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Recent Advances in Bio-Inspired Versatile Polydopamine Platforms for "Smart" Cancer Photothermal Therapy

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Abstract Although photothermal therapy (PTT) has been developed for fighting cancers, the degradative, toxic, and metabolic nature of photothermal conversion materials (PCMs) has prevented them from being clinically implemented. Taking advantage of the surface modification strategy of mussel-inspired dopamine chemistry and its excellent photothermal conversion effect, polydopamine (Pdop) represents a versatile PTT platform, providing strategies and methods for the construction of novel Pdop-functionalized PCMs. Thanks to its adhesion and secondary reactivity, Pdop can be deposited on virtually all substrates to improve their bioavailability and biocompatibility. Pdop-based PCMs could not be only functionalized with small biomolecules *via* chemical bonds and/or noncovalent force but also modified with functional polymers *via* either the "grafting to" or "grafting from" method. This review highlights the synthetic methods, therapeutic strategies, and designs of PCMs based on Pdop in recent years to explore its scope and limitations.

Keywords Polydopamine; Photothermal therapy; Drug delivery systems; Polymers; Tumor theranostics

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INTRODUCTION

Phototherapy, a treatment that involves exposing patients to light, has been used for thousands of years to help relieve a variety of conditions, such as psoriasis, vitiligo, and skin cancer.[1] The development of the laser has revolutionized phototherapy by providing a light source that emits photons in a coherent and narrow beam.[2] Photothermal therapy (PTT) that employs photothermal conversion materials (PCMs) to amplify the therapeutic effectiveness of light radiation has been developed.[3–6] PTT is an effective, selective, and nontoxic method that often reverses resistance, making it a complementary and alternative treatment.[7] In the past few decades, with the development of nanotechnology, PTT has attracted tremendous attentions (Fig. 1). Numerous inorganic and organic PCMs have demonstrated great potential for PTT of tumors and diseased tissue, producing positive results in both *in vitro* and *in vivo* studies.[8,9] Many reviews focused on the development of PTT and treatment protocols based on traditional or innovative PCMs, providing intuitive, vivid, and specific insights to the readers.[7,10–12] Noble and transition metal nanoparticles,[11,13] carbon nanomaterials,[14,15] synthetic colorants,[9,16] and conjugated polymers[17,18] are widely used in PTT due to their efficient photothermal conversion effect (Fig. 2). However, most of these agents have not yet been clinically implemented, due to concerns about potential long-term side effects.[19,20] The development of novel PCMs that consist of biocompounds derived from living organisms would be advantageous for *in vivo* applications, since it would obviate the

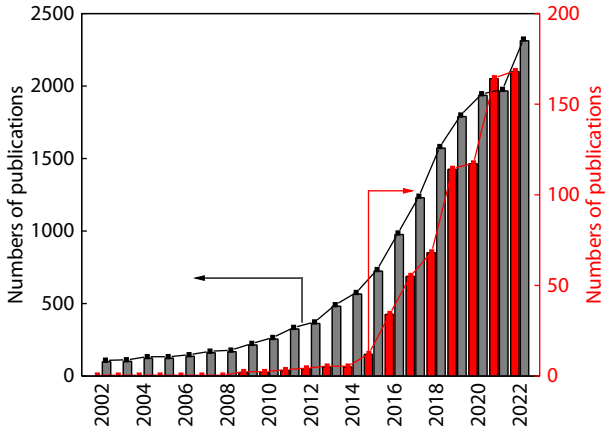

Fig. 1 Data statistics of publications with the topic of "photothermal therapy" (gray) and "photothermal therapy and polydopamine" (red) based on Web of Science searching conducted on November 11, 2022.

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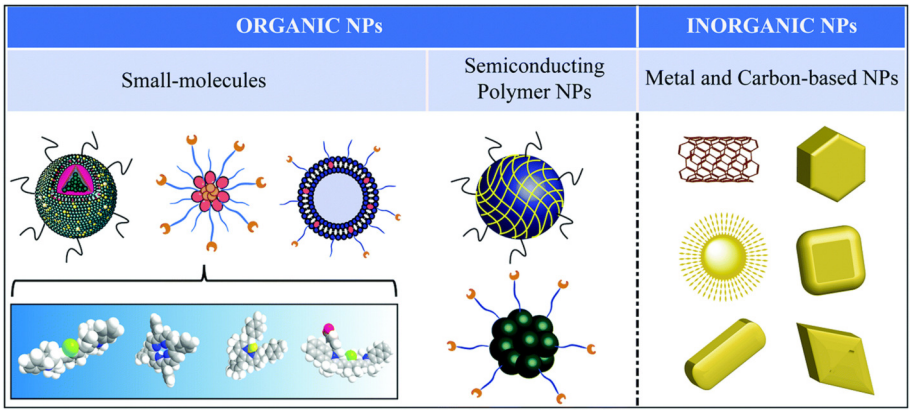

Fig. 2 Classification of PCMs. (Reproduced with permission from Ref. [5]; Copyright (2012) The Royal Society of Chemistry).

deleterious effects associated with the long-term retention of foreign substances in patients, and these agents could be metabolized, achieving biodegradation.[21,22] Melanin, a biopolymer, has been found in a variety of living organisms with good photothermal conversion efficiency, providing protection against ultraviolet radiation and absorbing light in the near-infrared range.[23] Dopamine, a precursor for melanin synthesis, has been used to generate biomimic nanoparticles with similar properties. Taking advantages of surface modification strategies of dopamine chemistry and its excellent photothermal conversion effect, polydopamine (Pdop) represents a versatile photothermal therapy platform, providing strategies and methods for the construction of novel polymer-functionalized PCMs. This review highlights the synthetic methods, therapeutic strategies, and designs of PCMs based on Pdop in recent years to explore its scope and limitations.

PDOP MODIFICATION STRATEGIES

Pdop became a popular adhesive polymer that can modify surfaces made of virtually all material chemistries, leading to its wide application in biological and biomedical fields.[24–26] Under alkaline and aerobic conditions, dopamine will self-polymerize to form Pdop nanoparticles[27,28] or a coating.[29,30] It is composed of dihydroxyindole, indoledione, and dopamine units, which are assumed to be covalently linked (Fig. 3).[31] Adhesion is one of the two most important characteristics of Pdop. When the surface has abundant amino, thiols, or sulfhydryl groups, dopamine undergoes Michael addition or Schiff base reaction to bind firmly to the substrate under oxidizing conditions.[32,33] Besides these, metal complexation plays a crucial role in Pdop adhesion on metal or metal oxide surfaces.[34] In general, Pdop can be coated on most surfaces of materials through noncovalent interaction, including van der Waals forces, metal complexation, hydrogen bonding, electrostatic forces, hydrophobic forces, and cation-π and π-π interactions.

The presence of amino and catechol groups on Pdop could be used as anchor points to further functionalize the Pdop-based materials, giving it secondary reactivity. To stabilize and enhance bioavailability and biocompatibility, Pdop-containing substrates could not be only functionalized with small biomolecules *via* chemical reaction and/or noncovalent force but also decorated with functional polymers *via* either the "grafting to" or "grafting from" method (Fig. 4). Consequently, Pdop-based materials offer a versatile platform for cancer therapeutics that can be combined with other drugs or detection methods to improve efficacy.

