

Review

A review of organic nanomaterials in photothermal cancer therapy

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Abstract: Photothermal therapy has inspired numerous interests due to its minimal invasion, easy to perform, and possibilities to treat embedded tumors in vital regions. In this review, examples where various types of photothermal nanoagents including carbon-based, organic near-infrared dye-based, polymer-based nanomaterials have been utilized to converse near-infrared light energy to heating within tumors are introduced. The pros and cons of these photothermal agents are discussed. Furthermore, the challenges and perspectives in the near future are also addressed.

Keywords: photothermal, near-infrared, dye, porphyrin, polymer, graphene.

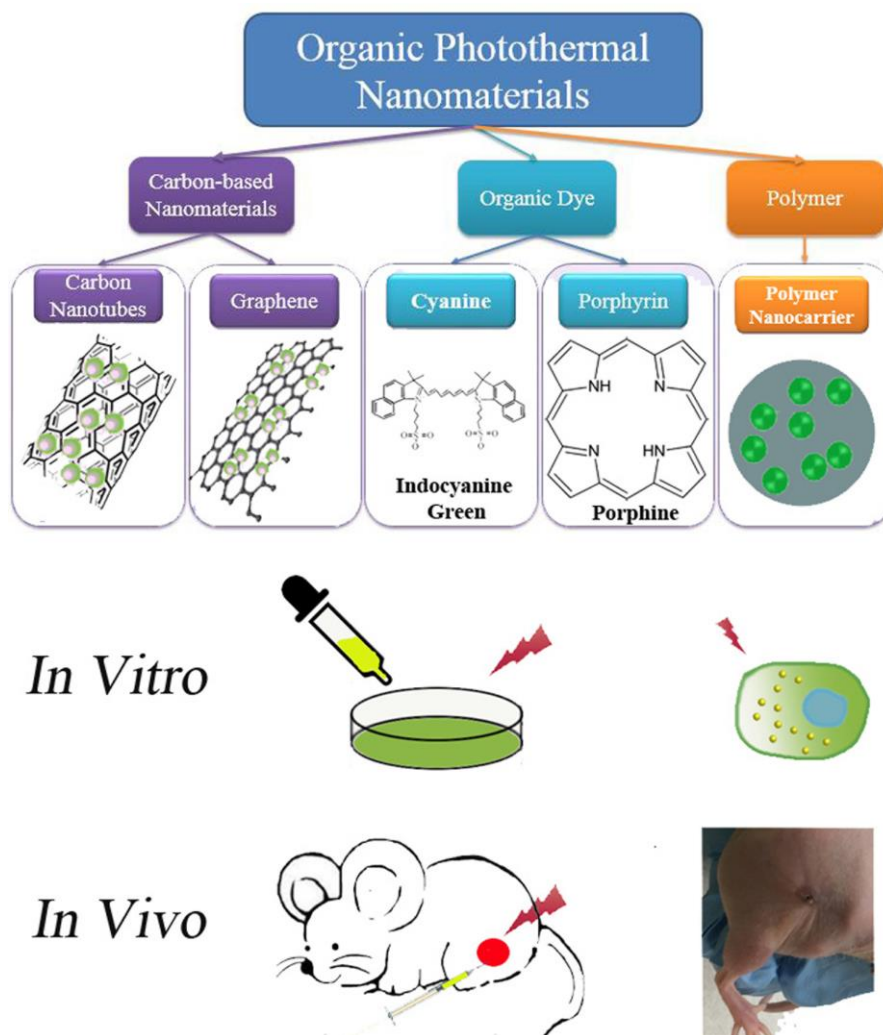
Introduction

Cancer is the second leading cause of death that accounts for more than 25% of the deaths in the United States (1). Currently, conventional cancer therapies including surgical excision, medical therapies such as chemotherapy and radiotherapy, and combination methods have their inherent drawbacks. Surgical excision usually fails to remove all cancerous cells resulting in serious morbidity. In addition, surgery is limited to large numbers of tumors which are adjacent to critical tissue structures. Furthermore, the severe side effects of chemotherapy and radiotherapy make the patient lots of sufferings.

Recently, hyperthermia has attracted lots of attention since it can lead to cell death via protein denaturation or rupture of the cellular membrane and subsequently result in tumor shrinkage due to removal of cancerous cells by macrophages,

which achieve numerous potential benefits over conventional cancer therapies including minimal invasion, easy to perform, and possibilities to treat embedded tumors in vital regions where surgery is not available. However, to cure underlying tumors, the activating energy source need not only adequately penetrate healthy tissues, but also efficiently kill tumors without invasion to surrounding healthy tissues (2). Therefore, specific energy-absorbing nanoagents are urgent, which can be localized in target tumors to absorb activating energy and facilitate thermal therapy. Currently, several heating resources such as laser light (3, 4), focused ultrasound (5, 6) and microwaves (7) have been employed in thermal cancer therapy.

