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A Review on Core–Shell Structured Unimolecular Nanoparticles for Biomedical Applications

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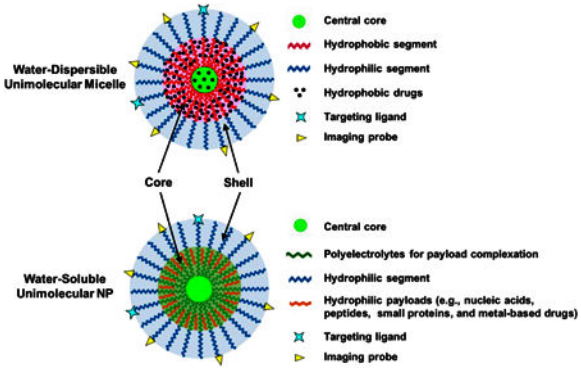
Abstract

Polymeric unimolecular nanoparticles (NPs) exhibiting a core-shell structure and formed by a single multi-arm molecule containing only covalent bonds have attracted increasing attention for numerous biomedical applications. This unique single-molecular architecture provides the unimolecular NP with superior stability both *in vitro* and *in vivo*, a high drug loading capacity, as well as versatile surface chemistry, thereby making it a desirable nanoplatform for therapeutic and diagnostic applications. In this review, we surveyed the architecture of various types of polymeric unimolecular NPs, including water-dispersible unimolecular micelles and water-soluble unimolecular NPs used for the delivery of hydrophobic and hydrophilic agents, respectively, as well as their diverse biomedical applications. Future opportunities and challenges of unimolecular NPs were also briefly discussed.

Graphical Abstract



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Keywords

Unimolecular nanoparticles; unimolecular micelles; drug delivery; nanomedicine

1. Introduction

Polymeric nanoparticle (NP)-based delivery systems have been extensively investigated to improve the diagnostic and treatment efficacy of a wide range of diseases, ranging from cancer [1–16] and cardiovascular diseases [17–26], to bacterial and viral infections [27–33]. Polymeric NPs are attractive for drug delivery applications because many polymers are biocompatible and biodegradable. Polymer chemistry is also very versatile, thereby making it possible to precisely control the molecular structure, NP morphology, and surface characteristics (e.g., zeta potential and ligand conjugation) of polymeric NPs. The design of polymeric NPs can drastically impact the safety, pharmacokinetics, pharmacodynamics, and ultimate *in vivo* fate of their payloads [6–9, 34–42].

Certain types of polymers can form NPs with a core–shell structure in aqueous media owing to the various types of inter/intra-molecular interactions, including electrostatic interactions, hydrophobic interactions, and hydrogen bonding [43–45]. A broad spectrum of payloads for therapeutic and diagnostic purposes have been delivered by polymeric NPs. The stability of the NPs, or the ability to control NP stability, is of great importance for *in vivo*/human applications. However, conventional polymeric NP systems, which mostly rely on relatively weak interactions as previously mentioned, often exhibit insufficient *in vivo* stability in terms of nanostructures [46–49]. Specifically, it is well-documented that dilution in the bloodstream, flow stress, environmental factors (e.g., pH and ionic strength), and interactions with serum proteins can lead to the disruption of the polymeric NPs before functioning [50–55]. For instance, a recent report attributed poor micelle stability to the failure of NK-911, a self-assembled polymeric micelle, at the early clinical stage as it bursts too rapidly after i.v. injection [55] Moreover, a recent study also found that more than 80% of the self-assembled PEG-polyester micelles dissociated within 1 h after intravenous administration [54].

Among all of the strategies that can be applied to address this instability issue, unimolecular NPs have received increasing attention because they are stable regardless of their concentration or the microenvironment [56]. The concept of unimolecular NPs was introduced in the 1990s [57–59]. Thereafter, development of the polymeric unimolecular NPs has been accelerated owing to their desirable characteristics as drug nanocarriers as well as versatile polymer chemistry [60–66]. In particular, polymeric unimolecular NPs formed by a single multi-arm polymer molecule containing only covalent bonds and exhibiting a core–shell structure are especially valuable for biomedical applications. Polymeric unimolecular NPs can be made from a variety of polymers. One way to classify unimolecular NPs is based on their chemical composition, which can be divided into two main categories: water-dispersible unimolecular micelles and water-soluble unimolecular NPs (Figure 1). Water-dispersible unimolecular micelles are typically formed by single/individual dendritic multi-arm amphiphilic block copolymers, conferring excellent *in vitro*

and *in vivo* stabilities [67, 68]. Their unique hydrophobic core is of particular interest in delivering hydrophobic therapeutics or imaging probes. Hydrophobic agents can be loaded into the hydrophobic core of the unimolecular micelles through hydrophobic interactions, hydrogen bonding, or covalent conjugation [67–69]. Water-soluble unimolecular NPs are typically formed by single/individual dendritic multi-arm water-soluble block copolymers [70, 71]. The cores of the water-soluble unimolecular NPs are usually polyelectrolytes (e.g., cationic or anionic polymers), which can be used to encapsulate hydrophilic payloads (e.g., nucleic acids, peptides, small proteins, metal-based drugs, etc.) via electrostatic interaction, hydrogen bonding, chelation, and/or ion–dipole interactions [70–72]. For biomedical applications, the shells of the unimolecular NPs are commonly formed by poly(ethylene glycol) (PEG) or other types of hydrophilic polymers (e.g., polyzwitterions) to provide good water dispersity, reduce opsonization during circulation in the bloodstream, and improve biocompatibility [68]. Both nanoplatforms have diverse applications.

This review focuses on the recent progress of the design and application of core–shell structured polymeric unimolecular NPs for various biomedical applications. Different types of polymeric unimolecular NPs and their diverse applications are highlighted. Future opportunities and challenges related to unimolecular NPs are also discussed briefly.

2. Types of Core–Shell Structured Unimolecular Nanoparticles

2.1. Water-Dispersible Unimolecular Micelles

Unimolecular micelles can be engineered using various types of organic NPs including dendritic polymers (e.g., hyperbranched polymers (HBPs) and dendrimers) and brush polymers as the initiating central core for the multi-arm amphiphilic block copolymers (Figure 1). Although inorganic NPs (e.g., Au NP, quantum dots, CuS NPs, and upconversion NPs) have also been employed as the central core of unimolecular micelles [73–79], those are beyond the scope of this review.

2.1.1 Unimolecular Micelles Based on Dendritic Polymers—Both HBPs and dendrimers are highly branched, three-dimensional dendritic macromolecules [80]. Their globular and dendritic architectures endow them with unique properties including abundant functional groups, intramolecular cavities, non/low entanglement, and low viscosity. HBPs and dendrimers differ in that dendrimers have regular structures, while HBPs have irregular structures [81, 82]. Dendrimers are synthesized step-by-step in an iterative fashion, while HBPs are typically synthesized via a one-step process [83]. Both HBPs and dendrimers have been widely used to fabricate unimolecular micelles.

2.1.1.1 Unimolecular Micelles Based on Hyperbranched Polymers: Hyperbranched polyesters are an attractive class of HBPs because they are biodegradable and biocompatible, which is extremely important if these molecules are to be used for drug delivery or other biological applications [84, 85]. Boltorn™ (e.g., H30 and H40) is one of the most studied hyperbranched polyesters, and its monomer unit is 2,2-bis(methylol) propionic acid [86, 87]. Because of its biodegradability, biocompatibility, globular architecture, and abundant functional groups, Boltorn hyperbranched polyesters have received a lot of attention in the design of nanoplatforms, including unimolecular NPs. Since H40 itself is hydrophobic,

when conjugated directly with PEG, it can also be used to encapsulate hydrophobic drugs [88]. However, due to the extremely small size (~3 nm) of H40, the drug (e.g., paclitaxel) loading level of H40-PEG unimolecular micelles is limited to less than 0.3 wt.% [88]. To significantly enhance the drug loading content, we and others reported H40-based unimolecular micelles formed by multi-arm amphiphilic block copolymers H40-polyester (e.g., poly (l-lactide) (PLA) and polycaprolactone (PCL))-poly(ethylene glycol) in aqueous media (Figure 2) [61, 89–96]. For example, H40 with –OH terminal groups was used as the macroinitiator to synthesize H40-PLA via ring-opening polymerization (ROP), followed by PEG conjugation via esterification [89, 90]. The H40-PLA formed a hydrophobic functional core for hydrophobic drug encapsulation, while the hydrophilic PEG shell provided the unimolecular micelles with good water dispersity. These core–shell structured unimolecular micelles can be a stable drug nanocarrier with a much higher drug loading level (for instance, ~12 wt.% for doxorubicin (Dox) [89] and ~33 wt.% for 5-fluorouracil (5-FU) [90]).

Zhang et al. also synthesized a temperature and pH dual-responsive unimolecular micelle based on H40 via reversible addition-fragmentation chain transfer (RAFT) polymerization [97]. The inner block was thermo-responsive poly(N, N-diethylacrylamide) (PDEAAM) and the outer shell was pH-sensitive cationic poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA). The size of the unimolecular micelles changed in response to both pH and temperature, which can be used for drug and gene delivery with a controlled release manner.

Hyperbranched polyglycerol (HPG) [98] is a type of water-soluble HBP that exhibits good biocompatibility and a low viscosity, prompting its use in drug nanocarrier systems. For example, a unimolecular micelle composed of an HPG core conjugated with diblock copolymer polycaprolactone-PEG (HPG-PCL-PEG) via amidization was reported [99]. These unimolecular micelles showed superior skin permeation of the entrapped payloads compared to the conventional cream formulation. Moreover, their good stability, low cytotoxicity, and ease of scaled-up production make them a promising nanoplatform for topical drug delivery.