PDOP-BASED PCMS FOR ENHANCED CANCER THERAPY

In 2013, Liu *et al.* prepared dopamine-melanin colloidal nanospheres that exhibited robust biocompatibility and biodegradability.[39] These Pdop-based nanoparticles offered a photothermal conversion efficiency of 40%, much higher than those of previously reported PCMs. Following the publication of this landmark research, Pdop-based PCMs have emerged in great numbers (Fig. 1). The properties of Pdop nanoparticles can be further enhanced by adding other functional materials. For example, by decorating Nd^{3+}-sensitized upconversion nanoparticles onto the surface of Pdop, a multifunctional core/satellite nanotheranostic was developed for *in vivo* imaging guidance PTT.[40] The Pdop core provides a high photothermal conversion efficiency and robust biocompatibility due to its natural features. Due to the its high adhesion, Pdop could be deposited on virtually all materials, endowing them with PTT or enhancing their PTT. Li and colleagues created Pdop-coated gold nanostars (Au-PEI@Pdop) to improve computed tomography (CT) imaging and cancerous tumor destruction through PTT.[41] The nanostars were able to convert the NIR laser into heat and had strong X-ray attenuation properties, allowing them to be used as a theranostic nanoplatform for efficient CT imaging and enhanced PTT *in vitro* and in the xenografted tumor model. Mn-complex modified $NaDyF_4$:Yb@$NaLuF_4$:Yb,Er@Pdop nanocomposites were synthesized (Fig. 5), which is based on the fact that Yb^{3+} and Er^{3+} induce upconversion luminescence imaging, Dy^{3+} and Mn^{2+} interferes with T2 and T1 in MRI, and Pdop strongly absorbs in the NIR region for PTT.[42]

Pdop-based PCMs for Synergistic Treatment

Pdop has a strong affinity for biomolecules due to its negative charge, abundance of π electrons, and functional groups (amine and hydroxyl), making it a desirable drug delivery system for combining other therapeutics to integrate materials for diagnosis and treatment. Pdop-coated selenide molybdenum ($MoSe_2$@Pdop), a photothermal nanocarrier, was developed by

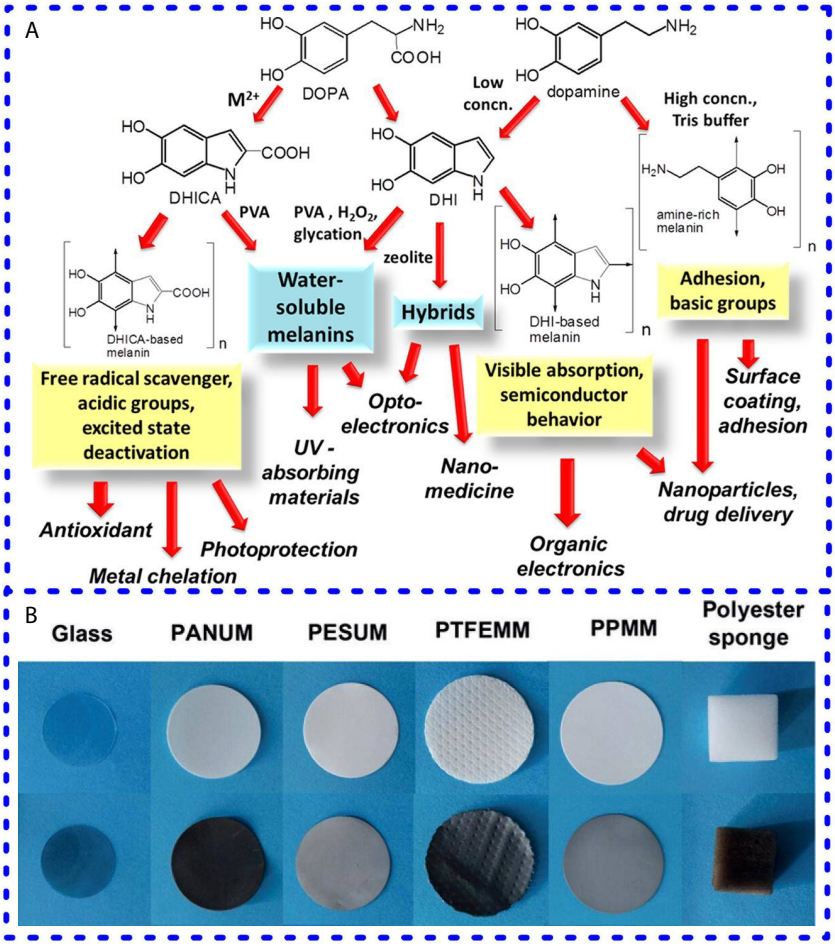

Fig. 3 (A) Unifying tailoring strategy for Pdop and eumelanin synthesis (Reproduced with permission from Ref. [26]; Copyright (2014) American Chemical Society); (B) Digital photographs of nascent substrates (up), PDA-coated substrates (bottom). PANUM: polyacrylonitrile ultrafiltration membranes; PESUM: polyethersulfone ultrafiltration membranes; PTFEMM: polytetra-fluoroethylene microfiltration membranes; and PPMM: polypropylene microfiltration membranes. (Reproduced with permission from Ref. [35]; Copyright (2016) Wiley-VCH).

Wang *et al.* for loading anticancer drug doxorubicin (Dox).[43] The Pdop layer can not only enhance the photothermal effect of $MoSe_2$ nanosheets, but also decrease their cytotoxicity and improve Dox loading. A nanoplatform (NRGO-GNS@DOX) was developed by Wang *et al.* that integrates Pdop-functionalized nanosized reduced graphene oxide (NRGO), gold nanostars (GNS) and Dox to be used for the combinational treatment of metastatic breast cancer (Fig. 6).[44] Upon NIR laser irradiation, the nanocomposites exhibited significant cytotoxicity in 4T1 breast cancer cells due to the hyperthermia elicited by the NRGO-GNS and the Dox-induced cytotoxicity. *In situ* one-step reduction-encapsulated method has been reported to synthesize a cancer theranostic agent as multicore-shell polydopamine-coated Ag nanoparticles, integrating amplified photoacoustic imaging, enhanced photothermal therapy, and photothermal promoted dual tumor microenvironment-coactivated chemodynamic therapy.[45] The 4T1 cell membrane loaded with cucurbitacin B was used to coat polydopamine (PDA) nanoparticles, resulting in a biomimetic nanoplatform with increased photothermal conversion efficiency and photostability.[46] A nanoplatform that combines Dox, imiquimod (R837), and folate onto Pdop to develop multifunctional nanoparticles is used as a combined photothermal therapy, chemotherapy, and immunotherapy in order to enhance cancer therapeutic effects.[47] By using these nanoparticles for NIR light-induced thermochemotherapy, local tumors can be destroyed while also elicit a systemic immune response that protects against tumor recurrence. Cisplatin-loaded Pdop nanoparticles have been fabricated through the supramolecular interaction of β-cyclodextrins with adamantyl groups (Fig. 7).[48] These nanoparticles demonstrated the ability to generate photoacoustic images, as well as to facilitate imaging-guided photothermal therapy, thus providing inspiration for the development of combinatorial nano-therapeutics. By functionalizing spherical zeolitic imidazolate framework-8 (ZIF-8) with Pdop, Janus nanoparticles with a hollow structure can be achieved using a mild synthesis strategy.[49] ZIF-8 domains with internal cavities can be used to store either hydrophobic or hydrophilic drugs. These nanoparticles, resulting from the combination of pH-sensitive ZIF-8 and the strong NIR absorption of Pdop, exhibited both photothermal conversion capacity and pH/NIR dual-responsive