In recent years, photothermal therapy (PPT) that employs light-activated heating to cure tumors receives tremendous attention since it can



Scheme 1. Organic photothermal nanoagents and in vitro and in vivo experiment

sufficiently destruct cancerous cells with minimal invasion to surrounding healthy tissues (8-10). Photothermal within tumor tissues results from energy conversion from light to heat, which increases temperature to kill tumors (11). Tissue damage is evident within minutes when the temperature of tissues reaches 55–95°C (12). Lots of natural light absorbers in tissues including water, hemoglobin, oxyhemoglobin, and melanin can converse light to heat, which results in hyperthermia damage in both tumors and healthy tissues. However, the near-infrared (NIR) light

induces minimal photothermal heating in both tumors and healthy tissues, since the absorption of biological tissues consisting of blood and water is lowest in a NIR region (700nm-900nm) (13). Therefore, specific photothermal nanoagents that can absorb NIR light to destruct the targeted tumor with minimal damage to the surrounding healthy tissues by conversing NIR light to heat have been widely developed and systematically investigated, which possess high photothermal conversion efficiency, and strong absorbance and good photostability in the NIR region (10). Besides,

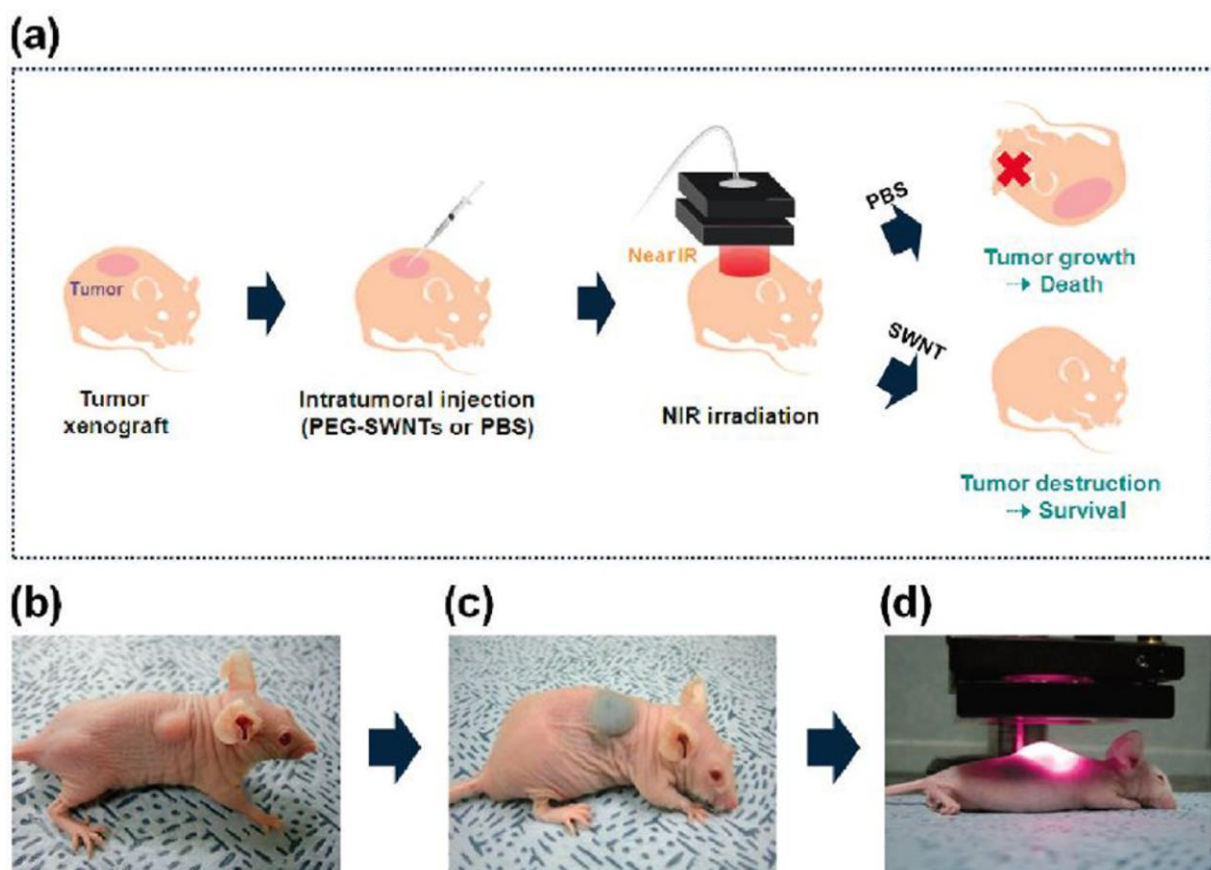


Figure 1. Photothermal treatments for *in vivo* tumor ablation using PEG-SWNTs: (a) schematic view of the procedure and results of PEG-SWNTs mediated photothermal treatment of tumors in mice; (b) photograph of a mouse bearing KB tumor cells ($\sim 70\text{mm}^3$); (c) photograph of a mouse after intratumoral injection of PEG-SWNTs solution ($\sim 120\text{ mg/L}$, $100\ \mu\text{L}$); (d) photograph of near-infrared irradiation (808 nm , 76 W/cm^2) for 3 min to tumor region. (Reprinted with permission from Ref. (46). Copyright (2009) American Chemical Society.)

