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EMERGING ADVANCED NANOMATERIALS FOR CANCER PHOTOTHERMAL THERAPY

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Abstract. As a new minimally invasive technique, photothermal therapy has attracted worldwide attention in the treatment of cancer. Photothermal therapy kills cancer cells by converting photon energy into heat energy. At the time of selection, the photothermal agents will be required to be water solubility, cytotoxicity, high photothermal conversion efficiency, metabolic pathway and so on. This report introduces the current research status of various nanoparticles used in photothermal therapy, and looks forward to the future development of photothermal therapy.

1. INTRODUCTION

In today's society, with the growing environmental problems and food safety problems, the incidence of cancer is also increasing. In the world, 12 million people have been diagnosed with cancer, and 7.6 million people died of malignant tumor, the data increases in different degree every year. Cancer has become one of the main diseases that threaten the safety of human life. Of all cancers, lung cancer, cancer of the stomach and liver cancer are most deadly. At present, the traditional methods of cancer treatments are chemotherapy, physical radiation therapy and surgical resection. These traditional cancer treatments are suitable for early cancer resection, while as for the advanced cancer, radiotherapy and chemotherapy will be the better choices. However the two treatment methods are of poor specificity, they will cause great damage to the human body. As for chemotherapy, many anticancer drugs are of poor water solubility, low stability and rapid metabolism, as a result, the drug will be quickly excreted out of the body, or engulfed by macrophages before reaching the target tumor tissue, resulting in a low effective dose. In addition, due to the low targeting of the drug carrier, many drugs will get into the normal tissues and organs. That will cause great harm to normal tissues due to high toxicity of drugs. As for radiation therapy, when radiation strikes the human body, it can damage the normal tissue at the same time as it kills the cancer tissue. Based on these questions, the researchers began to look for other anticancer therapies with high efficiency and low side effects to improve or replace many of the traditional therapies. In recent years, photothermal therapy (PTT) has attracted great attention due to its excellent tumor tissue dispelling ability and almost no damage to normal tissues. With the development of nanotechnology, it becomes possible to achieve specific photothermal therapy. Compared with conventional therapies such as surgery, chemotherapy and radiotherapy, photodynamic therapy has the following important advantages: (1) minor trauma; (2) low toxicity; (3) high targeting; (4) good applicability; (5) repeatable therapy; (6) palliative treatment;

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(7) it can improve the curative effect with the operation; (8) eradication of occult cancer; (9) protect the appearance and function of vital organs.

The near infrared wavelengths of 700~1000 nm is not easily to be absorbed by biological tissue, so it can penetrate the biological tissue maximally, so the near infrared wavelengths of 700~1000 nm is called the therapeutic window of biological tissue. Photothermal therapy works as a new means of cancer treatment. It makes use of the near infrared photothermal properties of the nanomaterials which can be injected into the body and then accumulated in tumor tissue by enhanced permeability and retention (EPR) effect [1,2]. Nanoparticles embedded in tumor cell absorb near infrared light and convert it into heat energy, which can cause tumor temperature increment until tumor cells are killed. The mechanism of photothermal therapy is that when the material absorbs photons, some of the energy is released in the form of photons, and the other is transformed into heat of the material itself, released in the form of heat. When the heat is transmitted to the normal tissues around the cancer tissue, the vessels of the normal tissue dilate, so the blood flow accelerates and the heat can distribute quickly, resulting the temperature increasing quickly. But because of the abnormal development of the tumor tissue, the blood flows in the tumor tissue is very slow, even lower than 5% of the normal tissue.

As a result of the disorder of internal structure, the cancer tissue has a small reaction to the thermal, so when it was exposed to a hyperpyrexia condition, it is difficult for tumor tissue to have a heat dissipation reaction, which will lead to a quickly-rise temperature. When the tumor tissue temperature rises to 42 degrees, it is enough to damage the cancer tissue and kill the tumor [3]. The photothermal agent injected into the body is excreted through two organs, the liver and the kidneys. When the dynamic diameter of photothermal agent is around 5 nm, it is efficiently cleared by renal clearance [4]. While when the dynamic diameter of photothermal agent is around 20-25 nm, it is efficiently cleared by liver clearance [5].

For photothermal therapy, a popular means of cancer treatment, it is very important to find a suitable photothermal agent to achieve an excellent effect in cancer tissue killing. Ideal photothermal reagents is required to have high photothermal conversion efficiency, good biocompatibility, non-toxic side effects, and can be degraded in vivo, or metabolized out of the body [6]. Recently, with the rapid development of nanomaterials, many kinds of nanomaterials have been used in clinical applications as photothermal agents. At present, there are four broad categories of materials that are widely used: (1) Noble metal nanoparticlesÿGold (Au), silver (Ag), platinum (Pt), (2) Carbon materials (Graphene oxide (GO) and carbon nanotubes (CNT)), (3) transition metal dichalcogenides (Copper sulfide (CuS), zinc sulfide (ZnS), bismuth sulfide (Bi_2S_3), tungsten sulfide (WS_2) and bismuth selenide (Bi_2Se_3)) (4) Organic and dye substances (Prussian blue (PB), indocyanine green (ICG), polypyrrole, polyaniline, dopamine, melanin, thiophene and so on). In this paper, recent developments and application of photothermal agents are reviewed, which will deepen people's understanding of this field and have profound implications for future design of ideal photothermal agents.

2. NOBLE METAL NANOPARTICLES

Noble metal nanoparticles have attracted wide attention due to the near infrared irradiation, and they have been widely used as photosensitizer in the treatment of living tumors. The electronic structures in conductive band of noble metal nanomaterials (gold, silver and platinum) have a large order of electromagnetic field due to their relatively orderly shock structure, and they also have good electromagnetic absorption capacity [7]. This phenomenon is known as surface plasmon resonance (SPR) effects. In recent years, nano sized noble metal nanomaterials with different scale, such as gold nanorods, gold nanoparticles, gold nanospheres and so on, have been widely used in photothermal therapy [8]. It is reported that gold and silver alloy nanomaterials with dendritic structure or hollow structure, gold silicon nanowires, magnetic or paramagnetic materials, carbon based materials can all improve the photothermal destruction of tumor cells.

2.1. Gold

Because of the strong surface plasmon resonance effect, gold nanoparticles are pretty ideal photothermal materials. The surface plasmon enhanced NIR laser absorption of AuNRs is better than that of any other gold and silver nanoparticles. Various nanostructures of gold nanoparticles (nanorods, nanostars, nanoshells, nanocages and nanobranches) are widely used because of their excellent stability, biocompatibility and non toxicity [9]. Therefore, by changing the shape of the AuNPs into AuNRs, researchers can not only change the absorption and scattering wavelengths from visible to near infrared regions, but also increase their absorption and scattering cross sections

