Review of Functionalized Nanomaterials for Photothermal Therapy of Cancers

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Abstract: Photothermal therapy (PTT) is recognized as a promising approach for cancer theranostics via the non-radiative conversion of light into heat energy. PTT treatment is able to reduce the adverse side effects of traditional chemotherapy. Some nanomaterials functionalized with unique physical and chemical properties have been integrated multiple imaging modalities and therapeutic function for applications. In the past decade, various nanomaterials for PTT applications have been reviewed but a comprehensive survey of all classes of photothermal nanomaterials developed in the recent years has not been done. A comprehensive discussion of PTT mechanisms using different nanomaterials and the application in combination therapy is useful to provide insights for new PTT materials development for diseases treatment in the future. In this review, the recent advancement of functionalized nanomaterials for PTT and the excellence of PTT combined therapies in the field of anticancer were discussed. The momentous property of nanomaterials tailored for advancing the noninvasive therapeutic approach of PTT was also highlighted. Due to a great deal of PTT nanomaterials have been developed in the past decades and reviewed in recent years, in this review, we only included the latest results reported during the past five years for discussion and comparison.

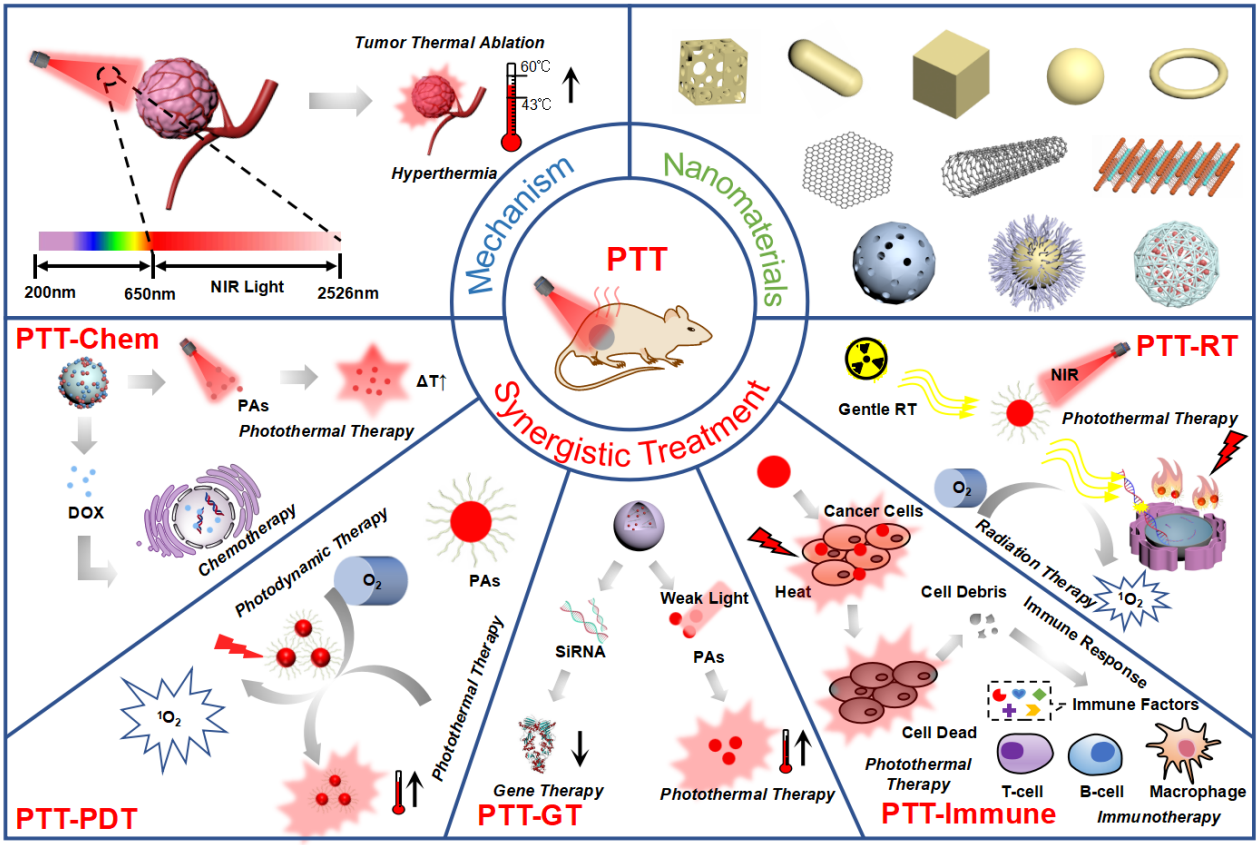
Keywords: Photothermal therapy, Cancer theranostics, Photothermal therapy mechanism, Nanomaterials, Combination therapy

Introduction

Cancer has been a critical threat to public health worldwide because of its high mortality and aggressiveness.[1] Moreover, cancer is a highly complicated pathema and causes massive deaths globally.[2] The statistics showed that about 8 million patients die from cancer-related diseases yearly.[3] Clinically, the current therapeutic options for treating cancer mainly include chemotherapy, radiotherapy and surgery, which are ordinarily accompanied with enormous collateral damage.[1] Despite chemotherapeutic drugs kill cancer cells, they may cause indirect severe harm to normal cells such as by means of oxidative stress. The radiation employed in radiotherapy may lead to sequelae, such as skin cicatrix and muscle fibrosis, after treatments. Surgical treatment may cause ramification to adjacent organs.[4,5] Consequently, the investigation of non-invasive and selective therapeutic technology has drawn wide attention. Researchers have devoted continuously to develop accurate diagnostic means and effective therapeutic strategy for cancer therapy (Scheme 1).

Cancer therapy may be improved potentially with the development of emerging therapies including photothermal therapy (PTT),[6,7] gene therapy,[8,9] immunotherapy,[10,11] photodynamic therapy (PDT),[12] and the combined application. PTT therapy by local elevation of body temperature has attracted the attention of clinicians.[13] Hyperthermia at a temperature of 41.8-45 °C can exert a therapeutic effect on malignant tumor cells in a hypoxic environment, while causing minimal injury to acroteria tissues.[14] The pathogens may notably slow down growth and enzymes in the virus may lose activity as the rise of body temperature. Therefore, photothermal-induced elevation of body temperature may be beneficial for anti-cancer applications.[15-18] PTT may offer distinctive advantages over other methods for cancer treatments because this technique can precisely target the lesions with

a steerable dose of external laser irradiation, thereby minimizing the damage to the surrounding healthy tissue. PTT is thus regarded as a promising non-invasive therapeutic strategy. It has been demonstrated that many types of cancers can be eliminated effectively with PTT.[19]



Scheme 1. A schematic illustration of functionalized nanomaterials for photothermal therapy of cancers.