the low cytotoxicity and high biocompatibility are required to lower side effects. During last decade, numerous inorganic photothermal agents have been extensively explored and studied *in vitro* and *in vivo* including noble metal nanostructures, such as Au (14-16), Ag (17, 18), and Pt (19-21), and transition metal sulfide or oxide nanoparticles (22-26). Although these inorganic photothermal nanoagents achieve high therapeutic efficacy in many preclinical animal models, the non-biodegradability and possible long-term cytotoxicity have significantly limited their future

clinical translation (27). To achieve excellent photothermal nanoagents with improved biocompatibility and lowered cytotoxicity, organic nanomaterials have been employed in photothermal therapy (as shown in Scheme 1). Carbon-based nanomaterials including graphene (3, 28), carbon dots (29, 30), and carbon nanotubes (CNTs) (31, 32) have been widely used in bio-fields owing to its high biocompatibility and low cytotoxicity. In recent years, carbon-based nanomaterials have been modified to be used as photothermal nanoagents (3, 33-35). In addition,

diverse nanomaterials combined organic NIR-dyes and micelles, liposomes or proteins have been successfully fabricated for photothermal cancer therapy (36, 37). Conjugated polymers have received significant interests to be used in photothermal cancer ablation due to strong NIR absorbance derived from extended π -electrons (38, 39). Furthermore various organic/inorganic nanocomposites have also been designed as theranostic agents aiming at imaging guided photothermal therapy.

Herein, recent advances in the development of organic based photothermal nanoagents have been reviewed. In addition, the current challenges and perspectives have been discussed.

Carbon-based Nanomaterials

Carbon nanotubes

Single-walled carbon nanotubes (SWNTs) have strong NIR absorbance, which have been well explored as photothermal nanoagents for photothermal cancer therapy due to its efficient light-to-heat conversion (40, 41). Zhou et al. (41) systematically studied the photothermal property of SWNTs and successfully developed folate conjugated SWNTs that could efficiently target onto tumor cells. *In vitro* and *in vivo* results clearly showed that folate conjugated SWNTs effectively improved photothermal ablation on cancerous cells. Therefore, SWNTs combined with appropriate tumor markers can be utilized as an effective photothermal nanoagent (30, 42-45). Moon et al. (46) demonstrated combined treatments of SWNTs and NIR irradiation to destruct solid malignant tumors *in vivo* (as shown in Figure 1). The tumors treated via SWNTs and NIR irradiation were completely destructed without harmful side effects or recurrence of tumors over 6 months, whereas the mice treated in other control groups failed to death, which suggests that SWNTs may potentially serve as an effective photothermal nanoagent in cancer therapeutics. In addition, metal nanoparticles coated SWNTs have also been widely developed

and investigated as photothermal nanoagents (47-50). For example, Wang et al. (47) developed noble metal and DNA modified SWNTs via an *in situ* solution phase synthesis method comprised of seed attachment, seeded growth, and surface modification with polyethylene glycol (PEG). The results presented that SWNTs-Au-PEG-folic acid (FA) nanocomposite offered noticeably enhanced photothermal tumor ablation efficacy due to the strong surface plasmon resonance absorption contributed by the gold shell. Currently, various CNTs based nanomaterials have been successfully fabricated as photothermal nanoagents and drug delivery systems, and been tested *in vivo*. For example, Zhang et al. (51) reported a self-amplified drug delivery system for the tumor photothermal therapy. In this system, multi-walled carbon nanotubes (MWNTs) with excellent photothermal effect were used as the vector, PEG as the shelter, CREKA peptide with special affinity for fibrin as the targeting moiety. With NIR illumination, the system revealed strong tumor targeting capacity and powerful photothermal therapeutic efficacy via *in vivo* temperature elevation, *in vivo* imaging and biodistribution experiment. In addition, Zhou et al. (30) developed a SWNT based thermo-sensitive hydrogel, which could be used as an injectable drug delivery system as well as a medium for photothermal transduction. By incorporating photothermal therapy and doxorubicin release, a higher tumor suppression rate on mice xenograft gastric tumor was found under NIR irradiation. Organ pathology detection involving heart, liver, spleen and kidney, proved no organ toxicity and favorable biocompatibility of SWNT based thermo-sensitive hydrogels. Compared with conventional inorganic photothermal nanoagents, SWNTs showed low cytotoxicity and high biocompatibility. However, the systematical investigation on long-term safety of SWNTs is still limited. Currently, most of studies on CNTs based photothermal nanoagents indicate that these nanoagents have great potential in clinical