2.1.1.2 Unimolecular Micelles Based on Dendrimers: Dendrimers are nano-sized, radially symmetric molecules with a well-defined, homogeneous, and monodispersed structure consisting of tree-like arms or branches [100]. It was first developed by Vögtle et al. in 1978 under the name of cascade polymers [101, 102]. Dendrimers can be prepared by the convergent or divergent synthesis approach [103, 104]. For the convergent strategy, it begins from the synthesis of dendrons that will eventually become the dendrimer shell. A dendrimer structure is then formed by coupling several dendrons to a multifunctional core [103, 104]. In contrast, the divergent strategy initiates growth at the core of the dendrimer and continues outward by the repetition of coupling and activation steps [103, 104]. So far, over 100 different dendrimers have been realized. Several of the most commonly referenced dendrimers include polyamidoamine (PAMAM) [105], poly(L-lysine) (PLL) [106], polyamide [107], polyester (PGLSA-OH) [108], and polypropylenimine (PPI) dendrimers [109]. The high level of control over the synthesis process gives dendrimers a perfect branching structure with a compact molecular structure, a high number of functional groups, and predictable properties. Due to these unique characteristics, tremendous progress on the

development of dendrimers for a wide range of biomedical applications has been witnessed in recent years [110–113]. Unimolecular micelles formed by dendrimer-based multi-arm star amphiphilic block copolymers have also been reported.

PAMAM dendrimers are the most common class of dendrimers suitable for many applications [114]. The original primary amino groups ($–NH_2$) on the surface of PAMAM have been modified into other functional terminals, such as –OH and –COOH, thereby allowing for versatile chemistry to form unimolecular micelles [115–121]. For example, we utilized an –OH functionalized generation 4 (G4) PAMAM (PAMAM-OH) dendrimer to grow amphiphilic block copolymer poly(L-lactide)-PEG (PAMAM-PLA-PEG) [115]. The resulting dendritic multi-arm amphiphilic block copolymer can form stable unimolecular micelles as a drug nanocarrier with a typical drug loading content around 20 wt.% [122]. Moreover, because of the ease of surface modification, the unimolecular micelle can be tailored with targeting ligands and imaging probes for multifunctionalities. Other types of polyesters (e.g., PCL and polyvalerolactone (PVL)) were also used as the hydrophobic segments in PAMAM-based unimolecular micelles [119–121].

2.1.2. Unimolecular Micelles Based on Brush-Shaped Polymers—Brush-shaped polymers are a special category of synthetic macromolecules with multiple side chains/polymers stemming from a polymer backbone [123–125]. There are three main strategies to synthesize brush-shaped polymers: “grafting through”, “grafting onto”, and “grafting from” [126–128]. In recent years, the investigation of brush-shaped core–shell unimolecular NPs has gained increasing attention. For example, a wormlike unimolecular micelle based on a densely grafted brush polymer polymethacrylate-g-(poly(ε-caprolactone)-b-poly(ethylene oxide)) (PGA-g-(PCL-b-PEO), prepared by “grafting onto” chemistry, was reported [129]. This polymer brush in an aqueous solution exhibited a uniform, wormlike conformation both before and after anticancer drug (DOX) encapsulation, as demonstrated by atomic force microscopy (AFM) images.

We also fabricated a unimolecular micelle system based on a brush-shaped amphiphilic block copolymer. The backbone of the brush-shaped polymer was poly(2-hydroxyethyl methacrylate) (PHEMA) and the side chains were poly(L-lactide)-poly(ethylene glycol) (PHEMA-PEG) [130]. The brush-shaped polymer was prepared via the “graft from” method and was able to form a stable unimolecular micelle for targeted drug delivery. Ito et al. also engineered a unimolecular NP formed by a branched graft copolymer poly(styrene-graft-PEO) that was synthesized via a “graft through” approach [60]. The polystyrene backbone of the brushed polymer served as a hydrophobic domain of the unimolecular micelle.

More recently, Tu et al. reported a unimolecular NP formed by a cyclic brush copolymer named poly(2-hydroxyethyl methacrylate-g-poly(N-isopropylacrylamide-st-N-hydroxyethylacrylamide)) (P(HEMA-g-P(NIPAAm-st-HEAAm)) (Figure 3) [131]. They found that the unimolecular micelles formed by these cyclic brush copolymers possessed better stability and a higher anti-proliferation effect compared to the ones formed by the bottlebrush analogues.

2.1.3. Other Types of Unimolecular Micelles—Unimolecular micelles formed by multi-arm amphiphilic polymers based on other types of central cores have also been reported. For example, polyhedral oligomeric silsesquioxane (POSS) with eight functional groups on the vertex of the silica cage has been used in the design of drug delivery systems due to its good biocompatible and non-toxic properties [132]. The eight corner functional groups can be conveniently used to grow multifunctional polymers. For instance, Fan et al. [133] reported a unimolecular micelle composed of POSS as the central core, PLA as the hydrophobic segment, and PEG as the hydrophilic block for drug delivery (Figure 4). In an aqueous solution, a stable unimolecular micelle with a unique core–shell structure was obtained as evidenced by DLS and TEM. The hydrophobic domain formed by POSS-PLA was loaded with the anticancer drug, DOX, with a high drug-loading content (18.5%) capable of sustained drug release.

β-CD has also been used to fabricate unimolecular NPs. β-CD is a cyclic oligosaccharide consisting of seven glucose molecules linked by α(1,4)-glucosidic bonds [134]. The 21 available hydroxyl groups on the surface of β-CD make it a suitable central core for unimolecular NPs. Lin et al. reported a β-CD-polystyrene-block-poly(3-hexylthiophene) unimolecular micelle as a potential drug nanocarrier [135].

2.2 Water-Soluble Unimolecular NPs

Water-soluble unimolecular NPs are generally designed for the delivery of hydrophilic payloads, such as metal-based compounds (e.g., platinum-based drugs), nucleic acids (e.g., siRNA and microRNA), peptides, and small proteins. These payloads are typically loaded into the unimolecular NPs, mainly through electrostatic interactions, hydrogen bonding, ion–dipole interactions, and chelation [70–72, 136–138]. Hence, polyelectrolytes are often incorporated into the design of such unimolecular NPs (Figure 1).

We reported a water-soluble unimolecular NP made of a hydrophilic multi-arm star block copolymer poly(amidoamine)-b-poly(aspartic acid)-b-poly(ethylene glycol) (PAMAM-PAsp-PEG) [136]. Carboplatin, a hydrophilic platinum-based drug, was complexed into the carboxyl-bearing PAsp segments through an ion–dipole interaction.

Jiang et al. reported a polyelectrolyte brush (PFNBr), which was a brush-like polymer consisting of a polyfluorene backbone and multiple positively charged poly(2-(dimethyl-amino)ethyl methacrylate) (PDMAEMA) side chains [72]. This unique cationic brush polymer can complex siRNA through electrostatic interactions and form an siRNA-complexed unimolecular NP. Its intrinsic fluorescence property also makes it a promising candidate for precise bioimaging.

We also reported a pH and redox dual-responsive unimolecular NP for the delivery of siRNA [137]. The unimolecular NP was formed by an H40-poly(aspartic acid-(2-aminoethyl disulfide)-(4-imidazolecarboxylic acid))-poly(ethylene glycol) (H40-P(Asp-AED-ICA)-PEG)) multi-arm star block copolymer. The cationic segments (P(Asp-AED-ICA)-PEG)) used for siRNA complexation contained disulfide bonds and were linked to the H40 core through pH-sensitive bonds. These pH and redox dual-response properties facilitate the release of the siRNA once they are taken up by the cells.

We recently reported a unique charge-conversional unimolecular NP made of multi-arm star block copolymer poly(amidoamine)–poly(aspartate diethylenetriamine-aconitic acid-*r*-imidazole)-poly(ethylene glycol) (PAMAM-PAsp(DET-Aco-*r*-Im)-PEG) for the delivery of positively charged peptides (Figure 5) [70]. In acidic conditions, the anionic PAsp(DET-Aco) segment can turn to positively charged PAsp(DET), thereby facilitating the release of peptides to function.

3. Unimolecular NPs for *In Vivo* Applications

Unimolecular NPs have been extensively investigated as drug nanocarriers for various therapeutic and diagnostic applications. In this section, we will summarize the state-of-the-art usage of unimolecular NPs for the delivery of therapeutic and diagnostic agents. Table 1 summarizes the representative core-shell structured polymeric unimolecular for biomedical applications.

3.1. Unimolecular NPs for Drug Delivery

The success of the therapeutic applications of unimolecular NPs critically depends on a rational design of the unimolecular NPs. Different therapeutic payloads may require distinctively different designs of unimolecular NPs. For instance, unimolecular micelles are used to deliver hydrophobic drugs, while water-soluble unimolecular NPs containing polyelectrolytes are needed to deliver charged payloads such as nucleic acids and peptides.

3.1.1. Unimolecular Micelles for Drug Delivery—Since Duncan and Kopecek introduced the concept of using polymers to deliver drugs back in the 1980s [139], the application of polymers in the drug delivery field has been explosively investigated. Polymeric micelles, due to their unique core–shell structure, have been extensively studied for delivering hydrophobic drugs [41, 42, 140–143]. It has been estimated that about 40% of the drugs in the market present poor water solubility [144, 145]. The inner hydrophobic core of the micelles can solubilize drugs through hydrophobic interactions and hydrogen bonding, while the hydrophilic shell can provide the micelles with good water dispersity and reduced opsonization. However, as aforementioned, the instability issue associated with traditional polymer micelles severely hinders their *in vivo* application [46–49]. Premature disruption of the micelles could lead to a burst release of the entrapped drugs, causing serious systemic toxicity and undermining their multifunctionality, including loss of specific tissue/cell targeting ability [50–52]. In contrast, judiciously designed unimolecular micelles can offer excellent *in vitro* and *in vivo* stabilities due to their covalent nature. It has been previously demonstrated that unimolecular NPs can transport hydrophobic guests into living cells under biologically relevant high-dilution conditions, which cannot be achieved by an analogous structure prepared by self-assembly [146].