Thermal treatment of cancer relies on the sensitivity of the cancer cells to heat. In other words, the tolerance of cancer cells to hyperpyrexia is lower than that of normal cells[20] as hyperpyrexia may cause irreversible damage to the membrane of cancer cells and promote protein denaturation.[21-24] Under these prerequisites, the thermal treatment could be a selective and effective therapeutic technique. In addition, the accumulation of exogenous photothermal agents (PTAs) in tumor cells is

higher than the surrounding normal tissue cells and that may further enhance the outcome of PTT.[25,26] For an ideal PTA, it should have a high photothermal conversion efficiency (PCE) and does not overlaps with the tumor background. More importantly, it should be preferentially accumulated in the lesions (target-specific). Currently, the development of novel PTAs is “blooming" in the scientific community.[27-31]

Benefited from the rapid development of nanotechnology, various nanomaterials with distinctive physical and chemical properties, such as light-to-heat, are suitable for PTT application.[32-36] In particular, photothermal nanomaterials can heap up in tumors by enhancing their permeability and retention effects (EPR).[37-39] In addition, nanomaterial-based photothermal agents (PAs) are capable of obtaining higher PCE than the simple PAs and they have great potential to integrate with multiple imaging and diversified therapeutic functions to treat cancer in a more efficient manner.[40] Regarding laser irradiation for the early cancer therapy, the heat generated by the external laser equipment may affect the surrounding healthy tissue when burning the lesion area.[41] This non-selective side effect limits the clinical application. Therefore, the research and development of photothermal effect that only causes local heating may show great application prospects. In addition, functionalized nanoparticles (NPs) can be tailor-made to convert the absorption of a specific light into heat to generate photothermal effect.[42-44] By applying the functionalized NPs, the heat generated can be limited in the tumor with a long wavelength laser irradiation. The external light irradiation can pass through the healthy tissue without significant side effects. Compared with ultraviolet and visible light, near-infrared (NIR) light has a deeper penetration ability in tissues and is relatively less harm to the body.[45,46] The NIR region is also called as biological window because water and biomolecules absorb

less light in that window, which makes NIR favorable for PTT application.[47] Therefore, various nanomaterial-based photothermal agents are engineered to possess excellent photothermal conversion effect in the NIR window area. Moreover, photothermal ablation of PTT combined with targeted tumor administration can synergistically improve the treatment index: (i) Improve cell membrane permeability. (ii) Increased drug cytotoxicity. (iii) Trigger drug release at the lesion. This strategy is of great significance in the treatment of drug-resistant cancer.[48]

Despite many advantages of PTT have been emphasized, PTT also has its own shortcomings. First, the limited penetration depth of light is the biggest problem of PTT. The tumors beyond the irradiation range may not be ablated completely. In addition, overheating of the tumor areas may cause damages to the surrounding normal tissue. The overexpressed heat shock proteins in some cancers may cause resistance to PTT. Furthermore, the low delivery efficiency of photothermal agents (PAs) to lesions may reduce the treatment efficiency.[49] To overcome the bottlenecks, scientists have devoted tremendous efforts, such as utilizing an advisable laser dosage,[50,51] optimal treatment time after administration,[25] enhancing the PCE of nanomaterials,[52-54] developing nanomaterials that absorb in the second NIR region,[55] cell-mediated nanomaterials delivery systems for PTT, and improving PTT performance by adjusting the shape,[56,57] size and physicochemical properties of NPs.[58-60]

During the past decades, the synthesis of nanomaterials and the development of PTT have been "mutually complementary". Due to the significance and rapid development of the field, many reviews on photothermal nanomaterials have been reported; however, a comprehensive summary of various newly developed photothermal nanomaterials and their PTT mechanism and the combined technology with other cancer therapies could be able to provide meaningful insights to overcome the

limitations of PTT therapy. In this review, we highlighted the tailored PTT nanomaterials reported during the last five years, mainly focusing on the noble metal-based nanomaterials, carbon-based nanomaterials, semiconductor-based nanomaterials, conducting polymer-based nanomaterials and small molecule-functionalized nanomaterials. The synergy of PTT integrated with other therapy was also discussed (Scheme 1).

The mechanism of light-tissue interaction, light-nanomaterial interaction and photostimulation

Light has been employed in diagnostic imaging and surgery in the medical domain.[61-63] It is important to understand the interaction between light and tissue, which determines the theragnostic effect. The reflection, scattering, transmission and absorption of light happens naturally both in the internal human tissues and the outside natural environment.[64] Light affects biological activities, such as oxygen consumption.[65] Light irradiation could produce thermal effects[64] or catalytic effects[66] and it also influences various metabolisms of living bodies by changing the activity of enzyme *in vivo*. In the view of the existence of these facts, it is an indispensable premise to premeditate light-tissue interaction before using light in clinical medicine. The effect of light-tissue interaction depends on the optical properties of the tissues and the wavelength of light. Since the optical properties of tissues are almost impossible to alter, the selection of suitable wavelengths of light for a specific application is thus the main tactic. The main optical activities between tissue and light are absorption, reflection and scattering. In terms of light absorption, tissues can absorb energy from light irradiation and make it an effective measure for combating pathema in clinical surgery.[62-64]

Photothermal therapy kills cancer cells by injecting materials with photothermal conversion

properties into the vicinity of tumor tissue intravenously, and then applying laser to the focus area. The irradiation time is generally between a few to dozens of minutes, resulting in local temperature rise of tumor tissue.[67,68] In general, there are three main mechanisms of photothermal therapy:

(i). The increase of temperature in the tumor area changes the permeability of tumor cell membrane, inactivates intracellular enzymes and proteins, and leads to the death of tumor cells.[69,70]

(ii). Due to poor capillary development and slow blood flow of cancer cells, their heat dissipation capacity is poor. Compared with normal cells, tumor cells have weaker tolerance to high temperature, which makes them easy to be killed by local heating.[71]

(iii). Local heating in the focus area will affect the expression of promoting and inhibiting genes related to apoptosis in tumor cells, and then cause apoptosis.[72]