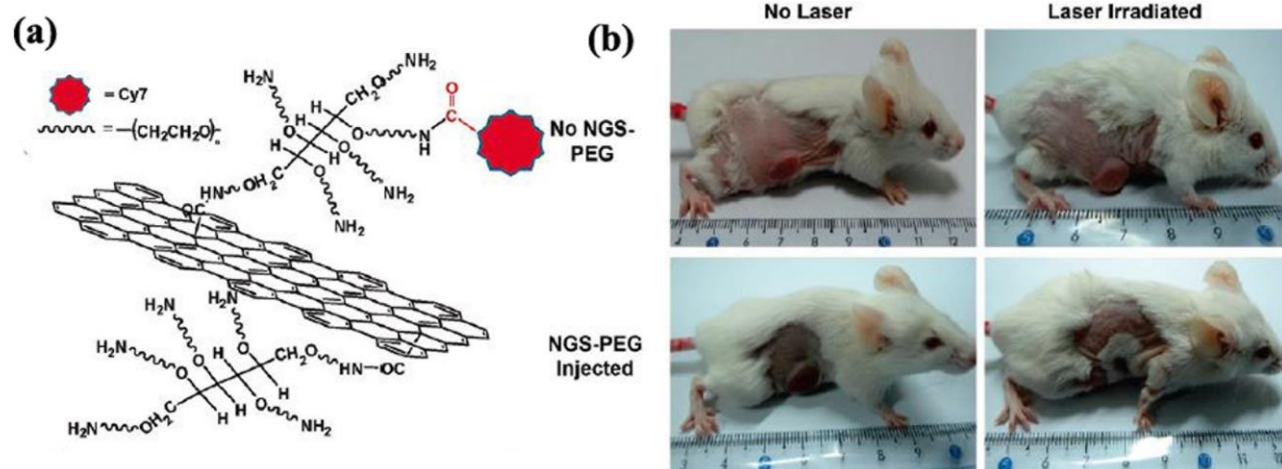


Figure 2. (a) A scheme of a NGS with PEG functionalization and labeled by Cy7. (b) Representative photos of tumors on mice after various treatments indicated. The laser irradiated tumor on NGS injected mouse was completely destroyed. (Reprinted with permission from Ref. (9). Copyright (2010) American Chemical Society.)

applications of tumor treatment, whereas the clinical studies have not been reported yet.

Graphene:

During past few years, two-dimensional graphene emerged as a rising material has received numerous interests, which has been successfully explored in biomedical applications at cellular level (52, 53). Functionalized graphene exhibits high solubility and stability in physiological environment and has been widely employed in the drug delivery system, cell imaging and cancer therapy (9, 35, 54-57). Graphene has strong optical absorption in NIR region, which makes it a promising candidate as a photothermal nanoagent in cancer therapy. For example, Yang et al. (9) developed PEG functionalized nanographene sheet (NGS) via conjugating amine terminated six-arm branched PEG to graphene oxide sheets (Figure 2a). In this report, NGS-PEG exhibited strong NIR absorbance and efficient tumor destruction under NIR laser irradiation *in vivo* (Figure 2b). No obvious side effect was noted for the injected mice by histology, blood chemistry, and complete blood panel analysis.

These results indicate that NGS-PEG is an excellent photothermal nanoagent. And Dai's group also developed nanosized, PEG functionalized reduced graphene oxide (rGO) sheets with high NIR absorbance and biocompatibility, which exhibited effective photothermal ablation *in vitro* (34). In addition, graphene has been modified to associate with different organic NIR dyes and metal nanoparticles to produce improved photothermal nanoagents (35, 58-61). Recently, Park and Lee's group successfully developed a pH-dependent and NIR-sensitive rGO hybrid nanocomposite via electrostatic interaction with indocyanine green (ICG) (62). The *in vivo* results showed that this nanocomposite can not only efficiently destruct localized cancerous cells but also be minimally invasive to surrounding healthy cells. Zhang and Chen's group synthesized cyanine dye grafted graphene oxide that exhibited severe cell damage owing to the enhanced photothermal effect in lysosomes, and thus generated synergistic photothermal efficacy with tumor ablation upon irradiation (35). Song et al. (59) produced a hybrid rGO-loaded ultrasmall plasmonic gold nanorod

Table 1. Organic dye in photothermal cancer therapy

Organic Dye	Nanocarrier	Wavelength of Laser (nm)	Cancer Types	Animal Model	Ref.
Indocyanine green (ICG)	Polymer functionalized reduced graphene oxide	808	MDAMB(MDA-MB-231)	Mice	(62)
	Nanoparticles made of lecithin and cholesterol	808	MCF-7 cells	Mice	(70)
	Dextran based block copolymers	808	MCF-7 cells	N/A	(71)
	Polymeric nanomicelles	808	HeLa cells	N/A	(72)
IR 780	Heparin-folic acid conjugate	808	MCF-7 cells	Mice	(68)
	Polymeric nanomicelles	808	CT26 colon carcinoma cells	Mice	(74)
	Human serum albumin nanoparticles	808	MCF-7 cells	Mice	(75)
IR 825	Polymeric nanomicelles	808	4T1 murine breast cancer cells and HeLa cells	Mice	(76)
	Polymeric nanomicelles	808	4T1 murine breast cancer cells	Mice	(77)
	Human serum albumin	808	4T1 murine breast cancer cells	Mice	(78)
	Human serum albumin	808	4T1 murine breast cancer cells	Mice	(78)
IR 820	Ferritin	808	4T1 murine breast cancer cells	Mice	(80)
	Polymeric nanoparticle	808	MCF-7 cells	N/A	(81)
	Polymeric nanoparticle	808	MCF-7 cells	N/A	(82)

vesicle with improved photoacoustic performance and photothermal effects. In addition, this hybrid could deliver cancer drug via NIR photothermal heating activation, which achieved amplified cancerous cell ablation *in vivo*, due to the combination of chemo and photothermal therapies. Compared with other NIR photothermal agents like gold nanomaterials and CNTs, the nanographene achieves many

favours including small size, high photothermal efficiency, and low cost, which has widely been employed as a novel photothermal nanoagent. However, despite large numbers of reports exhibit graphene achieves low cytotoxicity, the long-term safety concerns of graphene and its functionalized derivatives should be under investigation before its further clinical transition. Similar to CNTs, the clinical studies of graphene

based photothermal nanoagents have not been systematically published, although the graphene based photothermal nanoagents have been widely performed on preclinical animal models, especially mice.