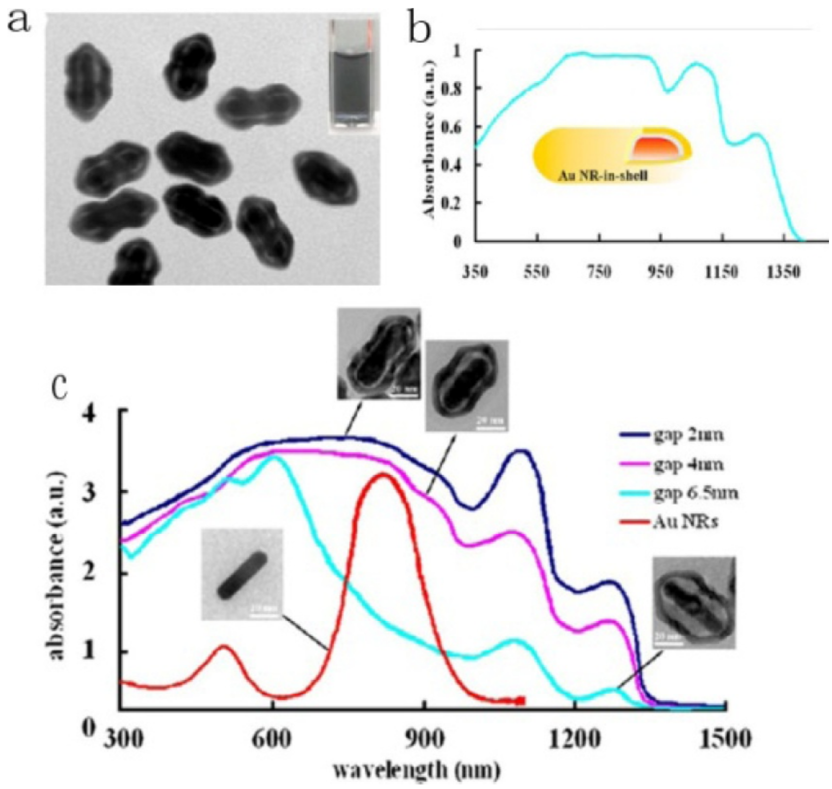


Fig. 1. (a) The TEM image of Au rod-in-shell. (b, c) The UV-vis-NIR spectra of Au rod-in-shells with diffenrent gaps and Au nanorods, measured at the same dosage amount of 50 ppm (in Au concentration), and their corresponding TEM images. Reprinted with permission from M. F. Tsai, S. H. Gilbert Chang, F. Y. Cheng // ACS nano **7** (2013) 5300. Copyright 2013 American Chemical Society.

(Gans theory). The application of AuNRs in photothermal therapy has been extensively studied [10,11].

Tsai et al. designed a rod-in-shell (rattle-like) structure with the size smaller than 100 nm. Firstly, they synthesised the Au NR, and then subjected to the formation of a Ag nanolayer on their surface by reducing $AgNO_3$ with a mixture of ascorbic acid (AA), cetyltrimethylammonium bromide (CTAB), and polyvinylpyrrolidone (PVP) forming Au NR@Ag [12]. This report is the first one to show in vitro and in vivo photothermal cancer therapy in the second NIR window (Fig. 1b). The Au rod-in-shell structure with Au/Ag nanoshell is formed by $HAuCl_4$ etching. After the etching, an Au NR embedded in a hollow Au/Ag shell with a distinct gap formed. Fig. 1a was the TEM of the as-prepared Au rod-in-shell structure. They evaluate the effective therapeutic effect of Au rod-in-shell nanoparticles in the second NIR window by changing the gap between the Au NR core and the Au/Ag shell (Figs. 1a and 1c). It is found that the as-prepared nanoparticle has a better anticancer efficacy in the laser ablation for solid tumors compared to Au NRs under the 808 nm diode laser. This study opens a new way for the application of gold nanorods in photothermal therapy.

Previous studies have found that there are dependent relationship between the size and toxicity for gold nanoparticles: Cytotoxicity is related to the particle size of gold nanoparticles [13] A kind of ultrasmall gold nanorods (8×2 nm, aspect ratio= 4) were synthesized by Song et al. [14]. In order to avoid the damage to normal cells and make use of excellent photothermal properties of gold, they functionalized the gold nanorods by surface modification and self-assembly with more operation functions. They coated the Au NP with hydrophilic brush poly(ethylene glycol) (PEG) and hydrophobic brush poly(lactic-co-glycolic acid) (PLGA) (AuNR@PEG/PLGA). The as-prepared NP can self-assemble into plasmonic vesicles, while the Au NRs embedded in the shell formed by the two kinds polymers, and then these two kinds of polymer extended to the aqueous environment helping to form a stabilize structure. This kind of vesicles (AuNR@PEG/PLGA) exhibit high photothermal effect and distinct photoacoustic signal, showing great potential in imageguided therapy. Chen et al. [15] have reported

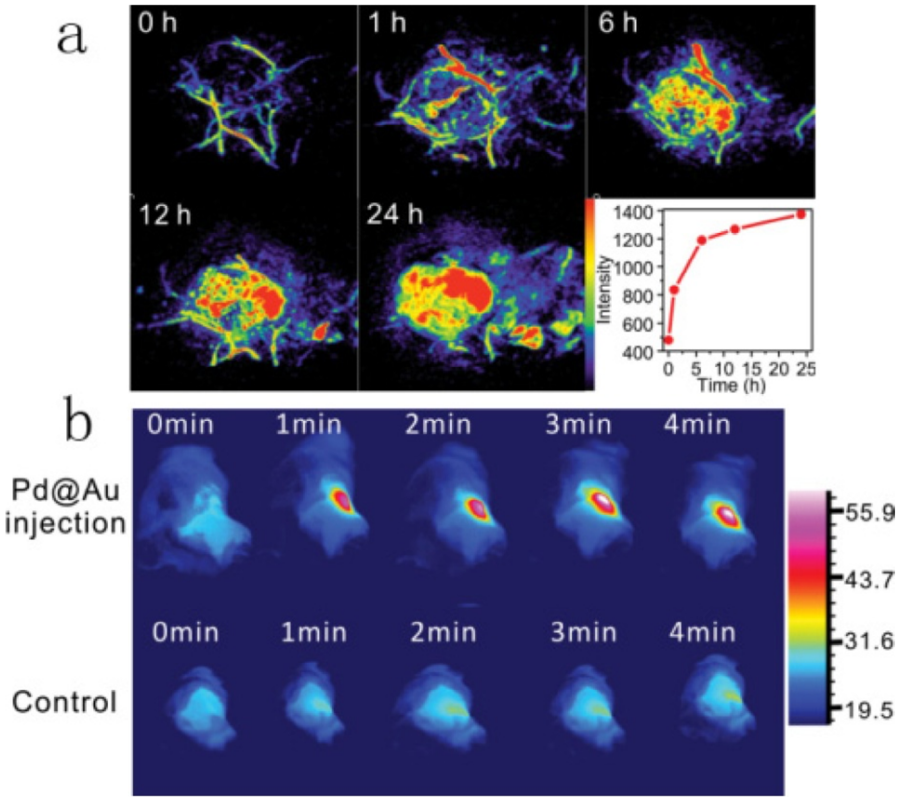


Fig. 2. (a) Photoacoustic imaging of Pd@Au-PEG in tumor sites and quantification photoacoustic signals of tumor site at different time. (b) Infrared thermal images of tumor-bearing mice with and with no Pd@Au-PEG injection under 0.5 W cm^{-2} 808 nm laser. Reprinted with permission from M. Chen, S. Tang, Z. Guo // Adv Materials **26** (2014) 8210. Copyright 2014 WILEY-VCH Verlag GmbH & Co.KGaA, Weinheim.

a new structure, Core-Shell Pd@Au Nanoplates with an average diameter of 30 nm and thickness of 4 nm, as theranostic agents for in-vivo photoacoustic imaging, CT imaging, and photothermal therapy. The as-prepared nanoplates are ultrathin freestanding hexagonal palladium nanosheets which are of well-defined thicknesses, sizes, and tunable surface plasmon resonance (SPR) which depended on their diameter and thickness of the 2D metal nanostructures. It was found in the NIR region [16] that the surface temperature of tumors of the mice which was injected Pd@Au-PEG reached ≈60 C only after 4 min under 0.5 W cm^{-2} 808 nm laser, while the control group only increased less than 3 °C in the same tumor sites (Fig. 2b). Which indicate that Pd@Au-PEG is a promising photothermal agent for cancer treatment.

Huang et al. report here rational design and synthesis of γFe_2O_3@Au core/shell magnetic gold nanoflowers (MG-NFs) for cancer theranostics. The as-prepared structure fully utilizing the photothermal properties and Surface-enhanced Raman spectroscopy (SERS) of gold nanoparticles [17]. In order to improve the biocompatibility of gold nanorods, Zhang et al. reported a gold nanorod (GNR) core with mesoporous silica shell (GNR@mSiO_2), realizing drug release and photothermal therapy. It is found that the outer coating of SiO_2 does not affect the photothermal effect of gold very much, and the thermal and optical intensity of GNR@mSiO_2 is enough to kill cancer cells.