Drug molecules can be encapsulated into unimolecular micelles via either physical encapsulation or chemical conjugation. All hydrophobic drugs can be easily loaded into unimolecular micelles via physical encapsulation through hydrophobic interactions and/or hydrogen bonding [61, 62, 91–93, 99, 120, 147, 148]. Thus, physical encapsulation is a more general and easier approach than chemical conjugation. However, chemical conjugation can offer stimuli-responsive drug release profiles [69, 149, 150]. We have

reported a series of drug-loaded unimolecular NPs for cancer treatment [62, 115, 116, 119, 130, 151, 152]. In order to improve delivery efficiency, various targeting ligands—such as folate (for folate receptor) [62], GE11 peptide (for epidermal growth factor receptor (EGFR)) [116], octreotide (for somatostatin receptor) [151], aptamer (e.g., A10 aptamer for prostate-specific membrane antigen) [152], and antibody (e.g., anti-CD105 monoclonal antibody (TRC105)) [115, 130]—were tagged to the surface of the unimolecular micelles for targeted cancer therapy. The resulting drug-loaded unimolecular micelles exhibited superior stability and tumor-targeting ability, as well as enhanced therapeutic efficacy. For example, aminoflavone (AF; an anticancer drug)-loaded and GE11-conjugated unimolecular micelles were tested in an orthotropic triple-negative breast cancer (TNBC) xenograft mouse model (Figure 6) [116]. GE11 peptide can bind specifically to EGFR, which is frequently amplified in TNBC tumors. The AF concentration in the tumor treated with AF-loaded, GE11-conjugated unimolecular micelles was about 72-fold and 10-fold higher than the AF concentration in the tumor treated with free AF and AF-loaded unimolecular micelles without GE11 targeting ligand, respectively (Figure 6 (B)). Remarkably, the AF-loaded, GE11-conjugated unimolecular micelles induced complete tumor regression at a significantly lower dosage (7 mg/kg) than the common dosage required for free drug (70–120 mg/kg) (Figure 6 (C)) [153–155], and this treatment did not result in any detectable systemic toxicity. A unimolecular micelle designed for the co-delivery of an anticancer drug (DOX) and an NIR-photothermal agent (benzo [1,2-c;4,5-c']bis[1,2,5]thiadiazole-4,7-bis(9,9-dioctyl-9H-fluoren-2-yl)thiophene (BBT-2FT)) for combination chemotherapy and photothermal therapy (PTT) was also reported [156]. The unimolecular micelle was formed by β-CD-poly(2-(diisopropylamino) ethyl methacrylate-oligo (ethylene glycol)-methyl ether-methacrylate) (β-CD-P(DPA-OEGMA)). The PDAP segment, with a pKa value around 6.4, is hydrophobic at neutral pH, and becomes hydrophilic in an acidic environment (pH < 6.4). The unimolecular micelles loaded with DOX and BBT-2FT showed pH-responsive drug release kinetics that enhanced the therapeutic effect against cancer cells by chemo-photothermal combination therapy. The combination therapy induced approximately 23-fold and 3-fold more cell death than chemotherapy and PTT alone, respectively.

Besides cancer therapy, drug-loaded unimolecular micelles have also been investigated for the treatment of other diseases. For instance, glaucoma is a common eye disease characterized by loss of retinal ganglion cells (RGCs), resulting in irreversible blindness. An RGC-targeted intraocular drug delivery system employing unimolecular micelles was engineered to deliver a neuroprotective drug, dehydroepiandrosterone (DHEA), to prevent RGC loss [157]. The unimolecular micelles were formed by multi-arm star amphiphilic block copolymers poly(amidoamine)–polyvalerolactone–poly(ethylene glycol) (PAMAM-PVL-PEG) conjugated with the cholera toxin B (CTB) domain that can bind specifically to GM1 ganglioside on the RGC surface. Following intravitreal administration, the CTB-conjugated (targeted) unimolecular micelles exhibited a much higher accumulation in the RGC layer than the non-targeted ones. Targeted unimolecular micelles can be detected at 7 days post-injection, while non-targeted micelles can only be detected one day post-injection. Moreover, in an acute *N*-methyl-D-aspartate-induced RGC death mouse model, the DHEA-loaded targeted unimolecular micelles exhibited a much better RGC protective effect than

the DHEA-loaded non-targeted ones after 14 days (>40 % of RGC being preserved for the targeted micelles vs. <20% of RGC being preserved for the non-targeted micelles).

A unimolecular micelle-based drug delivery system was also developed for the treatment of vascular diseases. Restenosis is the recurrence of blood vessel narrowing, leading to a restricted blood flow rate [158]. Globally, millions of patients receive open vascular interventions every year, but a significant fraction of these interventions eventually fail due to restenosis [159]. A perivascular drug delivery system consisting of drug (rapamycin)-loaded unimolecular micelles made of PAMAM-PVL-PEG and a thermosensitive hydrogel formed by PLGA-PEG-PLGA triblock copolymer (Triblock gel) was designed to inhibit restenosis after open surgery [122]. This hybrid perivascular drug delivery system provides sustained drug release for four months, while Triblock gel alone or unimolecular micelles alone only provide sustained drug release for one and two months, respectively. Remarkably, this hybrid perivascular drug delivery system produced a rare feat of 3-month restenosis inhibition in an animal model. Specifically, rapamycin-loaded unimolecular micelles in the Triblock gel inhibited restenosis by 80% and induced a larger luminal area (60% bigger) compared to its respective drug-free control.

Stimuli-responsive characteristics have also been incorporated into the unimolecular micelles to achieve controlled release of payloads to potentially achieve better therapeutic efficacy. Since NPs are largely taken up by cells through endocytosis, their subcellular trafficking pathways typically involve acidic endosomes and lysosomes. Therefore, pH-responsive unimolecular micelles have been engineered to control the drug release from the unimolecular micelles. For example, Haag et al. reported a pH-responsive unimolecular micelle formed by the hyperbranched amphiphilic block copolymer HPG-octadecane-18-PEG (HPG-C18-PEG) [160]. The amphiphilic C18-PEG block copolymer molecules were conjugated to the HPG core via a pH-responsive imine linker. In the acidic endocytic compartments, the imine linkers were cleaved quickly, thereby causing a more rapid drug (DOX) release, and subsequently leading to a better therapeutic efficacy compared to unimolecular micelles lacking a pH-responsive drug release profile in A549 lung cancer cells. Since the concentration of glutathione (GSH) (approximately 2–10 mM) is drastically higher than in the extracellular spaces (approximately 2–20 μM) [161–163], GSH-responsive unimolecular micelles for redox-responsive drug release have also been reported [96, 164, 165].

A GSH-sensitive unimolecular micelle composed of H40-PLA (as the hydrophobic core) linked to poly(2-ethoxy-2-oxo-1,3,2-dioxaphospholane) (PEP) (as the hydrophilic shell) through disulfide bonds was engineered to achieve GSH-responsive drug release [164]. GSH (2–10 mM) in the cytosol triggered the detachment of the hydrophilic PEP shell from the unimolecular micelle, which resulted in a rapid drug (DOX) release due to the disruption of the micelle structure, thereby enhancing growth inhibition in tumor cells.

Drug molecules with certain types of functional groups, such as –OH, $–NH_2$, and –C(O)–, can be covalently conjugated on unimolecular micelles to achieve stimuli-responsive drug release. We reported DOX-conjugated unimolecular micelles, where DOX was linked to the unimolecular micelles through a pH-sensitive hydrazone bond, thus taking advantage of the

13-keto position of the DOX molecule [69, 149]. Once taken up by cells through endocytosis, DOX can be easily cleaved from the unimolecular micelles in the acidic endocytic compartments. The DOX-conjugated unimolecular micelles exhibited a rapid drug release under acidic conditions. Specifically, 83% of the drug was released at a pH of 6.6 after 45 h, while only 15% of the drug was released at a pH of 7.4 after 45 h [149].

3.1.2 Water-Soluble Unimolecular NPs for Drug Delivery—Water-soluble unimolecular NPs are typically formed by employing polyelectrolytes to form the hydrophilic core and PEG as the hydrophilic shell (Figure 1). They have been used to deliver hydrophilic therapeutics, including small molecule drugs, genes, peptides, and proteins, mainly through electrostatic interactions and hydrogen bonding. More specifically, depending on the net charge of the biomacromolecule payload (e.g., nucleic acids, peptides, and proteins), unimolecular NPs are typically constructed with opposite-charged polyelectrolytes [70, 71, 137]. For small metal-based hydrophilic drugs, other interactions may also be utilized, such as ion–dipole interactions [136] and chelation [71]. Similar to self-assembled multi-molecular polymer micelles, multi-molecular polymeric NPs formed by electrostatic interactions, hydrogen bonding, and ion–dipole interactions possess insufficient *in vivo* stability because of their multi-molecular nature. Hence, the use of unimolecular NPs is more desirable.

