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FOCUS REVIEW

Polymeric nanocarriers incorporating near-infrared absorbing agents for potent photothermal therapy of cancer

Yuanyuan Zhang[1,3], Chung Yen Ang[1,3] and Yanli Zhao[1,2]

Applications of photothermal therapy (PTT) in the treatment of cancer have attracted a great deal of attention with the advancement of nanotechnology. A key advantage of this strategy is the fact that photothermal agents are capable of annihilating cancer cells with remote light irradiation while causing minimal damage to normal tissues. Because the incorporation of near-infrared (NIR) absorbing agents into self-assembled polymeric nanocarriers confers several benefits to PTT, in this review, we highlight recent advances in polymeric nanocarriers for the photothermal treatment of cancer. These polymeric nanocarriers can store and deliver NIR-absorbing agents to cancer cells and tumor sites, exhibiting significant cytotoxic effects upon treatment using external light irradiation. With the great success of photothermal cancer treatment both *in vitro* and *in vivo*, this approach exhibits promising potential for use in future clinical applications. To overcome the limitations of single photothermal treatment methods and to maximize their therapeutic efficacy, synergistic cancer treatment can be achieved by integrating NIR-absorbing agents with anticancer drugs or photosensitizers for combined photothermal–chemotherapy or photothermal–photodynamic therapy. Finally, we conclude this review by discussing various challenges and future perspectives in this field.
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INTRODUCTION

Recent developments in photothermal therapy (PTT) have led to major advances in the medical treatment of cancer.[1–3] It is well known that cells can only live and reproduce within a specific temperature range. In the case of tumor tissues, local hyperthermia at temperatures above 45 °C have been shown to directly trigger cancer cell death.[4,5] Excessively high temperatures can result in irreversible damage by loosening cell membranes and denaturing proteins, ultimately leading to the eradication of tumor tissues.[6] During the photothermal treatment of cancer, photo-absorbing agents can efficiently convert the absorbed light into heat energy under light irradiation with a specific wavelength. Owing to its noninvasive nature, localized hyperthermia for the ablation of targeted tumors by selective illumination of cancer sites induces no damage to un-illuminated healthy tissues and normal cells.[7] In order for PTT to be implemented in clinical applications, ideal photothermal agents should exhibit good biocompatibility, high photothermal efficiency, acceptable photostability and the ability to accumulate in specific tumor sites. Most importantly, it is preferable to use photothermal agents with strong absorption in the near-infrared (NIR) region (700–900 nm),[8,9] as NIR light allows for much deeper penetration through soft tissues with minimum absorption. NIR light also maximizes the efficiency of light utilization by light-absorbing agents and causes negligible damage to the surrounding tissues and cellular components. Therefore, numerous efforts have been made toward the design and preparation of biocompatible NIR-absorbing agents with strong NIR absorbance coefficients and high photothermal conversion efficiencies.[2,7]

The advancement of nanotechnology has endowed new opportunities for the further development of PTT. In the NIR light-to-heat conversion process, the performance of NIR-absorbing agents is critical for the successful ablation of malignant cells. To date, a variety of NIR-absorbing nanomaterials, such as gold nanostructures,[10–12] carbon nanomaterials,[13,14] copper sulfide nanoparticles,[15,16] conjugated polymers[17,18] and organic nanoparticles loaded with NIR-absorbing dyes,[19–21] have been successfully prepared and extensively exploited as photothermal therapeutic agents. Owing to their nanoscale sizes, these therapeutic systems not only possess prolonged blood circulation times but also passively increase tumoral accumulation via the enhanced penetration and retention effect.[22,23] Upon delivery into specific tumor sites, these systems can improve the treatment efficacy to the tumor cells and are accompanied by reduced side effects on normal tissue. Apart from relying on the passive targeting strategy of such agents to direct photothermal nanoagents into tumor sites, the nanosystems can also be fabricated with targeting

[1]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore, Singapore and [2]School of Materials Science and Engineering, Nanyang Technological University, Singapore, Singapore
[3]These authors contributed equally to this work.
Correspondence: Professor Y Zhao, Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore.
E-mail: zhaoyanli@ntu.edu.sg
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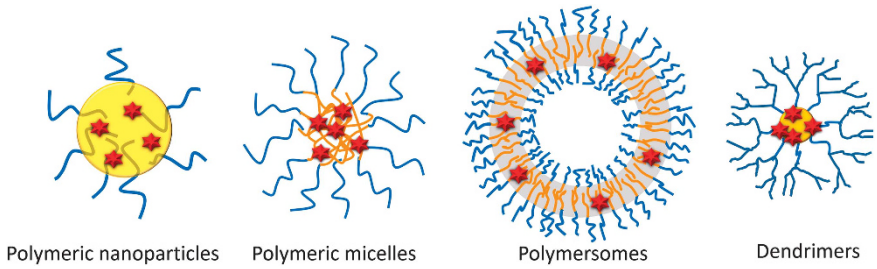


Figure 1 Schematic diagram of polymeric nanocarriers including polymeric nanoparticles, polymeric micelles, polymersomes and dendrimers.

ligands to induce selective endocytosis by specific cancer cells that are overexpressed with relevant receptors.

Polymeric nanocarriers such as polymeric nanoparticles,[24–26] polymeric micelles,[27–29] polymersomes[30,31] and dendrimers[32,33] have been extensively explored as delivery vehicles of chemotherapeutic drugs for the treatment of cancer (Figure 1). The encapsulation of various therapeutic agents in the polymeric nanocarriers can significantly prolong their circulation times, thereby reducing the side effects of the treatment without compromising its therapeutic efficacy. Because of their excellent treatment efficacy and biocompatibility, some of these polymeric anticancer nanosystems have already been tested in different stages of clinical trials or have even been approved for clinical use.[27,34,35] On the basis of a similar encapsulation principle, polymeric nanocarriers have also shown great promise for the delivery of NIR-absorbing agents to tumor sites and cancer cells after systematic administration.

Table 1 shows the structures, names and abbreviations of the polymeric materials that will be elaborated in this review. The concept of using polymers for biological applications has been widely accepted, and various polymeric materials have been adopted as integral parts in the construction of effective nanocarriers. The polymers of natural origin discussed in this article mainly consist of polysaccharides, including dextran, chitosan and heparin, which are often considered biocompatible for biological applications. With regard to synthetic polymers, some are already commercially available (for example, poly (lactic-*co*-glycolic acid) (PLGA), poly(styrene-*alt*-maleic anhydride) (PSMA) and poly(ethylenimine) (PEI)) and are used as ingredients in therapeutic nanocarriers. In recent studies, the idea of using synthetic polymers for biological applications has been revisited, and numerous new polymer-based materials have been developed (for example, poly (L-lysine)-*b*-poly(L-leucine) (PLL-PLLeu), poly(aspartic acid (decylamine)) (PAsp(DA)) and poly((*N*-isopropylacrylamide-*alt*-acrylamide) (pNIPAAm–pAAm)) via radical polymerization, condensation polymerization and ring-opening polymerization. Some polymers have been implemented as versatile nanocarriers for photothermal therapeutic agents.

Self-assembled polymeric nanocarriers can be easily prepared because of the availability of polymeric sources. Because these nanocarriers would be used for biomedical applications, it is of great importance that their biocompatibility in aqueous environments is ensured. Furthermore, considering the hydrophobic nature of therapeutic agents, the structures of these nanocarriers, including polymeric nanoparticles, micelles and dendrimeric nanocarriers, need a hydrophobic interior for the storage of organic NIR-absorbing dyes. For polymersomes, the dyes are incorporated in the discrete hydrophobic bilayers. Apart from conventional encapsulation strategies, an alternative route is to use amphiphilic polymers to modify inorganic substrates such as gold nanomaterials, forming polymeric hybrid assemblies. The incorporation of inorganic nanoparticles in polymeric assemblies can provide new possibilities for PTT with improved efficacy.

To overcome the limitations of various NIR-absorbing agents, the use of polymeric nanocarriers with versatile chemical structures undoubtedly improves the biocompatibility, photostability, aqueous solubility and multifunctionality of NIR-absorbing payloads,[36] significantly widening their application potential. Generally, NIR-absorbing agents can be incorporated into polymeric nanocarriers by physical loading, electrostatic interactions, coordination or covalent conjugation.

Although most single photothermal treatments that use polymeric NIR-absorbing systems have been reported to be highly effective for cancer cell destruction, the *co*-delivery of photothermal agents with other therapeutic agents, such as chemotherapeutic drugs, could be used to complement the PTT approach to ensure complete tumor ablation. With a well-designed, 'smart' polymeric nanocarrier, the encapsulated drug is expected to achieve triggered release at the tumor sites under various stimuli. Combined photothermal–chemotherapy is not only capable of causing cancer cell death by individual therapeutic approaches but also exhibits synergistic effects to achieve unprecedented therapeutic outcomes. In addition, photodynamic therapy (PDT), another type of effective phototherapeutic approach, could also be combined with PTT. PDT uses photosensitizers to generate highly toxic singlet oxygen or other reactive oxygen species to damage the cancer cells upon irradiation with suitable wavelengths of light. Although both PTT and PDT induce cytotoxicity of the cancer cells via different mechanisms, their combination into a single therapeutic entity that is distinct from combined photothermal–chemotherapy may also provide an enhanced therapeutic effect to cure cancer.