2.2. Silver

As an important member of the metal nanoparticles, compared to other metal nanoparticles, silver nanoparticles have unique physicochemical properties, excellent clinical application. For example, silver nanoparticles have a good inhibitory effect on bacteria and viruses, such as Staphylococcus aureus [18] and human immunodeficiency virus [19]. In addition, silver nanoparticles have excellent optical properties and narrow divergence peaks, and the localized surface plasmon resonance (LSPR) quality factor *Q* from UV to visible and near infrared bands of Ag is significantly higher than that of other common metals [20], such as Al and Au. Compared with other precious metals, the price of metal Ag is

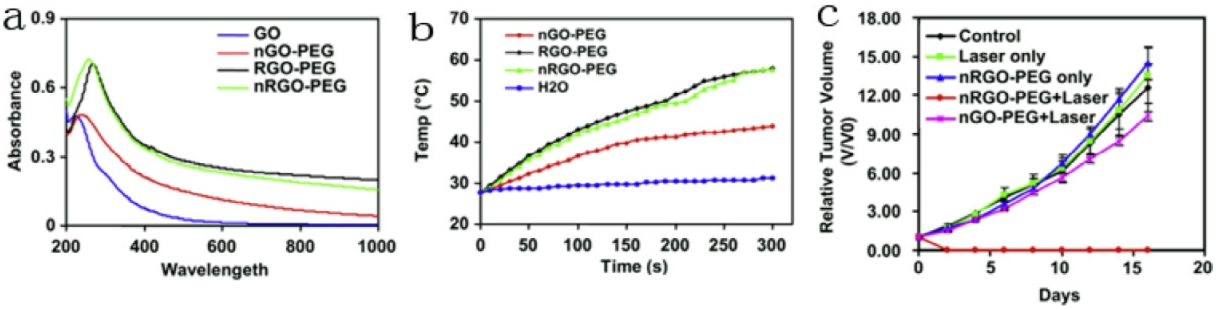


Fig. 3. (a) UVeVISeNIR spectra of as-prepared GO, nGO-PEG, RGO-PEG and nRGOPEG solutions at the graphene-concentration of 0.01 mg/ml. (b) Temperature change curves of water, nGO-PEG, RGO-PEG, and nRGO-PEG solutions exposed to the 808 nm laser at a power density of 1 W/cm^2. In vivo photothermal therapy study using intravenously injected nRGO-PEG. (c) Tumor growth curves of different groups of mice after treatment. The tumor volumes were normalized to their initial sizes. Reprinted with permission from J. Liu, K. Liu, L. Feng // Biomaterials Science **5** (2017) 331. Copyright 2011 Elsevier Ltd.

relatively low, so as to facilitate the widespread use of nano silver. Besides the photothermal property, silver nanoparticles also possess surface enhanced Raman scattering (SERS) effect, a kind of abnormal surface optical phenomenon. So the silver nanoparticles can often be used as a sensor. Nano silver, as a precious metal particle, has a strong absorption ability in the near infrared light. Nano silver exerts its photothermal effect through plasma resonance effects on the particle surface. When the light shines on the silver nanoparticles, the light will cause the free electron resonance of the nano silver surface, The electronic will absorb the light energy to form a kind of exothermic electron gas, after that the exothermic electron gas instantly transferred the energy to the silver nano particle dot matrix, and then the energy was transferred to the surrounding environment resulting in temperature rise [21].

Jeong Hoon Byeon et al. [22] report chitosan-conjugated dendritic Ag nanodendrites using Pd particles as seeds, using a serial continuous operations. The as-prepared nanodendrites were used as sensitizers for photothermal therapy. The researchers controlled the morphology and size of nanoparticles by controlling the synthesis conditions, and then they further tested their photothermal activities to kill HeLa cells under NIR irradiation. The research proof that incorporation of Pd with Ag exhibits good near infrared absorption capability and excellent photothermal conversion efficiency. The aerosol-based synthesis was developed for the first time. Simple process of reaction, nontoxic raw material, and continuous production make this synthesis method fitable for efficient photothermal therapy. Dong et al. [23] synthesized a kind of highly crystalline monodispersed multifunctional Yb^{3+}, Er^{3+}@Ag core/shell nanocomposites facilitating the same NIR 980 nm laser to achieve upconversion bioimaging and photothermal therapy at the same time. The addition of silver improved the biocompatibility of rare earth particles and endow the nanoparticles photothermal effect. The nanocomposites can reach the best mortality approaches 95% under 980 nm NIR light with a power density of 1.5 W cm^2, while Au nanoshells and Au nanorods need a higher power density, which shows great photothermal potential.

2.3. Platinum

Platinum nanoclusters, as one of noble metals, have many similarities with gold and silver nanoclusters, and have low biological toxicity. Platinum (Pt) nanoparticles have shown excellent biocompatibility no matter in vitro and in vivo [24]. These nanoparticles were widely used as catalysts for oxygen reduction reaction [25] and enzyme mimetics to scavenge reactive oxygen species in cancer cells [26]. Wang et al. [27] synthesized trifolium-like Pt nanoparticles (TPNs) with a green method, and the nanoparticles show minimal cytotoxicity and low systemic toxicity in vivo. It can easily reach 50 °C at the tumer sites under irradiation compared to the phosphate buffered saline(PBS) solution, exhibiting excellent photothermal potencial.

3. CARBON MATERIALS

3.1. Graphene

Graphene is a single-atomic-layer, two-dimensional system composed solely of carbon atoms arranged in a hexagonal honeycomb lattice. It has large specific surface area and exhibits excellent electrical, mechanical, optical and thermal property [28], which is reputed as the most promising carbon material in twenty-first Century. Compared with other materials, graphene oxide has large absorption coefûcient in the near infrared region, and contains more oxygen-containing functional groups, which makes it well-dispersed in aqueous solution. It also has a large surface area, with low toxicity and low production cost, so that it can be used as a new high biocompatible nanomaterial and be applied in the biomedical field. Graphene is widely used in photothermal therapy in cancer cells due to their unique electrical properties, optical properties and photothermal conversion ability [29]. Guo et al. [30] reported a kind of pH-responsive cyanine-grafted graphene oxide for fluorescence resonance energy transfer-enhanced photothermal therapy. GO can act as receptor to receive fluorescence from fluorescent dyes as donor in the presence of fluorescence resonance energy transfer (FRET), and grafted cyanine dye acts as the donor of near-infrared fluorescence (NIRF) [31]. This structure enhanced photothermal effect in lysosomal environment. Graphene itself has excellent photothermal effect, many researchers endue the nano particles to have the function of drug-loading by grafting multifunctional macromolecules on graphene, in order to achieve the combination of chemical treatment and thermal treatment. Zhang et al. [32] reported a kind of nanographene oxide functionalized with polydopamine as a versatile nanocarrier for chemotherapy and photothermal therapy. Yang et al. [33] studied how surface chemistry and size of nanoscale graphene oxide influence photothermal therapy of cancer. They found that reduced RGO-PEG and nRGO-PEG exhibited remarkable enhanced NIR absorption, compared to that of unreduced nGO-PEG and GO (Fig. 3a). So both RGO-PEG and nRGO-PEG were more effective than nGO-PEG in photothermal heating under the NIR laser irradiation (Fig. 3b). In vitro therapy of cancer cells reduced RGO-PEG and nRGO-PEG exhibited great effect of killing cancer cells (Fig. 3c).

Graphene show significant concentration-dependent cytotoxic and genotoxic effects, so when it is used in vivo, a safe concentration of graphene (lower than 10 $\mu g \cdot mL^{-1}$) [34] is needed in cancer treatments. Therefore, new structures of graphene based nanomaterials with effective photothermal therapies under low-power laser with low concentrations is required. Robinson et al. [35] reported a low concentration of rGONP-PEG (6.6 $\mu g \cdot mL^{-1}$) at a high NIR laser power (15.3 W cm^{-2}) to realize a high effeciency of PTT. Recently, Omid Akhavan and Elham Ghaderi [36] presented a kind of graphene nanomeshes applying in vivo photothermal cancer therapy which used only an ultralow concentration (10 $\mu g \cdot mL^{-1}$) of rGO based composites and an ultralow laser power (0.1 W cm^{-2}) in an in vivo tumor ablation, while reaching 100% efficiency of tumor death. Tian et al. [37] also reported a new structure of ZIF-8/GQD nanoparticles to combine chemotherapy and photothermal therapy together which exhibit great efficiency to eliminate cancer cells.