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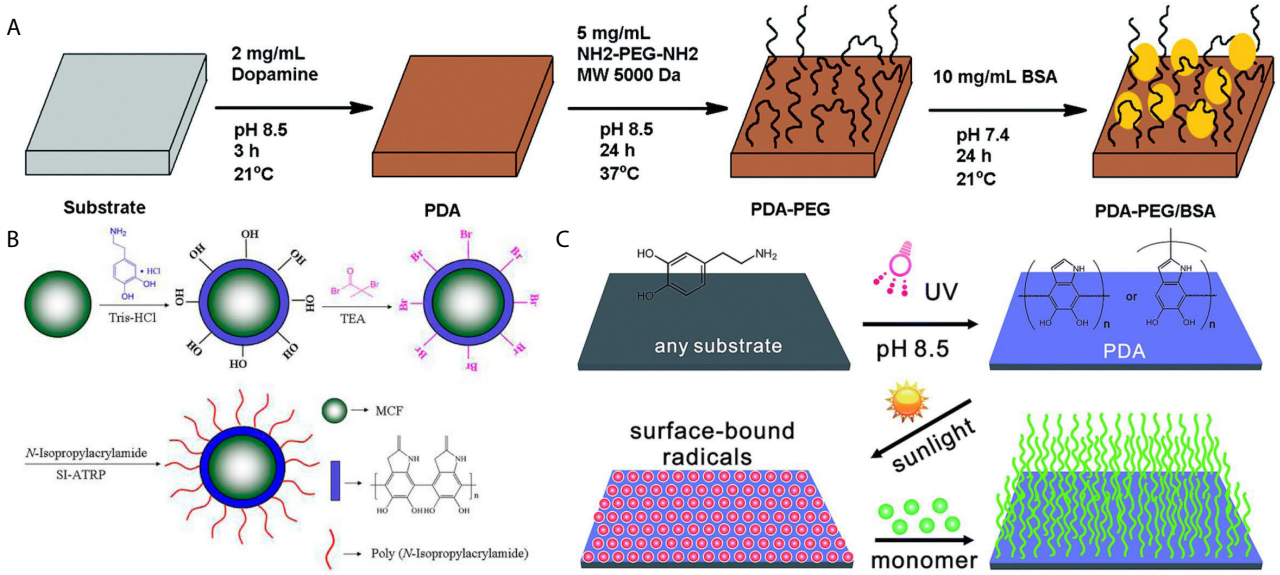

Fig. 4 Three methods of post-modifying Pdop materials with polymers: (A) grafting to (Reproduced with permission from Ref. [36]; Copyright (2018) American Chemical Society), (B) grafting from with ATRP (Reproduced with permission from Ref. [37]; Copyright (2013) Wiley-VCH), and (C) grafting from with UV-induced polymerization (Reproduced with permission from Ref. [38]; Copyright (2015) The Royal Society of Chemistry).

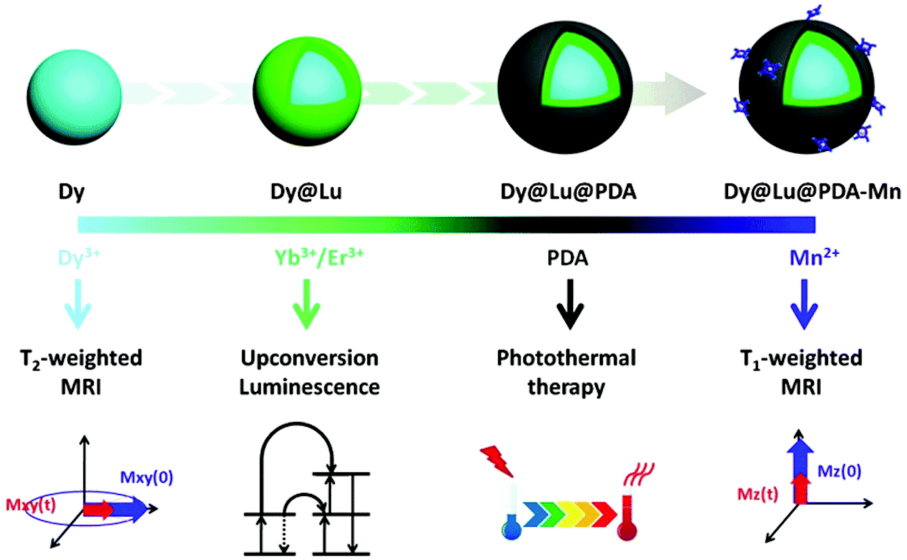

Fig. 5 Schematic illustration of synthesis of $NaDyF_4$:Yb (Dy), $NaDyF_4$:Yb@$NaLuF_4$:Yb,Er (Dy@Lu), $NaDyF_4$:Yb@$NaLuF_4$:Yb,Er@PDA (Dy@Lu@PDA), and Mn complex-modified $NaDyF_4$:Yb@$NaLuF_4$:Yb,Er@PDA (Dy@Lu@PDA–Mn) for T1-, T2-weighted MRI, upconversion luminescence imaging-guided photothermal therapy. (Reproduced with permission from Ref. [42]; Copyright (2016) The Royal Society of Chemistry).

drug release behavior, making them promising platforms for cancer treatment through collaborative photothermal and dual-drug chemical therapy. Mesoporous silica nanoparticles (MSNs) integrated with the photothermal agent Pdop, the model antigen ovalbumin and the antigen release promoter ammonium bicarbonate have been developed as the nanotherapeutic nanoplatform for melanoma PTT-immunotherapy.[50] The formulated nanovaccine exhibits excellent photothermal properties and effectively eliminates primary tumors. Cu-doped Pdop nanoparticles have been synthesized and embedded into microneedles for use in photothermal and chemodynamic synergistic therapy against skin melanoma.[51] This multimodal tumor therapeutic strategy uses the high photothermal effect (50.40%) from NIR irradiation to convert it into heat and the good Fenton-like catalytic activity of copper ions to produce toxic free hydroxyl groups, leading to the generation of a minimally invasive synergistic therapy. A multifunctional nanobeacon with a scout function for HSP90 mRNA fluorescence detection and NIR triggered drug release has been prepared for chemo-photothermal therapy.[52] By combining NIR with fluorescence imaging, it is possible to spatiotemporally release doxorubicin *via* the photothermal effect, potentially allowing for combined chemotherapy and photothermal treatment. A nanotherapeutic agent composed of a ZnO nanoparticle core, an interlayer of photosensitizer chlorin e6 (Ce6), and a Pdop outer layer was constructed by