In this review, we mainly describe the research advancements of photothermal therapeutic nanosystems using polymer-based nanoparticles as carriers of NIR-absorbing agents for potent photothermal cancer therapy. On the basis of the types of NIR-absorbing agents that are incorporated in these polymeric therapeutic systems for photothermal treatment, the following categories are highlighted in this review: (1) organic NIR-absorbing dyes; (2) gold nanostructures; (3) conjugated polymers; and (4) other NIR-absorbing nanosystems. Thereafter, we discuss recent developments in the combinational therapy with PTT. Finally, probable challenges and future prospects in this field are emphasized.

POLYMERIC NANOCARRIERS CONTAINING ORGANIC NIR-ABSORBING DYES FOR PTT

As compared with conventional inorganic nanomaterials or conjugated polymers, organic NIR-absorbing dyes, particularly cyanine dyes and their derivatives, possess promising properties for use in PTT applications because they possess unique advantages such as favorable biocompatibility and biodegradability. Upon NIR irradiation, the ground state electrons of cyanine

dyes are excited, where part of the energy could undergo radiative relaxation with fluorescence emissions. This property is often used for fluorescence bioimaging, which allows for the visual identification of microscopic cancer tumors and, consequently, more precise and highly efficient treatment. It should be noted that the emitted fluorescence generally falls into the NIR region, significantly reducing the interference of autofluorescence with enhanced contrast.

Table 1 Chemical structures of the polymers specified in this article

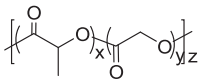
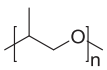
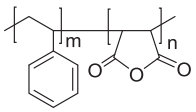
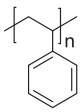
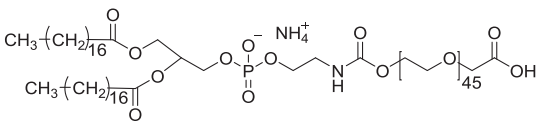
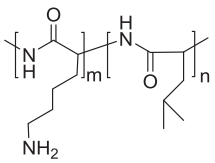
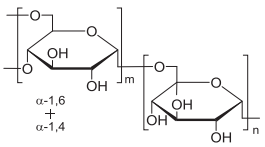
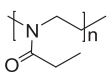
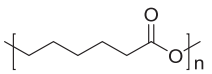
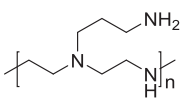
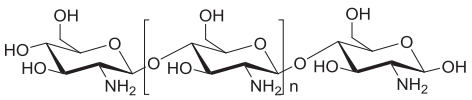
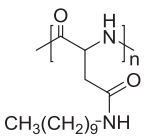
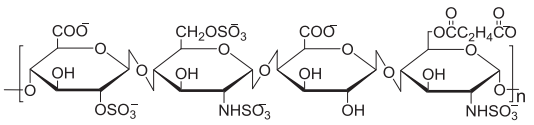
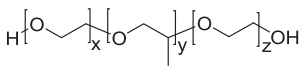
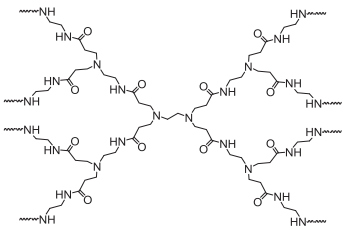
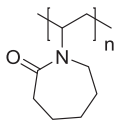
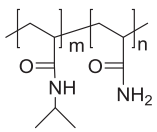
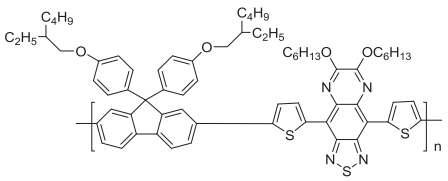
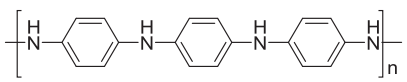
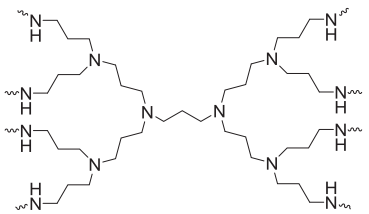
Name	*Abbreviation*	*Chemical structure*
poly(lactic-*co*-glycoloc acid)	PLGA	
poly(oxypropylene)	PPO	
poly(styrene-*alt*-maleic anhydride)	PSMA	
poly(styrene)	PS	
phospholipid-poly(ethyle ne glycol)	DSPE-PEG	
poly(L-lysine)-*b*-poly(L-leuc ine)	PLL-PLLeu	
dextran		
poly(2-ethyl-2-oxazoline)	PEOz	
poly(ε-caprolactone)	PCL	
poly(ethylenimine)	PEI	
chitosan		
poly(aspartic acid (decylamine))	PAsp(DA)	

Table 1 (Continued)

heparin		
polyoxyethylene-polyoxypropylene-polyoxyethylene	Pluronic (trade name)	
polyamidoamine dendrimer	PAMAM	
poly(*N*-vinylcaprolactam)	PNVCL	
poly((*N*-isopropylacrylamide-alt-acrylamide)	pNIPAAm-pAAm	
poly[9,9-bis(4-(2-ethylhexyl)phenyl)fluorene-*alt*-*co*-6,7-bis(4-(hexyloxy)phenyl)-4,9-di(thiophen-2-yl)thiadiazolo-quinoxaline	PFTTQ	
polyaniline		
polypropylenimine dendrimer		

Because some of the absorbed light energy from certain dyes can be converted into heat other than fluorescence after irradiation, these types of dyes have the potential to be used as theranostic agents in PTT applications. In order for the dyes to effectively perform photothermal treatment, the dyes should efficiently release their energy as heat during the internal conversion process. Some of the commonly used NIR-absorbing organic dyes for PTT are presented in Figure 2. These dyes exhibit extended conjugation that pushes the absorbed photons into the NIR region. In addition, their molecular structures contain a few methyl groups that can facilitate intramolecular rotation, promoting the internal conversion process to enhance the photo-to-heat conversion efficiency.

Although these NIR-absorbing dyes show excellent photothermal conversion efficiency, the free dyes cannot be directly used through systematic administration, hindering their further use in biomedical applications. In order for these dyes to be delivered into tumor tissues and cancer cells successfully, these dyes are commonly encapsulated in polymeric nanocarriers, which can significantly alter the bio-distribution of the NIR-absorbing dyes and prolong their circulation times in blood.

Indocyanine green-containing polymeric nanocarriers

Among the various organic NIR-absorbing dyes, indocyanine green (ICG) has been widely studied for the application of PPT since its

approval by the U.S. Food and Drug Administration (FDA) as a clinical NIR imaging agent on account of its good biocompatibility. ICG exhibits an absorption peak at ~780 nm, an emission band between 820 and 840 nm, and low interference with tissue chromophores.[37,38] As a potential theranostic agent, however, the application of free ICG is severely restricted by its physiochemical limitations, such as poor aqueous stability, concentration-dependent aggregation and nonspecific binding to proteins. To overcome these limitations, various polymeric nanocarriers such as PLGA,[39] poly (oxyethylene)-*b*-poly(oxypropylene), poly(styrene-*alt*-maleic anhydride)-*b*-poly(styrene)[40] and assembled capsules[41] have been used to encapsulate and stabilize ICG in aqueous solutions. These ICG-encapsulated nanosystems showed increased stabilities, as well as prolonged blood circulation times as compared with free ICG in water. The early study of ICG-containing nanostructures used through systemic administration was reported by Xing and co-workers,[42] where ICG-loaded phospholipid-poly(ethylene glycol) (DSPE–PEG) can self-assemble into nanostructures that showed efficient photothermal effects for cancer treatment *in vivo*. To study the size-dependent accumulation of ICG-loaded nanoparticles inside cancer cells, Cai and colleagues[43] developed a single-step assembly method for ICG-loaded PLGA–lecithin–PEG core-shell nanoparticles in three different sizes (39, 68 and 116 nm). It was demonstrated that the size of nanoparticles not only affected endocytosis and subsequent photothermal treatment efficiencies *in vitro* but also significantly influenced tumor internalization and photothermal therapeutic efficiencies *in vivo*. NIR imaging and photothermal cytotoxicity studies *in vivo* showed that the 68 nm ICG-containing nanoparticles presented the best therapeutic efficiency for inhibiting tumor growth. In addition, the same team also used other polymeric nanocarriers including PLGA-stabilized DSPE–PEG nanoparticles,[44] triblock copolymer poly (ethylene glycol)-*b*-poly(L-lysine)-*b*-poly(L-leucine) (PEG-PLL-PLLeu) micelles[45] and dextran-based block copolymer micelles[46] to load ICG for the imaging-guided PTT of cancer.

Targeting ligands such as folic acid (FA) have been widely used to functionalize nanocarriers to improve their therapeutic efficacies, because these ligands can selectively bind to overexpressed receptors on the surface of many types of cancer cells.[47] For example, it was reported that ICG was loaded inside folate-conjugated poly (2-ethyl-2-oxazoline)-*b*-poly(ε-caprolactone) (FA-PEOz-*b*-PCL) micelles, which can then be used for high-resolution NIR imaging.[48] Under NIR light irradiation, the micelles showed enhanced tumor ablation efficiencies due to the generation of heat by the light. To further improve the targeting capability of the micelles, two different ligands including FA and monoclonal integrin Rvβ3 were co-conjugated to the surface of the ICG-loaded PEGylated phospholipid micelles.[49] This dual targeting strategy led to enhanced endocytosis by cancer cells, and an *in vivo* study showed that these multifunctional nanostructures can be effectively used for cell imaging and selective photothermal cell destruction.

