drug delivery systems.

Very recently, we further synthesized polyacetal dendrimers with a β-cyclodextrin core and adamantane-terminated zwitterionic poly(sulfobetaine), then their host-guest recognition formed supramolecular amphiphilic LDBCs [128]. By varying the hydrophobic/hydrophilic ratio, the LDBCs could self-assemble into charge-reversible and pH-responsive biodegradable micelles and vesicles, which possessed excellent resistivity to protein absorption as well as good biocompatibility.

2.3. Other biodegradable dendrimers

Aside from the two classes of biodegradable dendrimers mentioned above, several biodegradable dendrimers were prepared by scientists. In 2008, Zimmerman et al. reported water soluble dendrimers with a biodegradable 1,3,5-triazaadamantane (TAA) unit at each branching point. In contrast with polyester dendrimers, that provide acidic products, this kind of dendrimers degrades to give products containing basic amine groups [129].

Using an economic, clean, simple, one-pot divergent-iterative approach, Bonifacio et al. synthesized a new family of water-soluble blue photoluminescent biocompatible and biodegradable “green” bifunctional dendrimers in supercritical carbon dioxide ($scCO_2$) [130]. Taking advantage of CO_2 as an alternative nonflammable, nontoxic and relatively low-cost solvent, the synthesis was clean and efficient.

In 2015, Nishikawa et al. described construction of DNA dendrimers consisting of several branched DNA units connected to each other using DNA ligase [131]. The self-assembling DNA dendrimers were with high immunostimulatory potency and could be used for effective delivery of immunostimulatory cytosine-phosphate-guanosine (CpG) DNA to immune cells. Recently, Ding et al. constructed programmable DNA dendrimers as efficient vehicles to deliver CpG immunostimulatory sequences for activation of the immune response [132]. After further modification with a typical cell-penetrating peptide on the surface of the dendrimers, the CpG loops-loaded DNA dendrimers demonstrated enhanced cell internalization and cytokines production.

2.4. Synthetic approaches for biodegradable dendrimers

Generally, dendrimers are synthesized utilizing either a divergent or convergent approach [6]. As demonstrated above, most reported biodegradable dendrimers were synthesized *via* interactive coupling in a divergent manner. Thereinto, the biodegradable units either formed during the synthetic process of the dendrimers, or derived from the

biodegradable monomers.

In the early days, biodegradable polyester dendrimers, especially polyester dendrimers based on bis-HMPA monomers, were prepared *via* esterification reaction of hydroxyls and carboxyl groups [55,59,60]. During the synthetic process, protection/deprotection reactions are needed, which not only makes the synthesis tedious and costly, but also brings the risk of forming defect since the removal of protecting groups may cause degradation of existing ester groups. To overcome these problems, orthogonal coupling strategies were proposed to synthesize polyester dendrimers, in which AB_2-type biodegradable monomers were employed [89]. Since the functional groups in the monomers were orthogonal, the protection/deprotection process could be avoided, and thus the synthetic efficiency was enhanced significantly.

In general, the biodegradable units are more vulnerable than non-degradable groups. Therefore, compared to the synthesis of non-degradable dendrimers, the preparation of degradable dendrimers prefers mild conditions. “Click” reactions refer to several kinds of reactions with advantages of high selectivity, high efficiency, and mild conditions, including CUAAC, thiol-ene and thiol-yne reactions [87,95]. The combination of orthogonal coupling strategy and “Click” reactions, first presented by Hawker et al., can extremely improve the synthetic efficiency of biodegradable dendrimers. By rational design of an AB_2-CD_2 monomer pair having orthogonal, “clickable” groups on each monomer, a sixth generation polyester dendrimer was obtained in six steps within a single day [90]. Similarly, Shen et al. proposed facile synthesis of polyester dendrimers *via* sequential click coupling of asymmetrical monomers, and a series of dendrimers with various architectures and functions were prepared by utilizing different monomers [92–94]. These strategies can also be employed to synthesize other kind of biodegradable dendrimers, such as polyacetal dendrimers, and several examples have already been reported [127,128].