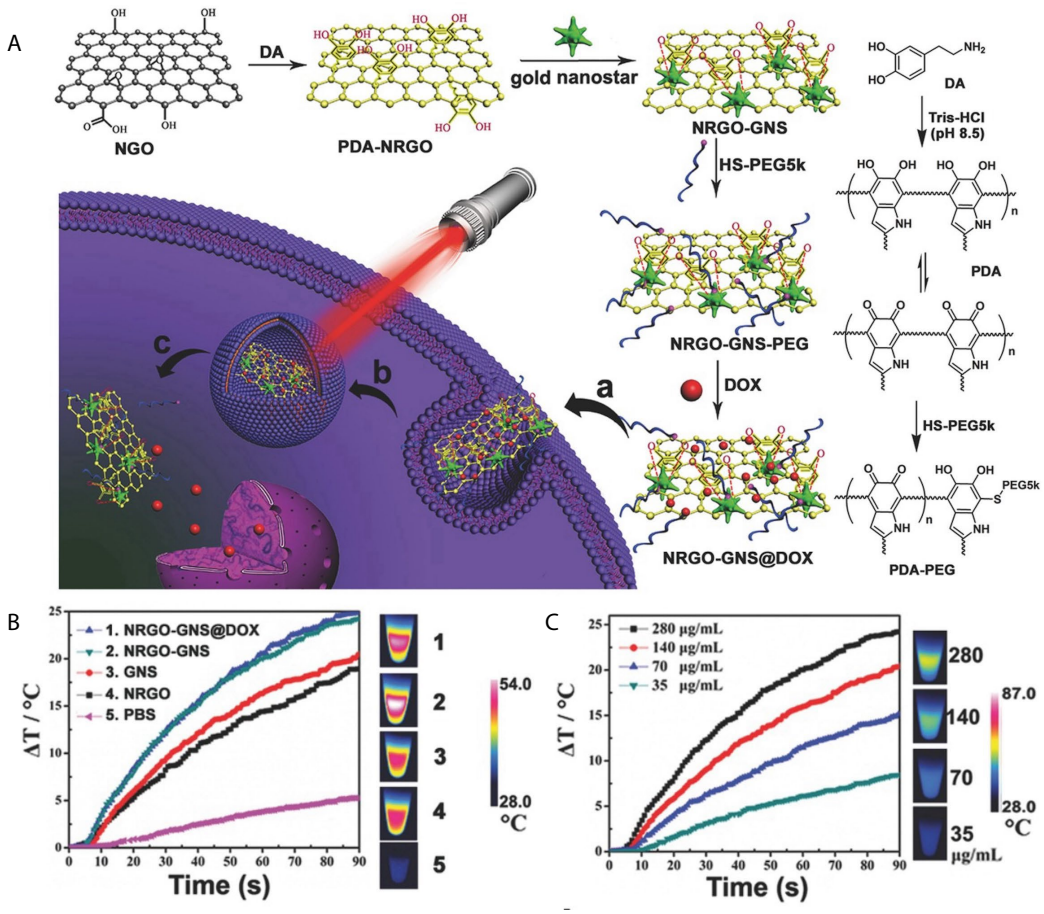

Fig. 6 (A) Schematic illustration for the preparation of NRGO-GNS@Dox nanocomposite for combined photothermal and chemotherapy of breast cancer, (B) temperature elevation of PBS, NRGO, GNS, NRGO-GNS, and NRGO-GNS@DOX suspensions (280 μg·mL^{-1}), and (C) concentration-dependent of NRGO-GNS@DOX aqueous suspension upon laser irradiation (4.0 W·cm^{-2}). (Reproduced with permission from Ref. [44]; Copyright (2016) WILEY-VCH).

combining PDT and PTT.[53] The as-prepared nanoparticles showed efficient generation of singlet oxygen and excellent photothermal conversion efficiency because of the presence of Ce6 and Pdop.

By using a template and porogen, the morphology of Pdop nanoparticles can be accurately controlled to produce solid,[28,54,55] mesoporous,[56] and hollow[57,58] structures (Fig. 8). Due to its unique hollow and porous structure, a high mass loading of biomolecules can be achieved, and the PCMs demonstrated remarkably high photothermal conversion capacitances. Hollow Pdop have been constructed by an improved surfactant-DMDES emulsion template method.[59] Due to their hollow structure and the good photothermal conversion efficiency, the Pdop capsules showed excellent photoacoustic imaging (PAI) ability and high Dox loading capacity *via* electrostatic interaction and *π*-*π* stacking. The Dox release was pH and NIR laser responsive to minimize the side effect, proving that it could efficiently ablate the tumor *in vitro* and *in vivo* experiments though chemo-photothermal synergistic therapy. A mesoporous Pdop-based theranostic agent that is superparamagnetic iron oxide coated with Pdop, modified with a targeted molecule of sialic acid and chelated with Fe^{3+} for T1/T2 dual MRI-guided cancer chemo-photothermal therapy has been developed.[60] The theranostic agent demonstrated excellent photothermal conversion capability and photostability, which could effectively encapsulate the Dox for its dual pH- and thermal-triggered release.

The combination of active tumor-targeting biomolecules with Pdop-based PCMs could result in more effective cancer PTT. Folic acid has been shown to bind to overexpressed folic acid receptors on many types of tumors, making it a potential targeting agent.[61–63] Pdop nanoparticles functionalized with folic acid and responsive to tumor acidity and NIR have been developed for co-delivery of Dox and epigallocatechin-3-gallate (Fig. 9).[64] The pH sensitivity and photothermal conversion capability of Pdop incorporated within the obtained materials enabled an increased drug release upon exposure to exogenous NIR irradiation and a lower pH, thus reducing the adverse effects of the drugs on healthy organs. Thanks to NIR, the cellular uptake of these drug delivery systems is significantly higher when compared with the free Dox group and the control group without NIR irradiation. Folic acid-functionalized Pdop-based nanomedicine has been found to improve the therapeutic activity of cinobufagin against cancer cells, most likely due to an increased targeting and accumulation of the compound at the site of the tumor.[65] Nanomedicine in combination with photothermal therapy exhibited an improved therapeutic effect against lung cancer. By loading the

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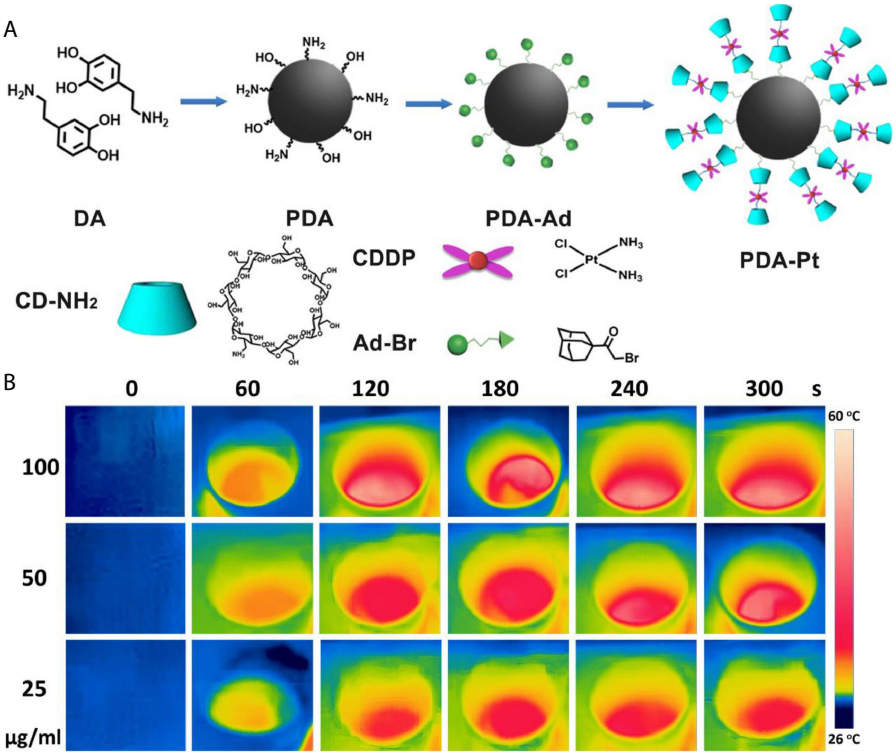

Fig. 7 (A) Schematic presentation of the fabrication of PDA-Pt NPs through supramolecular self-assembly, (B) infrared thermal images of PDA-Pt NPs solutions with different concentrations under NIR laser irradiation. (Reproduced with permission from Ref. [48]; Copyright (2021) Elsevier).