In addition to the use of ICG alone, other therapeutic molecules, such as the anticancer drug doxorubicin (DOX), can also be *co*-loaded in polymeric nanocarriers to achieve combined photothermal–chemotherapy. For instance, ICG and DOX were entrapped by PLGA

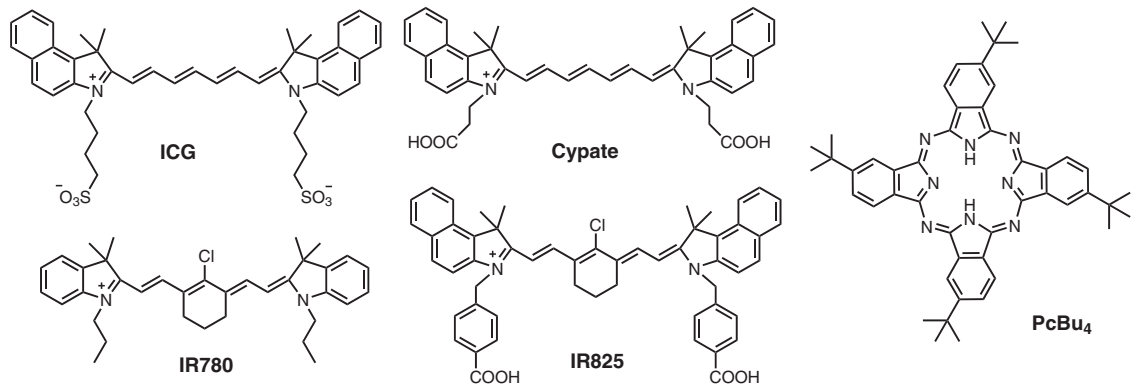


Figure 2 Chemical structures of different NIR-absorbing organic dyes encapsulated in polymeric nanocarriers for the photothermal treatment of cancer.

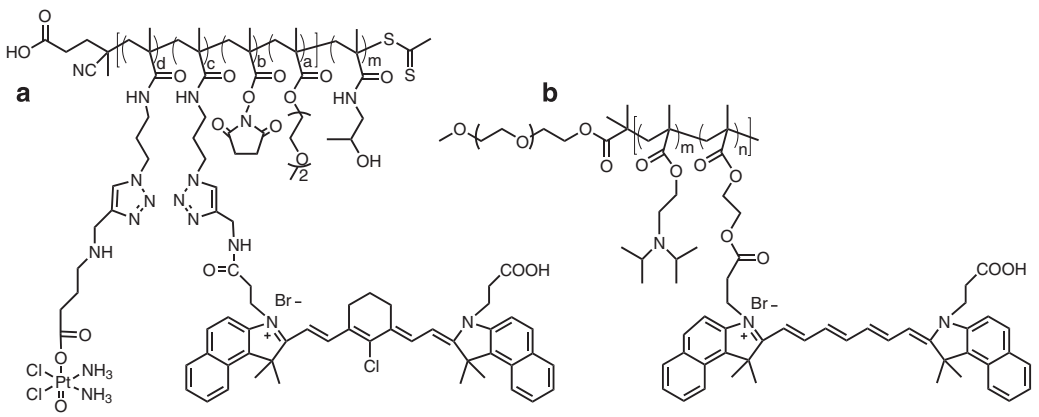


Figure 3 Representative chemical structures of polymer–cypate conjugates for the photothermal treatment of cancer. (**a**) Synthetic amphiphilic block copolymer prodrug–cypate conjugate, and (**b**) synthetic pH-responsive amphiphilic block copolymer–cypate conjugate.

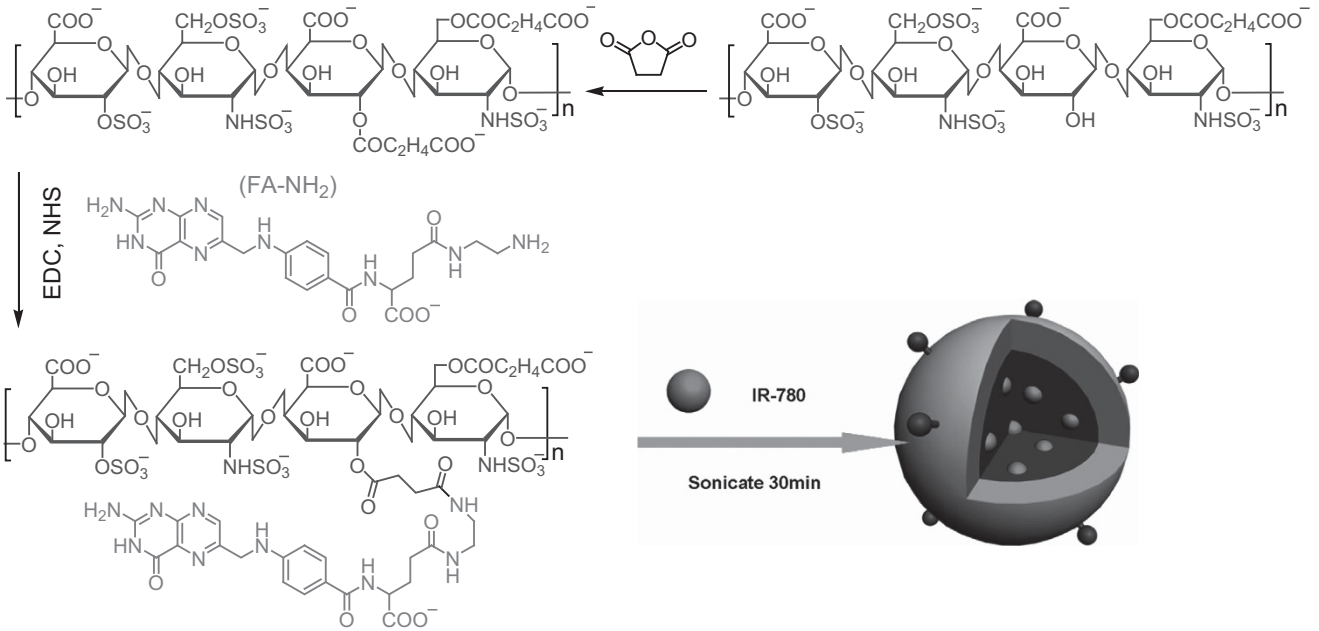


Figure 4 Synthesis of a heparin–folic acid conjugate and the assembly of IR780-loaded heparin–folic acid nanoparticles (reproduced with permission from Yue *et al.*[59]; copyright 2013 Elsevier). A full color version of this figure is available at *Polymer Journal* online.

nanoparticles modified with monoclonal antibodies for targeted combined photothermal–chemotherapy with NIR imaging capabilities.[50] A similar example was also reported by Cai and co-workers,[51] in which DOX and ICG were co-loaded in PLGA–lecithin–PEG polymeric nanoparticles using a single-step sonication method. The combined photothermal–chemotherapy not only synergistically induced DOX-sensitive MCF-7 and DOX-resistant MCF-7/ADR cell death *in vitro* but also completely ablated the tumor tissue without any tumor recurrence *in vivo*. Apart from the anticancer drugs, inorganic nanoparticles and ICG can also be encapsulated together by polymeric nanocarriers to achieve multiple therapeutic effects. For instance, Ma *et al.*[52] constructed dual-modal imaging-guided photothermal therapeutic agents using DSPE–PEG lipid micelles to encapsulate both ICG and superparamagnetic iron oxide nanoparticles. The superparamagnetic iron oxide nanoparticles were used as contrast agents for the enhancement of magnetic resonance imaging, while ICG served as an NIR fluorescence probe and heat generator for localized hyperthermia cancer therapy. This nanocomposite exhibited significant photothermal cytotoxicity, and the tumor was completely ablated by the hyperthermia treatment through photothermal effects.

Apart from conventional loading methods, complexation techniques can be used to achieve enhanced loading capacities inside polymeric nanocarriers. For example, Jian *et al.*[53] used PLGA-*b*-PEG micelles to load ICG with PEI, and uncovered that PEI could form highly robust and dense complexes with ICG, thus prominently reducing ICG outflow from the nanoparticles under physiological conditions. In addition, the use of electrostatic interactions is another feasible effect for improving ICG loading efficacies inside polymeric nanocarriers. Song *et al.*[54] introduced ICG to genipin cross-linked PEGylated chitosan nanoparticles through a self-assembly method via electrostatic interactions. Under NIR irradiation, the resulting nanoparticles exhibited improved stabilities and significant photothermal inhibition of the growth of mouse-bearing U87 tumors *in vivo*.

Cypate-containing polymeric nanocarriers

Although ICG has been widely used for NIR imaging and PTT, it cannot be easily functionalized for further biological applications because its disulfonate groups are highly chemically inert. Furthermore, the relatively high aqueous solubility of ICG may result in the pre-leakage of the dye during blood circulation, which tends to compromise the ultimate therapeutic efficacy of the carriers. To cope with this challenge, cypate, an ICG derivative, was developed as a replacement analog. Cypate has similar absorption and emission properties to ICG and possesses reactive carboxylic acid groups for easy conjugation with biologically active agents or other functional materials. For example, alkynyl-functionalized cypate and a Pt(IV) complex prodrug were simultaneously conjugated with an azido-containing block amphiphilic copolymer via click chemistry, and the conjugated cypate moieties in the formed micelles could result in photothermal temperature increases under NIR illumination (Figure 3a).[55] By using this strategy, a significant synergistic effect of combined photothermal–chemotherapy from this multifunctional system against cisplatin-resistant human lung cancer cells (A549R) was also observed. In addition to click reactions, cypate can also be conjugated to various substrates for PTT applications via direct esterification or amidation reactions of its carboxylic acid groups. Li and co-workers[56] reported the direct conjugation of the carboxylic acid groups of cypate and pendant hydroxyl groups on pH-responsive amphiphilic polymers via ester bond formation (Figure 3b). After the preparation of the dye-conjugated micelles, the localized NIR laser irradiation could trigger cytosol release of DOX through the hyperthermia effect and induced the photothermal destruction of cancer cells. In addition, *in vivo* experiments showed that this system could completely ablate tumor tissues with multi-drug resistance properties.