3. Applications of biodegradable dendrimers in drug delivery

Biodegradable dendrimers have been considered as promising candidates for drug delivery since they were developed, for the combination of biodegradability and the merits of dendrimers such as copious internal cavities and abundant surface functionalities [3]. Generally, drugs can either be entrapped into the internal cavities of dendrimers by physical encapsulation, or conjugated to the dendritic surface (Fig. 7). In addition, it has been reported several dendrimers can be used as drugs directly [6].

Using biodegradable dendrimers as drug or drug carriers has several advantages including the following: (a) the capacity to increase the solubility of hydrophobic drugs and protect them from degradation and undesired interactions with biological environment; (b) the possibility to prolong circulation time of drugs by protecting them from filtration and removal by the kidneys since nanoparticles larger than 5 nm exceeds the renal threshold and are less prone to be filtered by kidneys; (c) the chance to passively target to tumor tissues *via* enhanced permeability and retention (EPR) effect; (d) the potential to deliver different drugs *via* physical encapsulation and chemical conjugation at the same time, achieving synergetic therapy as well as tunable and improved pharmacodynamics; (e) the possibility to modify the dendrimer surface with functional molecules to endow them specific properties, such as imaging, surpassing biological barriers, targeting to specific tissues or cells, and so forth; (f) the ability to achieve controlled drug delivery by tuning dendrimer/drug interactions or by developing stimuli-responsive drug carriers; (g) the capacity to degrade to small fragments under physiological conditions and be expelled from body; and (h) the possibility to reduce side effects to normal tissues and organs, and to relieve the patients' pain.

3.1. Biodegradable dendrimers as drug carriers

3.1.1. Physical encapsulation

The idea of encapsulating drug molecules into the internal voids of dendrimers was proposed almost since they were synthesized. In the early years, the researches about using dendrimers as drug carriers mainly based on the widely used PAMAM and PLL dendrimers. Not until 2003, a biodegradable dendrimer based on glycerol and succinic acid was employed to deliver 10-hydroxy-camptothecin (CPT) to against various cancer cell lines [133]. Without introduction of additional compounds to the formulation, the solubility of CPT approximately increased an order of magnitude by using the dendrimers as carriers. In addition, compared to free drug, the cellular uptake of the dendrimer/drug complex enhanced 16-fold, along with cellular retention increased from 35% to 50% after 32 h. Furthermore, the dendrimer/drug complex demonstrated excellent *in vitro* anticancer activity against human breast adenocarcinoma (MCF-7), colorectal adenocarcinoma (HT-29), non-small cell lung carcinoma (NCI-H460), and glioblastoma (SF-268) cells, indicating great potential in cancer therapy.

To investigate the influence of molecular architecture of dendrimers on the encapsulation and release of drugs, Hildgen et al. synthesized a series of polyether-*co*-polyester dendrimers and studied drug encapsulation and release using methotrexate (MTX) as model [134]. The results revealed that increase in the number of branches and the size of internal cavities led to improvement of the encapsulation, while absence of aromatic rings as branching units dramatically cut down the loading capacity. The mechanism of encapsulation was associated with weak hydrogen bonding and hydrophobic interaction between the dendrimers and drugs. Furthermore, the authors concluded that the increase in the number of branches resulted in reduction of initial burst release, in contrast, absence of aromatic rings led to rapid drug release. Then in another paper, the authors evaluated potential of the MTX-

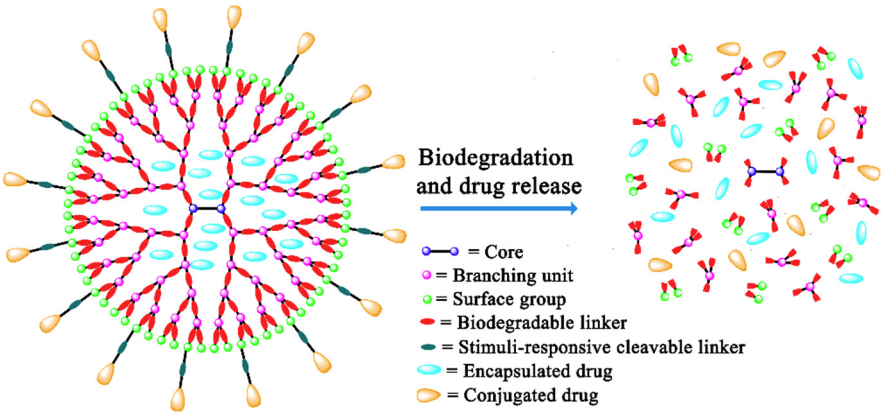

Fig. 7. Schematic illustration of biodegradable dendrimers as drug carriers.