X-ray, ultraviolet (UV) and near infrared (NIR) are the electromagnetic radiations can be utilized as the light sources for therapy.[73,74] NIR is an electromagnetic wave with a wavelength between microwave and visible light, which is a suitable light source for PTT therapy. Medical infrared is divided into near infrared and far infrared. The light in the NIR region has a relatively low absorption coefficient and strong penetrating capacity.[75] Light with longer wavelength has a deeper penetration power in tissues.[76] Thus, the NIR region is called “biological window”,[77,78] which is considered to be the vital mean for the diagnosis and therapy of deep body diseases. It is noteworthy that the penetration level of NIR light in lesions is found higher than that of natural tissues. The light at 630 nm can penetrate 0.9 mm in the normal brain tissue and penetrate 1.6 mm in the lung cancer lesions. It suggest that NIR light can be employed in PTT.[79]

In addition, nanoscience and technology are known as one of the three frontier fields. The rapid development of nano-biomedicine provides new ideas for the development of safe, efficient, specific and intelligent nanomaterials.[80-82] The size of nanoparticles is 100 times or even 1000 times smaller than that of cancer cells, so they can easily pass through the cell barrier. In addition, they can gather preferentially at the tumor site. It could be caused by the EPR produced by the tumor tissue microvascular permeability and the imperfect lymphatic drainage system.[83] To minimize side effects of the traditional anti-cancer therapy, the targeted therapy for carcinoma cells has been proposed.[81] The target-specific nano-drugs for PTT has been extensively investigated and applied to exterminate lesions selectively without or with minimum side effects towards the surrounding normal tissues.[84] After drug administration, the nano-system requires a suitable light stimulus to function. NIR light is definitely a favorable source of stimulation because low-power NIR can pass through deep tissues. It is thus capable of inducing the photothermal conversion of the nanomaterials and achieves the phototherapy of the pathological region under the irradiation of an external laser.[85] Therefore, the NIR-induced imaging and selective therapy of PTT have become a research hotspot currently.

The recently developed nanomaterials for photothermal therapy

The application of nanomaterials in the late-model cancer therapy has dramatically increased due to their unique compositions and properties. For instance, gold nanoparticles can perform photothermal conversion through the surface plasmon resonance (SPR).[86] It is noteworthy that nanomedicine induces endothelial leakage through NPs or the mechanism of enhancing the permeability of nanomaterials to tumors and EPR, which has a superiority target-specificity in the course of tumor treatment. For nanogels, it can interact with endothelial cells' adhesion connexins,

thereby enhancing the permeability of nanomedicine for effective accumulation.[87-89] As mentioned earlier, certain properties of nanomaterials such as size, shape and surface have a gigantic impact on their biocompatibility, biodegradability as well as photothermal properties. The research on PTAs is thus mainly focused on nanomaterials development. By taking the advantage of the optical absorption of NIR light, we can use nanostructures such as carbon nanotubes,[129] gold nanorods,[90] and graphene oxide sheets[91] to enhance photothermal therapy and treatment selective towards tumor tissues. In the past, noble metal nanomaterials exploited for PTT research have made great progress. In recent years, a great deal of neoteric nanomaterials developed for PTT have been gradually emerging in the field.[54,92,93]

(I) Noble metal-based Nanomaterials

The early study on PTT reagents is mainly focused on noble metal nanomaterials that comprise of Au, Ag, Pt and Pd.[94] These noble metal-based nanomaterials have good absorption of light and correspondingly high light-to-heat conversion efficiency and do not cause rapid photobleaching problems.[94] These nanomaterials motivate electrons by absorbing light energy and release the energy through a non-radiative decay. The energy released is in the form of heat,[95] which is the source of the photothermal effect of precious metal nanomaterials. Therefore, upon light irradiation, the noble metal-based nanomaterials can carry out photothermal conversion effect by converting light energy into heat energy.[86,96]

Gold-based nanoparticles (Au NPs) are the most studied noble metal nanomaterials. Some representative spherical Au NPs have SPR features.[97,98] These Au NPs absorb NIR light effectively and possess excellent photothermal conversion performance. Moreover, Au NPs are found to have

the advantage of low toxicity, stable photothermal conversion characteristics and well-defined surface chemistry.[99,100] Some Au NPs have been utilized as PTAs with distinctive SPR features in the NIR window.[98] The gold-based nanomaterial was first used for PTT in 2003.[101,18] Since then, a large number of studies have been reported. This may demonstrate the importance of gold-based nanomaterials in the PTT technology development. Au NPs have many specific-shaped hollow spherical structures,[102,103] core/shell,[104,105] nanorods,[106,107] nanocages,[108,109] nanoclusters[110] and chiral NPs.[111] Among them, gold nanorods have been extensively studied due to their absorption peak positions related to the aspect ratio and good PCE.[86] Moreover, gold nanorods have two characteristic absorption peaks. One is the longitudinal absorption peak and the other one is the lateral absorption peak at about 520 nm. Therefore, by adjusting the aspect ratio, the SPR area can be tuned and converted into NIR region.[112-115] By altering the size and/or shape of Au NPs and modifying their surface, the circulation and target specificity of Au NPs in the body can be enhanced to a large extent. Huang et al. prepared a series of Au nanorods with different aspect ratio and longitudinal SPR peaks.[116] The polyethylene glycol (PEG) and tumor-targeting ligand lactoferrin were used to modify these gold nanorods. They also employed these special gold nanorods to explore the influence of size and surface properties of gold nanorods on the internalization of tumor cells. Their results show that the Au nanorods with moderate width, length and lactoferrin modification exhibit significant tumor targeting effects. As a result, these Au nanorods are able to destroy the xenograft tumor under the irradiation with a 980 nm laser.

Recently, multifarious shapes of Au NPs have also been studied. Jing et al. prepared a sort of nanoarchitectonics on graphene oxide (GO) based on flower-shaped Au NPs (Fig.1a).[117] In the study,

a GO composite decorated with nanogold flowers was synthesized. Compared with the pure gold-based composite materials, it offers more obvious light-to-heat conversion performance. The temperature change of light irradiation time (irradiated with 808 nm) is more palpable. The aptamer DNA and PEG were further used to construct nanostructures. The aptamer AS1411 was grafted onto the flower-shaped Au-NPs to offer excellent stability and specificity under the complicated physiological conditions. Moreover, Zheng et al. designed a hybrid nanoplatform that was made of photothermal nanomaterials, Au nanostars (Fig.1b) and glycopolymer that is thermos-responsive and containing glucose and galactose.[118] It was found that the synthetic protocol shows admirable colloidal stability and exhibits high PCE. The one-photo photoluminescence quantum yield of gold nanobipyramids (GNBs) is found doubled compared to those well-studied gold nanorods in a similar SPR range, indicating that GNBs could achieve better imaging contrast in cancer diagnoses.[119] Moreover, compared with traditional gold nanoparticles, GNBs exhibited a more uniform shape, with adjustable absorption wavelength (700-1200 nm) and good chemical stability.[114,120,121] Furthermore, Li et al. contrived indocyanine green (ICG) conjugated mesoporous silica coated GNBs (GNBs@SiO_2-ICG)[122] and prepared for simultaneous FL/PA imaging-guided PTT (Fig.1c). The GNBs@SiO_2-ICG is capable of integrating various functions in a simplex platform to realize tumor nanotheranostics.