3.2 Carbon nanotubes

CNTs is a hollow tubular structure composed of carbon, which can be regarded as a monolayer or multilayer graphite hexagonal network plane formed by chiral-vector winding along the microtubule hollow, and it is a kind of special material of one-dimensional quantum structure (Fig. 4). Recently, carbon nanotubes (CNTs), as an excellent photothermal material, have received extensive attention and research. CNTs has a strong absorption in the near infrared region due to its unique optical absorption properties. It can effectively convert light energy into heat and achieve local thermal and thermal destruction of malignant tumor cells [38,39]. In addition as a photothermal material, that could simultaneously load drugs on their surfaces and synergistically combined chemotherapy with photothermal therapy to improve cancer treatment. Carbon nanotubes can be divided into single wall carbon nanotubes, multi walled carbon nanotubes, metal type and non-metallic type single wall carbon nanotubes. Among them, Single-walled carbon nanotubes (SWCNTs) is the most widely used in cancer therapy. From morphology, Single-walled carbon nanotubes are similar in size to biological macromolecules, and can enter cells by endocytosis agents, and thus they can smoothly get into the cancer cells during the blood circulation, so that they can maximize their effect of PTT. At the same time, due to the enhanced permeability and retention effect of SWCNTs (EPR), Single-walled carbon nanotubes can be targeted to accumulate in tumor cells. In addition, there is an expected development prospect of SWCNTs in the combination therapy of PTT and bio-imaging. Liu Zhuang's Research Group [40] covered two kinds of novel metal, gold and silver, in the surface of SWCNTs, then they modified the as-prepared nanoparticles with PEG and marked with folic acid. SWCNTs has excellent photothermal property, while the addition of noble nanoparticles provided excitation-source dependent surface-en-

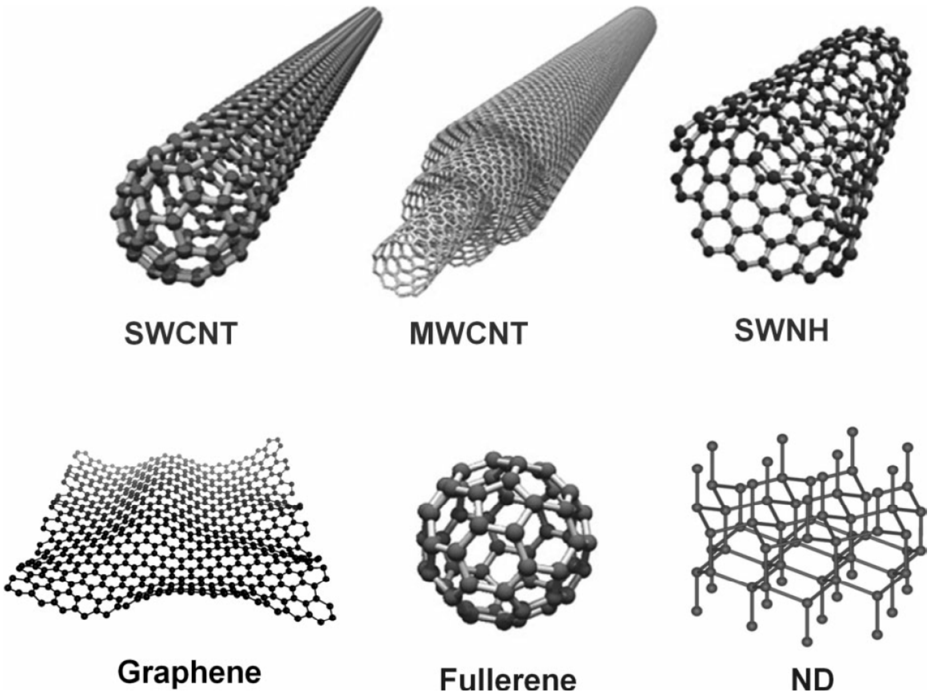


Fig. 4. Schematic representation of different CNMs. Reprinted with permission from G. Modugno, C. M. Moyon, M. P. D. Boldor // British Journal of Pharmacolo **172** (2015) 975. Copyright 2014 The British Pharmacological Society.

hanced Raman scattering (SERS) effect, meanwhile, they also enhance PTT effeciency. Under near infrared irradiation, this structure can enhance the tumor detection effect by surface enhanced Raman effect, and this structure can effectively inhibit the activity of cancer cells.

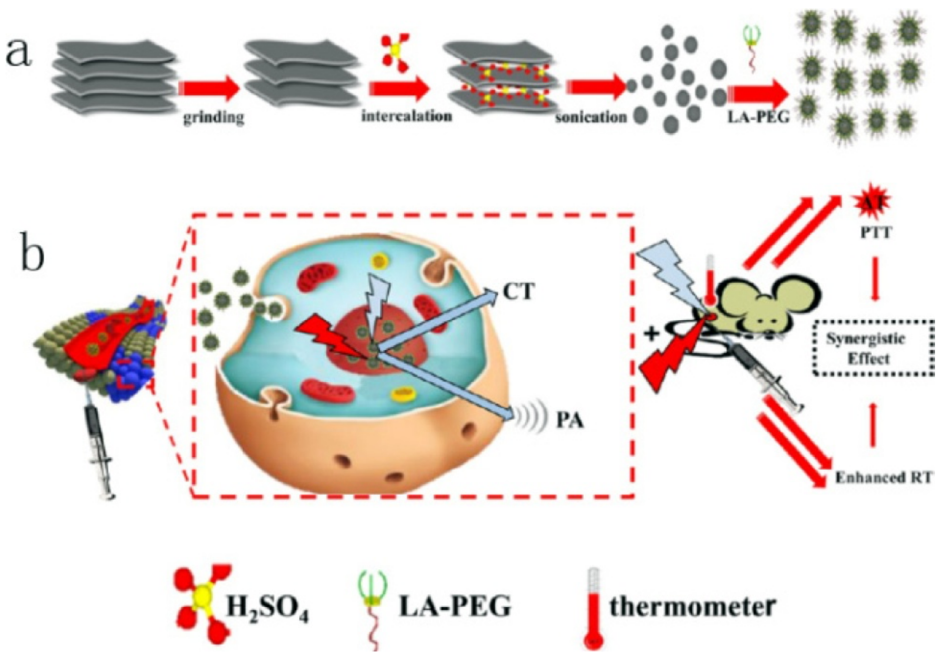
Lakshmi V. Nair et al. [41], tailored Cd and Zn (CdSe/ ZnSe) quantum dot to SWCNTs. This material exhibited great PTT effeciency, when exposed in 808 nm laser for 4 min, the temperature of FaQd@CNT reached 50–60 °C. Here Cd and Zn (CdSe/ ZnSe) quantum dot exhibited a maximum photoluminescence emission intensity around 556 nm for 450 nm excitation, so it showed good fluorescence imaging capability. After the modification with folic acid, the structure FaQd@CNT proved to have a great cellular targeting efficacy and a better photothermal efficiency than Qd@CNT.

Since CNTs is insoluble in water and organic solvents it is hard for the photothermal agents to accurately arrived at the tumor sites, so it is difficult to maximize photothermal thermal efficiency. As a result, it is necessary to have a surface functionalization using the macromolecular, such as Pluronic F-127 (PL-127) [42], polyethylene glycol (PEG), Polyhedral oligomeric silsesquioxane poly polyurethane (carbonate-urea) urethane, POSSPCU [43], and human serum albumin etc. In order to improve the biocompatibility and targeting of CNT, Radu Marches et al. [44] covalently grafted antibody molecules on the surface of CNT, as a result they successfully improved the targeting properties of CNT and applied it to photothermal therapy.