loaded dendrimer in treatment of Gliomas [135]. Generally, the delivery of drugs across the blood–brain barrier (BBB) is difficult, even with the help of dendrimer vectors. To overcome this hurdle, several D-glucosamine groups were attached to the dendrimer for enhancing BBB permeability and tumor targeting. The MTX-loaded glucosylated dendrimer carriers demonstrated promoted cellular uptake and anticancer activity both *in vitro* and *in vivo*, in comparison to MTX-loaded non-glucosylated dendrimers and free MTX.

Shen et al. carried out a series of researches about fabricating nanocarriers based on polyester dendrimers. In 2009, they proposed the facile synthesis of polyester dendrimers from sequential click coupling of asymmetrical monomers. This type of dendrimers was found to be dual pH- and temperature-responsive as well as display photoluminescence [42]. DOX was entrapped to the dendrimer and the loaded drug was released very slowly and steadily at 37 °C and physiological pH, while could be quickly released at acidic pH such as the lysosomal pH (pH 4–5). The endogenous photoluminescence could be exploited for monitoring drug loading and release. Recently, they further proposed the preparation of carriers called "nano-bomb" in which DOX-loaded dendrimers were encapsulated in nanoparticles with a size of about 45 nm formed from a PEGylated lipid DSPE-PEG (DSPE = 1,2-distearoyl-sn-glycero-3-phosphoethanolamine) and cholesterol (Fig. 8), based on the theory that nanoparticles with larger size were more desirable for accumulating in tumor tissues *via* EPR effect, while nanoparticles with smaller size (< 20 nm) were preferable for penetration in tumor [136]. Results showed these novel carriers based on polyester dendrimers could efficiently deliver active drugs into tumor cells as well as give rise to high therapeutic efficacy with few side effects.

In addition, the polyester dendrimers synthesized by the same group in 2013 were utilized for encapsulation of DOX after being PEGylated [44]. DOX was also encapsulated into the biodegradable PCA dendrimers reported by them in 2016 [113]. Benefitting from the binding interaction between PCA and the drug, the drug loading capacity was enhanced and the burst release was reduced. *In vitro* and *in vivo* evaluation indicated the biodegradable PCA dendrimers exhibited excellent potential as an efficient nanocarrier for drug delivery.

Incorporating the advantages of dendritic architectures such as copious functionalities and merits of self-assembly of block copolymers such as facility to control the morphologies and sizes of resulted assemblies, LDBCs are regard as promising candidates for construction of drug delivery systems. In 2003, thermo-reversible hydrogels based on LDBCs composed of citric acid dendrons and PEG were prepared by Namazi and Adeli [137]. The formed biodegradable hydrogels could be used to encapsulate several polar hydrophobic drugs such as 5-amino salicylic acid, mefenamic acid, and diclofenac. Moreover, they prepared dendritic-linear-dendritic triblock copolymers consisting of the same components and investigated their potential as drug carriers [138]. The above mentioned drugs could be entrapped to the dendrons and the formed polymer/drug complexes were stable at room temperature for > 10 months. Malkoch et al. presented LDBCs with bis-HMPA dendrons as connection of hydrophobic PCL chains and hydrophilic PEG segment [139]. The amphiphilic biodegradable polymer could self-assemble into doxorubicin (DOX)-loaded micelles and ordered honeycomb membranes with enhanced surface area. Recently, Li et al. presented RGD-conjugated LDBCs consisting of a polyester dendrimer core and hydrophilic PEG shells as unimolecular micelles for targeted drug delivery [100]. The hydrophobic core in the unimolecular micelles demonstrated strong capability for the encapsulation of anticancer drugs such as DOX, and it exhibited pH-dependent controlled release behavior of the payload. As previous described in Section 2.2, our group prepared pH-responsive charge-reversible and biodegradable micelles and vesicles self-assembled from LDBCs consisting of polyacetal dendrimers and linear zwitterionic polymer [128]. DOX could be encapsulated into the micelles and vesicles, and the DOX-loaded nanoparticles displayed a pH-responsive drug release manner. In addition, due to the charge-reversal behavior, the nanoparticles possessed excellent stability in blood circulation because of electrostatic repulsion with negatively charged proteins, while at the acidic environment of tumors tissues, they turned to be positively charged, facilitating the affinity with negatively charged cytomembrane. Therefore, the DOX-loaded nanoparticles exhibited higher internalization efficiency than the conventional PEG-coated nanocarriers and significant cytotoxicity