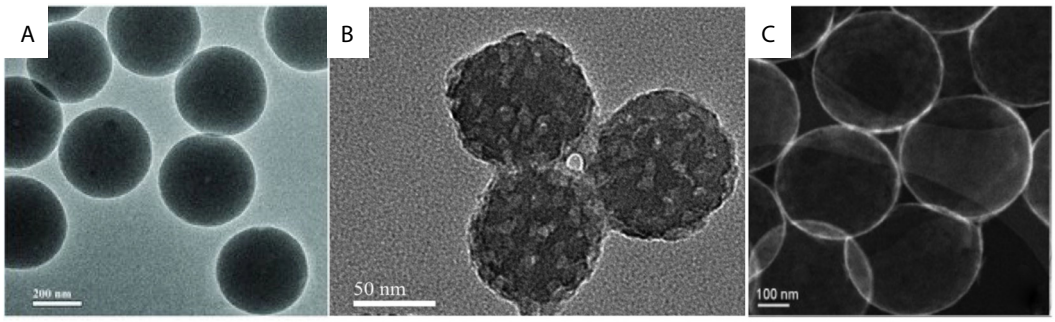

Fig. 8 Typical TEM image of (A) solid (Reproduced with permission from Ref. [54]; Copyright (2013) WILEY-VCH) and (B) mesoporous (Reproduced with permission from Ref. [56]; Copyright (2017) The Royal Society of Chemistry) Pdop nanoparticles, and STEM of (C) Pdop hollow spheres (Reproduced with permission from Ref. [57]; Copyright (2011) WILEY-VCH).

photosensitizer Ce6 onto mesoporous MnO_2 nanoparticles and coating them with folic acid-functionalized Pdop, a platform for photonic therapy is created.[66] The core-shell structure of MnO_2/Pdop enables efficient conversion of NIR light to heat. The use of a combination of O_2-strengthened Pdop and PTT resulted in effective tumor growth inhibition upon exposure to 660 and 808 nm lasers.

Pdop-based PCMs for Imaging-guided PTT

Thanks to the strong adhesion and metal-chelating ability of Pdop, Pdop-based magnetic resonance imaging (MRI) contrast agents that integrate imaging function with enhanced biocompatibility and PTT have been developed. Pdop-encapsulated gadolinium-loaded multi-walled carbon nanotube (MWCNT-Gd@PDA) were designed for dual-modality mapping guided PTT by positive signal of MRI as well as the black of the nanomaterials providing visual information.[67] The presence of a Pdop shell prevented gadolinium ion from escaping from the MWCNT, eliminating potential for inherent biological toxicity. Both *in vitro* and *in vivo* results showed that this nanosystem possessed precise spatial-temporal selectivity in comparison with conventional surgery and T2-MRI guided PTT. Gadolinium-functionalized nanocomposites were fabricated by encapsulating Fe_3O_4 nanoparticles in Pdop, and then chelating gadolinium onto their surface.[68] These nanocomposites exhibited excellent photothermal conversion efficiency and were able to induce significant contrast enhancement for both T1 and T2 imaging at very low concentrations of Gd and Fe, providing a promising platform for the development of novel diagnostic and therapeutic agents. Zhang *et al.* investigated the use of multifunctional Mn^{2+} complex-modified Pdop and dual emissive carbon dots-based

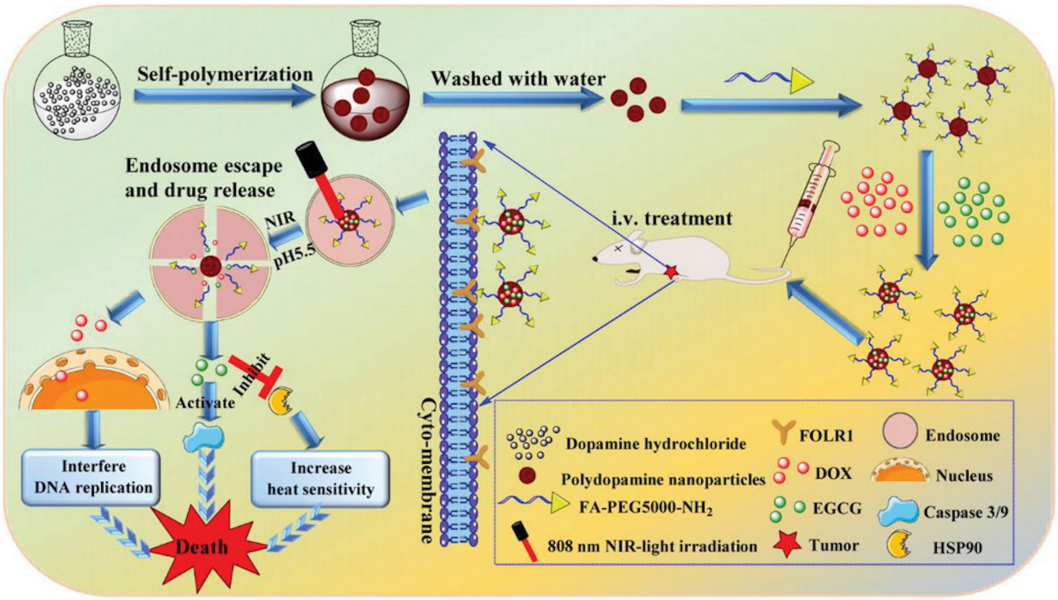

Fig. 9 Schematic illustration of DOX-EGCG/DPA-FA NPs mediated pH and NIR-controlled chemo-photothermal therapy. (Reproduced with permission from Ref. [64]; Copyright (2021) WILEY-VCH).