Because of its lipophilic nature, cypate can be directly loaded into polymeric self-assembled micelles with high loading contents. Chen and colleagues[57] demonstrated the development of a theranostic poly (ethylene glycol)-*b*-poly(aspartic acid (decylamine)) (PEG-*b*-PAsp

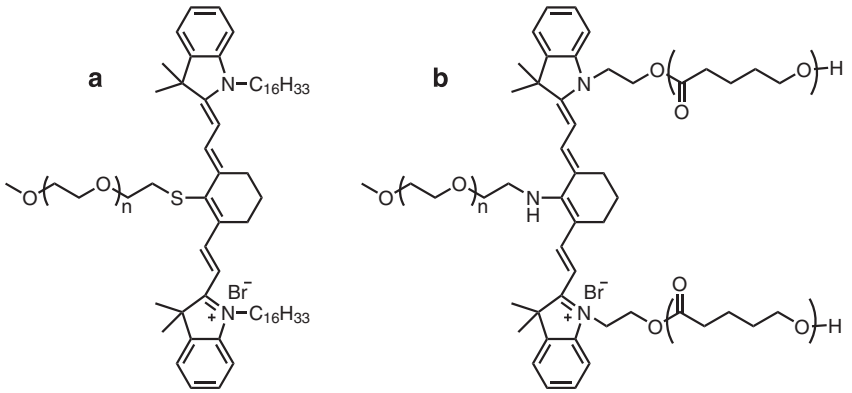


Figure 5 Representative chemical structures of polymer–IR780 conjugates for photothermal treatment. (**a**) PEG–IR780 conjugate, and (**b**) PEG-*b*-PCL block copolymer with IR780 as the linkage.

(DA)) micelle system encapsulating a cypate dye for long-term NIR fluorescence imaging of cancer. The *in vivo* experiments from the study exhibited that the micelles can generate significant photothermal damage of cancer cells via the destabilization of organelles, leading to successful tumor destruction upon NIR irradiation.

IR780-containing polymeric nanocarriers

Although the utilization of polymeric nanocarriers could improve the photostability of the loaded ICG and cypate and expand their use in biomedical applications, these dyes ultimately degraded under prolonged periods of NIR laser illumination. It is highly desirable to explore new NIR-absorbing dyes with excellent photostabilities under continuous and repeated light irradiation. IR780 is a dye that contains a rigid cyclohexenyl ring in the heptamethine chain and exhibits superior photostability over ICG and cypate.[58] Moreover, IR780 has similar fluorescence emissions and photothermal properties to ICG and cypate, but its improved photostability confers striking benefits as a robust theranostic reagent for fluorescence imaging and the photothermal treatment of tumors upon continuous and repeated NIR illumination.

To further improve the application potential for PTT, it is beneficial to use non-cytotoxic and biodegradable natural polymeric substrates as nanocarriers. On the basis of this principle, IR780 was loaded into micelles formed by FA-conjugated natural heparin polysaccharide.[59] Heparin micelles were simultaneously utilized for NIR fluorescence imaging and photothermal treatment both *in vitro* and *in vivo* on a folate-overexpressed tumor (Figure 4). In another study, Shieh and colleagues[60] incorporated IR780 and radionuclide rhenium-188 into amphiphilic poly(ethylene glycol)-*b*-poly(caprolactone) (PEG-*b*-PCL) self-assembled micelles, creating a multifunctional image-guided drug delivery system that permitted real-time monitoring of drug accumulation in a tumor, as well as intratumoral distribution and the kinetics of the released drug. In addition to the polymeric nanocarriers with normal sizes (generally between 50–200 nm) reported above, ultrasmall core-shell nanocarriers <20 nm in size have aroused much attention on account of their enhanced cellular uptake and increased aqueous stability for biological applications. Yang *et al.*[61] fabricated ultrasmall micelle@resin core-shell nanoparticles via a single micelle template method using resorcinol–formaldehyde resins as cross-linking agents. This modification of the resin shell significantly improved the aqueous stability and dispersity of the nanoparticles, and the nanoparticles can be stored for 3 months without aggregation. The hydrophobic dye IR780 was encapsulated into the hydrophobic core, and the resulting IR780-loaded nanoparticles served as theranostic agents for bioimaging and PTT both *in vitro* and *in vivo*.

The direct loading of dyes inside these self-assembled nanoparticles is a facile way of preparing polymeric photothermal agents. However, the nanoparticles tend to dissociate during blood circulation and are accompanied by the unexpected release of loaded cargoes, undoubtedly causing the low accumulation of dyes at the tumor sites. To improve the stability of the nanoparticles during the circulation process, polymeric nanocarriers self-assembled from IR780 dye-conjugated amphiphilic polymers were developed. Because the meso–chloro group in the cyclohexenyl ring of cyanine derivatives can be easily substituted with nucleophile reagents, Yuan *et al.* modified an IR780 derivative using sulfhydryl terminated PEG; the formed polymeric micelles without any other dye loading exhibited improved water solubility and photostability over the unmodified dye. In addition, the micelles could accumulate selectively at the mice tumor tissues, evidenced by fluorescence imaging, and the generated heat could lead to the complete ablation of tumors under laser irradiation without rendering any appreciable toxicity (Figure 5a).[62] Similar to the structure designed described above, PCL-*b*-PEG amphiphilic block copolymers with IR780 dye as the linkage between the two polymer blocks was also prepared (Figure 5b).[63] The self-assembled micelles acted as a multifunctional platform for NIR fluorescence imaging, PTT and the delivery of the anticancer drug DOX. Through this design, the DOX-loaded micelles exhibited a thermally triggered release of DOX under NIR irradiation, and thus displayed enhanced anticancer therapeutic efficacy through combined photothermal–chemotherapy.

IR825-containing polymeric nanocarriers

Many NIR-absorbing dyes have demonstrated excellent efficacies in the PTT treatment of cancer, and these dyes possess certain levels of fluorescence quantum yields. Although the emitted NIR fluorescence can be used for imaging, the excess loss of fluorescent energy ultimately compromises the photothermal therapeutic efficacy, especially for the treatment of the heat-resistant and refractory cancer cells. To address this challenge, Liu and co-workers designed a new NIR-absorbing heptamethine indocyanine dye (IR825) that exhibited excellent photostability, a high NIR-absorbing coefficient but low fluorescence quantum yields, which can improve the photothermal effect to the maximum extent. They proceeded by using a PEG-grafted amphiphilic polymer to solubilize this hydrophobic dye,[64] and the final formed micelles exhibited strong NIR absorbances and were accompanied by negligible quantum yields. The photostability

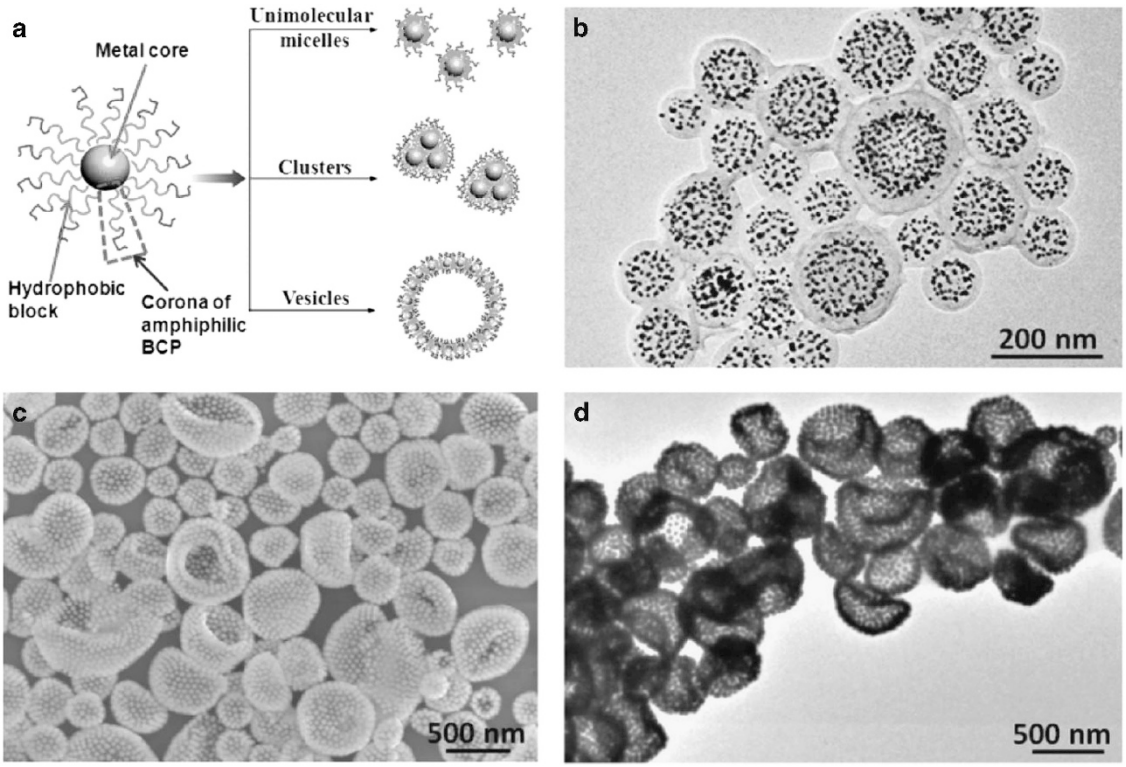


Figure 6 (**a**) Schematic illustration of amphiphilic plasmonic micelle-like nanoparticles composed of AuNP cores and amphiphilic block copolymer coronas and the assembly of the structures. (**b**) Representative transmission electron microscopy (TEM) image of vesicular assemblies of single micelle-like nanoparticles. (**c**) Scanning electron microscope (SEM) and (**d**) TEM images of vesicular assemblies of single micelle-like nanoparticles (reproduced with permission from He *et al.*;[71] copyright 2013 American Chemical Society). A full color version of this figure is available at *Polymer Journal* online.