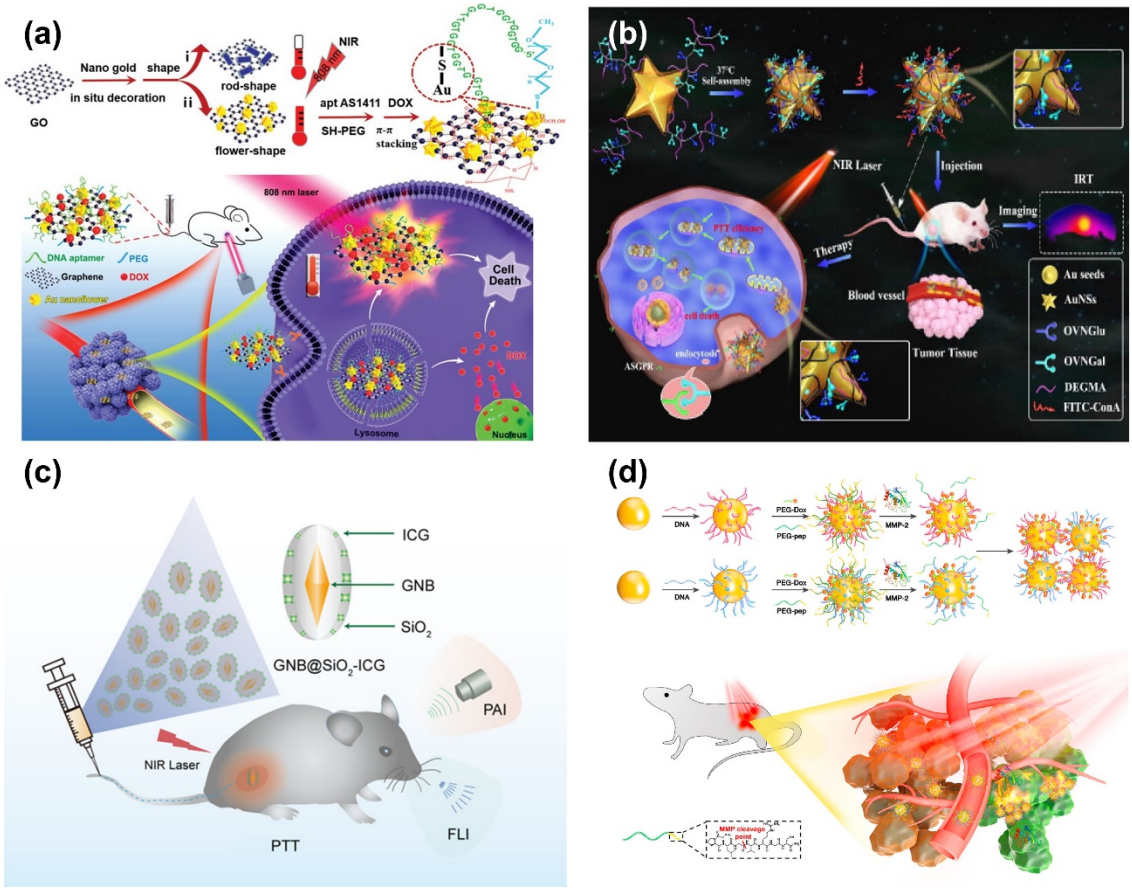


Figure 1. (a) Representative schemes illustrating preparation of nanoarchitectonics on GO based on flower-shaped Au NPs as a high-speed photothermal transform and drug delivery system for synergistic Chemo-PTT of tumor cells and tumor issues (Figure adapted from ref. 117 with permission). (b) Schematic illustration of the preparation of a hybrid nanoplatform and PTT application (Figure adapted from ref. 118 with permission). (c) Illustration of the Au nanobipyramid-based nanotheranostics for Dual-Modality imaging-guided PTT.[122] Reproduced from Li, C.; Mei, E.; Chen, C.; Li, Y.; Nugasur, B.; Hou, L.; Ding, X.; Hu, M.; Zhang, Y.; Su, Z.; Lin, J.; Yang, Y.; Huang, P.; Li, Z,. Gold-Nanobipyramid-Based NanoTheranosticss for Dual-Modality Imaging-Guided Phototherapy. ACS Appl. Mater. inter. 2020, 12, 12541-12548. Copyright 2020 American Chemical

Society. (d) Schematic illustration of MMP-induced aggregation of AuNPs in vivo for enhanced PTT of tumor (Figure adapted from ref. 124 with permission).

Apart from the study of gold-based nanomaterials with various shapes and morphologies, the application of dendritic gold nanoparticles in PTT has been demonstrated. Since the property of these dendritic gold nanoparticles can be altered because of hyper-branched nanostructures. The relationship between photothermal properties and the degree of branching of Au nanodendrites has also been investigated.[123] The results show that the optical feature of Au nanodendrites is adjustable and those with relatively low branching degree exhibit better PCE in the second NIR window. Moreover, the emergence of stimulating tumor-targeting strategy has brought a turning point for the effective clinical application of gold-based nanomaterials. In stimulus response therapy, due to the intensive EPR effect and the slower removal rate of larger assemblies, Au-NPs assemble into large aggregates at the lesions, thereby promoting the death of the tumor tissues. Yang et al. reported an assembly-based tumor targeting strategy to augment the accumulation of doxorubicin (DOX) tethered Au NPs in lesions for imaging-guided alliance treatment (Fig.1d).[124] Matrix metalloproteinase (MMP) responsive Au NPs were synthesized to possess strong NIR absorption property (at 724 nm) and extracellular assembly. Surprisingly, gold-based nanomaterials are not only useful for PTT treatment of cancer but also have many other medical applications, such as drug carriers and contrast agents for imaging diagnosis.[125-128] This may imply their latent capacity as a multifunctional drug.