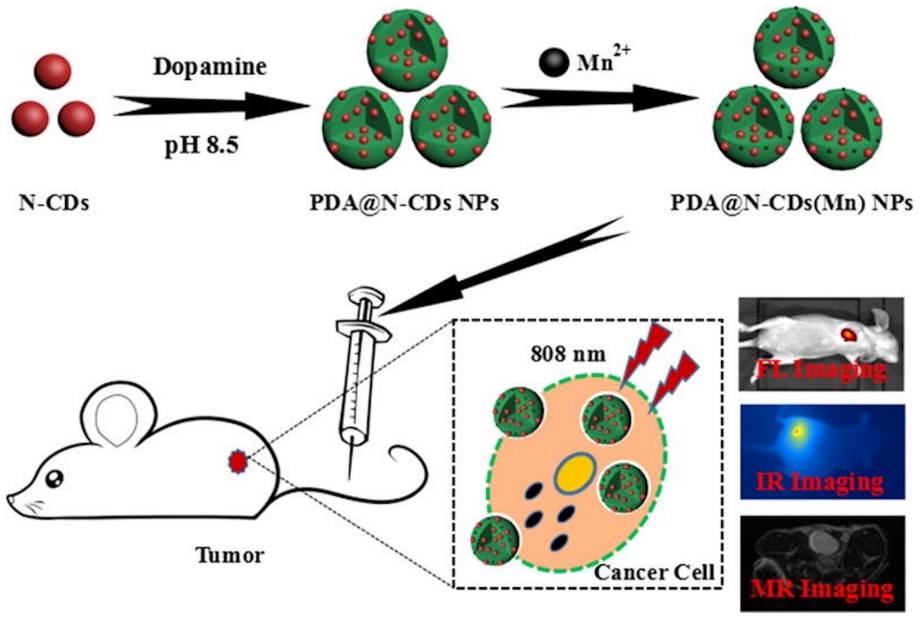

Fig. 10 Schematic illustration of the synthetic procedure and action mechanism of PDA@N-CDs(Mn) NPs and their application in fluorescent, photothermal, and magnetic resonance imaging. (Reproduced with permission from Ref. [69]; Copyright (2019) Elsevier).

nanoparticles for trimodality fluorescent, PTT and MRI *in vitro* and *in vivo* (Fig. 10).[69] These multifunctional nanoparticles exhibited green and red dual emission, high stability, and excellent photothermal effects (photothermal conversion efficiency of 28.2%). Core/shell nanocomplexes composed of Ce6-embedded mesoporous silica nanoparticle cores and Pdop and manganese ion shells improve MRI contrast effect with promising photothermal conversion efficacy.[70] *In vitro* and *in vivo* results demonstrated that the prepared nanocomplexes would be a promising potential for multimodal imaging-guided phototherapy. Multifunctional mesoporous Pdop nanoparticles loaded with glucose oxidase, Fe ions, and Pt nanoparticles have been demonstrated for synergistic cancer therapy.[71] The heat generated by Pdop under laser irradiation enhances the chemodynamic therapy (CDT) effect, providing a novel MRI-guided PTT-enhanced CDT synergistic nanomedicine platform for cancer therapy.

Pdop-based Hydrogel for Enhanced PTT

Hydrogel-based drug delivery systems provide a high-dose and constant release of therapeutic agents in pathological lesions and can avoid non-specific drug distribution in heathy tissues, which can significantly reduce the adverse effect of drugs and enhance their bioavailability.[72] Pdop can serve as either a chemical or physical crosslinker for polymer networks, depending on the formation of chemical bond and noncovalent interaction, respectively. A Pdop nanoparticle-knotted

poly(ethylene glycol) (PEG) hydrogel for on-demand drug delivery and combined chemo-photothermal therapy was designed and prepared, due to improved bioavailability, and minimized adverse effects of hydrogel (Fig. 11).[73] 7-Ethyl-10-hydroxycamptothecin (SN38), an anticancer drug, was loaded on Pdop NPs *via* π-π interaction, exhibited minimal leakage at physiological conditions and could be released upon exposure to NIR laser. *In vivo* results have demonstrated that the resulting hydrogel can efficiently suppress tumor growth by a combined chemo-photothermal therapy. A versatile hydrogel loading photothermal agents, chemotherapeutics, and immune-adjuvants have been reported to eradicate orthotopic tumors and inhibit metastasis by combinational therapy.[74] Pdop crosslinks with thiolated hyaluronic acid *via* thiol-Michael addition, endowing the resulting hydrogel with excellent photothermal property. The combination of Dox and an immune-adjuvant, CpG-ODN in a hydrogel results in a synergistic effect that includes effective chemotherapy and an evoked host immune response. A polyacrylamide/phytic acid/Pdop multi-component hydrogel was prepared by copolymerizing dopamine with acrylamide through a phytic acid crosslinker.[75] Due to the porous structure of the network and the strong NIR-absorption of Pdop, the hydrogel exhibits a high Dox-loading capacity (170 mg·g^{-1}) and efficient photothermal transduction efficiency (47.4%) even under 0.75 W·cm^{-2} of 808 nm NIR laser irradiation. To achieve effective antitumor efficacy at relatively low temperature, the siRNA-embedded nanogels are coated with Pdop which not only protects the nanogels against enzymatic degradation but also endows the nanogels with excellent photothermal conversion capacity under NIR light irradiation.[76] After surface PEGylation, this triple shield siRNA delivery complex is capable of effectively ablating tumors under relatively mild conditions.

Polymer-modified Pdop-based PCMs for Enhanced PTT

Modifying biomaterials with functionalized polymers can significantly affect the properties of the complexes, leading to improved bioavailability, biocompatibility, and anticancer properties.[77–79] Several noncovalent interactions play a crucial