As mentioned previously, a water-soluble PAMAM-PAsp-PEG unimolecular NP was engineered to deliver the platinum-based drug, carboplatin [136]. Carboplatin was complexed to the unimolecular NPs via pH-responsive ion–dipole interactions between the carboplatin and the carboxylate. The carboplatin-complexed unimolecular NPs exhibited excellent stability with a desirable pH-sensitive drug release profile. cRGD peptide (for integrin $\alpha_v\beta_3$-positive tumor targeting) was decorated on the surface of the unimolecular NPs for enhanced drug delivery efficiency. Liu et al. reported a unimolecular NP based on PAMAM (G3) that was conjugated with block copolymers poly(glutamic acid)-b-poly-(ethylene glycol) (PAMAM-PGA-PEG) to deliver 1,2-diaminocyclohexane-platinum(II) (DACHPt) through chelate complexation [71]. DACHPt-complexed unimolecular NPs displayed longer *in vivo* half-lives (13.2 h) than the self-assembled DACHPt-loaded micelles (7.1 h). The *in vivo* anticancer study showed that the tumor volume of the DACHPt-complexed unimolecular NP treated group was significantly smaller than that of the DACHPt-complexed self-assembled NP treated group (115 vs. 177 mm^3; note the original tumor size was 50 mm^3).

Delivery of nucleic acids is also of great interest to treat or prevent human diseases, such as genetic disorders and cancers [166, 167]. The polyplexes formed by the electrostatic interactions between cationic polymers and negatively charged genes have been widely explored to overcome the limitations associated with nucleic acids, such as limited cellular uptake due to their highly negatively charged nature, insufficient chemical stability, and short plasma half-life [168–170]. However, as aforementioned, polyplexes also exhibit poor *in vivo* stability due to various factors, including interactions with serum proteins (e.g., albumin) and *in vivo* dilution [171–174]. The use of unimolecular NPs could not only address the limitations with naked nucleic acids, but also provide excellent *in vivo* stability.

Chen et al. [137] engineered a pH and redox dual-sensitive unimolecular NP for siRNA delivery. The cationic core used for siRNA complexation contained GSH-cleavable disulfide bonds, thereby facilitating the decomplexation of siRNA from the unimolecular NPs. The cationic polymers were conjugated onto the H40 core via a pH-sensitive imine bond, which further facilitated siRNA decomplexation. The incorporation of imidazole in the unimolecular NP delivery system enhanced the endosomal escape capability of the NPs via the proton sponge effect. The resulting siRNA-complexed unimolecular NPs exhibited excellent stability. To enhance delivery efficiency, GE11 peptide was decorated on the surface of the unimolecular NPs, which was tested in EGFR-overexpressing TNBC cells. The *in vitro* gene silencing efficiency of the siRNA-complexed targeted unimolecular NPs (79 %) was comparable to the commercially available siRNA transfection agent, RNAiMAX (81 %). RNAiMAX is known to have severe cytotoxicity, whereas the unimolecular NPs exhibited a much better biocompatibility.

Unimolecular NPs can also be used to deliver peptides and small proteins. As mentioned earlier, a unique charge-conversional PAMAM-PAsp(DET-Aco-*r*-Im)-PEG unimolecular NP was developed for the delivery of a positively charged peptide, the pyruvate kinase isozyme M2 (PKM2) peptide (Figure 5) [70]. The PKM2 peptide is a fragment of the PKM2 protein that can specifically and efficiently bind with co-activator-associated arginine methyltransferase 1 (CARM1), and thus inhibits the interaction between PKM2 and CARM1 [70]. The non-methylated PKM2 peptide (nonmethyl-peptide), but not the methylated PKM2 peptide (methyl-peptide), can inhibit the CARM1-mediated methylation of PKM2. In a lung tumor metastasis mouse model, the bioluminescence intensities of lung-metastatic cells in the non-methyl PKM2 peptide-loaded unimolecular NP treated group were 5-fold lower than those in the methyl PKM2-peptide-loaded unimolecular NP treated group, indicating that the PKM2 peptide delivered by the unimolecular NPs successfully inhibited breast cancer lung metastasis by disrupting the metabolic energy balance in cancer cells (Figure 7).

Dai et al. [175] fabricated a dendritic poly(amido amine)-b-poly(ε-caprolactone)-b-poly(d-gluconamidoethyl methacrylate) (PAMAM-PCL-PGAMA) block copolymer for the delivery of Concanavalin A (Con A) protein. Con A is a carbohydrate-binding protein, and thus can bind to the sugar molecules in dendritic polymers. These unimolecular NPs were more stable than those self-assembled from their linear counterparts. Similarly, host–guest interactions (e.g., cyclodextrin and adamantane) or biotin/avidin interactions could also be potentially incorporated into the unimolecular NP systems.

3.2. Unimolecular NPs for Bioimaging

Bioimaging is a prominent area of research aiming at extending or developing novel tools for diagnosis with high specificity and quality [176, 177]. Most of the bioimaging probes currently used are small molecular compounds, such as organic fluorescent agents for optical imaging, metal ions for magnetic resonance imaging (MRI), and radiolabeled molecules for positron emission tomography (PET) [177, 178]. Although they have shown some utility, clinical applications of these bioimaging probes are still hindered by low specificity and sensitivity, instability, and potential toxicity [179–181]. Unimolecular NPs

have emerged as an excellent candidate for bioimaging probes. Their high loading capacity and versatile chemistry allow encapsulation or conjugation of imaging probes for enhanced diagnosis.

Optical imaging utilizes photons emitted from fluorescence or bioluminescence probes. It is a fast and inexpensive approach [176, 182]. DOX, a common anticancer drug, is also fluorescent (red) and thus it is suitable for optical imaging. Hence, DOX-encapsulated unimolecular NPs can be used for optical imaging. For instance, Xu et al. reported an aptamer-conjugated and DOX-loaded unimolecular micelle to target prostate cancers [152]. A10 aptamer, which can specifically recognize the prostate-specific membrane antigen (PSMA) abundantly expressed on the surface of prostate cancer cells, was used as the targeting ligand. In tumor-bearing mice, the DOX fluorescence intensity measured by optical imaging suggests that targeted unimolecular micelles exhibited a much higher tumor accumulation than non-targeted micelles and free DOX. However, one concern with utilizing imaging probes loaded into NPs via physical encapsulation to localize the NPs *in vitro* and *in vivo* is that the imaging probes are continuously released from the NPs. Therefore, physically encapsulated imaging probes may not result in the precise localization of the NPs. Owing to the large number of surface functional groups on the unimolecular NPs, imaging probes can also be covalently linked to the NPs. For example, to track the unimolecular NPs, Cy5.5 molecules were conjugated onto the distal ends of the PEG arms [116, 118]. Another approach to endow the unimolecular NPs with optical imaging properties is to fabricate the NPs with fluorescent building segments. We also reported a self-fluorescent unimolecular micelle system for targeted drug delivery. The unimolecular NPs were formed by H40-**b**iodegradable **p**hoto-**l**uminescent **p**olymer-poly(ethylene glycol) (PEG) (H40-BPLP-PEG) [183]. The hydrophobic BPLP segment was self-fluorescent, thereby making the unimolecular micelle self-fluorescent that is suitable for optical imaging. Self-fluorescent unimolecular micelles can also serve as drug carriers for cancer-targeted delivery. The combination of its intrinsic fluorescence properties and its capability of drug delivery holds great promise for cancer theranostics.

Pu et al. reported a bottom-up strategy to construct water-soluble fluorescent unimolecular NPs based on the cationic oligofluorene-conjugated POSS dendritic polymer for fluorescence amplification in cellular imaging [184]. The high quantum yields (e.g., 0.85 in water and 0.80 in PBS) and good signal amplification capability of POSS-based molecules allow for high quality biological imaging even with a small amount of indicator dyes, thereby avoiding the undesirable side effect of elevated dye concentrations. The emission wavelength, charged nature, and diameter of POSS-based fluorescent unimolecular NPs can be easily adjusted through chemical modification of the fluorescent arms so as to fulfill the different requirements of specific applications.

Another widely used bioimaging modality is MRI, which is an extremely versatile anatomical imaging technique that generates high quality images [185, 186]. Paramagnetic contrast agents (e.g., gadolinium (Gd)) can enhance the signal intensity of T1-weighted MRI images [187]. However, the commercial products for Gd-based agents, such as Gd-DTPA (Magnevist®; DTPA: diethylenetriaminepentaacetic acid), Gd-(DTPA-BMA) (Omniscan; DTPA-BMA: di-ethylenetriaininepentaacetic acid-bis(methylamide)), and Gd-DOTA

Dotarem®; DOTA: 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid), often exhibit a rapid clearance rate and no specificity [188, 189].

Unimolecular NPs can be used to adequately address these concerns. Li et al. reported a unimolecular micelle formed by H40-star-(PCL-b-POEGMA/Gd/FA) for cancer-targeted MRI [148]. *In vitro* MRI experiments revealed considerably enhanced T1 relaxivity for Gd-loaded unimolecular micelles (18.14 s^{-1} mm^{-1}) compared to that of small molecular DOTA–Gd complexes (3.12 s^{-1} mm^{-1}). Further *in vivo* MRI experiments in rats showed prominently positive contrast enhancement in the major organs. Specifically, in the first 20 min, the contrast-to-noise ratio (CNR) in the heart, kidney, and liver dramatically increased. Both the heart and kidney reached the highest CNR at 20 min post-injection, while the CNR of the liver reached a maximum at 20 h post-injection.