In general, some Au NPs show a strong local SPR effect. These Au-based nanomaterials have strong absorption or scattering ability to light and its resonance wavelength (535 nm) can be regulated

by nanomaterial preparation conditions. These properties grant Au NPs a variety of applications. Although noble metal nanomaterials have significant photothermal effects in the cancer therapy, there are still some problems to be solved. Typically, Au NPs are non-biodegradable and hence further tracking and measurement after application is indispensable. In addition, the light stability of Au NPs also deserves attention because some structures become weaker or unstable due to the "thawing"[128] that could depress the photothermal conversion efficiency. Therefore, it is an urgent and challenging task to be explored further for noble metal-based nanomaterials with high light stability.

(II) Carbon-based nanomaterials

The restriction of noble metal-based nanomaterials in PTT has prompted researchers to search for other inorganic materials as the ideal PTAs. Alternatively, carbon-based nanomaterials comprised of carbon nanotubes (CNTs),[129] graphenes,[130] graphene oxides (GO),[131] carbon dots,[132] nanodiamond[133] and activated carbon[134] were developed. Among various carbon-based nanomaterials, CNTs have remarkable light-to-heat conversion properties in the medical fields.[135,136] Applications of CNTs have contained drug carriers and bioimaging probes.[137] However, there are multifarious factors including the size, dosage, surface chemistry and/or elemental ingredients that may affect the toxicity of CNTs. Therefore, CNTs are often converted with diverse surface chemical properties to reduce toxicity.[138] Similar to other PTAs,[139] PEG coating is generally utilized to functionalize CNTs because PEG may be able to improve the biocompatibility and prolong the blood circulation time of CNTs.[140,141] Moreover, it is noteworthy to highlight that a reliable methodology for the synthesis of CNTs materials and making them accurately targeting lesions is crucial for the realization of practical application. Lu et al. investigated the single-walled carbon nanotubes

(SWNTs) with good water solubility, biological stability and low toxicity.[142] The SWNTs can be coupled with an imaging agent CY7, and then the dye-coupled SWNTs can be combined with antibodies to make them specifically targeting pancreatic tumors for imaging-guided photothermal therapy (irradiated with 808 nm). The transmission electron microscopy (TEM) characterization showed that the morphology of the material in each step of the synthesis process has no significantly changes (Fig.2a). SWNTs can also be dispersed uniformly in solution without aggregation by applying ultrasonic dispersion.

Graphene is a two-dimensional nanomaterial composed of sp^2-hybridized carbon atoms arranged in a hexagonal honeycomb shape[143] and it has large specific surface area, good flexibility, high thermal conductivity, high carrier mobility and good biocompatibility. Therefore, it can be employed as a multi-functional material for many biomedical applications[144,145] including biosensors,[146] tissue scaffold engineering,[147] anti-microbial therapies,[148] bioimaging[149] and PTT[150]. However, graphene has a fatal weakness of high hydrophobicity that makes it extremely tough to be applied in medical care. Nonetheless, graphene oxide (GO) is customarily employed as preferred materials. GO has several oxygen-based functional groups compared to graphene. The functional groups primarily include hydroxyl and epoxy groups located on the basal plane of the sheet and the hydroxyl, carboxyl, carbonyl, phenol and lactone structures situated at the sheet edge.[151,152] These functional groups greatly reduce the strong hydrophobicity of graphene. More specifically, the hydrogen-oxygen bonding capability of hydroxyl and epoxy groups remarkably improve the stability of GO in polar solvents,[153] while the hydroxyl and carboxyl groups on the sheet edge make GO more impressionable for modification and functionalization.

GO is well known for its light-to-heat conversion properties. It can convert laser energy into heat energy and enables hyperthermia to destroy tumor cells.[154] Liang et al. developed a nanocomposite (NCGO-FA)[155] and followed the materials were loaded with DOX through π−π stacking and electrostatic attractions to form NCGO@DOX-FA nanomaterials. The NCGO@DOX-FA nanoplatform bears a number of merit properties such as ultra-high surface area, high drug loading, good targeting specificity, PCE and photostability (irradiated with 808 nm). Chang et al. exploit a versatile nanoplatform with $BaHoF_5$ nanoparticles deposited on GO. The synthesized nanocomposite (GO/$BaHoF_5$/PEG) showed prominent biocompatibility and could be accumulated in lesions via the EPR effect.[156] The heat shock protein 90 (HSP90) inhibitor NVP-AUY922 can be loaded into GO/$BaHoF_5$/PEG to perform sensitized PTT (irradiated with 808 nm) against cancer (Fig.2b). Further studies conducted by Deng et al. demonstrated a tumor-killing strategy for ultra-rapid low-temperature PTT (LTPTT) employing GO loaded with SNX-2112 (irradiated with 808 nm) and FA (Fig.2c).[157] A distinct mechanism was proposed, in which the ultra-rapid LTPTT over-activated autophagy causes rapid induction of apoptosis of tumor cells and the T cells promote the innate immune ability and actively participate in the attack of lesions.