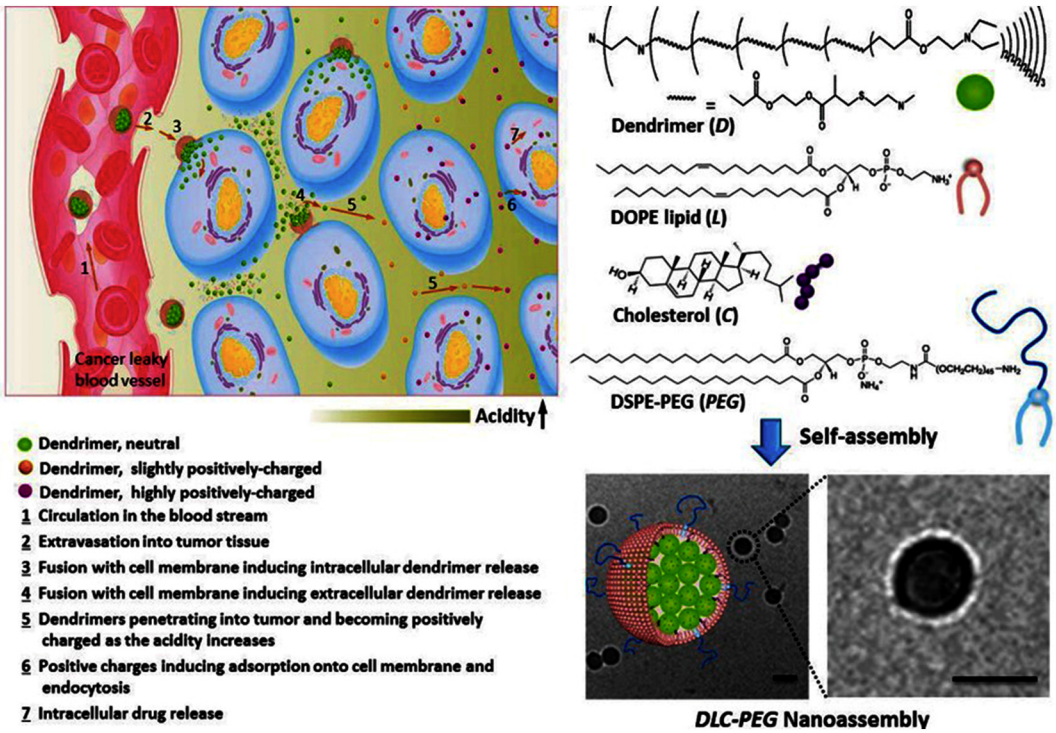

Fig. 8. "Nano-bomb" carriers based on biodegradable dendrimers. Readapted with permission from Ref. [136]. Copyright © 2014, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

against cancer cells, indicating a considerable potential in developing novel drug carriers for cancer therapy.

Biodegradable dendrimers were also used for fabricating pressurized metered-dose inhalers, reported by Rocha et al. very recently [140]. Surface PEGylated polyester dendrimers were employed to formulate carriers in propellant-based, portable oral-inhalation devices, and *in vitro* experiments were carried out to determine their potential for local and systemic delivery of drugs to and through the lungs. The dendrimers exhibited highly compatibility with the model pulmonary epithelium, but showed toxicity profiles much more favorable than non-degradable PAMAM dendrimers, indicating that they were promising candidates for developing drug delivery systems that can be tailored to target the lung tissue to treat local diseases, or the circulation, using the lungs as pathway to the bloodstream.