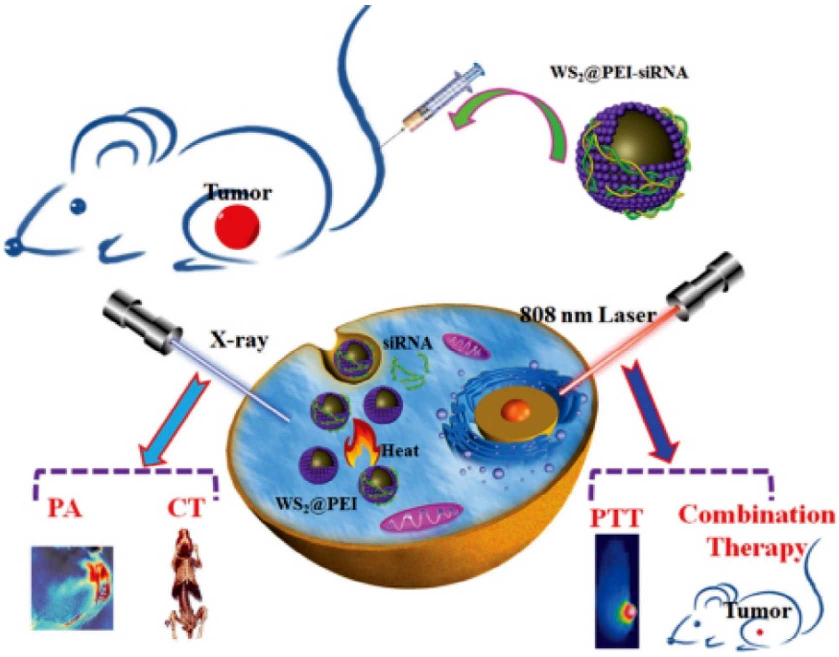
4. TRANSITION METAL CHALCOGENIDE

Transition metal dichalcogenide (TMD) have caused great upsurge of research on biomedical application due to its good thermal effect. This kind of material is mostly layered structure, such as tungsten disulfide and molybdenum disulfide. TMD materials have a wide absorption band in the near infrared region, and these materials also have high extinction coefficient in the near infrared and visible light [45], meanwhile they can also produce tunable absorption characteristics accompanied by layered structure changes, which make it possible for the application of photothermal therapy. Materials such as Bi_2Se_3 [46-49], Bi_2S_3 [50-53], Ag_2S and CuS [54-57], have been widely used in the photothermal treatment of cancer.

WS_2 as a new photothermal agentÿYong et al. [58] prepared multifunctional nanomedicine based on WS_2 quantum dots (QDs) by a facile and “green” method (Scheme 1a) through physical grinding and



Scheme 1. (a, b) Schematic illustration of WS_2 QDs for dual-mode CT/PA imaging and PTT/RT synergistic therapy. Reprinted with permission from C. Zhang, Y. Yong, L. Song // Adv Healthcare Mater. **5** (2016) 2776. Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.



Scheme 2. Schematic illustration of the design of WS_2@PEI-siRNA in the improved PTT platform and dual-mode CT/PA imaging. Reprinted with permission from Y. Yong, X. Cheng, T. Bao // ACS nano **9** (2015) 12451. Copyright 2015 American Chemical Society.

ultrasonication for simultaneous biomedical imaging and combined RT and PTT of tumors (Scheme 1b). And it was proved to have excellent efficiency for cancer eliminating. Zhang et al. [59] reported a multifunctional WS_2@polyetherimide (PEI) nanoplatforms for imaging guided gene-photothermal synergistic therapy of cancer. Herein, the PEI work as the carrier to transport si-RNA into cells to inhabit the translation of specific mRNA into protein (Scheme 2).

As photothermal materials, Bi_2Se_3 is also in the research upsurge recently. Researchers realize the combination treatment of cancer by changing the morphology of materials, surface modification and

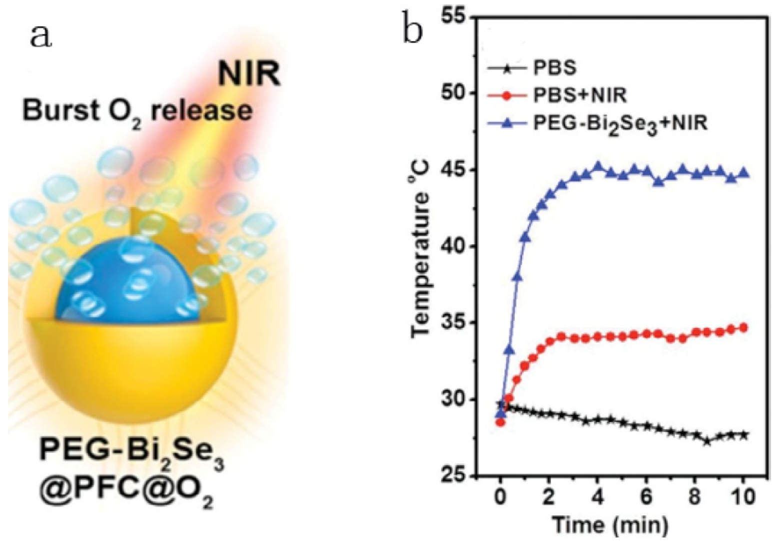


Fig. 5. (a) A Schematic showing burst release of oxygen from PEG-Bi_2Se_3@PFC@O_2 under stimulation by an NIR laser. (b) Temperature changes of tumors monitored by the IR thermal camera during laser irradiation. Reprinted with permission from G. Song, C. Liang, X. Yi // Adv Mater **28** (2016) 2716. Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

incorporating other nanoparticles. Song et al. [48] have synthesized a new structure, core–shell MnSe@Bi_2Se_3-PEG, through a cation exchange method as new theranostics for multimodal imaging and synergistic thermoradiotherapy. The nanostructure can be used for both T_1- and T_2-weighted MR imaging for the existance of the paramagnetic MnSe core, it's also can be used for CT imaging and enhanced RT as well as high NIR optical absorbance to enable PTT for the existance of the Bi_2Se_3 shell. Song et al. [46] synthesized a Bi_2Se_3 hollow structure using a facile one-pot cation exchange method and Kirkendall effect with liquid PFC loaded inside the hollow structure, and then modified with PEG on the surface (Fig. 5a). PFC act as an O_2 carrier. The temperatures of tumors injected with PEG-Bi_2Se_3 increased to 45 °C, while those control groups were not able to heated (final temperature 35 °C) (Fig. 5b). Therefore, PEG-Bi_2Se_3 could be served as an effective photothermal agent to locally enhance the tumor temperature under exposure to the NIR laser. And their research group also synthesized $FeSe_2$/Bi_2Se_3 nanostructures successfully [49] through cation exchange which can provide contrasts in tetra-modal MR/CT/PA/PET imaging and PTT.

5. ORGANIC AND DYE SUBSTANCES

5.1. Prussian Blue

As an old dye, prussian blue (PB) is an approved by the U.S. Food and Drug Administration(FDA) with the low cost of the raw materials, good biocompatibility, well biological safety and simple preparation method. Charge transfer transition between Fe^{2+} and Fe^{3+} in the structure of the Prussian blue making the nanoparticles possess good absorption in the near infrared region, so that it has high photothermal conversion efficiency. Fu [60] synthesized a kind of Prussian blue nanoparticles with an average particle size of 42 nm, and had a comparison of the extinction coefficient in the follow 4 materials: Prussian blue nanoparticles (1.09×10^9 $M^{-1}cm^{-1}$ at 808 nm), gold nanorods (5.24×10^9 $M^{-1}cm^{-1}$ at 808 nm), carbon nanotubes (7.9×10^6 $M^{-1}cm^{-1}$ at 808 nm), $Cu_{2-x}Se$ (7.7×10^7 $M^{-1}cm^{-1}$ at 808 nm), which show great potencial of PB in PTT. In the light of the near infrared irradiation, Prussian blue show the same magnitude of molar extinction as gold nanorods, although the ratio of molar extinction coefficient is smaller than gold nanorods, but the molar extinction ratio of PB is larger than carbon nanotubes and copper selenium over several orders of magnitude. Gold nanoparticles, as the first photothermal therapy light agent, have pretty high photothermal conversion efficiency, but they are difficult to be widely used in clinical cancer treatment because of their high price. Fu compares the temperature changes of PB solutions at different concentrations under 808 nm near the infrared light for 10 minutes (Fig. 6a). When the solution with a concentration of 500 ppm, the temperature can rise to 60 °C after irradiation. When the Prussian blue solution of 50 ppm and gold nanorods