PET imaging has become increasingly popular in both preclinical and clinical settings as this non-invasive imaging modality is tomographic in nature, has excellent tissue penetration as well as high sensitivity and specificity, and can observe functional changes over a short time period [190, 191]. As such, PET-based nanomedicine has gained increasing attention during the last decade. The use of unimolecular NPs for PET imaging has also been reported. For instance, Xiao et al. [150] engineered a unimolecular micelle made of a hyperbranched amphiphilic block copolymer (Figure 8). NOTA (a macrocyclicchelator for ^{64}Cu-labeling) and cRGD peptide (for integrin $\alpha_v\beta_3$-positive tumor targeting) were linked to the surface of the unimolecular micelles. *In vivo* PET imaging demonstrated a higher tumor accumulation of ^{64}Cu-labeled targeted unimolecular micelles (e.g., 5.7 % ID/g at 4 h post injection) than the non-targeted ones (e.g., 2.6 % ID/g at 4 h post injection). Injection with a blocking dose of cRGD peptide, along with ^{64}Cu-labeled targeted unimolecular micelles, significantly reduced tumor uptake (e.g., 3.2 % ID/g at 4 h post injection) to a level similar to the non-targeted ones, indicating integrin $\alpha_v\beta_3$-specific binding of ^{64}Cu–labeled targeted unimolecular micelles. In addition, DOX was also conjugated to the unimolecular micelles via a pH-labile hydrazine bond, allowing for optical imaging as well. The *ex vivo* fluorescence imaging of the excised tumors also revealed a higher tumor accumulation of targeted micelles compared to the non-targeted control.

3.3. Unimolecular NPs for Nanotheranostics Applications

Nanotheranostics, the use of nanotechnology for the integration of therapy and diagnostics, may offer new opportunities for “personalized nanomedicine” [192–194]. Unimolecular micelles can conveniently incorporate therapeutic and diagnostic agents to achieve multifunctionality due to their excellent stability, high loading capacity, and versatile chemistry [67, 68]. Therefore, unimolecular micelles can be a desirable platform for nanotheranostics [115, 130, 150, 152, 183, 195–199].

We developed a multifunctional unimolecular micelle for targeted neuroendocrine (NE) cancer theranostics [195]. The unimolecular micelle was formed by multi-arm star amphiphilic block copolymer PAMAM-PVL-PEG conjugated with KE108 peptide as a targeting ligand and Cy5 dye as an optical imaging probe (abbreviated as PAMAM-PVL-PEG-KE108/Cy5) (Figure 9). The targeted unimolecular micelles exhibited a much higher tumor accumulation than that of the non-targeted micelles in an NE-tumor-bearing mouse

model based on *in vivo* optical imaging. Moreover, the drug (thailandepsin A (TDP-A))-loaded targeted unimolecular micelles induced the highest antitumor efficacy (92 % tumor reduction compared to the control group) without detectable systemic toxicity.

Hu et al. fabricated a theranostic unimolecular NP formed by hyperbranched polyprodrug amphiphiles consisting of a hyperbranched core conjugated with reduction-activatable camptothecin (CPT) prodrugs and MRI contrast agent (Gd-DOTA), and hydrophilic coronas functionalized with guanidine residues (abbreviated as H-P(CPTM-co-DOTA(Gd))-b-P(OEGMA-co-GPMA), thus enabling a combination of chemotherapy and MRI [196]. Upon cellular internalization, CPT in its active form was released from the polyprodrug unimolecular NPs under intracellular cytosol reductive conditions (e.g., cytosol GSH ~10 mM). Synchronously, the MR contrast performance was also enhanced (~9.6-fold) in the reductive environment due to the hydrophobic-to-hydrophilic transition of the hyperbranched cores. Furthermore, the unimolecular NP exhibited a long blood circulation time ($t_{1/2}$ ~10.6 h), enabling this unimolecular NP to be a promising candidate for synergistic imaging/chemotherapy.

The tumor-targeted combination of chemotherapy and computed tomography (CT) imaging enabled by a unimolecular micelle system has also been demonstrated [197]. The unimolecular micelle was formed by a 21-arm star-like triblock polymer of β-cyclodextrin-[poly(ε-caprolactone)-poly(2-aminoethyl methacrylate)-poly(poly(ethylene glycol) methyl ether methacrylate)]$_{21}$ [β-CD-(PCL-PAEMA-PPEGMA)$_{21}$] (Figure 10). The micelles can encapsulate anticancer drugs, such as DOX, and serve as a template for fabricating small gold NPs AuNPs) for CT imaging. *In vivo* CT imaging revealed that the CT signals in the tumor sites treated by β-CD-(PCL-PAEMAPPEGMA)$_{21}$/AuNPs/DOX unimolecular micelles were significantly higher than those of Omnipaque, a commercially available iodinated contrast agent for CT imaging. Specifically, compared to pre-injection, the magnitude of CT value improvement in the tumor sites was much greater in the unimolecular micelle treated group (32, 54, 65, or 71% of increase after 0.5 1, 2, or 4 h post injection, respectively) than in the Omnipaque treated group (18, 26, 36, or 43% of increase correspondingly). Moreover, the unimolecular micelles induced ~87% tumor reduction compared to the control group (PBS). Collectively, this platform holds great promise for combination CT imaging and chemotherapy.

4. Conclusions and Future Perspectives

In this review, we have surveyed recent progress on unimolecular NPs, including the architecture of water-dispersible unimolecular micelles and water-soluble unimolecular NPs, as well as their potential therapeutic and diagnostic applications. In contrast to multi-molecular self-assembled polymeric NPs, unimolecular NPs can offer excellent *in vitro* and *in vivo* stabilities due to their covalent nature. In addition, multifunctional unimolecular NPs can be conveniently fabricated due to their unique chemical structures and versatile chemistry. Unimolecular NPs, and in particular, unimolecular micelles, have been extensively investigated for targeted cancer therapy and, more recently, for targeted cancer theranostics. Unimolecular NPs have also been explored to treat a number of other diseases including vascular and eye diseases, as well as genetic disorders. Their diverse polymer

chemistry makes it possible to design numerous desirable unimolecular NP platforms for different applications.

Despite their promise, some challenges exist for clinical translation. First, the synthesis process for the multi-arm polymer molecules used to form the unimolecular NPs may be more complex than for linear polymers. Thus, more facial polymer synthesis and conjugation strategies to fabricate well-defined multi-arm polymers are highly desirable. Of note, once a well-controlled scale-up synthesis process for the multi-arm polymers is established, it is expected that the unimolecular NPs will exhibit better reproducibility and quality assurance than multi-molecular self-assembled polymeric NPs. The unimolecular NPs can readily form in an aqueous solution and stay as intact NPs during freezing drying and the re-dispersion process, while the formation of multi-molecular nanoplatforms requires the optimization of various parameters, including concentrations, temperatures, solvents, and processing parameters. The stability of multi-molecular nanoplatforms is also affected by a number of processes (e.g., freezing drying and re-dispersion) and various factors (e.g., concentration, flow stress, interaction with serum proteins, etc.). The second challenge is a lack of fundamental understanding of the interactions between unimolecular NPs and cells/tissues. In contrast to some of the well-investigated drug delivery systems (e.g., liposomes and multi-molecular polymer micelles), exploration of core-shell structured unimolecular nanoparticles is still largely limited to small animal (e.g., mouse) experiments. Thus, more in-depth understanding of the interactions between unimolecular NPs and cells/tissues, and more comprehensive investigation on their *in vivo* behaviors including pharmacokinetics, pharmacodynamics, and biosafety needs to be carried out before clinical translation.

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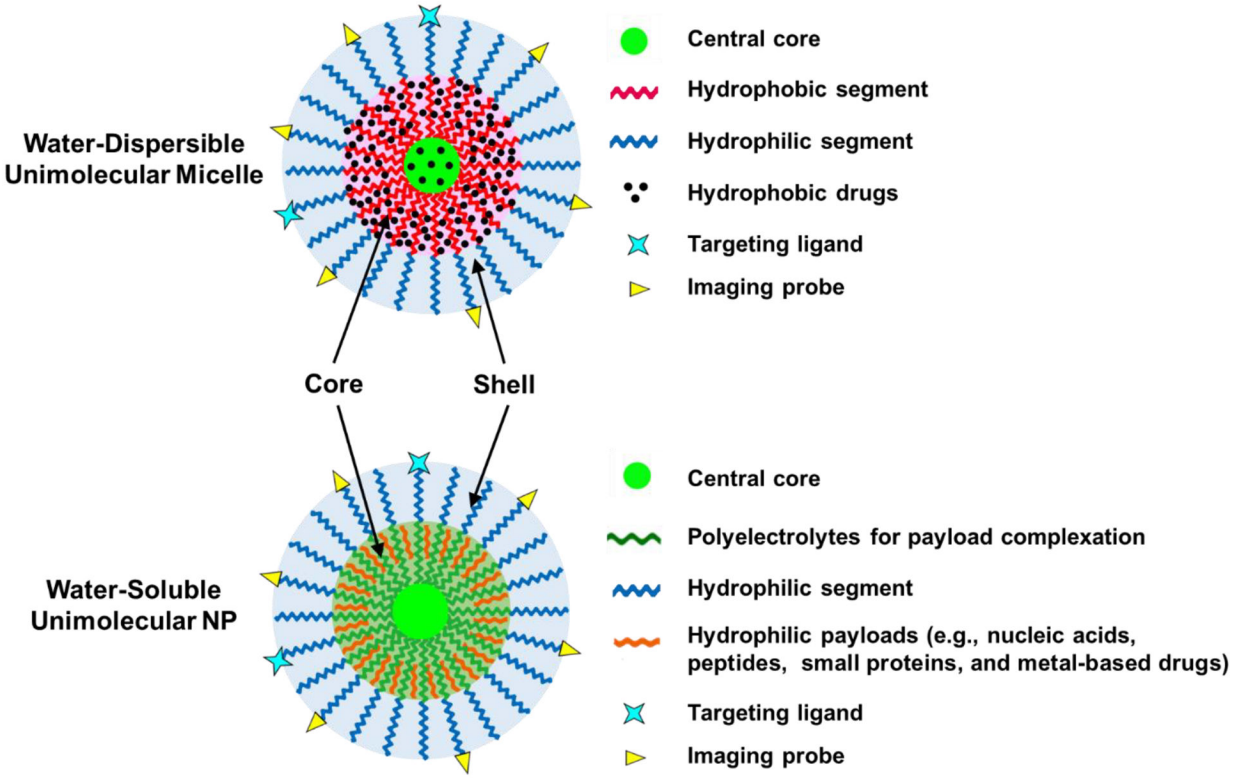

Figure 1:

An illustration of a representative multifunctional water-dispersible unimolecular micelle and a water-soluble unimolecular NP. The functional core of the water-dispersible unimolecular micelle is formed by hydrophobic segments and is used to encapsulate hydrophobic drugs. The functional core of the water-soluble unimolecular NP is typically formed by polyelectrolytes and is usually used to encapsulate hydrophilic payloads. The hydrophilic shell for both types of unimolecular NPs is typically formed by hydrophilic segments, such as PEG and polyzwitterions. The hydrophilic shell provides the NP with good water dispersity and better biocompatibility. It also helps to reduce opsonization during circulation in the bloodstream.