Although successful drug encapsulation using biodegradable dendrimers has been obtained as described above, limitations to this strategy still exist. The most important drawback of the physical encapsulation is the rapid and uncontrolled drug release. Building dendrimers with sufficiently dense architectures may relieve the burst release of entrapped drugs in some extent. However, synthesizing dense dendrimers usually requires multiple repetitive reaction steps, which increases cost and the risk of defect formation [20]. Therefore, alternative strategies for preparing drug carriers based on biodegradable dendrimers need to be explored.

3.1.2. Chemical conjugation

To address the limitations encountered with drug encapsulation, the chemical conjugation strategy was proposed and extensively studied by scientists. The linkers between the drugs and the dendrimers can remarkably affect the activity of the dendrimer–drug conjugates and the drug release profile, thus need to be well designed. Several types of generally used linkers for covalently attaching drugs to dendrimers are listed in Fig. 9, including (1) ester groups which can be cleaved by esterase enzymes within the cell; (2) acid-labile acetal/ketal, hydrazone, or *cis*-aconityl groups, which are easily degraded at acidic conditions in tumor or inflammation tissues and intracellular endosomal/lysosomal compartments; (3) disulfide groups which can be readily reduced by glutathione within the cytosol. By using these stimuli-responsive linkers, smart controllable drug delivery can be achieved [141].

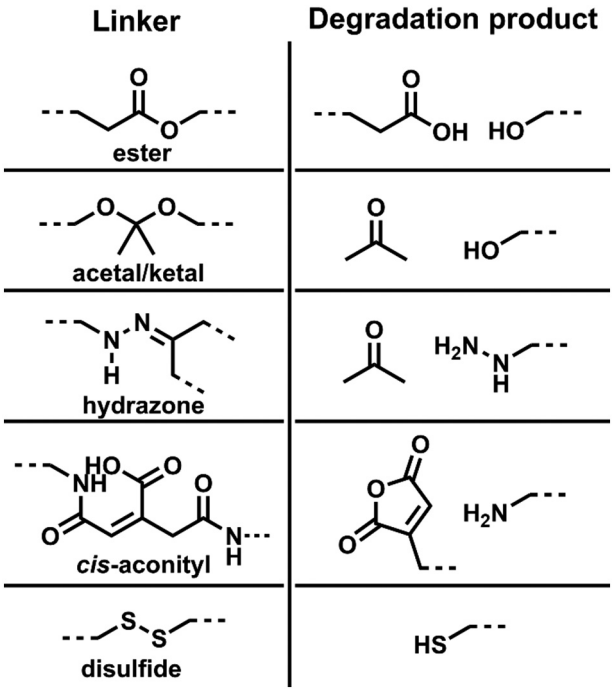

Fig. 9. Commonly used stimuli-responsive cleavable linkers and their degradation products.

Despite various dendrimer-drug conjugates were designed and prepared in past decades, only a few examples involved the biodegradable dendrimers. In 2002, Frechet et al. reported the conjugation of DOX to hydrazine groups terminated bis-HMPA dendrimers *via* acid-labile hydrazone linkages [59]. The drug release exhibited a pH-dependent manner: at pH = 7, nearly no DOX release was observed, whereas at pH < 6, the drug release was drastically accelerated, resulting in complete release in several days. The cytotoxicity of the drug was remarkably reduced (80–98%) after attaching it to the dendrimer, while the dendrimer-drug conjugates demonstrated excellent inhibition to proliferation of cancer cells.

Self-immolative dendritic prodrugs using DOX and CPT as tail units were prepared by Shabat et al. at 2004 [142]. These dendritic structures had unique degradable backbone and cleavage functionalities, which allowed a cascade decomposition response to single external stimuli. Thus stimuli-responsive drug release and degradation of the dendrimers happened simultaneous, which could be triggered by catalytic antibody 38C2. In comparison to traditional monomeric prodrugs, the inhibition to cancer cell growth of these dendritic prodrugs enhanced significantly. Then in their following research, trimeric prodrug platforms were developed using the same strategy [143]. Interestingly, it was possible to incorporate three different drug molecules including DOX, CPT and etoposide on the same prodrug platform, which effectively allowed triple-drug therapy in a single system.