Organic Dye-Based Nanomaterials

Cyanine Derivatives

Numerous cyanine derivatives have been synthesized as NIR dyes that are mainly utilized in fluorescent imaging during recent years (63-65). The cyanine derivatives have been simultaneously employed as an efficient photothermal agent as well as a fluorescent imaging probe due to its strong NIR absorbance and partial conversion from optical energy to heat (36, 66, 67). However drawbacks including limited aqueous stability, rapid body clearance, and poor cellular uptake severely limit the direct use of free NIR dyes in photothermal cancer therapy (68). To sufficiently utilize NIR dyes, various nanocarriers containing NIR dyes have been designed as photothermal nanoagents. Among various cyanine derivatives, ICG is one of the most commonly employed medical imaging dyes and approved by US Food and Drug Administration (FDA) for clinical use on patients, which has been widely investigated for photothermal cancer therapy (69). Different groups have successfully developed ICG-containing nanocarriers that present better stability than free ICG, and excellent tumor ablation efficacy (62, 70-73). For example, Jian et al. recently developed novel ICG-encapsulated hybrid polymeric nanomicelles (PNMs) by coassociating the amphiphilic diblock copolymer poly(lactico-glycolic acid)-b-poly(ethylene glycol) (PLGA-b-PEG) and hydrophobic electrostatic complexes composed of ICG molecules and branched poly(ethylenimine) (PEI) that showed effective cancer imaging and photothermal cancer ablation (72). In addition, various nanocarriers including micelles, liposomes, polymers and proteins have been developed to connect to other cyanine derivatives that have

been employed in fluorescent imaging and photothermal therapy, such as IR780 (68, 74, 75), IR825 (76-79), and IR820 (80-82). Table 1 shows recent advances of organic dye containing nanocarriers in recent years. Currently, cyanine derivative containing nanocarriers have been widely investigated via *in vitro* and *in vivo* experiments. Cai et al. (83) developed doxorubicin (DOX) and indocyanine green (ICG) loaded PLGA-lecithin-PEG nanoparticles (DINPs) via a single-step sonication method, which achieved a combination of chemotherapy and photothermal therapy (Figure 3a). Compared with chemotherapy or photothermal therapy alone, the combined treatment with laser irradiation synergistically suppressed MCF-7 and MCF-7/ADR tumor growth *in vivo* and with no tumor recurrence (Figure 3b). Recently, Kang et al. (84) reported that a single nanocarrier combined diagnostic bioimaging fluorescence and photothermal therapeutic can be used to simultaneously and accurately diagnose and ablate tumors. In the report, thermo-responsive poly(dimethylaminoethyl methacrylate-co-N-isopropylacrylamide) sulfobetaine (PDNS) was used as a nanocarrier to contain IR825 and boron dipyrro-methane (BODIPY). The *in vitro* and *in vivo* results exhibited promising photo-thermolysis-based cytotoxicity, which revealed potential clinical applicability of multifunctional theranostic agents.

Compared with the direct use of free organic NIR dyes, NIR dye containing nanocarriers achieve significantly improved stability in different physiological environments and photothermal conversion efficiency (10, 70). However, the poor photostability of the small organic NIR dyes under continuous high-power laser irradiation still exist even in nanocarriers. In addition, although ICG and several nanocarriers including liposomes and polymeric nanoparticles have been approved by FDA for clinical use (85), most studies about organic NIR dyes based photothermal nanoagents