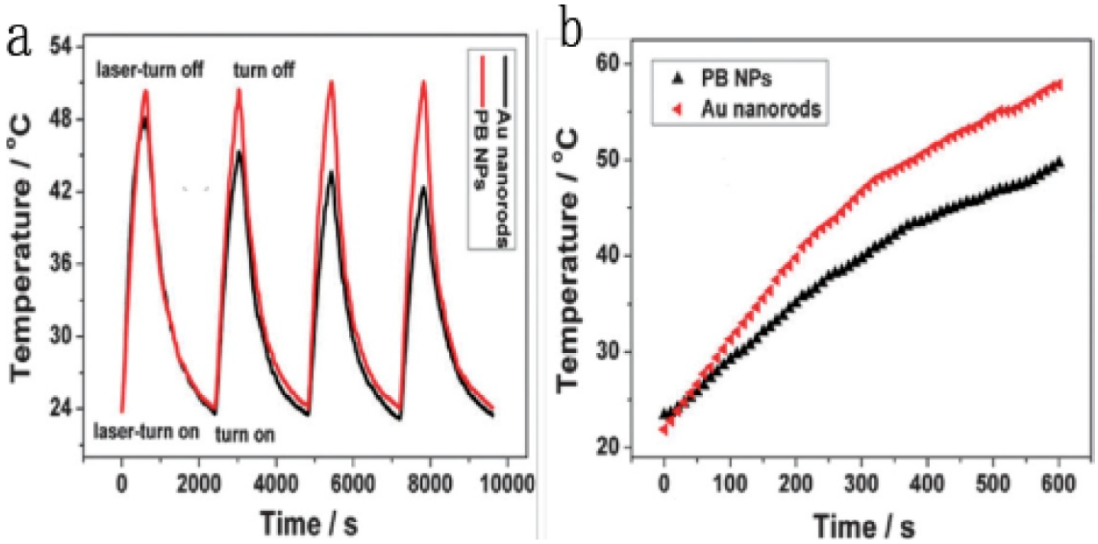


Fig. 6. (a) Temperature variations of PB NPs (50 ppm) and CTAB-capped Au nanorods (16 ppm) under the continuous irradiation of 808 nm laser for 4 cycles; (b) temperatures of aqueous dispersions of PB NPs and CTAB-capped Au nanorods with the same concentration (50 ppm) under the irradiation of 808 nm laser for 10 min. Reprinted with permission from G. Fu, W. Liu, S. Feng, X. Yue // Chemical Communications **48** (2012) 11567. Copyright 2012 Royal Society of Chemistry.

solution of 50 ppm are irradiated at near infrared light of 808 nm, the comparison of thermal and optical conversion efficiency is as follows (Fig. 6b). Although Prussian blue has a slightly lower photothermal conversion efficiency than gold nanorods, it is sufficient to kill cancer cells.

Chen et al. [61] synthesized red blood cell (RBC) membrane camouûaged hollow mesoporous Prussian blue nanoparticles (HMPB@RBC NPs). Doxorubicin (DOX), as a model drug is encapsulated within HMPB@RBC NPsÿused to combined photothermal therapy with chemotherapy to treat cancer. The encapsulation of RBC cell membrane can improve the immune evading capability of HMPB obviously. Therefore DOX@HMPB@RBC NP can accurately target into tumor cells by target enhanced permeability and retention (EPR) effect (Fig. 7a). The structure exhibits very high molar extinction coefficients and photothermal conversion efficiency, when the solution of this nanoparticle was exposed to an 808 nm NIR laser at a power density of 1 W·cm^{-2}ÿthe temperature can increase 30.2 °C in 5 min. In researching the effect of DOX@HMPB@RBC NPs in vivo antitumor therapy, the control group was only increased to 41.1 C under 808 nm laser irradiation, while the local temperature of tumor of the mice injected with HMPB@RBC NPs or DOX@HMPB@RBC NPs was as high as 60.6 °C, suggesting that DOX@HMPB@RBC NPs can effectively absorb the NIR light energy and convert it into local heat in vivo (Fig. 7b). From the size of the tumor can be seen that anticancer effect of DOX@HMPB@RBC NP is excellent (Fig. 7c).

Chen et al. [62] reported a nanoparticle—PEGylated PB-DOX NP, The nanoparticles are used in combination therapy for cancer, PTT and chemotherapy. and an excellent photothermal conversion efficiency is up to 36.7%. Li et al. [63] recently reported a drug delivery system based on a doxorubicin (DOX) blending phase-change material of 1-pentadecanol loaded hollow magnetic prussian blue nanoparticles, HMNP-PB@Pent@DOX. The innovation of this magnetic response of PB NP is that they used a phase-change material (PCM) 1-pentadecanol (Pent), which is regarded as a biocompatible phase-change material incorporated by FDA, and here they adopted this material as the agent to load/lock antitumor drug (Scheme 3). The material PCM possesses the advantage of large latent heats of enthalpy change, leading to solid–liquid or liquid–solid phase transformation at a relatively constant temperature [63]. When 808nm near infrared light is irradiated to the as-prepared PB NP, photothermal effects will occur for the existence of PB. When the temperature rises above 42 degrees, "Pent" will change from solid to liquid, and DOX will release. The presence of magnetite ensures the targeting ability of particles, and the release of gas enhances the ability of photoacoustic imaging to further pinpoint cancer. The combination of photoacoustic,