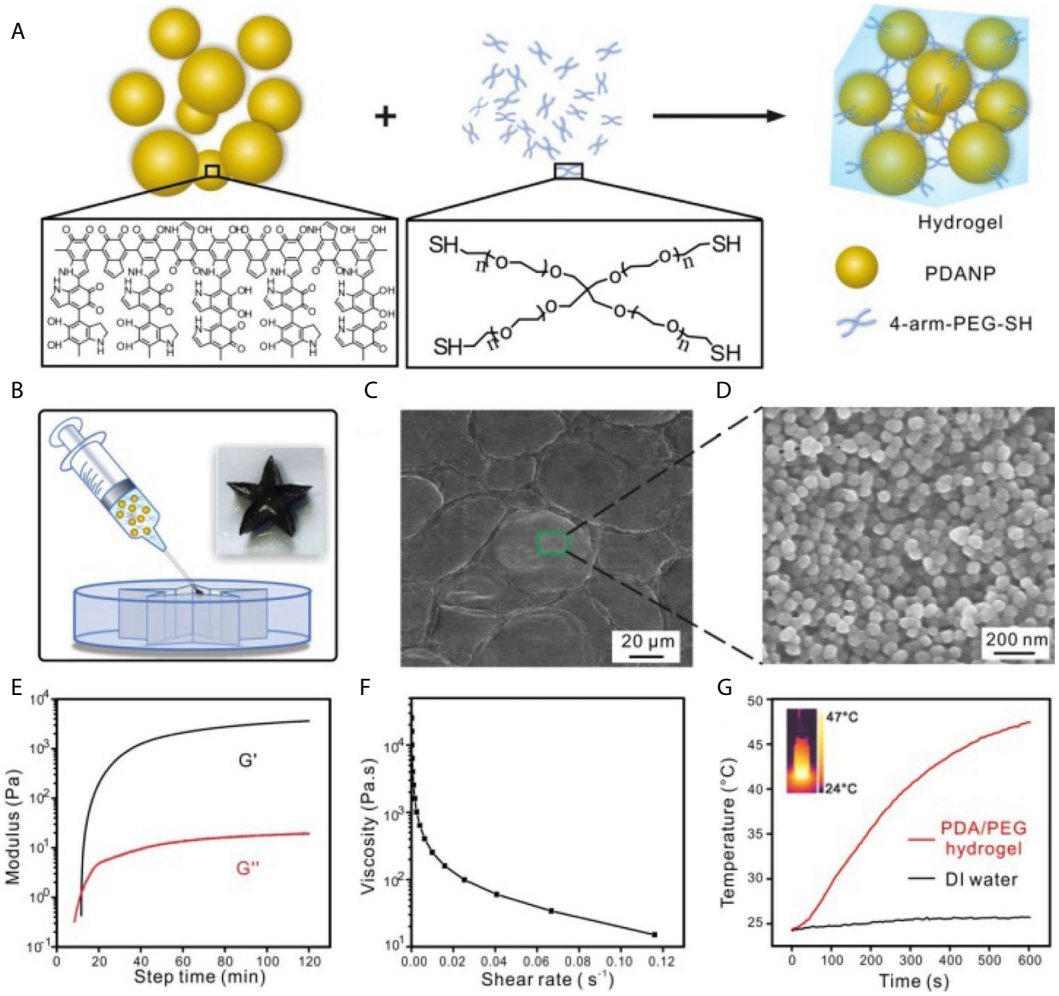

Fig. 11 Preparation and characterization of the PDA-knotted PEG hydrogel. (A) Preparation of PDA/PEG hydrogel. PDANPs were used as a cross-linking agent to cross-link 4-arm-PEG-SH. (B) Fabrication of a star-shaped PDA/PEG hydrogel. (C, D) SEM images of PDA/PEG hydrogel. (E) Dynamic *G'* and *G"* moduli of PDA/PEG hydrogel. The mixture of 4-arm-PEG-SH and PDANPs was blended by a Vortex mixer for 10 min. After that, the rheology of the mixture was measured by a hybrid rheometer. (F) The shear-thinning behavior of PDA/PEG hydrogel. (G) Photothermal effect of PDA/PEG hydrogel irradiated with NIR light at 3.6 W·cm^{-2} for 10 min. (Reproduced with permission from Ref. [73]; Copyright (2021) American Chemical Society).

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role in the construction of polymer-modified Pdop nanomaterials, including hydrogen bonds, *π-π* stacking, charge transfer, and hydrophobic interactions. A pH- and NIR light-responsive drug delivery system has been developed to target tumors by electrostatically adsorbing hyaluronic acid (HA) onto the nanoparticle surface.[80] The nanomedicine showed synergistic effects against tumors through chemotherapy and photothermal therapy in both *in vitro* and *in vivo* studies. Pdop and HA-coated liquid perfluorocarbon nanoparticles were prepared to take advantage of good photothermal conversion effect of Pdop, the ultrasound imaging properties of the liquid fluorocarbon, and the active tumor-targeting of HA (Fig. 12).[81] Pdop has been shown to effectively convert NIR laser energy into heat for PTT, which can induce a phase change of the liquid perfluorocarbon, generating microbubbles, enhancing ultrasound imaging signals, and promoting drug release.

Pdop has numerous functional groups that can act as anchor points to form covalent bonds with functional polymers *via* Schiff base reactions or/and Michael addition reactions.[82–84] Thus, Pdop-based materials could be further modified with biopolymers though "grafting on" or "grating from" strategies. Inspired by the simple and low-cost "grafting on" approaches, various polymer-modified Pdop nanomaterials have been demonstrated. The fabrication of camptothecin-containing polymeric prodrugs was achieved by polymerizing a pH-sensitive related comonomer *via* reversible addition-fragmentation transfer (RAFT).[85] The pH-sensitive polymeric prodrug was attached to the surface of the Pdop nanoparticles through amidation chemistry for combination of chemotherapy with photothermal therapy. Pdop-coated lanthanide-based nanocomposites have been successfully constructed and functionalized with PEG and folic acid for early diagnosis and treatment of tumors (Fig. 13).[86] The nanocomposites could be effectively triggered by 808 nm laser irradiation to produce an excellent photothermal conversion efficiency of 32.3%, due to the strong NIR absorption of Pdop. Nanocomplexes (PPy-PDA-PEG@DOX), consisting of a polypyrrole core, a Pdop shell, PEG linkages, and Dox, were designed to enhance PTT against cancer cells in NIR range.[87] The nanocomplex demonstrated good photothermal stability and conversion efficiencies of 23.1% and 30.8% in the NIR-I and II biowindows, respectively. A targeted theranostic nanoplatform has been fabricated though the modification of Pdop-coated LAPONITE®-Fe_3O_4 nanoparticles with PEGylated phenylboronic acid *via* Michael addition.[88] The nanoplatforms displayed excellent biocompatibility and photothermal conversion efficiency under NIR laser irradiation, making them ideal for use in MRI and photoacoustic imaging-guided cancer cell PTT. PEGylated PPy@Fe^{3+}-chelated Pdop nanocomposites with a uniform core-shell structure were designed and prepared.[89] The cores of PPy and Pdop contribute to the photothermal ablation of tumors, while the PEG shells provide the nanoparticles with good biocompatibility and MRI signal-enhancing ability. Spherical Pdop/mesoporous calcium phosphate hollow Janus nanoparticles have been reported and further functionalized with indocyanine green (ICG), methoxy-poly(ethylene glycol)thiol and Dox.[90] The resultant nanoparticles possess excellent biocompatibility, a competent drug loading capability, high photothermal conversion efficiency, and pH/NIR dual-responsive properties, providing photoacoustic imaging-guided synergistic cancer chemo-phototherapy *in vitro* and *in vivo*. Multifunctional nanotheranostics for MRI guided combinatorial chemotherapy and PTT for cancer have been designed and constructed.[91] Biamino polyethylene glycol was modified on the surface of Mn_3O_4@Pdop for further conjugation with folic acid, improving the ability to target tumors and the stability in physiological conditions. Upon 808 nm NIR laser irradiation,

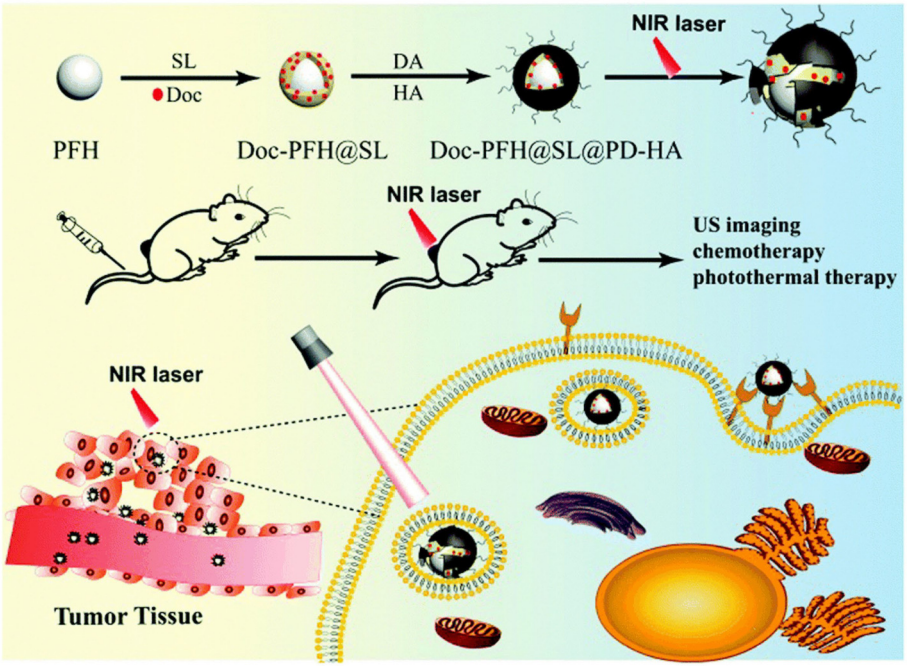

Fig. 12 Design of core-shell Doc-PFH@SL@PD-HA for ultrasound imaging-guided photothermal-chemotherapy. (Reproduced with permission from Ref. [81]; Copyright (2019) The Royal Society of Chemistry).