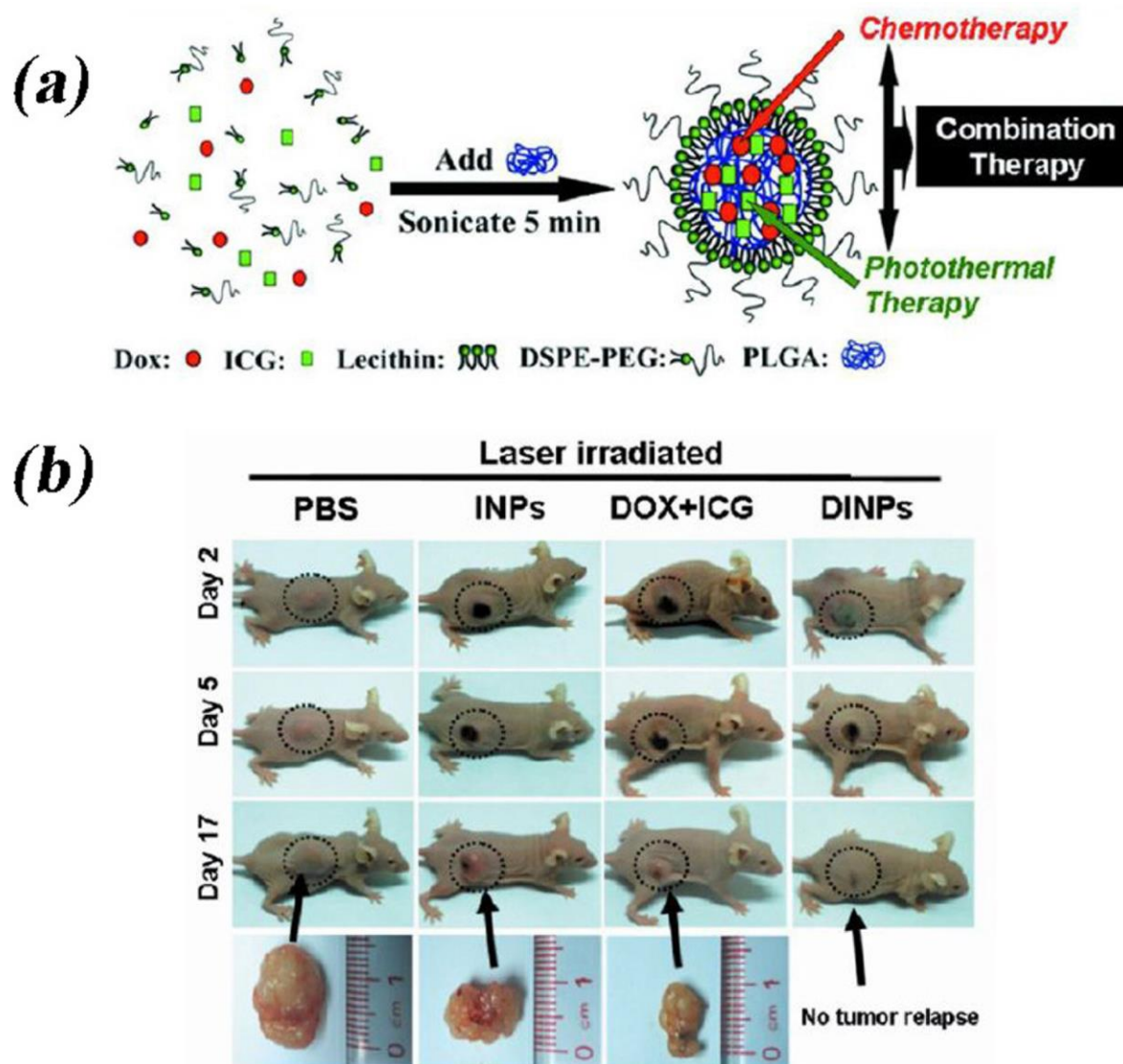


Figure 3. (a) Schematic illustration of the single-step sonication to synthesize DINPs, and (b) *In vivo* chemophotothermal therapy of DINPs. Representative photos of mice bearing MCF-7 tumors and excised tumors on 17 d after treatments. The tumors were marked with dashed circles. Combined treatment of DINPs yielded higher synergistic therapy effect and no tumor recurrence was noted over a course of 17 days. (Reprinted with permission from Ref. (83). Copyright (2013) American Chemical Society.)

are currently in various stages of preclinical development.

Porphyrin Derivatives

Porphyrin and its derivatives are another type of organic dyes which have been employed in photothermal cancer therapy (86). For example,

Zheng et al. (87-89) developed liposome-like nanoparticles called "porphyrinsomes" via self-assembly of porphyrin lipids. These porphyrinsomes could absorb and convert optical energy into heat with high efficiency due to the high porphyrin packing density. *In vivo* experiments clearly showed high tumor ablation efficiency under laser

irradiation. Further developments have been also performed in their studies. Magnetic resonance imaging-sensitive and non-photobleachable porphyrins were successfully developed as efficient photothermal nanoagents via incorporating manganese ions into porphyrin nanoparticles (90). In addition, different types of porphyrins have been applied in photodynamic therapy, ultrasound imaging, positron emission tomography (89, 91, 92). Recently, Nie et al. (93) developed a porphyrin-based micelle via self-assembling from a hybrid amphiphilic polymer comprising PEG, poly(D, L-lactide-co-glycolide) and porphyrin. Under NIR laser irradiation, the combination of photothermal effect and synergistic chemotherapy conferred great chemosensitivity to cancer cells and achieved tumor regression using about 1/10 of traditional drug dosage, which could avoid side effects of chemotherapy. Our group also developed a biocompatible porphyrin functionalized graphene oxide (PGO), which was used as a photothermal platform for brain cancer therapy (3). The

graphene oxide was exfoliated and conjugated with porphyrin via π - π interactions, which showed improved photothermal conversion efficiency resulting in ablation of brain cancer cells *in vitro*. Further studies of *in vivo* distribution and photothermal effect are underway.

Although porphyrin are highly biodegradable and biocompatible, and can be used as efficient nanocarriers and light absorbers with interesting multi-functions. The relatively short absorption wavelength (600-700 nm) severely limits the conversion efficiency *in vivo* (10). Therefore, improved porphyrin based photothermal agents with strong NIR absorbance is expected in the near future. In addition, the preclinical and clinical studies on porphyrin based photothermal nanoagents are necessary before their future clinical transition.