experiment of the dye-loaded micelles proved that the photothermal effect did not decrease upon extended irradiation. In addition, *in vivo* experiments showed that the IR825-loaded micelles could efficiently accumulate in the tumor tissues after intravenous injection and completely ablate the tumor tissues under low-power laser irradiation.

Tetra-*t*-butylphthalocyanine-containing polymeric nanocarriers

Another example of an NIR-absorbing dye other than cyanine derivatives used for PTT is tetra-*t*-butylphthalocyanine ($PcBu_4$). $PcBu_4$ possesses acceptable photostability properties compared with ICG and cypate. Lim *et al.*[65] prepared Pluronic-based nanoparticles encapsulating the hydrophobic $PcBu_4$ dye, and the resulting therapeutic system exhibited robust photothermal effects superior to the ICG-loaded nanoparticles that were used as a control. Furthermore, the hybrid system was capable of selectively accumulating at the tumor tissues in the *in vivo* models, and the generated heat can successfully suppress tumor growth upon continuous NIR irradiation.

POLYMER/GOLD ASSEMBLIES FOR PTT

Gold nanomaterials have received a great deal of attention for use in cancer diagnosis and therapy owing to their unique optical and localized surface plasmon resonance properties. The optical properties of gold nanomaterials primarily depend on the particle sizes and the shapes of the nanostructures. Gold nanomaterials strongly absorb light at their resonance wavelengths and convert light into heat energy, which enables the thermal ablation of cancer cells. To improve the biocompatibility, aqueous stability and functionality, several types of gold nanostructures, including gold nanoparticles (AuNPs), gold nanorods (AuNRs), gold nanoshells (AuNSs) and hollow gold nanospheres (HAuNSs) have been employed as ingredients of polymeric assemblies for use in photothermal treatment.

Gold nanoparticle-integrated polymeric assemblies

Among the various gold nanostructures, AuNPs are readily prepared and have been extensively explored in biomedicinal applications. Generally, AuNPs exhibit strong visible absorption with heat generation, showing their potential application for the detection and photothermal treatment of cancer. To increase the colloidal stability and biocompatibility of AuNPs, they were either retained inside polymer-based nanocarriers or conjugated on the surface of polymeric nanocarriers. For example, Iodice *et al.* reported the loading of AuNPs inside large PLGA-based nanoparticles with lipid-PEG as a stabilizer. The hybrid nanostructure was stable under physiological conditions and showed enhanced photothermal-induced cytotoxicity against cancer cells as compared with bare AnNPs that were used as the control.[66] Among these polymeric nanocarriers, special attention has been given to dendrimers because of their highly branched and unique three-dimensional architectures with high and stable drug loading capacities. Several studies have been reported in the literature pertaining to the use of dendrimers as carriers for the stabilization of AuNPs. Hence, the integration of AuNPs with dendrimers could impart them with excellent aqueous stability and biocompatibility for use in biomedical applications.[67–69]

However, the visible absorption wavelength of AuNPs limits their use in further clinical applications because visible light is strongly absorbed and scattered by biological tissues, thus lowering the availability of light and enhancing the photodamage of normal tissues. To address this challenge, various amphiphilic polymers have been

applied to mediate the aggregation of gold nanoparticles, and to induce the red-shift of AuNP absorption into the NIR region.[70] Nie and co-workers[71] used the self-assembled amphiphilic block polymer poly(ethyl oxide)-*b*-polystyrene (PEO-*b*-PS) as a nanocarrier to encapsulate AuNPs, forming amphiphilic plasmonic micellar hybrid nanoparticles. Interestingly, the nanocomposites can further self-assemble into various superstructures such as individual micelles, aggregated clusters and vesicles when AuNPs were dispersed in different solvent media (Figure 6). Upon aggregation, the plasmonic peaks of the vesicular assemblies exhibited a bathochromic shift into the NIR region, and subsequent *in vivo* experiments showed that the heat generated form the vesicular assemblies can effectively ablate the mouse 4T1 tumors under laser irradiation at 808 nm. Similar research findings were also reported by Song *et al.*,[72] in which thiolated PEG and thiolated hydrophobic block copolymers were used to coat AuNPs and to induce the self-assembly of individual hybrid nanoparticles into plasmonic polymeric vesicles with large hollow cavities. These plasmonic vesicles were not only capable of loading and releasing anticancer drugs but were also used as theranostic agents based on the effects resulting from the combination of plasmonic imaging with PTT.

In addition to the traditional assembly of polymeric plasmonic nanostructures, another facile method of preparing AuNP self-assembly was developed through the *in situ* formation of aggregated AuNP coatings on polymeric assemblies as nanotemplates.[73,74] For example, DOX-loaded PLGA nanoparticles were reported as templates to deposit Au films, whereby the heat generated upon NIR irradiation can induce the dissociation of the nanocomposites and the subsequent release of DOX.[75] The combination of PTT with chemo-treatment indicated a synergistic therapeutic effect against HeLa cells *in vitro*, resulting in enhanced cytotoxicity and shortened treatment times. To overcome the inherent thermodynamic instability of the assembled polymeric nanotemplates, Dai *et al.*[76] used DOX-loaded interlayer cross-linked micelles as the template for the Au deposits. The resulting nanocomposites exhibited excellent stability with negligible DOX leakage in a physiological environment. When the nanocomposites were delivered into the intracellular environments of cancer cells, acidic/reduction cellular conditions caused the release of DOX, the disassembled nanocomposites can re-aggregate and shift the absorption into the NIR region, demonstrating that these nanocomposites can be used as an ideal NIR photothermal agent.

Gold nanorod-integrated polymeric assemblies

AuNRs with unique optical properties are superior to their AuNP counterparts. The absorption band of AuNRs could be easily shifted to the NIR region by simply increasing aspect ratios, thereby promoting longitudinal absorption properties. However, the synthesis of AuNRs often requires the use of cetyltrimethylammonium bromide (CTAB) as a surfactant, and the presence of CTAB on AuNRs confers systemic toxicity to the cells, thereby reducing their biocompatibility. For biomedical applications, it is necessary to use more biologically benign molecules or polymers to replace the stabilizing CTAB coating to improve the biocompatibility of AuNRs. Various types of thiolated biocompatible polymers have been developed and used to replace CTAB via strong thiol-Au coordination. For example, Choi *et al.*[77] reported the preparation of thiolated dextran-coated AuNRs for tumor-targeted delivery and studied their photothermal ablation efficiencies under NIR irradiation. Similarly, Kim *et al.*[78] prepared AuNR-embedded polymeric nanoparticles, in which the AuNRs were first modified with thiolated PCL followed by wrapping with a Pluronic polymer to improve their water stability. In another study, Li *et al.*[79] developed hybrid nanoparticles with polyamidoamine (PAMAM) dendrimers and AuNRs as the core with stretched hydrophilic PEG as the polymeric shell. The hybrid dendrimer nanoparticles exhibited excellent photothermal conversion capabilities upon NIR irradiation, resulting in considerable tumor volume reduction. For targeted PTT applications, arginine–glycine–aspartic acid (RGD) peptides were conjugated on the PAMAM shell, and the resulting polymer was used as a stabilizing agent coated on the AuNRs.[80] The obtained nanocomposites could efficiently target and destroy A375 cancer cells *in vitro* and *in vivo* under NIR irradiation.

