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Recent advances in the development of organic photothermal nano-agents

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ABSTRACT

Recently, photothermal therapy (PTT) has attracted tremendous attention because of its high efficacy in tumor ablation and minimal damage to normal tissues. While many inorganic nanomaterials, especially various gold nanostructures and nanocarbons, have been extensively explored for near-infrared (NIR) light triggered PTT in the past decade, a variety of organic photothermal agents have also emerged in recent years, aiming at replacing their inorganic counterparts which usually are not biodegradable. In this mini-review, we will summarize several typical classes of recently developed NIR-absorbing organic PTT nano-agents, which include NIR dye-containing micelles, porphysomes, protein-based agents, conjugated polymers, and organic/inorganic nanocomposites. The development of imaging-guided PTT and combination therapy will be introduced as well. Finally, the perspectives and challenges in the future development of PTT will be discussed.

1 Introduction

Photothermal therapy (PTT) which uses light-induced heating to burn cancer has attracted much interest in recent years as a minimally invasive strategy to destruct cancerous cells without damaging surrounding healthy tissues [1–4]. Effective photothermal agents should possess strong absorbance, high photothermal conversion efficiency, and good photostability in the near-infrared (NIR) region (700–950 nm), in which the absorbance by biological tissues, blood and water is the lowest [5–7]. In addition, the agents used in PTT should be nontoxic and show high tumor-homing ability in order to improve therapeutic efficacy without toxic side effects. In recent years, a large variety of NIR-absorbing inorganic nanomaterials, such as different noble metal (e.g. Au, Ag, Pt) nanostructures [8–13], carbon nanomaterials [3, 4, 6, 7, 14], as well as transition metal sulfide or oxide nanoparticles [15–21], have been widely explored by many research teams including ours as photothermal agents for PTT ablation of cancer *in vitro* and *in vivo*. Despite the high therapeutic efficacy obtained in many pre-clinical animal models, the non-biodegradable nature and

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potential long-term toxicity concerns of these inorganic nano-agents have significantly delayed their future clinical translation [22, 23].

As a potential replacement for inorganic photothermal agents, NIR-absorbing organic nanomaterials have been developed by many groups in the past few years for applications in PTT (Table 1). Various nanocomplexes encapsulating, adsorbing, or covalently linking NIR dyes to micelles, liposomes, or even proteins, have been fabricated and successfully used for photothermal tumor ablation [24–26]. Conjugated polymers with extended π-electrons are another type of organic agent with strong NIR absorbance, and have also been found to be robust photothermal agents [27–30]. In addition, a number of organic/inorganic nanocomposites with multiple functionalities integrated in single-nanoparticle systems have also been developed, aiming at realizing imaging-guided PTT

Table 1 A summary of the various kinds of organic nanomaterials explored in photothermal therapy

Organic PTT nano-agents	Typical samples	Size (nm)	Laser irradiation	Experimental details	Refs.
NIR dye containing micelles	ICG-PL-PEG	17.6	808 nm, 1.25 W/cm^2, 5 min	Intravenous injection. Dose = 25 mg/kg (ICG)	[24]
	HF-IR-780	92–121	808 nm, 0.8 W/cm^2, 5 min	Intravenous injection. Dose = 1.4 mg/kg (IR-780)	[31]
	IR825–PEG	25	808 nm, 0.5 W/cm^2, 5 min	Intravenous injection. Dose = 10 mg/kg (IR825)	[40]
	ICG/DOX loaded PLGA-lecithin-PEG NPs	86.3	808 nm, 1 W/cm^2, 8 min	Intratumoral injection. Dose = 1.375 mg/kg (ICG)	[33]
	IR825@C18P MH-PEG-Ce6	107	808 nm, 0.3 W/cm^2, 6 min 660 nm, 2 mW/cm^2, 1 h	Intravenous injection. Dose = 5 mg/kg (Ce6) 13 mg/kg (IR825)	[50]
Porphysomes		100	658 nm, 1.9 W/cm^2, 1 min	Intravenous injection. Dose = 42 mg/kg	[57]
Protein-based photothermal agents	SQ-BSA	~8	680 nm, 20 W/cm^2, 30 min	Intravenous injection	[65]
	HSA-IR82	~8	808 nm, 0.7 W/cm^2, 10 min	Intravenous injection. Dose = 1.3 mg/kg (IR825)	[67]
	FRT-IR820	12	808 nm, 0.5 or 1 W/cm^2, 10 min	Intravenous injection. Dose = 20 mg/kg	[66]
Conjugated polymers	Polyaniline	115.6	808 nm, 2.45 W/cm^2, 5 min	Intratumoral injection. Dose = 5 mg/kg	[29]
	Polypyrrole	55	808 nm, 1 W/cm^2, 5 min	Intravenous injection. Dose = 10 mg/kg	[30]
	PEDOT:PSS-PEG	80–90	808 nm, 0.5 W/cm^2, 5 min	Intravenous injection. Dose = 10 mg/kg	[28]
Other organic photothermal agents	Dpa-melanin CNSs	70	808 nm, 2 W/cm^2, 5 min	Intratumoral injection. Dose = 1 mg/kg	[72]
	PB-PEG NCs	~60	808 nm, 0.8 W/cm^2, 5 min	Intravenous injection. Dose = 10 mg/kg	[74]
Organic-inorganic nano-composites	SPIO@DSPE-PEG/ICG	29.9	808 nm, 0.64 W/cm^2,10 min	Intratumoral injection. Dose = 10 mg/kg (ICG)	[79]
	IR825@PAH-IONP-PEG	60	915 nm, 0.7 W/cm^2,5 min	Intravenous injection. Dose = 10 mg/kg (IR825)	[32]
	IONP@PPy-PEG	100	808 nm, 1.5 W/cm^2,5 min	Intravenous injection. Dose = 8 mg/kg (PPy)	[18]
	Fe_3O_4@PPy-PEG/DOX	150	808 nm, 425 mW/cm^2, 25 min	Intratumoral injection. Dose = 1 mg/kg (DOX)	[25]

or combination cancer therapy [18, 31–33]. Herein, we will review recent advances in the development of organic PTT agents, and discuss perspectives and challenges in this rapidly progressing direction.