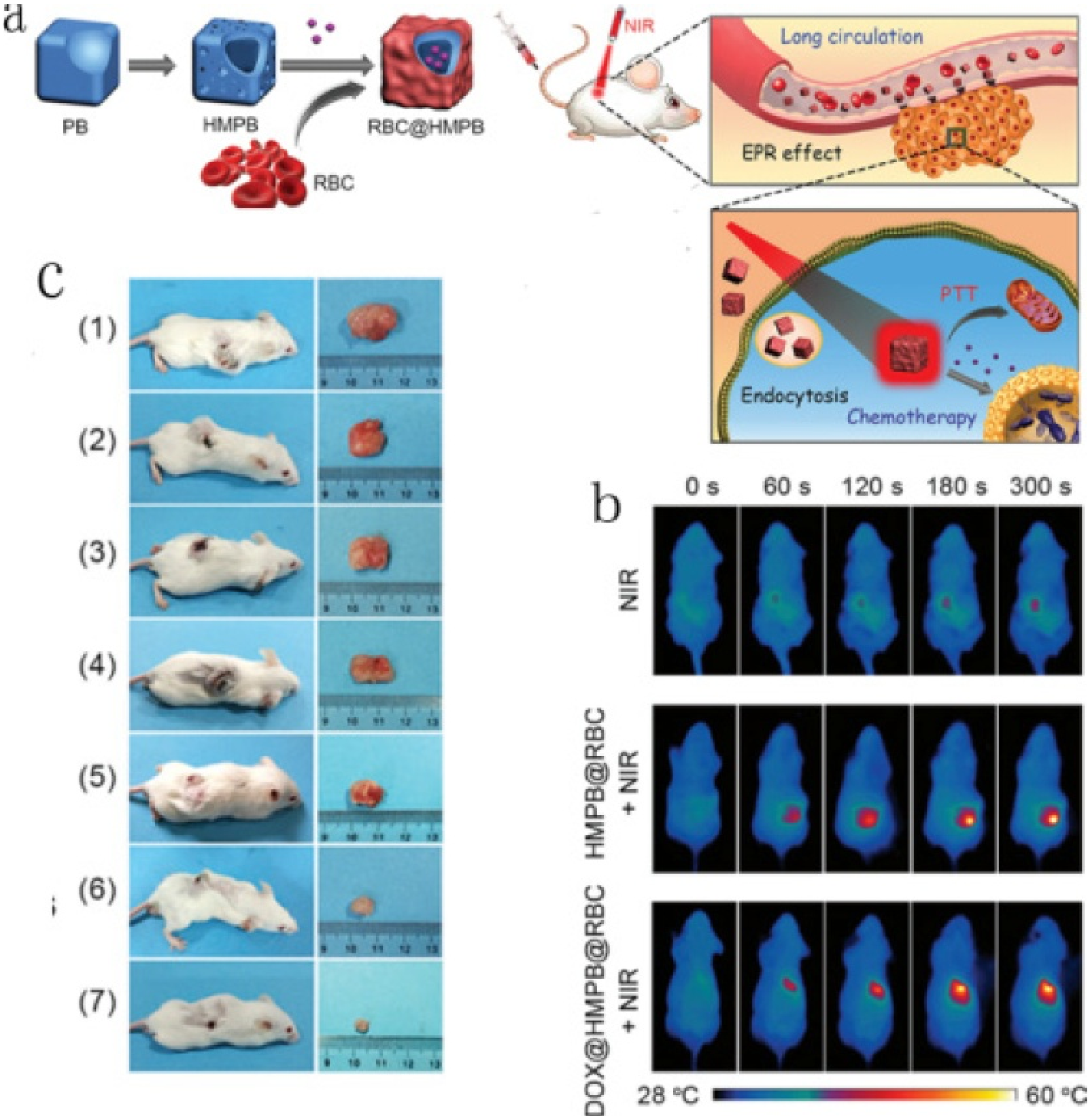
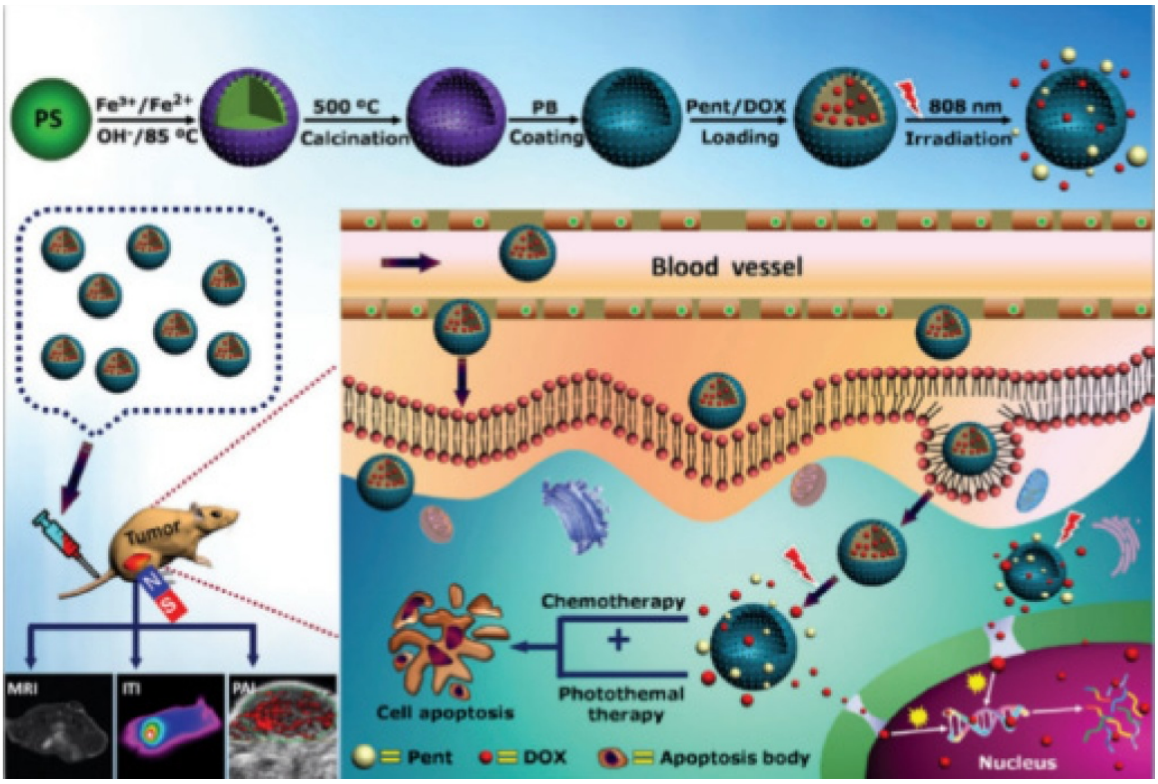


Fig. 7. (a) Illustration of the preparation of drug loaded HMPB@RBC NPs, and the synergistic photothermal-/chemotherapy of cancer;(b) Infrared thermal images of tumor-bearing mice treated with HMPB@RBC NPs and DOX@HMPB@RBC NPs under 808 nm laser irradiation. (c) Photographs of representative mice after different treatments. Reprinted with permission from W. Chen, K. Zeng, H. Liu // Adv Funct Mater **27** (2017) 1605795. Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

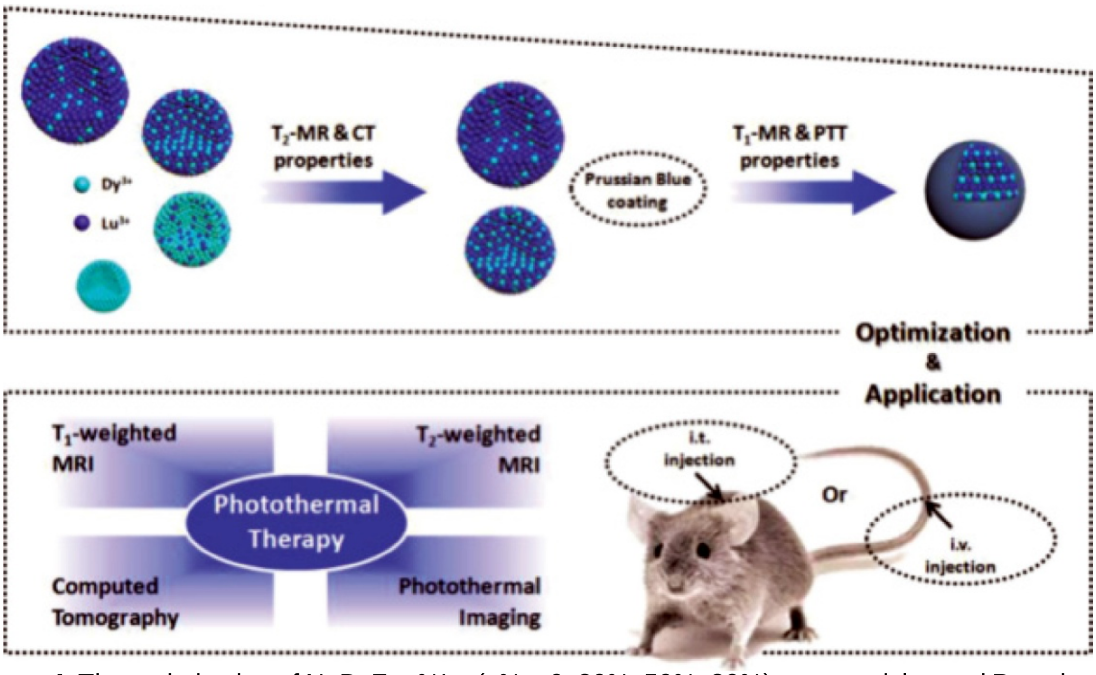
targeted, photothermal therapy and chemotherapy has greatly improved the anti-cancer effect.

Prussian blue, as a good photothermal agent, has T1-weighted MR itself. Therefore, most recent studies have applied it to joint anticancer therapy. Liu et al. [64] synthesized a versatile cancer diagnostic nanoparticle that coated a layer of Prussian blue on the outer layer of the rare earth fluorescent agent, synthesizing the structure of NaDyF4:50%Lu@PB (Scheme 4).