Previously in Section 2.1.1, the "bow-tie" dendrimers based on bis-HMPA monomers were discussed. In a subsequent study, DOX was attached to the surface of the dendrimer *via* an acid labile hydrazone linker [144]. Upon intravenous injection to BALB/c mice with C-26 colon carcinoma tumors, dendrimer–DOX conjugates prolonged the circulation time with a half-life of 16 h, and their tumor uptake was nine-fold higher than free DOX at 48 h. A single injection of the dendrimer–DOX conjugates to BALB/c mice effectively inhibited the progression of the tumor, and the antitumor effect was similar to that of liposomal DOX (Doxil).

Conjugation of drugs to the dendrimers improves the drug release kinetics by avoiding burst release, however, the physical behavior such as solubility of the dendrimer will be changed too, and in most cases, this change is not desirable. To maintain the solubility of the resulted dendrimer-drug conjugates, only a few drug molecules are allowed to attach to the dendritic surface, which may lead to low drug loading capacity [20]. To address this issue, dendrimers with internal functional groups will be promising. This type of biodegradable dendrimers was reported by Shen et al. in 2013 (Fig. 10) [145]. Polyester dendrimers with internal hydroxyls were synthesized and CPT was conjugated *via* ester groups, forming dendrimer-drug conjugates like unimolecular micelles. This novel dendritic polymer–drug conjugate could achieve high drug loading capacity (up to 17.4 wt%) without change of the physical properties, thus is very promising as drug delivery systems.

3.2. Biodegradable dendrimers as drugs

Some dendrimers with inherent therapeutic effect can be directly used as drugs. During the last twenty years, several nondegradable dendrimers were proposed to be used as antimicrobial or antiviral drugs, including the most successful VivaGel®, a sulfonated PLL dendrimer, which is currently undergoing phase I/II clinical trials [146–148]. And in 2009, Blanzat and Turrin et al. presented the synthesis of biodegradable poly(phosphor-hydrazone) dendrimers with terminal phosphonic acid and alkyl chain groups which could be used as HIV antivirals for CEM-SS and MT-4 cells [149]. *In vitro* inhibitory assays were performed to investigate the influence of the length of the alkyl chain on the efficiency of these inhibitors. The highest antiviral activity was achieved using the dendrimer with a short C3 alkyl chain,