2 NIR dye-containing micelles

In the past decades, a large number of small organic NIR dyes, many of which are cyanine derivatives, have been synthesized, mainly for applications in fluorescent imaging [34–37]. Dye molecules with strong NIR absorbance in fact can also be used as photothermal agents, as their absorbed optical energy is partially converted into heat in addition to their fluorescence emission. Several commonly used NIR dyes in PTT are listed in Fig. 1 [24, 31, 38–41]. Generally speaking, many NIR dyes can simultaneously serve as a fluorescent imaging probe as well as a photothermal agent [24, 34, 36]. With small molecular weights, NIR dyes are usually excreted shortly after injection, without rendering much long-term toxicity concern. Among various NIR dyes, indocyanine green (ICG) is approved by US Food and Drug Administration (FDA) for clinical use on patients [42]. Its safety is therefore not a problem. However, the direct use of free NIR dyes for PTT is not popular because of their limited aqueous stability (ICG suffers from concentration-dependent aggregation), nonspecific binding to proteins, and lack of tumor-targeting specificity [31, 43–47]. To overcome these limitations, many nanocomplexes, such as micelles self-assembled from amphiphilic polymers, containing NIR dyes have therefore been developed as photothermal nano-agents for cancer treatment. For example, ICG-containing nanostructures self-assembled with phospholipid–polyethylene glycol (PL–PEG) showed much better stability than free ICG [24, 48, 49]. Irradiation of tumors by an 808-nm laser after intravenous (i.v.) administration of ICG–PL–PEG offered excellent efficacy in tumor suppression, while free ICG only had a limited effect. Multifunctional heparine-folic acid–IR-780 nanoparticles (HF-IR-780 NPs) were synthesized by self-assembling a heparine–folic acid conjugate and IR-780 through ultrasonication [31]. Efficient ablation of folate receptor positive tumors was achieved after i.v. injection of HF–IR-780 and subsequent NIR laser irradiation of tumors. Recently, our group reported a new generation of organic PTT

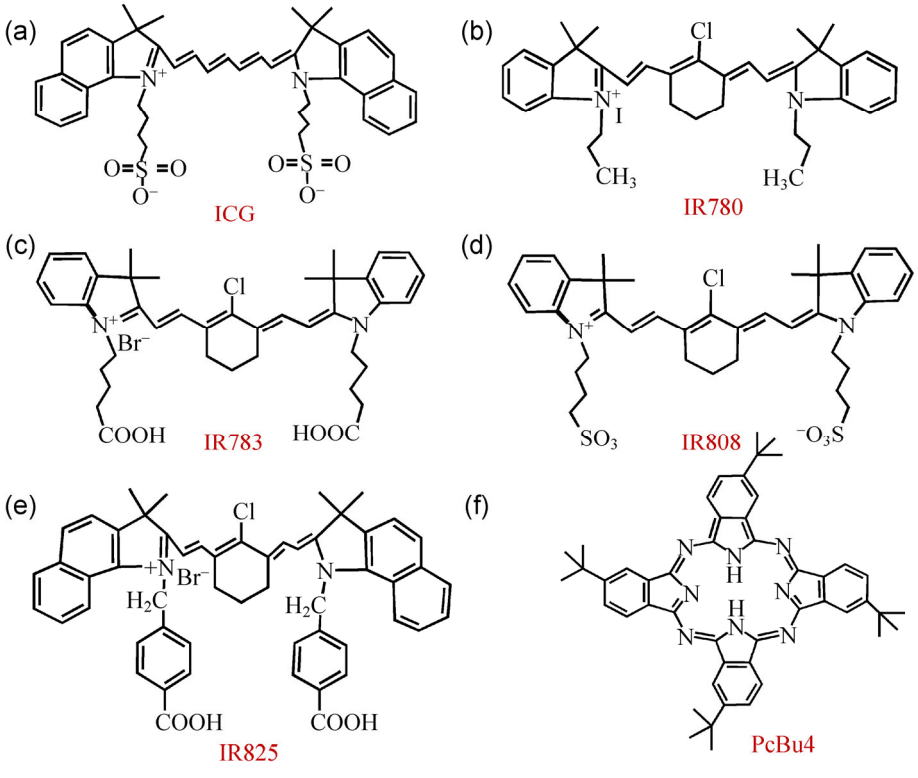

Figure 1 The chemical structures of different organic NIR dyes.

agents based on PEGylated micelles encapsulating a heptamethine indocyanine dye, IR825 [40]. The IR825–PEG nanoparticles showed much better photothermal stability compared to ICG, efficient tumor passive homing as a result of the enhanced permeability and retention (EPR) effect of cancerous tumors, and were able to induce effective photothermal tumor ablation under NIR laser irradiation.

In addition to NIR dyes, other therapeutic molecules can be co-loaded into these micelles to realize combination therapy, in which different therapeutic strategies are involved to kill cancer in a synergistic manner. In a study by Cai and co-workers, PEGylated micelles encapsulating a chemotherapy drug, doxorubicin (DOX), together with ICG, were fabricated and used for combined photothermal and chemotherapy, which appeared to be rather effective not only to wild-type tumors, but also towards multidrug resistant tumors as demonstrated in their *in vivo* studies [33]. Very recently, our group reported a new type of multifunctional theranostic nanomicelles by loading IR825 inside micelles formed by a PEGylated amphiphilic polymer, which was pre-conjugated with chlorin e6 (Ce6), a widely used photodynamic agent. Combined photothermal and photodynamic therapy under the guidance of multimodal imaging was realized in this work, demonstrating remarkable synergistic in inhibiting tumor growth [50]. Similar strategies have also been proposed by several other groups in their recent studies [51–54].

Compared with free organic NIR dyes, NIR dye-containing micelles show a number of advantages including significantly improved stability in different physiological environments, enhanced photothermal conversion efficiency due to the aggregation-induced blocking of photophysical processes other than internal conversion and thermal relaxation, prolonged blood circulation half-lives, as well as the possibility of realizing either passive tumor homing by the EPR effect or active tumor targeting with the help of targeting ligands. Nanomicelles also provide a versatile platform into which multiple imaging and/or therapy functions can be integrated. However, some small NIR dyes, ICG for example, are not very stable under continuous high-power laser irradiation, making repeated photothermal heating not that realistic. Encapsulation of these molecules inside micelles or other nanocomplexes may not be able to completely resolve this problem.