Polymer-Based Nanomaterials

During the last decade, conductive polymers with conjugated molecular structures have been widely used in biomedicine, especially in cancer

Table 2. Polymer based photothermal nanoagents

Polymer	Wavelength of Laser (nm)	Cancer Cells	Animal Model	Ref.
Polyaniline nanoparticles	808	A431 cells	N/A	(39)
Polypyrrole nanoparticles	808	4T1 murine breast cancer cells	Mice	(95)
Polypyrrole hollow microspheres	808	U87-MG cells	Mice	(96)
Polypyrrole Nanoparticles	808	HeLa cells	N/A	(96)
Albumin-Polypyrrole Nanoparticles	808	4T1 murine breast cancer cells	Mice	(98)
Polypyrrole Nanowire Arrays	810	MCF-7 cells	N/A	(100)

therapy. As shown in Table 2, various NIR absorbing conjugated polymers have been successfully developed and investigated as photothermal nanoagents for cancer therapy. In 2011, Yang et al. (39) first developed conjugated polymer nanoparticles as photothermal nanoagents for cancer therapy. In this report, water soluble polyaniline nanoparticles showed excellent colloidal stability and NIR absorption. *In vitro* and *in vivo* experiments demonstrated effective ablation of cancerous cells under NIR irradiation. Liu et al. (94) developed a novel organic photothermal nanoagent based on poly-(3,4-ethylenedioxythiophene):poly(4-styrenesulfonate) (PEDOT:PSS), a conductive polymer mixture with strong NIR absorbance, for *in vivo* photothermal treatment of cancer (Figure 4a). The *in vivo* experiments exhibited PEDOT:PSS-PEG nanoparticles achieved excellent therapeutic efficacy in a mouse tumor model under NIR light irradiation at a low laser power density (Figure 4b). The results of the blood test and histological examination revealed no apparent toxicity of PEDOT:PSS-PEG to mice with 40 days.

In addition, polypyrrole (PPy) nanomaterials have been widely developed and investigated in biomedical applications owing to high conductivity, superior stability and excellent biocompatibility. Besides, the strong absorbance of PPy in the NIR region makes PPy nanomaterials a promising candidate for effective cancer ablation as photothermal nanoagents (95, 96). In 2012, Liu et al. (38) developed PPy nanoparticles as a novel photothermal nanoagent with great stability in different biological media and little dark toxicity. This photothermal nanoagent produces heating under NIR laser irradiation resulting in effective cancerous cells ablation *in vitro* and *in vivo* without noticing side effects after treatment. Subsequently, Dai and Yue et al. (96) successfully constructed uniform PPy nanoparticles via a one-step aqueous dispersion polymerization method. Similarly, the as-

prepared PPy nanoparticles also exhibited good colloidal stability and high photothermal conversion efficiency due to strong NIR absorption and good photostability. *In vitro* assays clearly showed high cell ablation efficiency. Recently, various types of complicated PPy-based nanomaterials have been prepared as photothermal nanoagents (97-101). For example, Lee et al. (100) developed an electro responsive drug release system based on PPy nanowires via electrochemical deposition of a mixture of pyrrole monomers and biotin as dopants in a sacrificial template. The results showed strong photothermal effects synergistically maximized the chemotherapeutic efficacy.

Besides, nanocomposites combined inorganic nanoparticles and polymers have received tremendous attention to produce theranostic agents aiming at imaging guided photothermal therapy, which can real-time track the laser treatment of photothermal agents by imaging. Dai et al. (102) developed a nanotheranostic agent via loading the organic dye ICG into 1,2-distearoylsn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)] (DSPE-PEG) coated super paramagnetic iron oxide nanoparticles (IONP), which was simultaneously used as fluorescent/magnetic resonance dual-modal imaging probes and photothermal agents. Similar nanocomposites like IONP/PPy (23), Fe₃O₄/PPy-PEG (103), Gd-PEG-PPy (99), Au-PPy (97) and etc. (104-106), have been widely developed and investigated in recent years, which showed improved theranostics efficiency.

Compared with small organic NIR dyes, conjugated polymers based photothermal nanoagents usually present superior photothermal stability under continuous laser irradiation. However, the unclear safety concerns of these polymers are the most important challenges that need to be addressed in the near future. Although nanocomposites can achieve multiple functionalities in imaging and cancer therapy, the use of inorganic nanomaterials may