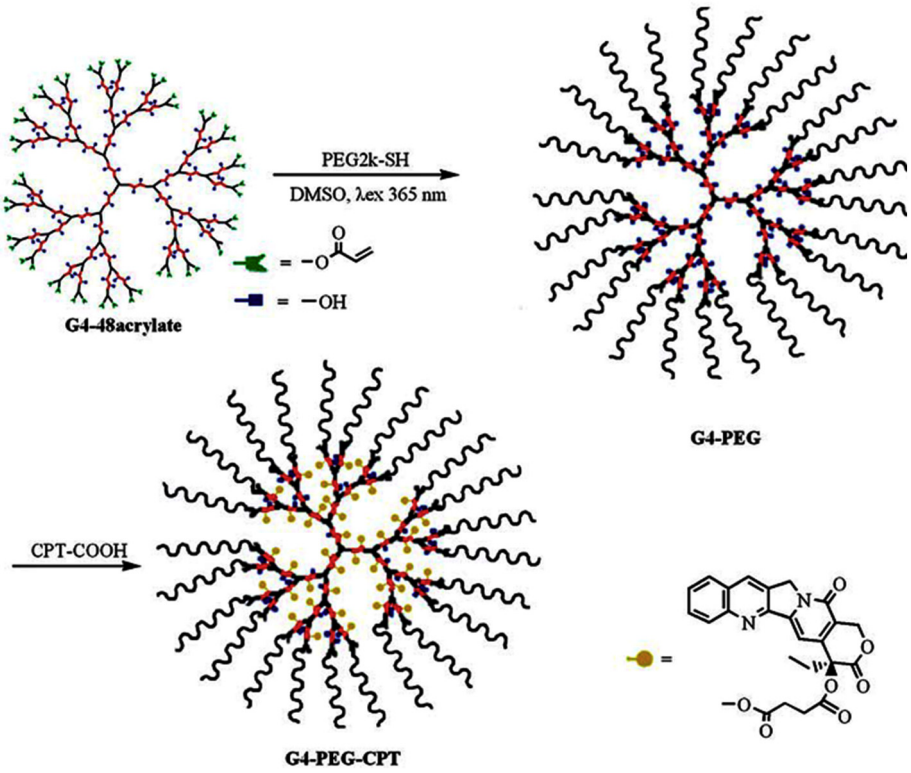

Fig. 10. Polyester dendrimers with internal conjugated CPT. Readapted with permission from Ref. [145]. Copyright © 2012, Royal Society of Chemistry.

which could interact with the lipophilic portion of the V3 loop.

In 2015, Gu et al. reported a bioinspired tryptophan-rich peptide dendrimers as a new type of dendritic peptide drugs for efficient tumor therapy [150]. This first reported therapeutic dendrimers showed remarkable supramolecular interactions with DNA through the tryptophan residues (indole rings and amino groups), and exhibited significant antitumor activity both *in vitro* and *in vivo*. Although no data about whether this dendrimer is biodegradable was supplied, it paved the way for developing novel therapeutic dendrimers.

Recently, Shen et al. reported, for the first time, a biodegradable polyacylthiourea (PATU) dendrimer with innate and potent anticancer and anti-metastatic activities (Fig. 11) [94]. The dendrimers were facilely synthesized from sequential click coupling of orthogonal monomers with high yield. The embedded thiourea groups in the dendrimer could chelate to copper ions, which is a very important micronutrient for the proliferation of cancer cells. Therefore, the dendrimer's *in vivo* anticancer activity resulted from the depletion of bioavailable copper and the subsequent suppression of angiogenesis and cellular proliferation. In comparison to some clinically used cytotoxin drugs, the dendrimer exerted intrinsic anticancer activity *via* non-cytotoxic pathways and resulted in higher therapeutic efficacy, yet without cytotoxin-induced side effects.

4. Conclusions and perspectives

Biodegradable dendrimers are promising candidates for developing novel smart drug delivery systems for the combination of the merits of biodegradability and unique structural features of dendrimers. In past decades, a large number of biodegradable dendrimers with different architectures and properties were successfully designed and synthesized for different purposes. Some of these dendrimers were employed to fabricate drug carriers *via* physical encapsulation or chemical conjugation, and a few of them even could be used as drugs directly. In comparison to nondegradable dendrimers, biodegradable dendrimers possess all merits of dendrimers, further show the advantages of being degrade into small fragments which can be metabolized or excreted from body. Several recent researches manifested that the biodegradable dendrimers exhibited significant superiority and great potential in the field of drug delivery.

However, in spite of remarkable progress have been made in the synthesis and application of biodegradable dendrimers, the clinical use of biodegradable dendrimers has still not reached the success of linear polymers and some limitations still need to be addressed. Firstly, most of the reported biodegradable dendrimers are polyester dendrimer, and many of them undergo undesirable hydrolysis, not to mention that degradation of polyester produces acid byproducts, which may cause local inflammation, thus the synthesis and application of new families of biodegradable dendrimers need to be explored. Secondly, the encapsulation of drugs to dendrimers generally accompanies with low drug capacity and inevitable burst release, while the conjugation strategy encounters the problem of inaccurate and inhomogeneous conjugation as well as low efficiency. Finally, the synthesis of most biodegradable dendrimers remains to be tedious and expensive. In fact, these obstacles may explain the much smaller number of reports involving the application of biodegradable dendrimers, in comparison to the large number of works reporting the design and synthesis of biodegradable dendrimers. Numerous efforts need to be made to explore new methodologies for preparing novel biodegradable dendrimers and more efficient drug carriers based on them. Once these problems are addressed, the superiority of biodegradable dendrimers will be fully displayed and they may play a much more important role in developing advanced drug delivery systems.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this review.