3 Porphysomes

Porphysomes invented by Zheng and co-workers are obtained by self-assembly of porphyrin lipids into liposome-like nanoparticles (~100 nm diameter). Porphysomes can absorb and convert light energy into heat with high efficiency due to the high porphyrin packing density, making them promising candidates in PTT [55, 56].

In 2011, porphysomes were developed as a theranostic agent in PTT for the first time by Zheng's team [57]. Porphysomes containing 30 mole% cholesterol exhibited high tumor accumulation and long serum half-life after systemic administration. High efficiency in tumor ablation was achieved under laser irradiation in their *in vivo* experiments (Fig. 2) [55–57]. By changing the ways that porphyrin-lipid assembles were formed, ultra small porphyrin nanodiscs and large porphyrin shell microbubbles were fabricated in their later studies, for applications in photodynamic therapy and ultrasound imaging, respectively [58, 59]. Furthermore, metal ions can be introduced into these porphysomes owing to the intrinsic metal chelating property of the porphyrin ring. For example, ^{64}Cu, a radioisotope, can be simply inserted into porphysomes for positron emission tomography (PET) [60]. In addition, manganese ions can also be incorporated directly into the building blocks of porphysome nanoparticles to enable T1 contrast in magnetic resonance (MR) imaging [61]

Porphysomes self-assembled from simple monomers are enzymatically biodegradable and highly biocompatible. Meanwhile, porphysomes can be utilized as efficient nanocarriers as well as imaging probes with many interesting functionalities. However, the relatively short absorption wavelength of porphyrins (600–700 nm) somewhat limits the tissue penetration depth when porphysomes are used in PTT. The development of new generations of porphysomes with strong NIR absorbance (e.g. with peaked absorbance wavelength longer than 800 nm) is expected to resolve this problem.

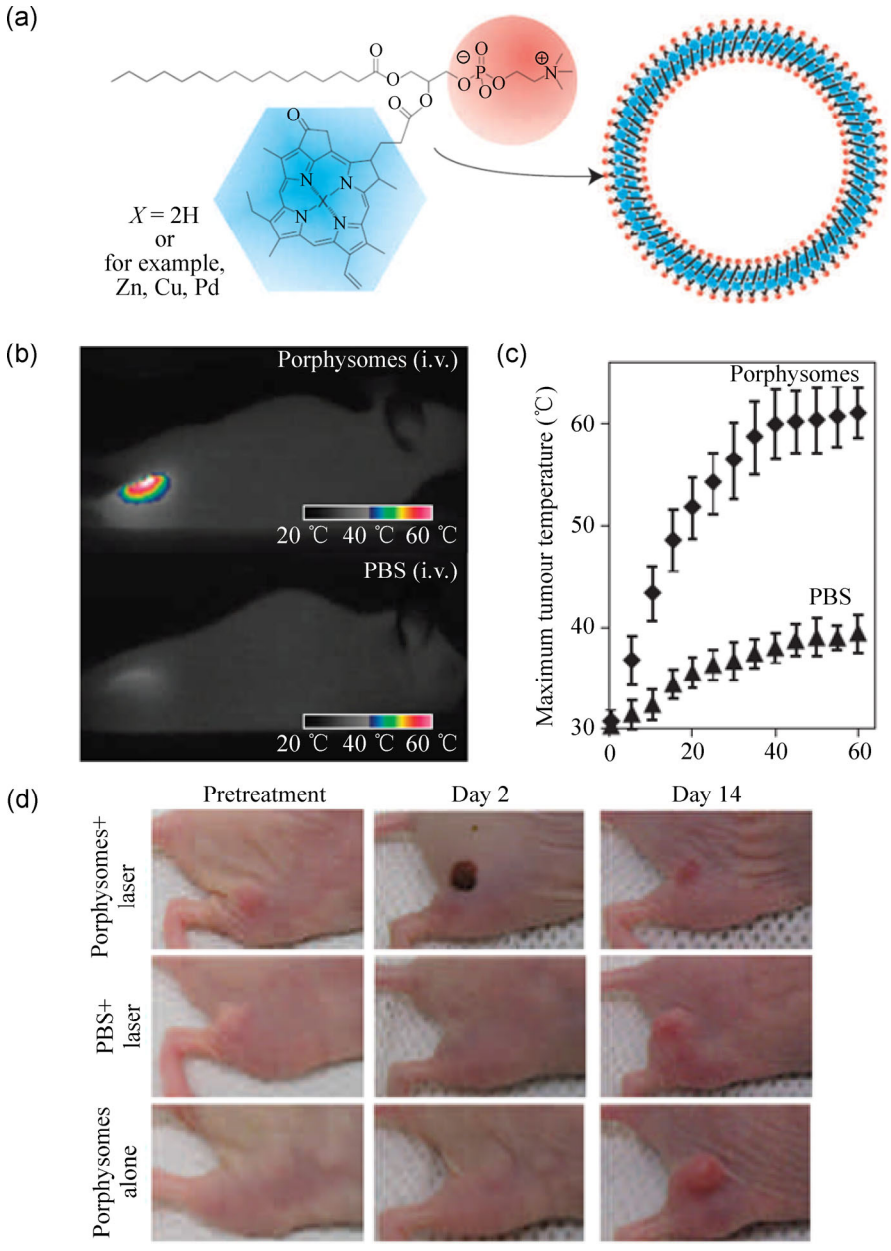

Figure 2 Porphysome nanovesicles generated by porphyrin bilayers for applications as photothermal agents. (a) Schematic representation of a porphysome. Infrared thermal images (b) and temperature increases (c) of tumors on mice i.v. injected with porphysomes upon NIR laser irradiation. (d) Photographs showing therapeutic response to photothermal therapy using porphysomes. Tumors were completely ablated after porphysome-based PTT. (Copyright Nature Publishing Group. Reproduced from Ref. [57] with permission.)