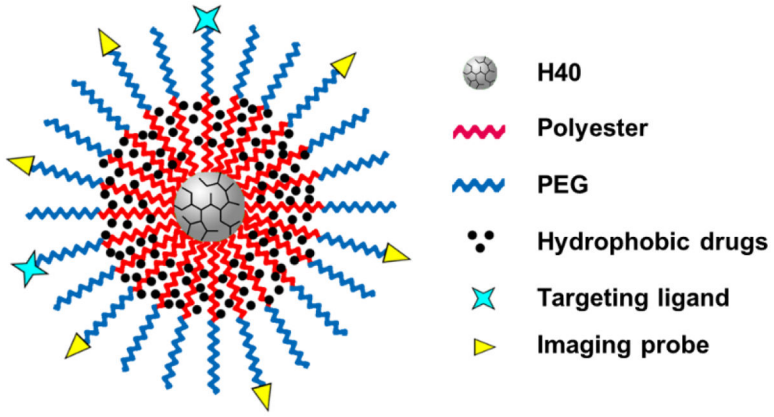

Figure 2:
A representative illustration of an H40-based unimolecular micelle formed by a single multi-arm star amphiphilic block copolymer H40-polyester (e.g., (PLA) and (PCL))-PEG.

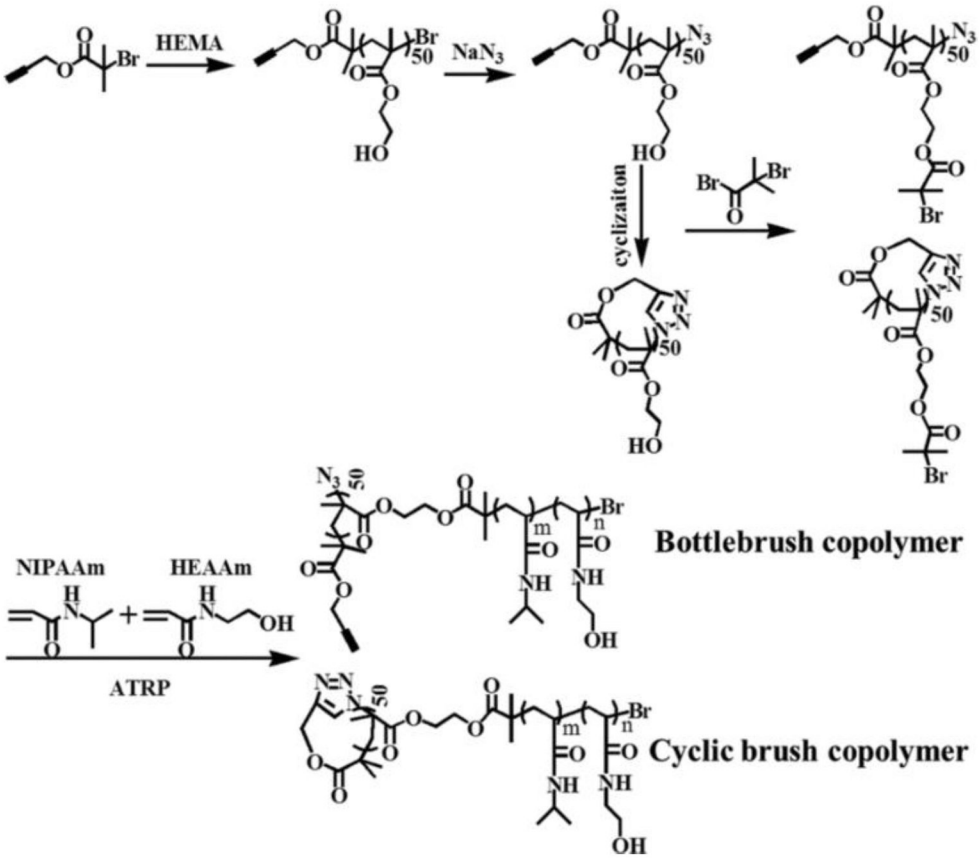

Figure 3:
Synthesis of cyclic brush and bottlebrush copolymers. Reproduced with permission from Ref. [131].

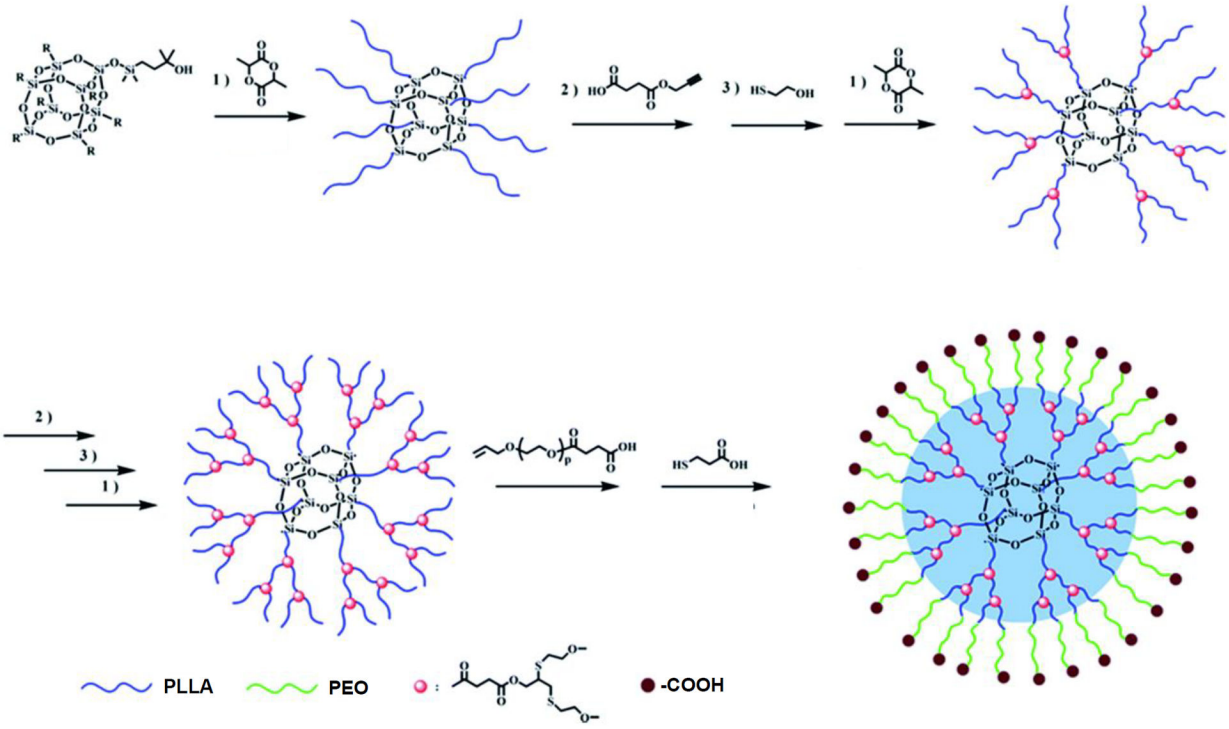

Figure 4:
Schematic illustration of the core–shell structured unimolecular micelle formed by the amphiphilic block copolymer POSS-(G3-PLLA-b-PEO-COOH)$_8$. Reproduced with permission from Ref. [133].

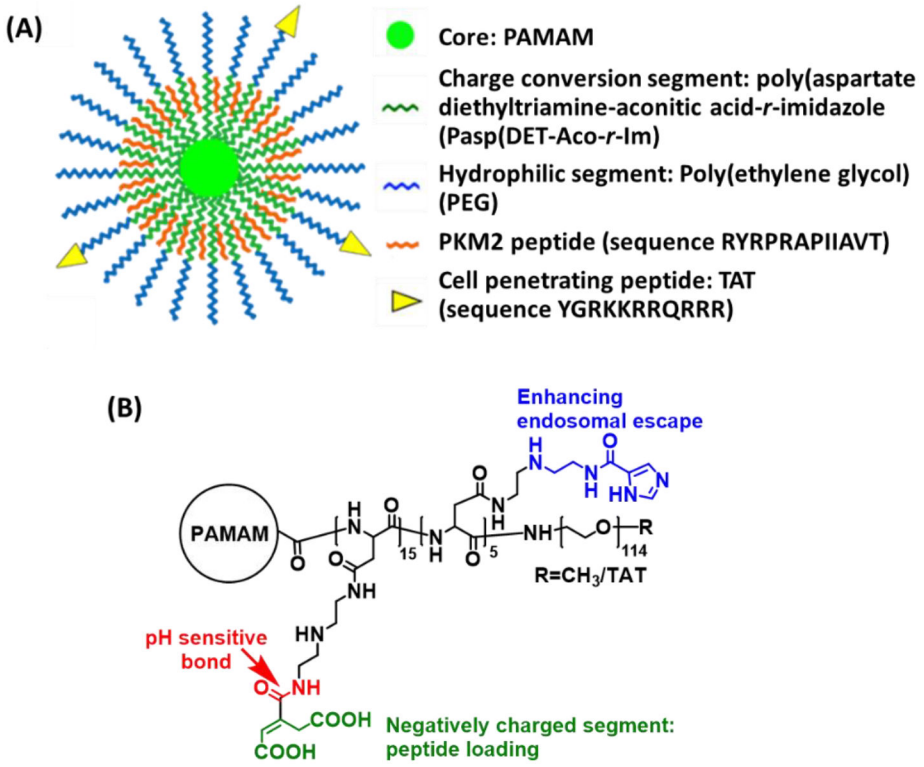

Figure 5.