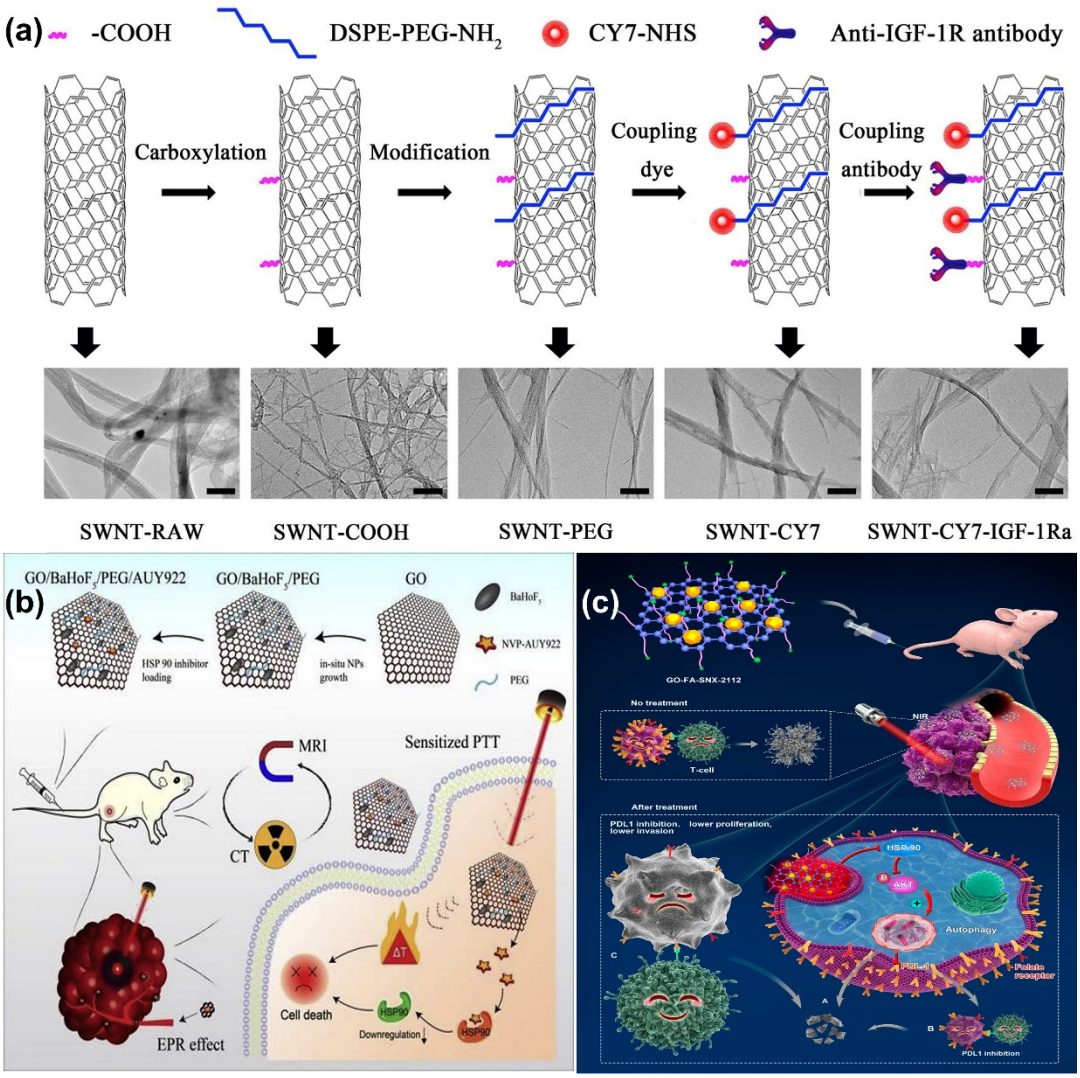


Figure 2. (a) Schematic illustration and TEM images in the synthesis procedure of nanotubes. The bar is 100 nm (Figures adapted from ref. 142 with permission). (b) Illustration of construction procedure of GO/BaHoF5/PEG/AUY922 and its application in MR/CT dual-modal imaging and HSP inhibitor-sensitized tumor photothermal ablation (Figures adapted from ref. 156 with permission). (c) Schematic structure of GFS and its application for LTPTT of tumor to induce over-activation of autophagy.[157] Reprinted with permission from Deng, X.; Guan, W.; Qing, X.; Yang, W.; Que, Y.; Tan, L.; Liang, H.; Zhang, Z.; Wang, B.; Liu, X.; Zhao, Y.; Shao, Z. Ultrafast Low-Temperature Photothermal Therapy Activates Autophagy and Recovers Immunity for Efficient Antitumor

Treatment. ACS Appl. Mater. inter. 2020, 12, 4265-4275. Copyright 2020 American Chemical Society.

Graphitic carbon nanocages (GCNCs) are distinctive hollow and porous graphene-based nanoparticles with a large inner cage with diameter of tens of nanometers and thin graphitic shell with a thickness of several nanometers.[158] GCNCs exhibit predominant physicochemical capabilities and have been widely investigated in various fields.[159,160] Guo et al. studied the combined effect of a 808 nm laser and microwave to deactivate chitosan (CS)-coated GCNCs (CS-GCNCs) and 5-fluorouracil (5Fu) to treat antagonism cancer.[161] It was found that the cytotoxicity of the modified GCNCs can be reduced and the release rate of 5Fu was slower than that of GCNCs. The system achieves sustained release. Besides, carbon dots (CDs) show great development prospects for biomedical applications due to the dominants of facile preparation, remarkable water solubility, ease of surface modification, good photostability and biocompatibility.[161-164] Moreover, CDs could generate reactive oxygen species (ROS) simultaneously under laser irradiation (at 650 nm) to realize the combination of photothermal therapy and photodynamic therapy.[165,166] Zhao et al. reported the lysosome targetable CDs, which can synchronously produce ROS and heat under a 635 nm laser irradiation.[167] The results demonstrated the potential application in PTT-PDC synergistic cancer therapy.

Taken together, carbon-based nanomaterials have been successfully applied in PTT for tumor treatment because of their merit property in drug transport and biomedical imaging; however, their poor dispersion in water greatly limits their practical use in clinical. Surface attached with PEG or coated with functional polymer may help the carbon-based nanomaterials disperse uniformly in

aqueous solution and enhance the absorption capacity of the nanomaterials to NIR light. Therefore, to realize the synergy therapy, further efforts on the modification of carbon-based nanomaterials are required.

(III) Semiconductor-based nanomaterials

In addition to carbon-based nanomaterials, certain semiconductor nanomaterials, such as semiconductor copper chalcogenides[168] and semiconductor polymer,[169] have been recognized as PTT ablation thanks to their specific unique features. Copper chalcogenide compounds ($Cu_{2-x}E$, E=S, Se, Te) are a typical type of semiconductor materials that can generate numerous copper vacancies during the crystallization process.[170,171] The copper vacancies form high mobility multiple hole carriers and the co-oscillation of these hole carriers can induce a strong regional SPR effect in the nanocrystal.[172,173] In particular, the plasmonic $Cu_{2-x}E$ nanocrystals with a copper-poor stoichiometry emerge strong localized SPR band in near-infrared region, which can fleetly transform laser energy into heat energy for tumor ablation.[174,175] CuS NPs were initially utilized as a PTA for ablating tumor cells under a 808 nm laser radiation.[176] After that, a series of related studies were reported. Wang et al. exploited some $Cu_{2-x}S$-based nanomaterials including Cu_9S_5 nanocrystals,[177] CuS superstructur[178] and CuS@nanogel-DOX nanocomposites.[179] Recently, a new method for constructing CuS-Au hetero-structures in aqueous without the addition of reducing agent has been developed.[180] The application of CuS nanoplates as an effective reducing agent to generate CuS-Au hetero-structures through the galvanic exchange route was also studied. According to the experimental results reported, by regulating the molar ratio of Au/Cu in the reaction, the size and quantity of Au nanocrystals on CuS nanoplates can be controlled. The CuS-Au hetero-structures obtained possess a strong local SPR

absorption in NIR region (irradiated with 1064 nm) and the PCE achieved is 36.5%.