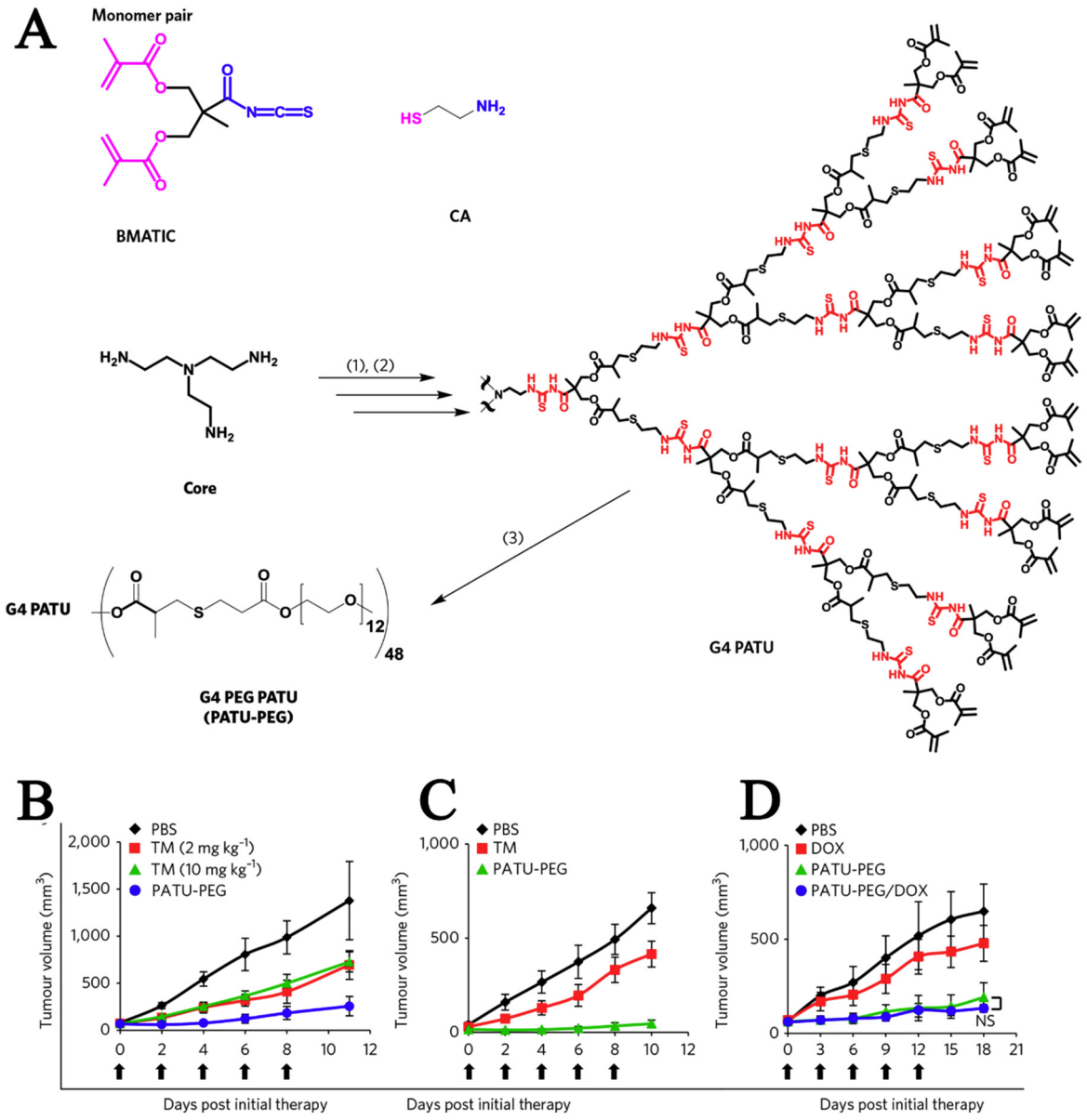

Fig. 11. (A) Synthetic route of PATU dendrimer. Tumor inhibitory effect of PATU-PEG against (B) BCap37, (C) SW620 and (D) MCF-7/ADR tumors. Readapted with permission from Ref. [94]. Copyright © 2017, Nature Publishing Group.

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