4 Protein-based photothermal agents

Proteins with inherent biocompatibility have been extensively explored as drug carriers for decades. Recently, several groups have also reported protein-based photothermal nano-agents particularly for imaging-guided PTT [26, 62–64]. Early this year, Wang and co-workers reported that squaraine (SQ) can be bound to the hydrophobic domain of bovine serum albumin (BSA) via hydrophobic interaction and hydrogen bonding [65]. The resulting BSA–SQ complex showed enhanced fluorescence emission and was used for imaging guided photothermal treatment of cancer *in vivo*. In a more recent work, Chen and

co-workers reported a novel "chameleon" theranostic platform based on NIR dye (a new cyanine green, IR820)–loaded ferritin (DFRT) nanocages, which showed strong NIR absorbance and was employed for photoacoustic/fluorescence multimodal imaging-guided PTT [66].

For fluorescent imageable photothermal agents, high fluorescent quantum yield (QY), which is required in fluorescent imaging, will reduce the photothermal conversion efficiency as more absorbed optical energy is converted into emitted light instead of heat. In our very recent studies, we uncovered an interesting imageable photothermal agent by complexing a NIR dye, IR825, with human serum albumin (HSA), the most abundant human protein [67]. The resulting HSA–IR825 nanocomplex exhibited strong fluorescence under 600 nm excitation, useful for *in vivo* imaging, together with a rather high absorbance peak at 810–825 nm for photothermal tumor ablation. Using such protein-based agents, both fluorescent imaging and PTT can be conducted with different wavelength channels without compromising the performance of either. The rapid renal excretion of IR825 in this formulation together with the great biocompatibility of HSA could limit the long-term toxicity concern of this agent.

In our latest follow-up study, HSA conjugated with diethylenetriamine pentaacetic acid (DTPA) chelated Gd^{3+} was then complexed with IR825 [68]. The resulting HSA–Gd–IR825 nanoprobe was utilized for multimodal fluorescence/MR imaging-guided PTT (Fig. 3). Interestingly, both *in vivo* fluorescence and MR imaging revealed that HSA–Gd–IR825 after intratumoral injection can migrate into nearby sentinel lymph nodes (SLNs). Surgical removal of the primary tumors, together with photothermal ablation of SLNs induced by HSA–Gd–IR825 resulted in significantly reduced lymphatic tumor metastasis and greatly prolonged animal survival.

Although protein-based drug delivery is an old topic, the development of protein–dye complexes as photothermal agents is rather new. As natural carriers, proteins raise less safety concern for clinical use compared with synthetic carriers. The unique interactions between proteins and some NIR dyes, although in need of more in-depth understanding, make such complexes useful in imaging-guided PTT. It is expected that other therapeutic molecules, such as chemotherapy drugs, may also be easily integrated into these protein-based PTT agents for future use in combination cancer therapy.

5 Conjugated polymers

Conductive polymers with conjugated molecular structures have been widely used in organic electronics for many years. Their applications in biomedicine, especially cancer therapy, did not receive significant attention until 2011–2012, when a number of groups reported the use of various NIR- absorbing conjugated polymers for photothermal cancer ablation (Fig. 4).

Polyaniline nanoparticles (PANPs) were the first conjugated polymer to be used as a photothermal agent for cancer ablation [29]. Due to its transition from the emeraldine base (EB) to the emeraldine salt (ES) in presence of oxidative species in an intracellular environment, the optical absorbance peak of polyaniline is red-shifted toward the NIR region, making it a promising candidate for PTT.

Polypyrrole (PPy) nanomaterials have received great attention in bioelectronics and biomedical application due to their high conductivity, outstanding stability and good biocompatibility. PPy nanoparticles are usually produced by polymerization of pyrrole monomer through microemulsion methods. The strong absorption of PPy NPs in the NIR region can create a significant NIR photothermal effect for effective cancer ablation. In 2012, our group developed PPy nanoparticles as a new type of photothermal agent [27]. With great stability in different biological media and little dark toxicity, after being injected into tumors PPy nanoparticles can induce strong heating under NIR laser irradiation which effectively destroys tumor cells *in vivo*. Subsequently, several different groups have also separately demonstrated the use of PPy nanoparticles for photothermal cancer treatment [30, 69, 70].

Poly(3,4-ethylenedioxythiophene):poly(4-styrenesulfonate) (PEDOT:PSS), which is a complex between the conjugated polymer PEDOT and the negatively charged polymer PSS, exists as nanoparticles in aqueous solutions and also exhibits strong absorbance in the NIR region. In 2012, our group successfully