In addition, CuS has recently been developed as a Fenton-like agent for chemodynamic therapy,[181-183] which is an emerging tumor therapy mean with high specificity and minimal invasiveness.[184,185] CuS catalyzes the endogenous hydrogen peroxide (H_2O_2) to produce hydroxyl free radicals through copper ions to eliminate tumors.[186] Wang et al. reported a hollow Cu_9S_8 theranostic nanoplatform (Fig.3a).[187] Compared with Cu_9S_8 NPs, the especial external area of hollow Cu_9S_8 was enhanced, which overwhelmingly increased the number of active sites for the catalysis of the Fenton-like reaction. Therefore, it improves therapeutic performance. Moreover, the predominant photothermal capability of the material promotes the generation of hydroxyl radicals in the Fenton-like reactions (irradiated with 808 nm).

CuS NPs have also made great progress as a favorable PTA in combination with other NPs for tumor treatment. By taking the advantages of photothermal efficiency and in vivo biodegradability of CuS NPs,[188,189] the combined application of CuS-NPs and SiO_2 NPs has achieved synergistic therapeutic effects.[190,191] Zhang et al. fabricated a nanocomposite based on CuS@mSiO_2@MnO_2 that responds to the tumor environment (TME) (Fig.3b).[192] With respect to their methodology, manganese dioxide (MnO_2) is utilized to catalyze H_2O_2 decomposition to produce O_2 and toxic hydroxyl radicals in TME. When the CuS core is irradiated with NIR (915 nm), a good PTT effect can be obtained. In addition, Sun et al. employed the degradability of honeycomb MnO_2 in TME to design triumphantly a PTT-PDT therapeutic nanoplatform that integrated tumor targeting and O_2 release functions (Fig.3c).[193] The nanoplatform was loaded with CuS NPs and ICG and then further was wrapped in hyaluronic acid (HA). The PTT effect of CuS-NPs and ICG molecules is triggered under 808 nm

laser irradiation and exhibits satisfactory photostability. Furthermore, Qi et al. contrived melanin as a biological template and folic acid (FA) as a stabilizer to fabricate a method for HA to modify CuS nanodots.[194] Since both melanin and CuS have strong near-infrared absorption ability, the prepared CuS-melanin-FA composite nanoprobe exhibited high PCE for PTT of cancer (irradiated with 808 nm).

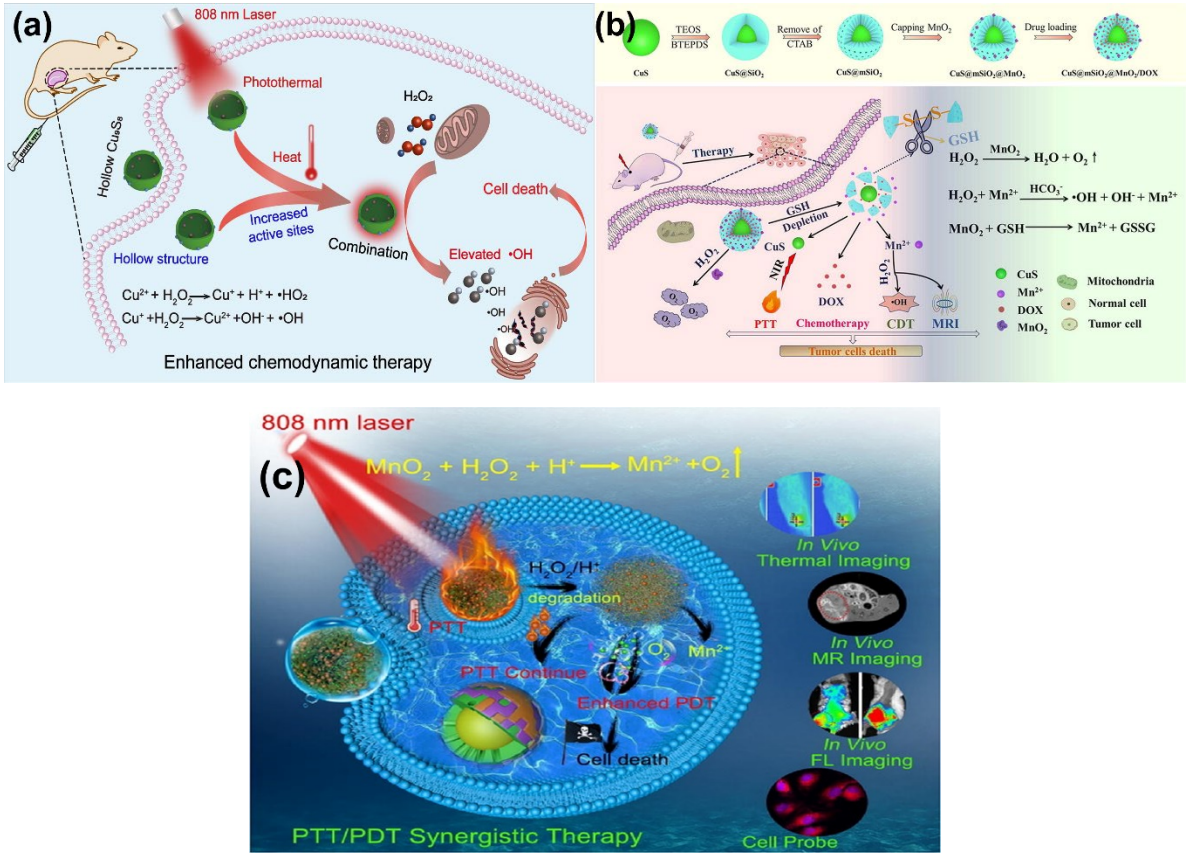


Figure 3. (a) Schematic diagram of combining increased active sites with photothermal to enhance chemodynamic therapy performance enabled by hollow Cu_9S_8 NPs (Figures adapted from ref. 187 with permission). (b) Illustration of preparation procedure for CuS@mSiO$_2$@MnO$_2$/DOX nanocomposites and their smart theranostic mechanism for treatment of cancer cells (Figures adapted

from ref. 192 with permission). (c) Schematic illustration for the synthesis of MCIH (MnO_2-CuS-ICG-HA) nanoplatform and the nanoenzyme-catalyzed behavior of MCIH used in PTT and improved PDT by the single 808 nm laser irradiation for the treatment of cancer (Figures adapted from ref. 193 with permission).