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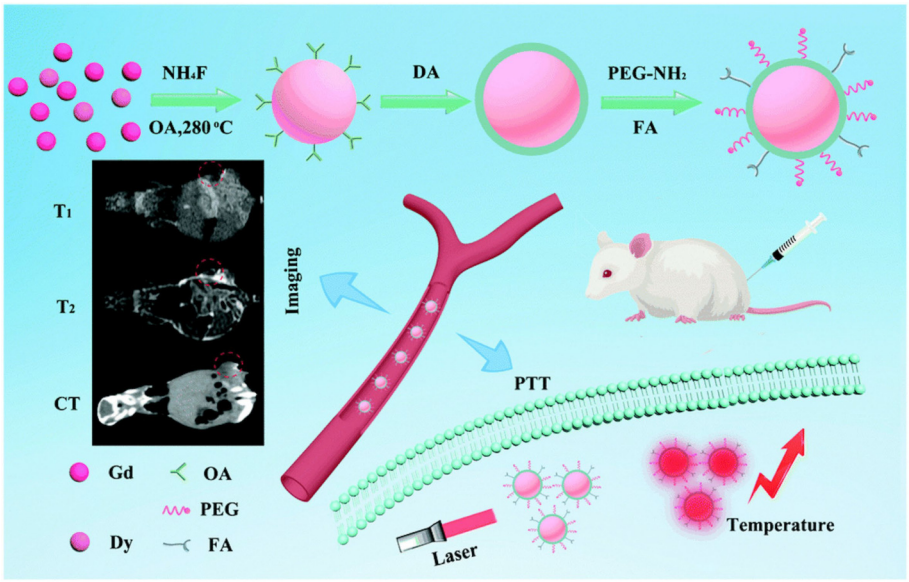

Fig. 13 Schematic illustration of the preparation of $NaGdF_4$:Dy@PPF as a theranostic agent for trimodal imaging-guided PTT. (Reproduced with permission from Ref. [86]; Copyright (2019) The Royal Society of Chemistry).

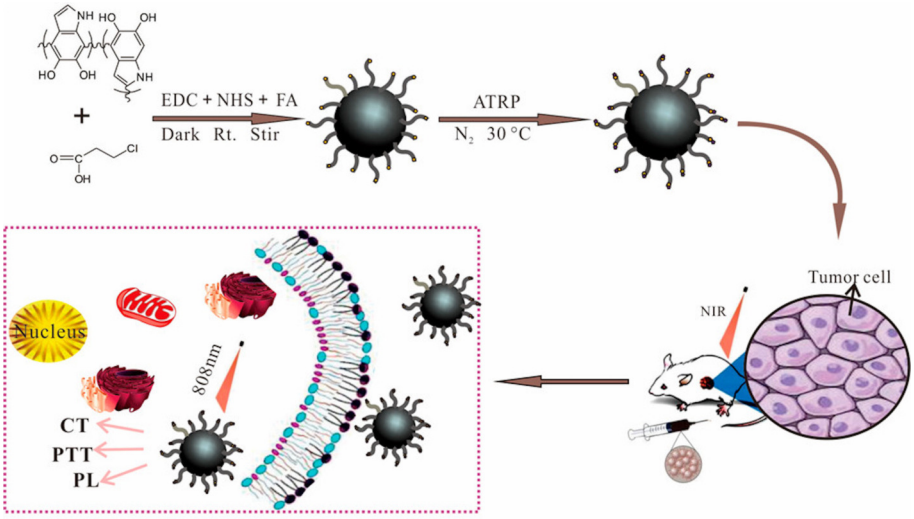

Fig. 14 Design and synthesize schematic illustration of FEDA nanoparticles for multifunctional photothermal agent. (Reproduced with permission from Ref. [97]; Copyright (2021) American Chemical Society).

nanotheranostics exhibits high therapeutic efficiency and low side effects of drugs, providing highly effective MRI guided synergetic chemo-/photothermal therapy for cancer treatment. The biocompatibility of IR820 was improved by encapsulating with Pdop under alkaline conditions and then modifying with methoxy polyethylene glycol amine *via* Michael addition, leading to the fabrication of an agent with enhanced photothermal properties.[92]

Surface-initiated polymerizations are an attractive "grafting from" method for creating well-defined polymer brushes with complex architectures on Pdop nanoparticles.[38,93–96] Zhang *et al.* developed a Pdop-based multifunctional reagent consisting of europium(III) complexes which was grafted from the surface by surface-initiated atom transfer radical polymerization (Fig. 14).[97] The nanocomplexes exhibited both bright X-ray CT and photoluminescence dual-mode imaging efficiency and an excellent PTT effect both *in vivo* and *in vitro*. The modification of Pdop coated silica nanoparticles with poly(*N*,*N*-diethylacrylamide) was carried out by SIATRP.[98] The resulting product exhibited a strong near-infrared photothermal effect and facilitated the loaded Dox release.

CONCLUSIONS AND PERSPECTIVE

Generally, inorganic PCMs are poorly biometabolized, while organic materials could have potential problems with leakage and toxicity of degradation products during their long-term retention. It is believed that there is still considerable potential for improvement in the synthesis and properties of PCMs. Thanks to the adhesion and secondary reactivity of Pdop, numerous Pdop-based PCMS have been developed with excellent photothermal conversion and combined with other theranostics to enhance therapeutic efficacy. In this review, we

highlight the recent advances in versatile Pdop platforms for PTT. By using a template and porogen, the morphology of Pdop nanoparticles can be controlled to form solid, mesoporous, and hollow structures with an excellent photothermal conversion efficiency. Thanks to the adhesion nature, Pdop can be coated on bulk substrates to improve their bioavailability and biocompatibility, which can be further enhanced by combining with functional nanomaterials and/or biomolecules. The presence of functional groups (amino and catechol) on Pdop endows it with secondary reactivity, making it useful for functionalization as anchor points. Pdop-containing substrates could not be only conjugated with small biomolecules *via* covalent bonds and/or noncovalent interaction but also decorated with polymers *via* either the "grafting to" or "grafting from" method. The transition from basic research to clinical applications has traditionally been lengthy and complex, but it is reasonable to believe that the development of Pdop-based PCMs can help to expedite and improve the progress of tumor theranostic methodology.

BIOGRAPHY

Mei-Fang Zhu obtained her PhD degree in Materials Science in 1999 from Donghua University (DHU, Shanghai). Currently, she is a Professor at DHU and a member of the Chinese Academy of Science. She also serves as the Dean for the College of Materials Science and Engineering in DHU and the Director of the State Key Laboratory for Modification of Chemical Fibers and Polymer Materials. She has long been engaged in research on the fundamental chemistry, properties, and applications of fiber materials, organic/inorganic hybrid nano-materials, smart hydrogels and biomaterials for green energy, environment, and healthcare.

NOTES

The authors declare no competing financial interest.

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