Considering that polymeric hybrid assemblies with hydrophobic cores can serve as reservoirs to store hydrophobic agents, polymer-modified AuNRs have been used as NIR-responsive nanocarriers to deliver drug loads to targeted tumor sites. Zhong and co-workers[81,82] reported the preparation of AuNR hybrid micelles by coating the AuNRs with biodegradable lipoylated poly(ethylene glycol)-*b*-poly (caprolactone) (Lip-PEG-*b*-PCL) block copolymers with or without the targeting cyclic RGD (cRGD) ligand. In their study, DOX was retained in the hydrophobic core, and no pre-matured release was observed under physiological conditions. Upon NIR irradiation, the loaded drug could be released swiftly by heat that was generated from the AuNRs even at low-power illumination. Cytotoxicity studies showed that the antitumor activity could be significantly enhanced under mild laser irradiation *in vitro*, and cRGD-modified micelles

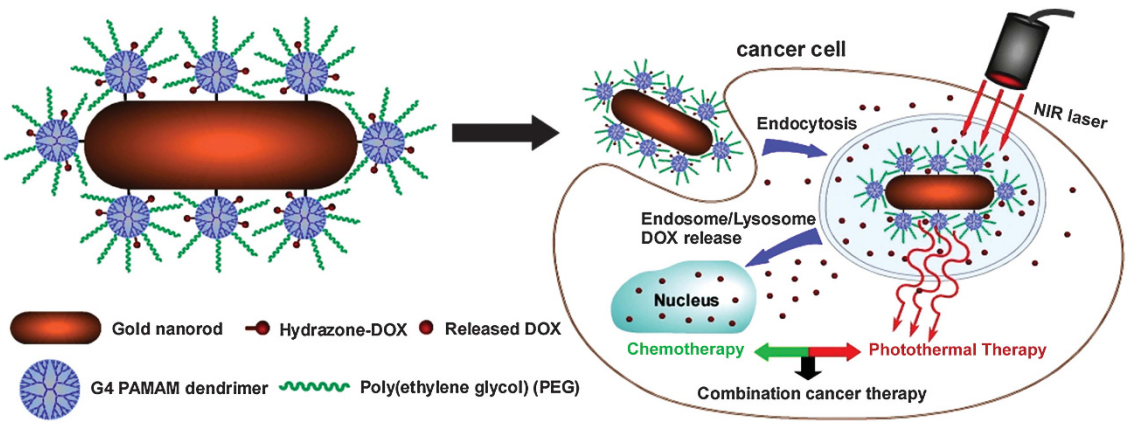


Figure 7 Schematic illustration of AuNR hybridized by a pH-sensitive PEGylated PAMAM dendrimer–DOX conjugate for combined photothermal–chemotherapy (reproduced with permission from Li *et al.*[87]; copyright 2014 Elsevier).

could completely inhibit human glioma xenograft growth in a nude mouse model *in vivo*. For more sensitive NIR illumination triggered release, the modification of AuNRs with a thermo-responsive polymer is a preferable choice. Park *et al.*[83] used AuNRs entrapped within thermal-responsive polymeric micelles as drug carriers to deliver DOX to cancer cells. It was demonstrated that localized photothermal heating under NIR illumination not only enhanced the cytotoxicity of DOX with a slight increase in local temperature but also thermally triggered an efficient release of DOX from the thermo-responsive nanocomposites. In addition, Liu *et al.*[84] prepared a temperature-responsive poly(ethylene glycol)-*b*-poly(*N*-vinylcaprolactam) (PEG-*b*-PNVCL) polymer that was capable of forming a polymer corona on the surface of AuNRs. More importantly, significant release of the loaded drug can be observed as a result of local overheating under NIR irradiation with a power density as low as 250 mW.

While the encapsulated drugs can be triggered to be released from AuNR-containing nanocomposites for chemotherapy under mild irradiation, combined photothermal–chemotherapy was also achieved for the ablation of tumors, particularly if a sufficient amount of laser output power density was adopted. An early example of AuNR-containing polymeric nanocomposites for the combined photothermal–chemotherapy was reported by Yeh and co-workers[85] in 2010. They prepared paclitaxel-loaded PLGA nanoparticles with *co*-conjugated Fe_3O_4 nanoparticles and quantum dots inside. Finally, AuNRs were attached on the surface of the nanocomposites via electrostatic interactions. These multifunctional nanocomposites can be effectively used for optical imaging and magnetic resonance imaging, as well as for combined photothermal–chemotherapy. Later, Liao *et al.*[86] developed PEG-*b*-PCL-based polymersomes *co*-loaded with DOX and AuNRs. The loaded DOX can be released efficiently under NIR laser irradiation, owing to the disassembly of the polymersome nanocarriers resulting from the generated heat. In addition, an *in vivo* experiment showed that the combined therapeutic effects led to complete removal of C26 tumor tissue in mice. Other than direct loading of drugs into the hydrophobic core of nanocarriers, an alternative tactic is to convert drugs into stable nanocarrier-drug conjugates through biologically cleavable covalent bonds, which would further prevent undesired leakage of the drug during circulation. Li *et al.*[87] used PEG-modified PAMAM dendrimers to wrap the AuNRs via thiol-Au coordination prior to the conjugation of DOX using an acid-labile hydrazone linkage (Figure 7). In this system, the nanocomposites remained stable under physiological conditions. Under acidic endo/lysosomal conditions, however, the hydrozone bond was cleaved, leading to the subsequent release of DOX. Most importantly, combined photothermal–chemotherapy exhibited synergistic therapeutic efficacy as compared with PTT or drug treatment alone, showing great potential for use in cancer treatment.

Using a similar strategy to polymer-mediated AuNP re-aggregation, AuNRs with an amphiphilic polymer coating can also self-assemble into well-defined discrete nanostructures, driven by the amphiphilic nature of the polymers. For instance, Duan and co-workers found that

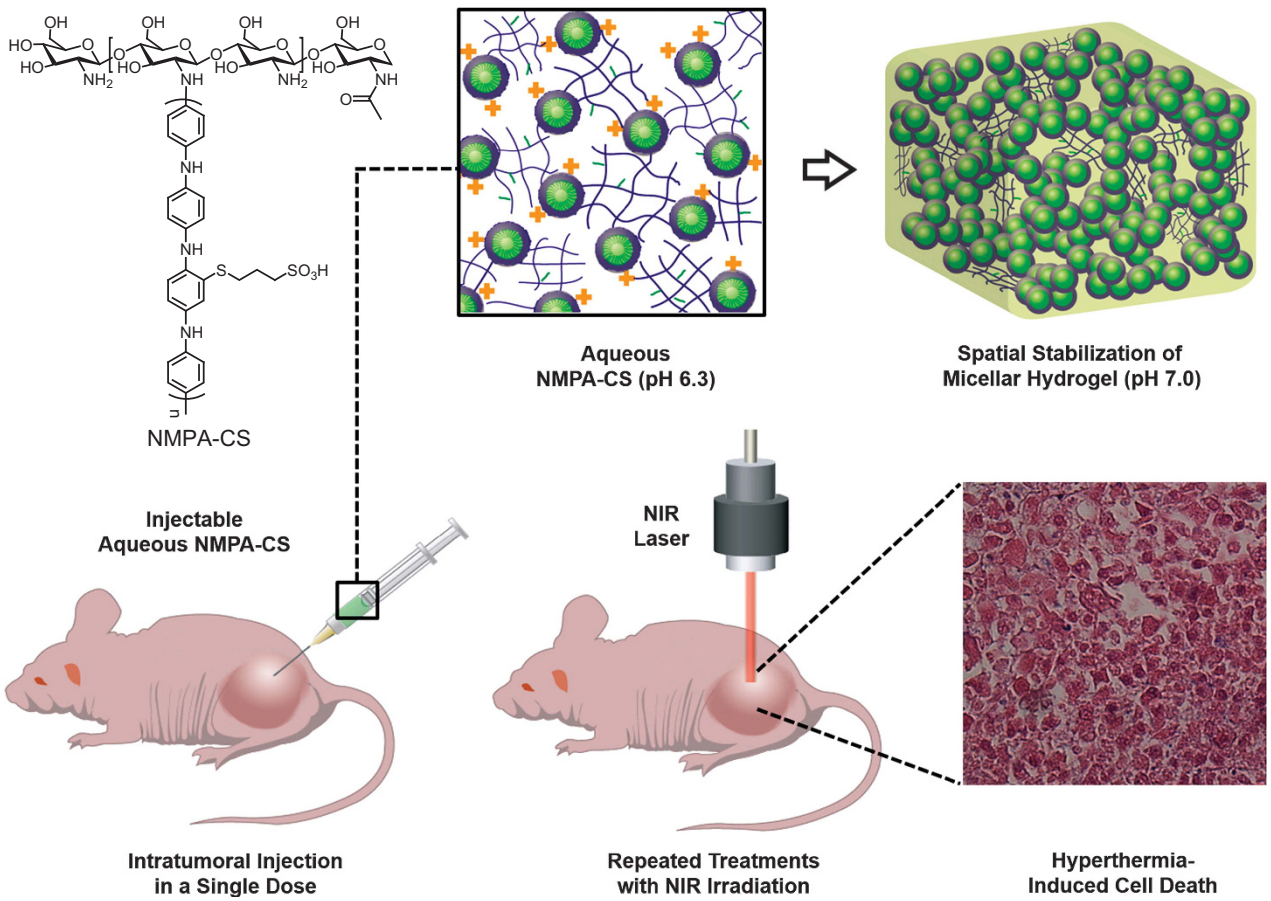


Figure 8 Chemical structure of a chitosan derivative (NMPA-CS) containing self-doped polyaniline side chains, and the mechanism of its photothermal treatment of tumors (reproduced with permission from Hsiao *et al.*[94]; copyright 2014 Elsevier).

PLA- and PEG-coated AuNRs could self-assemble into vesicles with increased interparticle plasmonic coupling. The self-assembly of these vesicles can be totally destroyed by enzymatic degradation or NIR illumination, which was followed by the release of encapsulated DOX.[88] In addition to the AuNR-induced PPT effect, additional loading of DOX inside the vesicles conferred synergistic photothermal–chemotherapy effects, showing better cancer cell-killing efficiency than either of the single treatments when used alone.