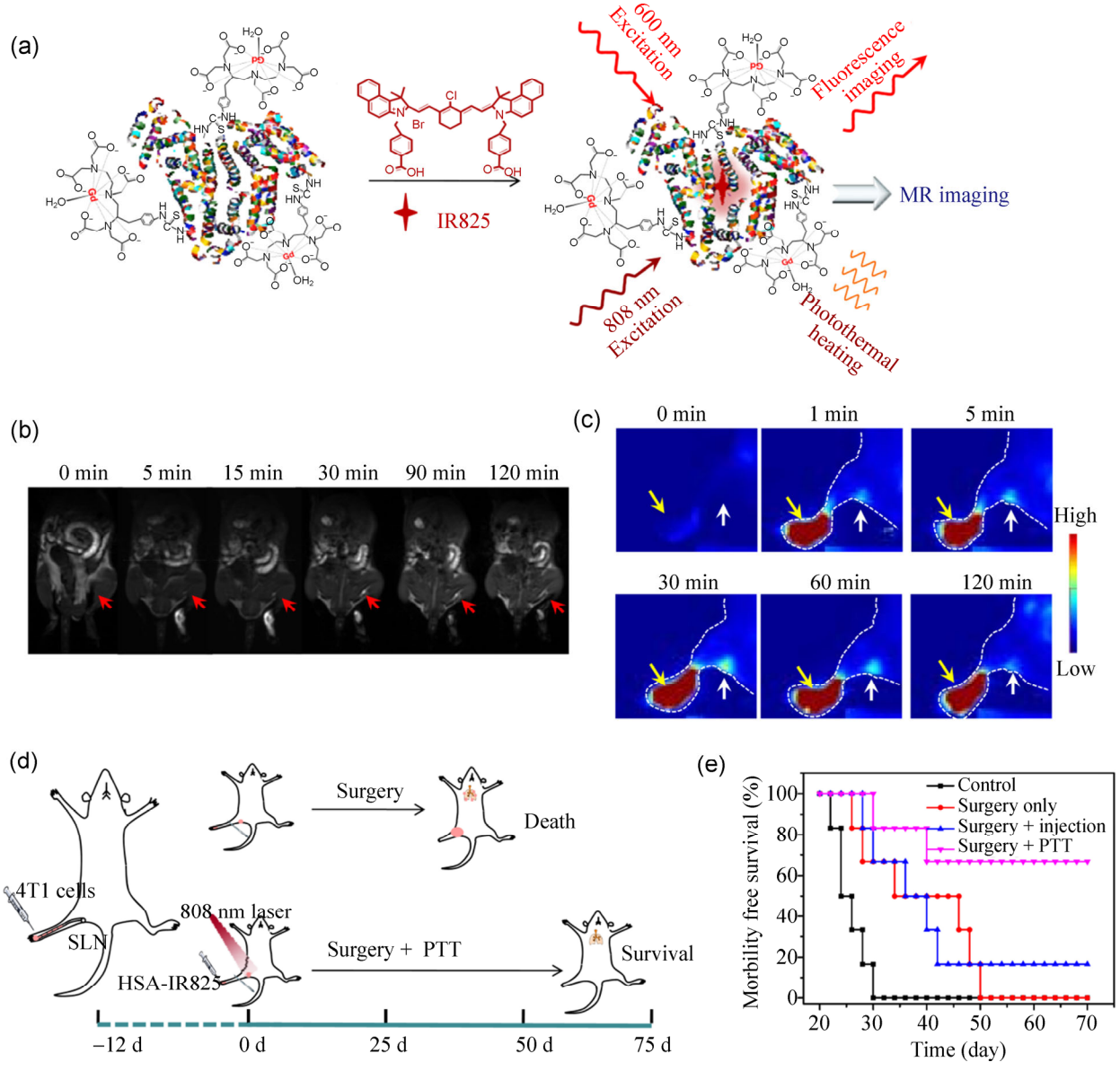

Figure 3 Protein-based photothermal agents for imaging-guided PTT. (a) A schematic illustration to show the formation of HSA-Gd-IR825 nanoparticles. (b) T1-MR images of mice after injection of HSA-Gd-IR825 into the primary tumor. Red arrows point to the SLNs. (c) *In vivo* fluorescence images of mice after injection of HSA-Gd-IR825 into the tumor growing on their hint paws. Yellow and white arrows point to the primary tumors and the SLNs, respectively. (d) A scheme showing the design of our animal experiment. (e) Morbidity free survival of different groups of mice after various treatments indicated (6 mice per group). (Copyright Elsevier Ltd. Reproduced from Ref. [68] with permission.)

developed a novel PTT agent based on functionalized PEDOT:PSS [28]. PEGylated PEDOT:PSS nanoparticles fabricated by a layer-by-layer polymer coating method showed excellent stability and exhibited a stealth-like behavior after intravenous injection with a long blood circulation half-life, which enabled rather effect tumor homing of these nanoparticles as a result of the EPR effect. Highly effective *in vivo* photothermal ablation of tumors was then realized in our mouse model experiments.

Besides serving as photothermal agents, conjugated polymers can also be used as drug delivery platforms as evidenced in our recent studies [25, 71]. It was found that several types of aromatic therapeutic molecules such as chemotherapy drugs DOX and 7-ethyl-10-hydroxycamptothecin (SN38), and a photodynamic