(A) Illustration of the unimolecular NP for PKM2 peptide delivery. (B) Chemical structure of PAMAM-PAsp(DET-Aco-*r*-Im)-PEG. Reproduced with permission from Ref. [70].

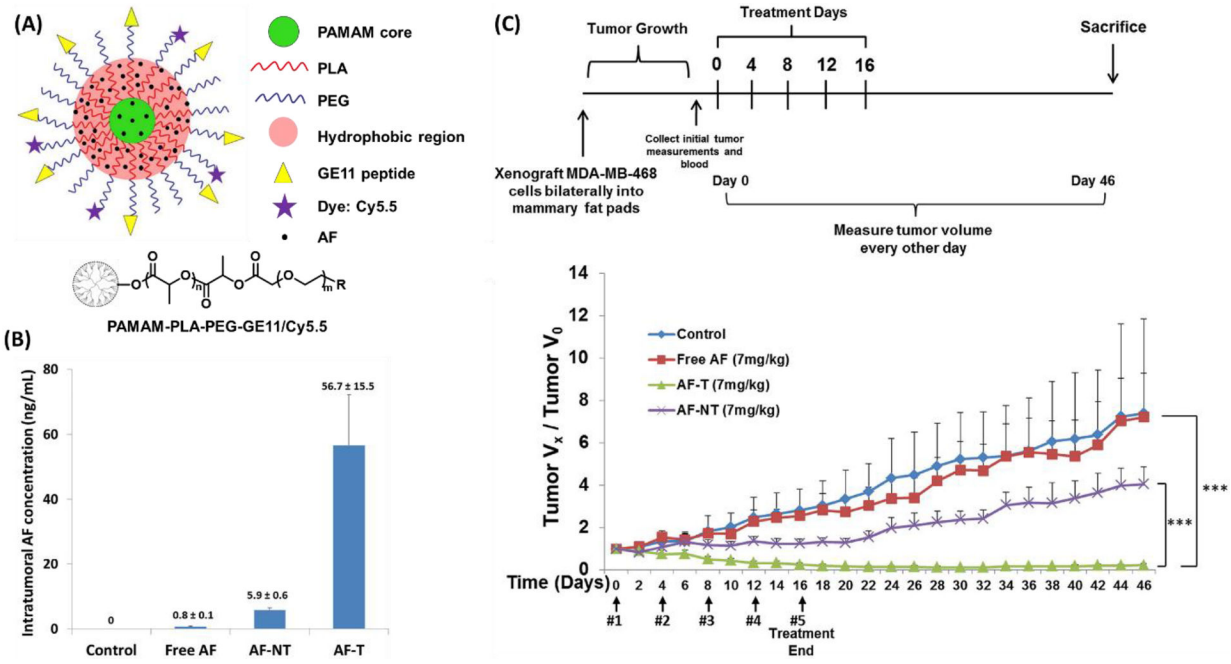

Figure 6:

(A) A schematic illustration of multifunctional unimolecular micelles formed by multi-arm star amphiphilic block copolymer PAMAM–PLA–PEG–OCH_3/Cy5.5/GE11 for targeted triple-negative breast cancer therapy. (B) Graphical representation of AF concentration in the tumors of nude mice treated with saline control, free AF, and AF encapsulated in GE11-conjugated targeted (AF-T) or non-targeted (AF-NT) micelles as determined by LC/MS/MS. (C) Anticancer study of AF-loaded, GE11-conjugated unimolecular micelles in an MDA-MB-468 TNBC xenograft mouse model. Reproduced with permission from Ref. [116].

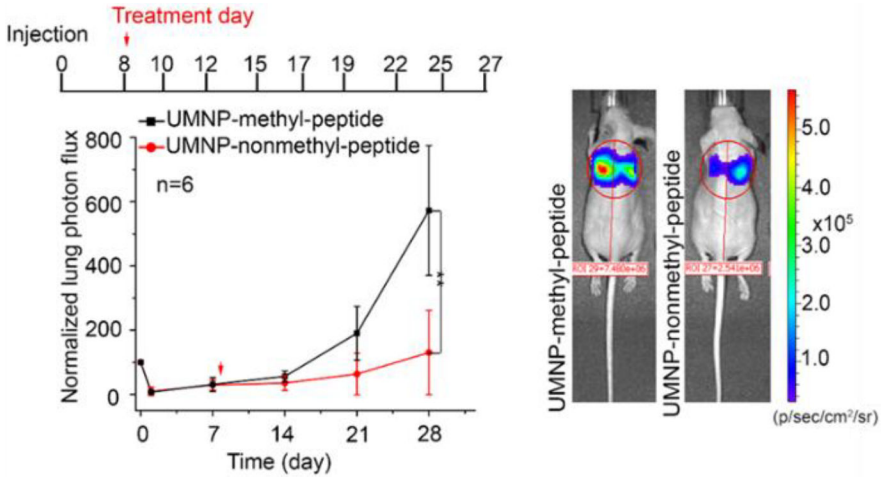

Figure 7.

Inhibition of PKM2 methylation using a competitive PKM2 peptide reduces tumor lung metastasis *in vivo*. Bioluminescence at indicated times was measured in the lung when mice (n=6) were treated with unimolecular NPs loaded with methyl PKM2 peptide (UMNP-methyl-peptide) or unimolecular NPs loaded with non-methyl PKM2 peptide (UMNP-nonmethyl-peptide). Representative bioluminescence images of mice after four-week treatment with UMNP-methyl-peptide (n=4) or UMNP-nonmethyl-peptide (n=5) via retroorbital injection at the indicated times after tumor introduction. The color scale depicts the photon flux (photons per second) emitted from the xenografted mice. Reproduced with permission from Ref. [70].

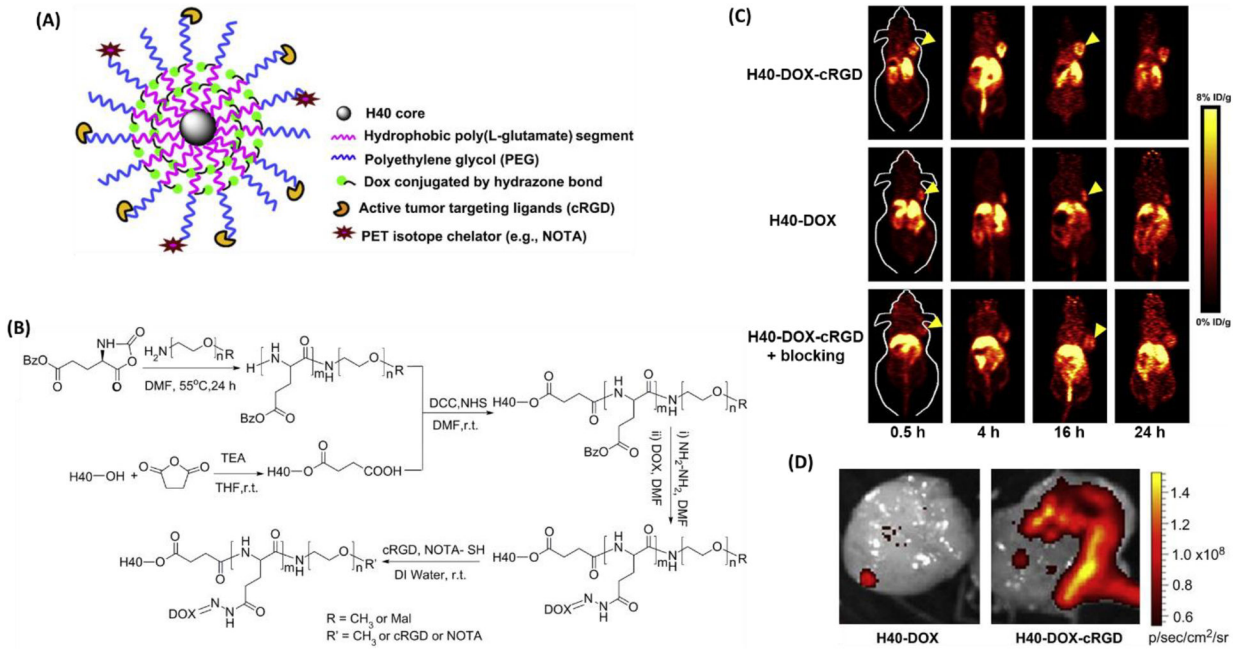

Figure 8:

(A) A schematic illustration of the multifunctional unimolecular micelle formed by H40-P(LG-Hyd-DOX)-b-PEG-OCH_3/cRGD/NOTA(^{64}Cu). (B) The synthetic scheme for H40-P(LG-Hyd-DOX)-b-PEG-OCH3/cRGD/NOTA(^{64}Cu). (C) PET imaging of ^{64}Cu-labeled nanocarriers in U87MG tumor-bearing mice. (D) *Ex vivo* fluorescence imaging of excised U87MG tumors, with the excitation and emission set for DOX fluorescence. Reproduced with permission from Ref. [150].