Other gold nanostructure-incorporated polymeric assemblies

Other gold nanostructures have also shown great potential in PTT applications. These gold nanostructures are commonly stabilized and delivered by polymeric nanocarriers for photothermal treatment. Barhoumi *et al.*[89] reported the coating of AuNSs with a thermoresponsive copolymer pNIPAAm–pAAm to shield the encapsulated peptide ligands. Upon illumination with NIR light, the generated heat can induce significant degradation of the copolymer, which was followed by exposure of the peptide ligand for cell binding. This approach revealed the potential of these gold nanostructures for use in tumor-targeted drug delivery and photothermal treatment. In addition, HAuNSs have displayed more effective photothermal efficacies than solid gold nanostructures, owing to their superior NIR-absorbing capabilities. You *et al.*[90] developed a polymer-based nanotherapeutic system, in which glycolipid-like polymer micelles were used to encapsulate PTX and HAuNSs. By using the HAuNSs as the heat generator, the hybrid micelles exhibited significant toxicity to tumor cells under NIR light irradiation both *in vitro* and *in vivo*. This design can be regarded as an excellent demonstration of gold nanostructures for combination photothermal–chemotherapy with superior tumor eradication efficacy.

CONJUGATED POLYMER-INCORPORATED POLYMERIC ASSEMBLIES

Conjugated polymers have been widely used in the field of optoelectronic devices because of their excellent electrical and optical properties. Recently, some of these conjugated polymers have been used as the new generation of NIR-absorbing agents for cancer treatment. However, many of these conjugated polymers are hydrophobic and non-biocompatible, hindering their further use in biomedical applications. To increase their clinical application potential, it would be of great interest and importance to load these conjugated polymers inside biocompatible polymeric nanocarriers. Liu and co-workers[91] developed a donor–acceptor conjugated polymer (PFTTQ) that was encapsulated within a DSPE–PEG matrix to form polymeric micelles with superior dispersity and stability. The micelles can efficiently convert NIR light energy into heat and could therefore efficiently ablate HeLa tumor cells in mice. In their follow-up research, the same conjugated polymer, PFTTQ, and the anticancer drug DOX were *co*-loaded inside NIR-responsive micelles for use in combined photothermal–chemotherapy.[92] Upon NIR laser irradiation, a hydrophobic-hydrophilic transition of 2-diazo-1,2-naphthoquinone moieties of the polymer occurred, causing the micelles to dissociate for the rapid release of the encapsulated DOX. With the additional hyperthermia effect caused by PFTTQ, the hybrid assemblies showed synergistic therapeutic efficiencies as compared with sole treatment against MDA-MB-231 cancer cells *in vivo*.

Another approach to increase the aqueous solubility and biocompatibility of the conjugated polymers is the introduction of additional biocompatible hydrophilic polymers via covalent bonds. Sung and co-workers[93] prepared an amphiphilic chitosan matrix with conjugated polyaniline side chains. This hybrid polymer can self-assemble into monodispersed micelles in a neutral aqueous environment, but

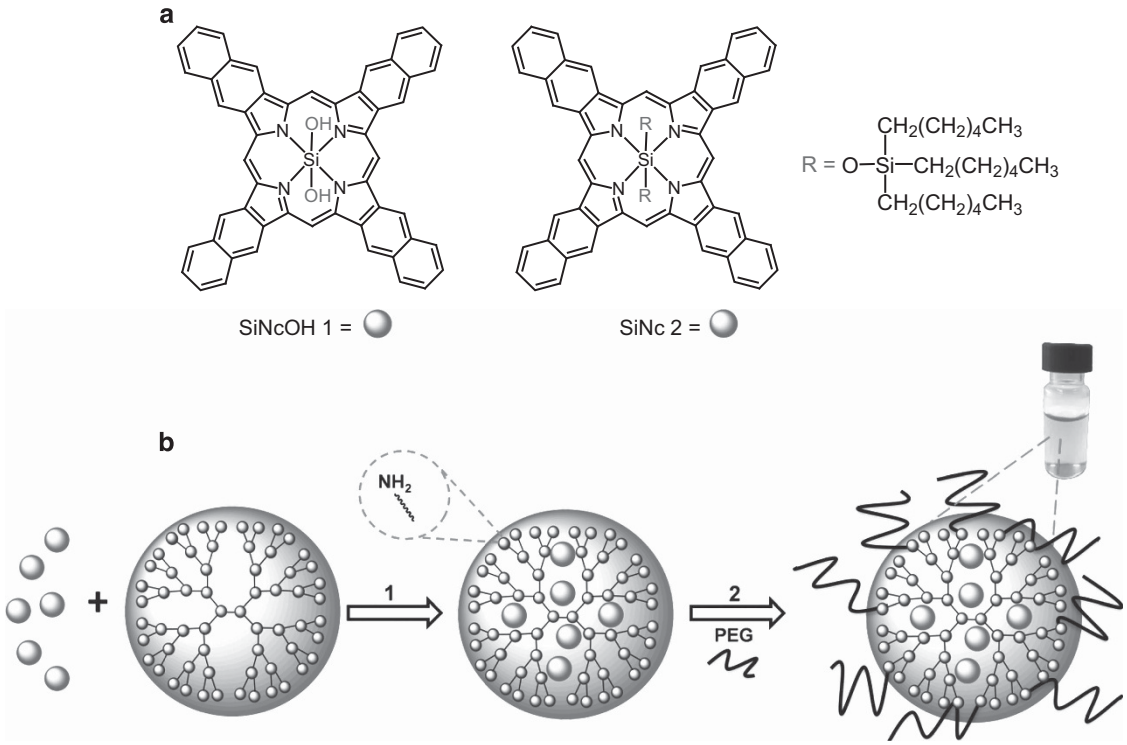


Figure 9 (**a**) Chemical structures of the parent silicon naphthalocyanine (SiNc) and the substituted derivative. (**b**) Schematic illustration of the fabrication of a SiNc-loaded theranostic nanoplatform (reproduced with permission from Gomaa *et al.*[103]; copyright 2015 Royal Society of Chemistry). A full color version of this figure is available at *Polymer Journal* online.

was readily transformed into a cross-linked gel when the local pH value decreased. After directly injecting the micelles at an infected abscess site in a mouse model, the micelles quickly formed colloidal gels and were distributed over the entire acidic abscess. After illumination of the infected abscess site with an 808 nm laser, the colloidal gel converted NIR light into heat and caused the thermolysis of bacteria and repair of the infected wound without residual implanted materials. Moreover, their studies also showed that this material could be efficiently delivered and retained at tumor sites without any leakage, which favored the photothermal treatment of cancer under repeated NIR irradiation (Figure 8).[94] This *in vivo* investigation revealed that the hydrogel at the tumor tissue provided better therapeutic efficacy after multiple treatment sessions as compared with pure HAuNS treatment as the control.

OTHER INORGANIC NIR-ABSORBING AGENT-INCORPORATED POLYMERIC ASSEMBLIES

In addition to the Au nanostructures used as NIR agents mentioned above, other inorganic agents, such as Mg nanoparticles (MgNPs) and CuS nanoparticles (CuSNPs), have also been wrapped with amphiphilic copolymers to form spherical hybrid nanoparticles for the potent photothermal treatment of cancer. Unlike the heavy metal element gold, Mg nanomaterials are more biologically benign for biomedical applications because the element Mg is abundant in the human body. Furthermore, MgNPs can easily biodegrade into ions that would be eliminated quickly by the human body. Locatelli *et al.*[95] reported the synthesis of MgNPs and their surface functionalization with a PLGA-*b*-PEG block copolymer. The heat generated from the formed hybrid micelles can be regulated by varying the laser intensity at 810 nm, just like other photothermal agents. Although the photothermal efficiency of MgNPs in this study appeared to be lower than that of conventional gold nanomaterials, MgNPs are still considered promising candidates for future PTT application owing to their excellent biocompatibility and biodegradability. In addition, CuSNPs have also been widely used as NIR-absorbing agents on account of their commercial availability, low cytotoxicity, high stability and intrinsic NIR region absorption. Zhang *et al.*[96] prepared multifunctional nanocomposites by *co*-conjugating CuSNPs with Cy5.5-modified hyaluronic acid polymeric nanoparticles, in which the emitted fluorescence of dye Cy5.5 was quenched by the loaded CuSNPs. Upon the delivery into tumor tissues, the acidic environment in the tumor tissues caused the degradation of the nanocomposites, thereby regaining strong fluorescence from Cy5.5. After intravenous administration of the nanocomposites into SCC7 tumor-bearing mice, the recovered fluorescence from Cy5.5 and photoacoustic signals of CuSNPs can be clearly observed in the tumor sites over time. Most importantly, tumor growth was efficiently inhibited as a result of the generated hyperthermia effect.