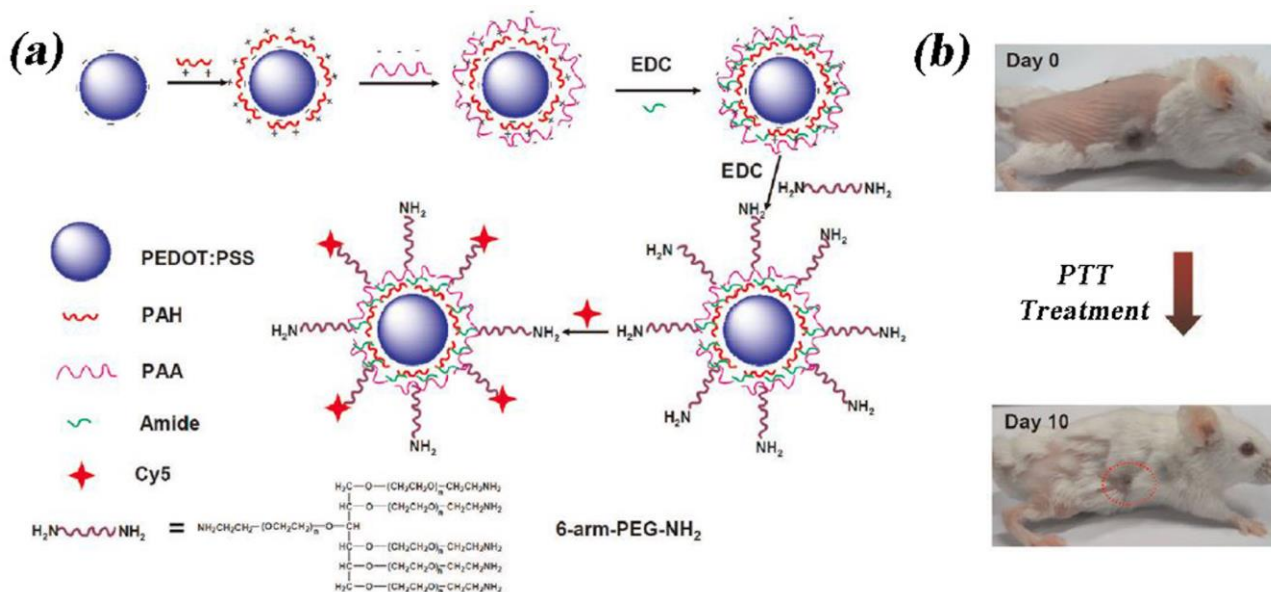


Figure 4. (a) Scheme showing the fabrication process of PEDOT:PSS-PEG. Note that a linear structure is drawn for simplification purposes to represent the branched six-arm-PEG-amine. (b) Representative photos of a PEDOT:PSS-PEG-injected mouse at day 0 before PTT treatment and at day 10 after treatment. The tumor color turned obviously darker after PEDOT:PSS-PEG injection at 48 h pi (left). Complete tumor elimination was achieved after PTT treatment (right). (Reprinted with permission from Ref. (94). Copyright (2012) American Chemical Society.)

limit their future clinical use, which still need large numbers of attention to improve for imaging guided photothermal therapy. Despite several polymeric nanoparticles that utilized as drug delivery system in cancer treatment have been approved by FDA (85), most polymeric nanoparticles that utilized in photothermal treatment have not been systematically investigated in clinical studies.

Conclusions and Perspectives

In this review, a brief overview of organic photothermal nanoagents is summarized to introduce the recent advances. Carbon based nanomaterials can be used as nanocarriers as well as photothermal agents. The organic NIR dye-containing nanocarriers are highly biodegradable, which may be much easier to be employed in clinical compared with inorganic counterparts.

Polymer-based photothermal nanoagents have also been reviewed.

Although organic photothermal nanoagents have been systematically developed and investigated in recent years, there are still several challenges that should be addressed before their future clinical translation: (1) Although carbon based nanomaterials showed high biocompatible and low cytotoxicity *in vitro* and *in vivo* experiments, the long-term experiments are still few. (2) Despite lots of organic NIR dyes have been explored in photothermal therapy, indocyanine green is still the only FDA-approved organic dye. However, the poor photothermal stability severely limits its future applications; (3) The long-term safety concerns of conjugated polymers is still blur, which may be of great interest in the future research. (4) Although photothermal nanoagents have received

tremendous attention, efforts in engineering and clinical fields are few, which are necessary to design special medical instruments. (5) Recent advances mainly concentrate on photothermal nanoagents synthesis, the clinical reports are limited. Therefore, in the next stage, the researches related to photothermal therapy might focus on several following fields: (1) The systematic investigation on long-term safety of carbon-based nanomaterials and conjugated polymers should be addressed in the near future; (2) The studies of organic NIR dyes with superior photothermal stability on human safety are necessary; (3) The assisted instruments for photothermal therapy should be systematically developed; (4) The preclinical and clinical experiments should be systematically performed before future clinical translation.

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Abbreviations:

BODIPY boron dipyrro-methane;
CNTs carbon nanotubes;

DINPs	DOX and ICG loaded PLGA-lecithin-PEG nanoparticles;
DOX	doxorubicin;
DSPE-PEG	1,2-distearoylsn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)];
FA	folic acid;
FDA	Food and Drug Administration;
ICG	indocyanine green;
IONP	iron oxide nanoparticles;
MWNTs	multi-walled carbon nanotubes
NGS	nanographene sheet;
NIR	near-infrared;
PDNS	poly(dimethylaminoethyl methacrylate-co-N-isopropylamide) sulfobetaine;
PEDOT:PSS	poly-(3,4-ethylenedioxythiophene):poly(4-styrenesulfonate);
PEG	polyethylene glycol;
PEI	poly(ethylenimine);
PGO	porphyrin functionalized graphene oxide;
PLGA	poly(lactico-glycolic acid);
PNMs	polymeric nanomicelles;
PPy	polypyrrole;
PTT	photothermal therapy;
rGO	reduced graphene oxide;
SWNTs	single-walled carbon nanotubes;

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