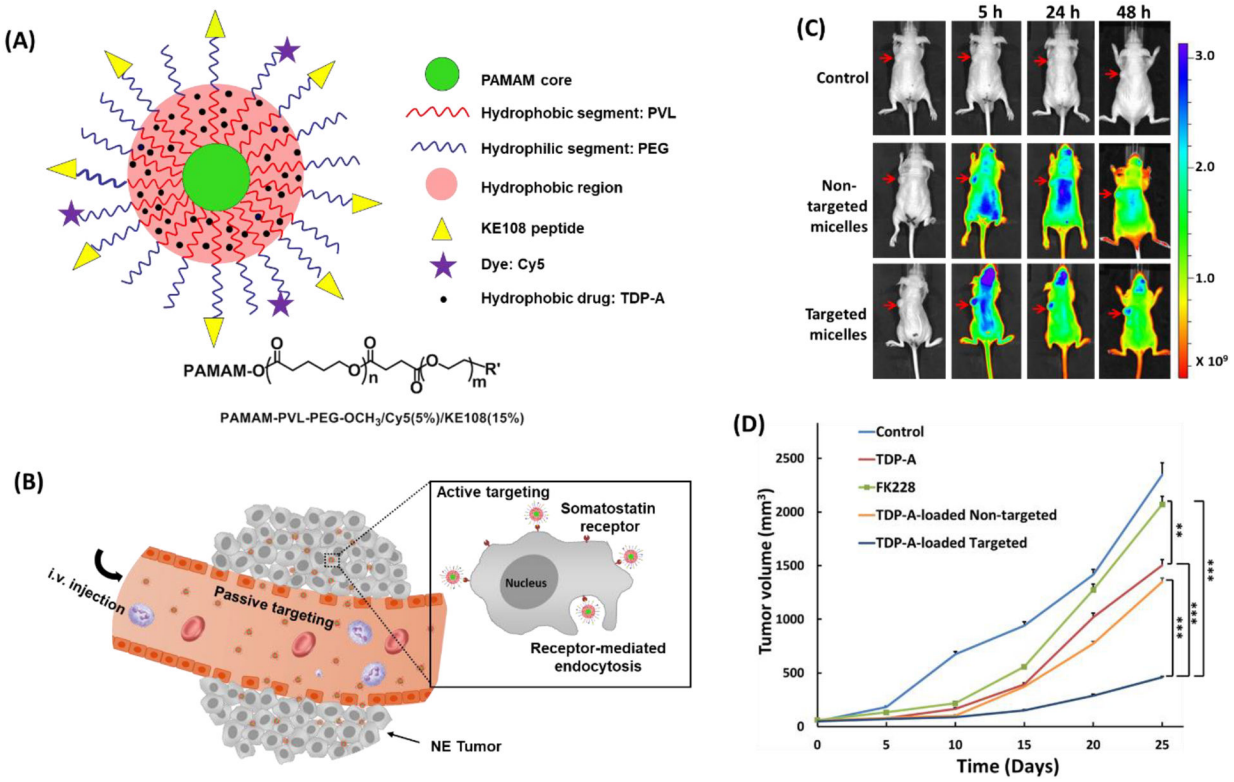

Figure 9:

(A) A schematic illustration of the multifunctional unimolecular micelle formed by the multi-arm star amphiphilic block copolymer PAMAM–PVL–PEG–OCH_3/Cy5/KE108 for targeted NE cancer therapy. (B) A schematic illustration of the passive and active tumor targeting capabilities exhibited by the multifunctional unimolecular micelles after i.v. injection. (C) *In vivo* near-infrared fluorescence imaging of subcutaneous BON tumor-bearing mice treated with saline (control), non-targeted micelles conjugated with Cy5, and targeted micelles conjugated with KE108 and Cy5; arrows point to the tumor sites. (D) *In vivo* anticancer efficacy of different TDP-A formulations in BON tumor xenografts. Reproduced with permission from Ref. [195].

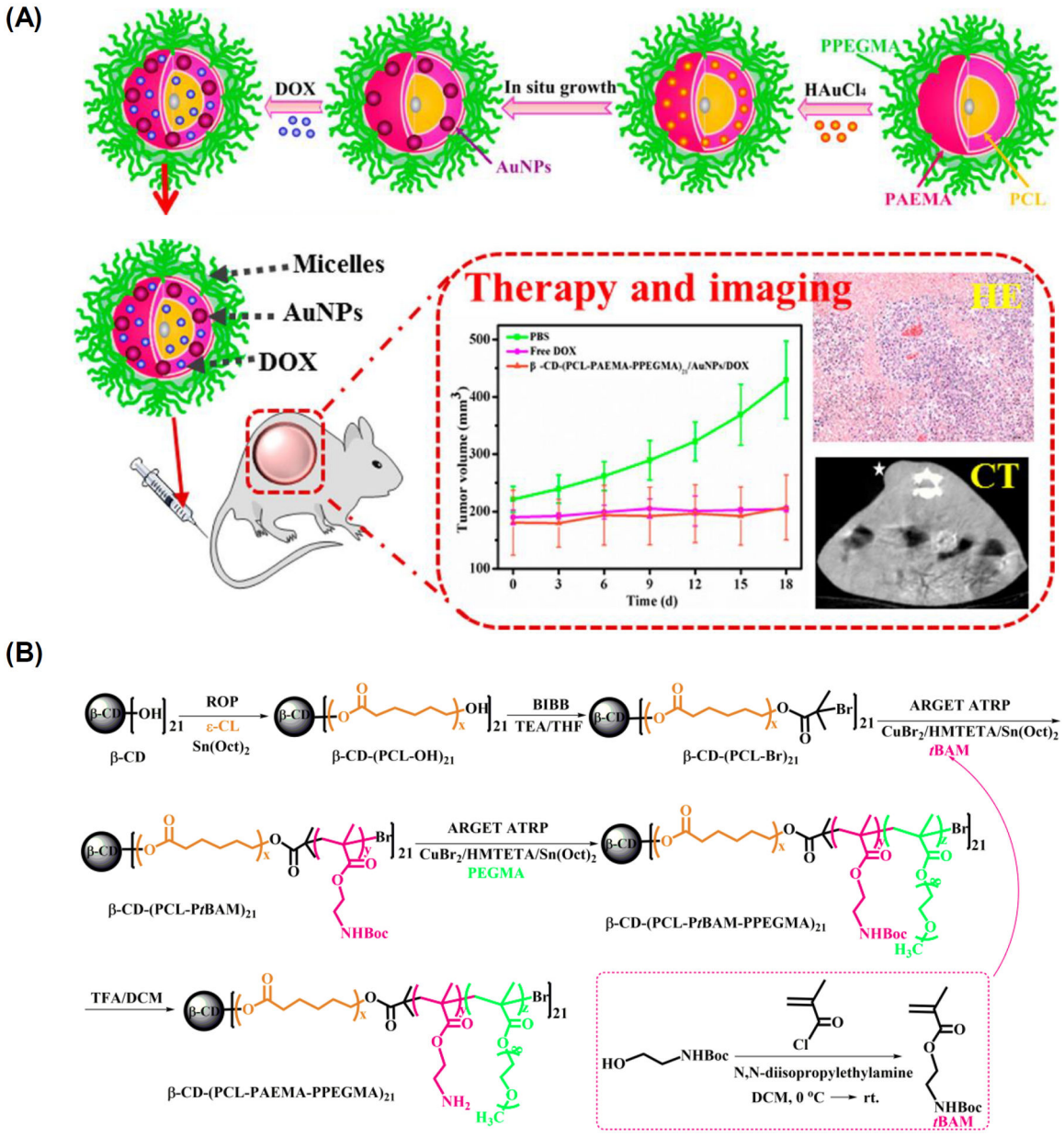

Figure 10.

(A) Schematic representation of the fabrication of a dual-functional β-CD-(PCL-PAEMA-PPEGMA)$_{21}$/AuNPs/DOX nanoplatform for cancer theranostics. (B) Synthetic route of β-CD-(PCL-PAEMA-PPEGMA)$_{21}$. Reproduced with permission from Ref. [197].

Table 1:

Representative polymeric unimolecular NPs for biomedical applications.

	Chemical composition	Therapeutic payloads	Imaging Probes	Reference
Water-dispersible unimolecular micelles	H40-PLA-PEG	DOX	-	62
	H40-PCL-PEG	Resveratrol	-	151
	PAMAM-PLA-PEG	DOX	^{64}Cu (PET)	115
	PAMAM-PVL-PEG	TDP-A	Cy5 (optical imaging)	120
	PGA-g-(PCL-b-PEG)	DOX	-	129
	POSS-(G3-PLLA-b-PEO-COOH)$_8$	DOX	-	133
	β-CD-P(DPA-co-OEGMA)	DOX + BBT-2FT	-	156
	H40-BPLP-PEG	DOX	BPLP (self-fluorescent)	183
	H-P(CPTM-co-DOTA(Gd))-P(OEGMA-co-GPMA)	CPT	DOTA/Gd (MRI)	196
	β-CD-(PCL-PAEMA-PPEGMA)$_{21}$/AuNPs	DOX	AuNPs (CT imaging)	197
Water-soluble unimolecular nanoparticles	PAMAM-PAsp-PEG	Carboplatin	Cy5 (optical imaging)	136
	PAMAM-PGA-PEG	DACHPt	-	71
	PFNBr-PDMAEMA	siRNA	-	72
	H40-P(Asp-AED-ICA)-PEG	siRNA	Cy5 (optical imaging)	137
	PAMAM-PAsp(DET-Aco-r-Im)-PEG	Peptide	-	70