COMBINATION OF PTT WITH PDT

Integration of dual phototherapeutic agents into one platform

The combination of PTT with PDT could be achieved by integrating NIR-absorbing agents and photosensitizers into a single polymeric nanocarrier. In this hybrid system, the dual phototherapeutic agents can execute their therapeutic properties independently via different mechanisms without any interference. By using this approach, chlorin e6 (Ce6) has often been used as additional cargo for PDT because of its commercial availability, NIR-absorption, rapid elimination from the body, and high singlet oxygen generation efficiency. For example, Liu and co-workers[97] pre-conjugated the photosensitizer Ce6 to a PEGylated amphiphilic polymer, followed by loading of the NIR-absorbing dye IR825, which resulted in self-assembled multifunctional micelles. Because Ce6 is capable of chelating Gd^{3+} ions, the micelles could also be utilized as a T1 contrasting agent for magnetic resonance imaging applications. Overall, the hybrid system can be used for magnetic, fluorescence, and photoacoustic imaging of tumors in mouse models. Thereafter, combined photothermal–PDT was carried out, achieving a synergistic antitumor effect both *in vitro* and *in vivo*. This work presents a polymeric nanocarrier-based theranostic platform with great potential for use in multimodal imaging and the combination therapy of cancer. An additional study reported by Chen *et al.* showed the *co*-loading of cypate and Ce6 inside biodegradable PEG-*b*-PAsp(DA) micelles. The obtained systems can be used to achieve precise anatomical tumor localization, evidenced by the dual photoacoustic/NIR imaging modalities, accompanied by superior anticancer efficacy via sequential combination of PTT with PDT.[98]

In another study, Lin *et al.*[99] reported the modification of AuNPs with thiol terminated poly(ethylene glycol)-*b*-poly(styrene) (PEG-*b*-PS), which can then self-assemble into monolayer polymer-based vesicles. The plasmonic vesicular assemblies of AuNPs showed strong absorption in the NIR region, which was favorable for the PTT of cancer. The subsequent encapsulation of the photosensitizer Ce6 with a high loading efficiency enabled the versatile functionality of the vesicles by enabling NIR fluorescence/thermal/photoacoustic imaging-guided PTT and PDT. In addition, Kim *et al.*[100] prepared a chitosan-functionalized Pluronic nanogel for the loading of AuNRs and Ce6 for use in combined photothermal–PDT. By adjusting the loading method to avoid direct contact between Ce6 and the AuNRs, the quenching of Ce6 fluorescence was eliminated, thereby enabling both photothermal and photodynamic treatments. As compared with the treatment of PDT or PTT alone, an enhanced antitumor efficacy was observed for the combined photothermal–PDT both *in vitro* and *in vivo*.

However, the main disadvantage of this method is the complex composition of therapeutic systems resulting from the integration of different therapeutic agents into a single nanocarrier, which limits their translational potential. In addition, the incorporation of excessive therapeutic agents may give rise to the potential risk of unexpected side effects.

Use of dual-functional phototherapeutic agents

Apart from preparing dual phototherapeutic nanosystems containing both NIR-absorption and photosensitizing agents for the realization of combination therapy, another method that uses a single photoactive dye that simultaneously possesses PTT and PDT properties is desired. In this case, no excessive phototherapeutic agents would be needed in the therapeutic systems. By using the dual-functional phototherapeutic agents alone, the complications involved in the material preparation could be minimized with less concern over side effects. For instance, several studies reported that the ICG dye possesses both PTT and PDT properties; nevertheless, PDT applications of this dye are not commonly exploited.[101] Chen and co-workers prepared PEG-*b*-PAsp(DA) micelles with a *co*-loading of ICG and DOX. Their experiments showed that this combined system could facilitate enhanced cellular uptake and tumor accumulation both *in vitro* and *in vivo*.[98] The multifunctional micelles can trigger severe photothermal damage on tumor tissues upon light irradiation. In addition, the generation of singlet oxygen species from the loaded ICG via the photodynamic effect *in vitro* was validated using dihydroethidium as an intracellular probe. The synergistic cytotoxicity of anticancer drugs with light-induced heat and singlet oxygen species could successfully eradicate tumors without observing any re-growth.

Another NIR photoactive dye, naphthalocyanine, exhibits strong absorption in the NIR region and also holds great promise for use in

fluorescence imaging and dual phototherapy. Recently, Taratula *et al.*[102] prepared a multifunctional platform by encapsulating substituted silicon naphthalocyanin into the interior of polypropylenimine dendrimer micelles followed by modification with PEG (Figure 9). This hybrid therapeutic agent exhibited minimal side effects and remarkable combinational phototherapeutic efficiency after imaging-guided tumor identification and localization, thereby causing significant cytotoxicity on DOX-resistant ovarian cancer cells due to efficient conversion of light into heat and the generation of reactive oxygen species.

In addition, natural chlorophyll (Chl) extracted from natural plants tends to be regarded as an ideal NIR fluorescent imaging-guided photosensitizer for PDT.[103,104] Chu *et al.*[105] initially discovered that Chl possessed photothermal effects in their study, and subsequently carried out research on the combined photothermal–PDT of cancer. Combined therapy was realized by the encapsulation of Chl in Pluronic micelles prior to *in vivo* applications. It was observed that tumor growth was completely suppressed by the photothermal and photodynamic synergistic effects of Chl upon laser irradiation.

CONCLUSIONS AND PERSPECTIVES

In this review, we have discussed a variety of NIR-absorbing agents loaded in polymeric nanocarriers for PTT applications. The latest advances in NIR-absorbing agents, as well as in polymer design and self-assembly have been summarized. To realize the full potential of PTT, biocompatible and amphiphilic polymers are generally preferred as delivery vehicles, as they improve the stability and solubility of NIR-absorbing agents and reduce their cytotoxicity. Most importantly, these photothermal nanotherapeutic agents could be passively accumulated in tumor tissues and selectively endocytosed by cancer cells owing to their nanoscale size and modifications with relevant tumor targeting ligands, thereby maximizing their therapeutic efficacies and lowering their side effects. Many of these applied photothermal agents, especially organic NIR-absorbing dye-loaded polymeric nanocarriers, are fully biocompatible and biodegradable *in vivo* and serve as safe therapeutic agents for promising clinical uses. Numerous studies have indicated that these therapeutic agents can effectively eradicate cancer cells and destruct tumor tissues under NIR light illumination. By integrating diagnostic (for example, NIR imaging and photoacoustic imaging) or therapeutic (for example, chemotherapy and PDT) functionalities in a single therapeutic nanosystem, the obtained multifunctional nanoparticles can offer new opportunities in cancer theranostics with unprecedented therapeutic outcomes.

Encouraged by various excellent therapeutic results both *in vitro* and *in vivo*, these polymeric nanocarrier-based photothermal agents show great potential for applications in the efficient and safe treatment of cancer. However, several challenges in the field need to be addressed before achieving the clinical translation of these developed systems. Despite the great achievements in the treatment of cancer, additional research efforts should be devoted to advancing clinical applications. First, detailed preclinical safety concerns of these nanosystems should be thoroughly studied. These studies include the pharmacodynamics, pharmacokinetics and long-term toxicity using various animal models. Second, most organic NIR-absorbing dyes suffer from low photostability, which hinders their applications. Therefore, research must focus on continuously searching for new dyes that exhibit excellent photostability and biocompatibility. The next aspect of using polymeric photothermal agents for PTT applications pertains to the safety concerns of the light source used. In many successful demonstrations of PTT cancer treatment *in vivo*, a laser with high power density is often used as the light source for the photoillumination process. In these studies, the laser powers exceed the maximal value permitted by American National Standard for Safe Use of Lasers (ANSI) regulations (that is, 0.33 W cm^{-2} for 808 nm continuous wave laser). The use of these high power lasers can induce skin injuries on the sites of illumination, resulting in a major safety concern over the clinical application of PTT. Thus, it is crucial to develop new types of NIR-absorbing agents that exhibit superior NIR-absorption coefficients coupled with excellent photothermal conversion efficiencies. Finally, research attention should also be devoted to the development of smart and biodegradable photothermal agents integrated with targeting ligands, as well as diagnostic, imaging and therapeutic properties for versatile therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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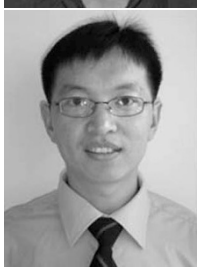
Yuanyuan Zhang obtained his BSc degree in Chemistry in 2004 and MS degree in Polymer Chemistry and Physics from Soochow University China in 2007 under the supervision of Professor Xiulin Zhu. Currently, he is a PhD candidate under the supervision of Professor Yanli Zhao in the School of Physical and Mathematical Sciences at Nanyang Technological University, Singapore. His research interests focus on the synthesis and characterization of organic NIR-absorption dye containing polymeric nanocarriers for combinational photothermal–chemotherapy of cancer.

Chung Yen Ang received his BSc (Hons.) degree with First-Class Honours in Chemistry from Nanyang Technological University, Singapore in 2012. Currently, he is pursuing his PhD studies under the supervision of Professor Yanli Zhao at Nanyang Technological University and co-supervision of Dr Tamil Selvan Subramanium at Institute of Materials Research and Engineering. His research focuses on developing organic materials for various biological applications including drug delivery, photodynamic therapy and bio-detection.



Yanli Zhao is currently an Associate Professor at Nanyang Technological University, Singapore. He received his BSc degree in Chemistry from Nankai University in 2000 and his PhD degree in Physical Chemistry there in 2005 under the supervision of Professor Yu Liu. He was a postdoctoral scholar with Professor Sir Fraser Stoddart at University of California Los Angeles (October 2005 to November 2008) and subsequently at Northwestern University (January 2010 to August 2010). In between (December 2008 to December 2009), he was a postdoctoral scholar with Professor Jeffrey Zink at University of California Los Angeles. He has published over 200 scientific papers, and received several awards including the TR35@Singapore Award in 2012 and the Singapore National Research Foundation Fellowship in 2010. His current research focuses on the development of integrated systems for diagnostics and therapeutics, as well as porous materials for gas storage and catalysis.