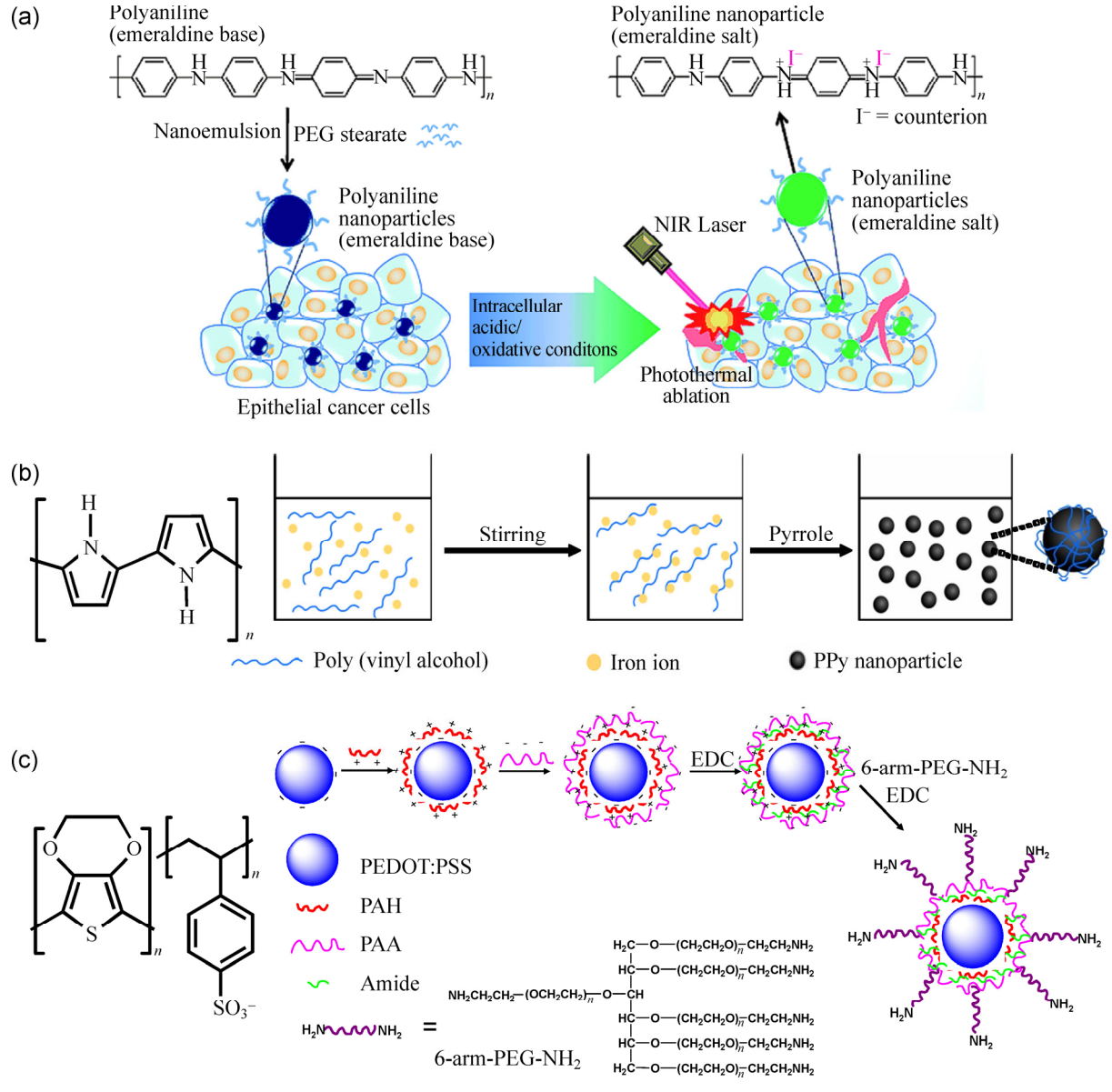

Figure 4 Conjugated polymers for photothermal therapy of cancer. (a) Schematic illustration of the preparation of organic photothermal agents based on polyaniline nanoparticles and their application in the photothermal ablation of epithelial cancer cells by NIR laser irradiation (Copyright WILEY-VCH Verlag GmbH & Co. KGaA. Reproduced from Ref. [29] with permission). (b) PVA-coated PPy nanoparticles used for *in vivo* photothermal therapy (Copyright WILEY-VCH Verlag GmbH & Co. KGaA. Reproduced from Ref. [27] with permission). (c) Scheme showing the preparation of PEGylated PEDOT:PSS nanoparticles for *in vivo* photothermal therapy (Copyright American Chemical Society. Reproduced from Ref. [28] with permission).

agent Ce6, can be successfully loaded onto PEDOT:PSS–PEG nanoparticles through π–π stacking and hydrophobic interaction. The drug-loaded conjugated polymers can be utilized for combination cancer therapy, showing obvious synergistic therapeutic effect [71].

Compared with small NIR dyes, conjugated polymers usually exhibit rather robust photothermal stability even after a long period of continuous laser irradiation. Owing to their unique structure, many conjugated polymer can serve as promising multifunctional drug carriers for potential applications in combination cancer therapy. However, although many *in vitro* and *in vivo* studies have indicated that conjugated polymer nanoparticles with suitable surface coatings are not obviously toxic [28, 29, 69],

the exact biodegradation and metabolism behavior of these polymers remains a largely unknown question to be addressed by future investigations.

6 Other organic PTT agents

In addition to the abovementioned various types of organic photothermal nano-agents, there have been a number of other organic nanoparticles used in PTT cancer treatment in recent years. In 2012, Lu and co-workers presented a novel PTT agent based on dopamine–melanin colloidal nanospheres (Dpa–melanin CNSs) for *in vivo* cancer therapy [72]. Melanin is a nature pigment polymer found in the human body while dopamine is a biomolecule already used in the clinic. Dpa–melanin CNSs showed great biodegradability as well as high photothermal conversion efficiency due to the NIR absorbance of melanin, enabling effective photothermal treatment of cancer as demonstrated in their animal studies.

Prussian blue (PB), which has been approved by FDA for the treatment of radioactive exposure in the clinic, has also been investigated as a photothermal agent by several groups including ours [73–75]. In our latest work [74], PEGylated PB nanocubes (PB-PEG NCs) were fabricated and i.v. injected into tumor-bearing mice, enabling *in vivo* PTT under the guidance by both photoacoustic imaging and T1-weighted MR imaging. Strictly speaking PB is not an organic agent. Nevertheless, its biocompatible nature together with strong NIR absorbance as well as intrinsic MR contrasting ability, make it an interesting imageable photothermal agent.

7 Organic–inorganic nanocomposites

In recent years, introducing imaging strategies during therapy, namely theranostics, has been proposed to be a promising way to improve treatment efficiency. In the case of photothermal cancer treatment, imaging is able to provide valuable information about the tumor location, size, and shape to allow full light coverage of the tumor during laser irradiation. The real-time tracking of a photothermal agent by imaging is also a meaningful way to decide the best timing of laser treatment. Considerable efforts have thus been devoted to the development of organic/inorganic nanocomposites as theranostic agents aiming at imaging guided PTT. In such nanocomposites, iron oxide nanoparticles (IONPs) have been the most popular inorganic component, owing to their ability to offer great contrast in T2-weighted MR imaging, and the fact that several formulations of IONPs have already been approved by FDA for clinical use.

In a recent work by Dai and co-workers, a biodegradable nanotheranostic agent was fabricated by loading the organic dye ICG into 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)] (DSPE–PEG) coated superparamagnetic IONPs [76]. The nanocomposite was utilized for fluorescence/MR dual-modal imaging guided PTT. We have reported a new kind of organic/inorganic nanocomposite based on a IR825, which in the presence of a cationic polymer forms J-aggregates with red-shifted and significantly enhanced absorbance at ~915 nm [32]. After complexing with IONPs and further surface PEGylation, the resulting nanocomposite can be utilized for *in vivo* MR imaging-guided PTT triggered by at 915 nm, which interestingly appeared to be optimal in PTT applications, due to its improved tissue penetration compared with 808-nm light and much lower water heating in comparison to 980-nm light (Fig. 5).