The $NaDyF_4$:50%Lu@PB and $NaDyF_4$:80%Lu@PB that they synthesized exhibit broad absorption from 600 to 900 nm (NIR wavelength). It is similar to the absorption properties of the free PB solution. These results ensured that $NaDyF_4$:50%Lu@PB and $NaDyF_4$:80%Lu@PB nanocomposites could operate as a potential agent for NIR light-mediated PTT. In the experiment by regulating the contents of lutetium elements, they contrasted the different wavelength of irradiation on 808 nm and 785 nm near-infrared light, finding the



Scheme 3. Schematic illustration of the design and synthesis of HMNP-PB@Pent@DOX for NIR guided synergetic chemo-photothermal tumor therapy with trimodal imaging in vivo. Reprinted with permission from J. Li, F. Zhang, Z. Hu // Adv Healthcare Mater. **6** (2017). Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.



Scheme 4. The optimization of $NaDyF_4$:x%Lu (x% = 0, 20%, 50%, 80%) nanoparticles and Prussian blue coated $NaDyF_4$:x%Lu (x% = 50%, 80%) nanocomposites for application in multifunctional imaging-guided photothermal therapy by intraveneously or intratumoral injection. Reprinted with permission from Y. Liu, Q. Guo, X. Zhu // Adv Funct Mater**26** (2016) 5120. Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

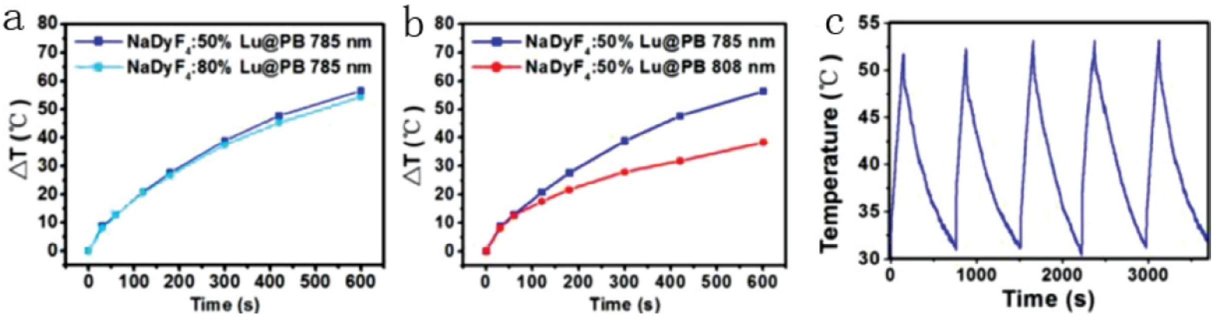
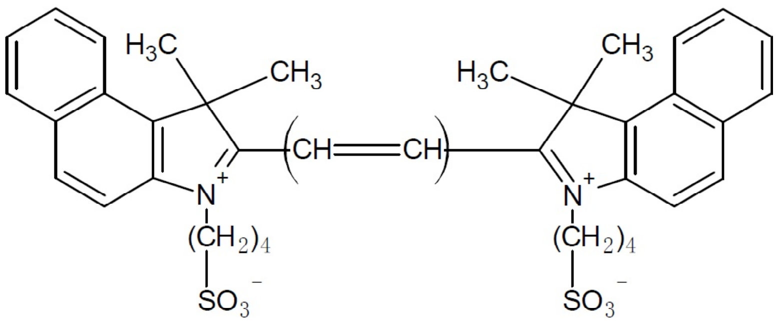


Fig. 8. (a, b)Heating curves of 200 mg mL-1 NaDyF$_4$:50%Lu@PB (785 nm), NaDyF$_4$:80%Lu@PB (785 nm), andNaDyF$_4$:50%Lu@PB (808 nm) under laser irradiation at the power density of 1.33 W cm^{-2}, respectively. (c) Temperature variations of NaDyF$_4$:50%Lu@PB (200 mg mL^{-1}) under the continuous irradiations of 785 nm laser for five cycles. Reprinted with permission from Y. Liu, Q. Guo, X. Zhu // Adv Funct Mater**26** (2016) 5120. Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.



Scheme 5. Equation of indocyanine green.

best condition of the highest thermal efficiency (Fig. 8). Excellent photothermal conversion efficiency is demonstrated under the near infrared light at 785 nm, and 50% lutetium element content.

Cai et al. [65] have synthesized a hollow Prussian blue structure with perfluoropentane (PFP) and doxorubicin (DOX) inside, forming a DOX@PFP@HMPB structure. This versatile structure can be implemented the abilities of ultrasound (US)/photoacoustic (PA) dual mode imaging guided and chemo-thermal tumor therapy. The as prepared nanoparticle exhibits great photothermal conversion properties with large molar extinctioncoefficient (1.2×10^{11} M^{-1}cm^{-1}) and high photothermal conversion efficiency up to 41.4% and ultrahigh drug loading capacity up to 1782 mg g^{-1} of DOX.

5.2. Indocyanine green

The indocyanine green dye molecule (Scheme 5) is a large ð conjugate system, which determines the main absorption of dye in the range of 600-850 nm. Due to the absorption of indocyanine green dye in the near infrared region, the electron energy of the indocyanine green dye increases after laser irradiation, and the electron transition occurs from the ground state to the singlet excited state. When electrons fall from a single excited state to the ground state, energy is released in the form of light and heat, so that the compounds have the ability to emit fluorescence and photothermal conversion. In addition, it has the characteristics of high molar extinction coefficient, high fluorescence quantum yield, good stability, low melting point and large tunable range of maximum absorption wavelength. At the same time, ICG is the only molecule with near infrared optical properties approved by the US FDA for clinical diagnosis. However, ICG is concentration dependent aggregation, poor stability, nonspecific protein binding, and lack of targeting properties [66]. ICG can degrade rapidly in organisms, with a half-life of only 2~4 min [67]. In order to overcome the above shortcomings, and maximize the PTT efficiency, a great deal of research is being carried out. Li et al. [68] synthesized a kind of block copolymers, poly(oligo(ethylene glycol) methacrylate)-block-poly(furfuryl methacrylate) (POEGMA-bPFMA), are by sequential (RAFT) polymerization forming the polymeric micelles which are used to encapsulate ICG and DOX. It can greatly increased the water solubility of ICG. Chen et al. [69] synthesized a novel structure, GNS-ICG-BSA nanotags, which can be used as a theranostic probe, SERS imaging probe and intracellular thermometer. ICG-encoded SERS probe is uneasy to be influenced by the cellular microenvironment and worked as the monitor of PTT in various cell types. In order to overcome the shortcoming of rapid photolysis of ICG in aqueous solution, Kuo et al. [70] and Li et al. [71] also conjugated ICG with gold nanoparticles, achieving the combination of PTT and PDT two cancer treatments. In order to improve the water solubility and biological compatibility of indocyanine green dye, Sheng et al. [72] coated ICG with Human Serum Albumin by programmed and assembly, also realizing the aim to improve the photothermal efficiency of ICG.

In addition, the organic photothermal conversion nanomaterials have the characteristics of absorption range, easy regulation and biodegradability, Some organic compounds have also been found to have photothermal effects and have been used in cancer therapy. For example, organic conductive polymers, polypyrrole [73,74] have high productivity and good stability, and have strong near infrared absorption. Polyaniline [75], dopamine melanin [75], also proved to have photothermal effect, and used in the diagnosis and treatment of cancer.

6. CONCLUDING REMARKS

In summary, we have reviewed recent significant progress of materials for Photothermal Therapy. Due to the fascinating properties of low cost, highly localized, specific tumor treatment, less side effects and minimally invasive, photothermal therapy has increasingly attracted much attention. As outlined here, many remarkable nano-materials have been developed for photothermal therapy, ranging from carbon materials, organic polymers, dyes, transition metal compounds and precious metals. However, there are still a series of questions to be solved, such as excessive heat effect, toxicity, difficulty to metabolize and so on. Therefore, future endeavors should focus on the fabrication of photothermal reagents with (1) high conversion efficiency, (2) high biological security, (3) accurate targeting. In addition, the future photothermal material should be conducive to combining with biological imaging, drug treatment and other means to achieve excellent efficacy in anticancer.

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