Nanocomposites composed of conjugated polymers and IONPs have also been reported in several recent studies [18, 25, 77–79]. In our work, we used PPy to encapsulate ultra small IONPs [18]. The resulting multifunctional IONP@PPy nanoparticles after PEG coating can serve as a contrast agent for *in vivo* MR and photoacoustic dual-modal imaging. Such *in vivo* imaging-guided PTT leads to effective *in vivo* tumor ablation. In another recent study, our group developed a new class of drug carrier based on PEGylated Fe_3O_4@PPy (Fe_3O_4@PPy–PEG) core–shell nanoparticles for combination cancer therapy (Fig. 6) [25]. In addition to serving as a NIR-absorber in PTT, the PPy shell can also be utilized for loading of chemotherapy drugs. In addition, the magnetic Fe_3O_4 nanocluster core can enable magnetically controlled drug delivery and offer contrast in MR imaging. Our *in vivo* cancer treatment study demonstrated the high therapeutic efficacy of combined photothermal and chemotherapy

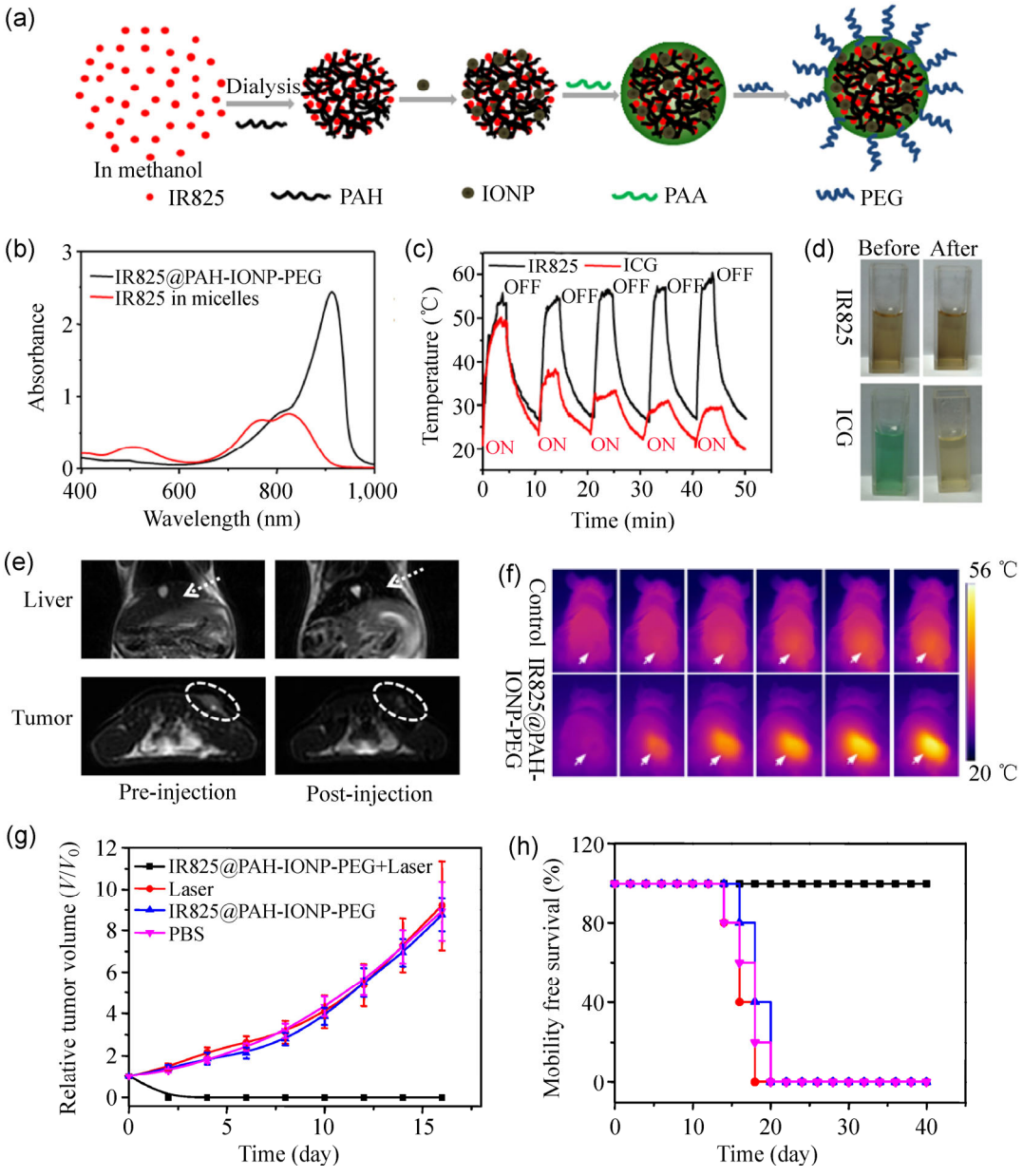

Figure 5 J-Aggregates of organic dye molecules complexed with IONPs for imaging-guided PTT under 915-nm light. (a) A schematic showing the fabrication process of IR825@PAH-IONP-PEG nanocomposite. (b) UV–vis–NIR absorbance spectra of IR825@PAH-IONP-PEG and IR825 in PEGylated micelles at the same IR825 concentration. (c) and (d) Optical stability of IR825@ PAH-IONP-PEG and ICG solution after multiple cycles of laser-induced photothermal heating. (e)–(h) *In vivo* imaging-guided photothermal therapy. (e) T2-weighted MR images of mice before and 24 h after i.v. injection of IR825@PAH-IONP-PEG nanoparticles. (f) IR thermal images of 4T1 tumor-bearing mice without (upper row) or with (lower row) intravenous injection of IR825@PAH-IONP-PEG (1 mg/mL, 24 h post-injection (p.i.)) under 915-nm laser irradiation for 5 min. (g) Growth of 4T1 tumors in different groups of mice after treatment. (h) Survival curves of mice after various treatments. (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced from Ref. [32] with permission.)

using this multifunctional theranostic agent.

The integration of organic with inorganic components is able to afford nanocomposites with multiple functionalities in imaging and therapy, useful in cancer theranostics. However, for future clinical use, more functionalities usually accompanied by sophisticated nanostructures, are not always necessary or meaningful. Carefully designed theranostic platforms

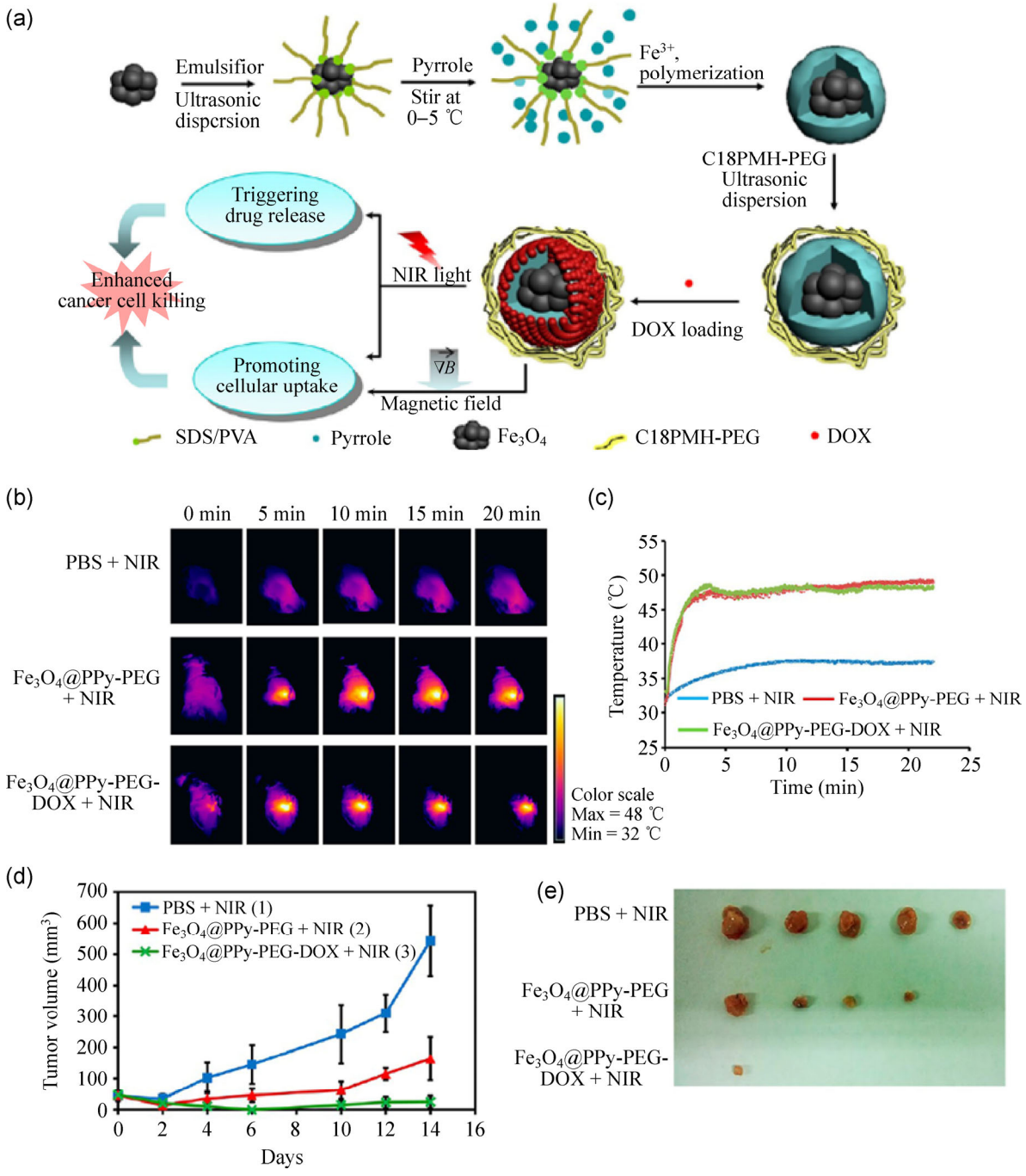

Figure 6 Iron oxide@polypyrrole nanoparticles as a multifunctional drug carrier for remotely controlled cancer therapy with synergistic antitumor effect. (a) Schematic illustration to show the synthesis of Fe_3O_4@PPy-PEG nanoparticles, the subsequent drug loading, and the remotely controlled cancer cell killing under dual physical stimuli. (b) IR thermal images of tumor-bearing mice exposed to the NIR laser after intratumoral (i.t.) injection with PBS, Fe_3O_4@PPy-PEG, or Fe_3O_4@PPy-PEG-DOX. (c) Tumor temperatures of mice during laser irradiation as indicated in (b). (d) Tumor growth curves of different groups of mice after various treatments indicated (5 mice per group). (e) Photos of the tumors collected from different groups of mice at the end of treatment (day 14). (Copyright American Chemical Society. Reproduced from Ref. [25] with permission.)

with each of their functionalities being able to enhance/promote their other functions may be of great interest in future research.

8 Conclusions and perspectives

A variety of organic NIR-absorbing nano-agents have emerged in the past few years for applications in photothermal cancer treatment. Many of these nano-agents, especially NIR dye-containing nanocomplexes (micelles, liposomes, protein complexes), are biodegradable and there may be fewer obstacles to their future clinical translation compared with their inorganic counterparts. Imaging-guided PTT and combination cancer therapy have also been demonstrated using various organic nanocomplexes or organic/inorganic nanocomposites. The eventual goal of researchers in this area is to develop PTT as a useful tool for clinical cancer treatment.

Despite the encouraging results obtained using organic nanomaterials in PTT cancer treatment as summarized in this mini-review, there are still a number of challenges ahead in respect of their future clinical translation: (1) Among many NIR dyes explored in PTT, ICG is still the only FDA-approved one. However the poor photothermal stability of ICG somewhat limits its PTT efficacy, especially if a high laser power is needed in the treatment. (2) Regarding the safety of these organic agents, most NIR dyes apart from ICG have not yet been tested on humans. The long-term safety concerns for conjugated polymers may be even more serious. (3) In addition to improvement/optimization of materials, efforts from engineers and clinicians are also needed to design special medical instruments and clinical protocols so that the clinical use of PTT will become possible. Nevertheless, although the widespread clinical use of PTT may still need some time, such cancer treatment strategies, particularly when combined with other therapeutic approaches and delivered by suitable platforms, may offer new opportunities in cancer treatment.

Acknowledgements

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