The semiconductor polymer is actually a conjugated polymer. The material has semiconductor property because of its special π-π conjugation structure in the main chain. Therefore, it is called semiconductor polymer.[195] Due to this special structure, semiconductor polymers have excellent optical property and stability. They are considered to be one of the most potential materials in the biomedical field due to easy surface functionalization and good biocompatibility.[196,197] The structure of semiconductor polymers determines their properties and functions. The recently reported structures of semiconductor polymers include copolymers (such as polyfluorene (PFO)[196], poly(phenylene acetylene) (PPE)[198]) and D-A semiconductor polymers (such as donor structures: fluorene and thiophene and benzothiadiazole/benzoselenidazole;[196] receptor structures: PFPV, PFBT, PFBS, PF-BTDBT).[199] These materials have been widely studied in the biomedical field.[198,199] Moreover, the semiconductor polymer nanomaterials with NIR absorption property have become a research hotspot in recent years. It is because their strong tissue penetration ability. These new semiconductor polymer nanomaterials with weak fluorescence intensity and NIR absorption convert most of the energy into heat energy after absorbing light energy and have high PCE.[199] Therefore, they are frequently used in the field of photothermal therapy.

At present, the preparation methods of semiconductor polymer nanoparticles mainly include re-

precipitation, microemulsion and self-assembly method.[198,199] However, these methods have many shortcomings such as complicated operation, poor purification of nanoparticles, uncontrollable of size and poor size dispersion. To improve these drawbacks, various surface functionalization methods have been adopted for the preparation of new semiconductor polymers, which mainly include amphiphilic molecular modification,[200,201] surface silylation[202] and phospholipid encapsulation.[203] Through further surface modification, the polymeric nanomaterials have the functions of tumor targeting, environmental stimulation response and drug loading. Yu et al. selected a polystyrene maleic anhydride (PSMA) as an amphiphilic polymer to modify the polymer PFBT.[204] The prepared nanoparticles were found with good colloidal stability and were coupled with biomolecules via the hydrophilic carboxyl group for cell targeting. The materials have made a great progress in cell specific imaging. Xu et al. designed a pH/photothermal multi-stimulus responsive triblock polymer PSNiAA.[205] After doped it into a semiconductor polymer PDPP3T nanoparticles by co-precipitation method, it is successfully loaded with anticancer drug DOX, and constructed pH/photothermal multi-stimulus responsive intelligent nano-diagnostic and therapeutic agent PDPP3T@PSNiAA-DOX NPs. The material has a stable structure, uniform size and excellent photothermal property (irradiated with 785 nm). Compared with small molecular photothermal therapeutic agent ICG, it shows better photobleaching resistance. Moreover, the coating of PSNiAA makes the drug-loading rate of diagnostic and therapeutic agents reach 24.1%, which promotes the synergistic treatment.

In general, semiconductor-based nanomaterials are favored by most researchers because of their good photothermal stability, low cytotoxicity and controllable particle size and morphology.[195-197] Nevertheless, the semiconductor nanomaterials also have bottlenecks in photothermal therapy

applications. For example, certain semiconductor materials, such as copper-based nanomaterials,[176] have relatively low PCE under a 808 nm NIR laser irradiation. A higher laser power is required to ablate tumors. To overcome this obstacle, a 980 nm laser is usually used to irradiate the lesions but the vital problem is that 980 nm NIR radiation can be also absorbed by water. Consequently, normal tissues may be also damaged. Therefore, it is still a long way to go to realize good semiconductor nanomaterials for practical use in PTT.

(V) Conducting polymer-based nanomaterials

The conductive polymers (CPs) such as polyaniline (PANI),[206] polypyrrole (PPy),[207] polythiophene[208] and their derivatives show significance in a variety of biomedical applications including controlled release of drugs, biosensors and neural prostheses. CPs have been considered as a neoteric generation of modern organic nanomaterials.[209] Besides, the optical absorption capacity of CPs enables their potential applications in PTT. Compared with noble metal nanomaterials, CPs have a much lower cost and good biocompatibility.[31,210,211] However, the PTT mechanism of CPs is largely different from that of inorganic nanomaterials. When the materials stimulated by a specific light, a biopolaron is formed. Subsequently, it decays into a photon band and generates heat.[212,213] Moreover, the optical absorption peak (516 nm) of nano-architectured CPs can be shifted during the doping process.[214] More specifically, the dopants could facilitate the generation of gaps between bands, which results changes in the excitation energy level. This special property is employed for improving the conductivity of conductive polymers.

PANI received extraordinary attention because of their unique π-conjugated structures, which result in high conductivity under acidic conditions. Moreover, the distinct redox property is

appropriate for the facile synthesis, inexpensive preparation, and the oversimplified and highly doped chemistry.[215-217] Recently, the application of polyaniline in the field of nano-medicine including cell stimulation, drug delivery and tissue engineering has received great attention.[218] Although PANI can be highly functionalized with oxidizing groups, the aggregation between PANI particles hinders the development of PANI in many areas.[211] Some researchers have investigated the feasibility of using PANI as a coating material for neural probes and confirmed that the PANI film displayed good biocompatibility.[219,220] PANI is the first reported pH-responsive organic polymer for PTT therapy with surpassing stability.[221] PANI exists in two states of emeraldine base (EB) and emeraldine salt (ES) and can be converted into each other via protonation and depronation reactions at different pH conditions.[222] Under strong acidic conditions, PANI can be transformed from EB state into ES state and thus it causes absorption shift from visible to NIR region (about 1100 nm), which is promising for PTT applications.[223] However, the pH required for the transformation of this state is significantly lower than the pH of the tumor microenvironment (pH 5.4-7.0), which severely restricts the clinical application of PANI as a pH-responsive agent in PTT.[224] Therefore, adjusting the pH response ranges of polyaniline is an extremely significant investigation. Some research groups attempted to focus on self-doping effects and increasing the charge transfer rate for adjustments. For example, the introduction of acid groups in the main chain of PANI caused strong absorption in a wide pH range due to the self-doping effect. However, the problem is that the self-doped PANI could only be dispersed in a strong alkaline solution. It is thus not suitable for biological applications. Moreover, the Au@PANI presented a predominant NIR absorption (740 nm) over a pH range of 6.5-8.0 because of the enhanced charge transfer rate.[225] Nevertheless, the introduction of non-biodegradable Au

nanoparticles may cause long-term toxicity, which is a non-negligible problem.[226,227] In order to overcome the obstacles, Tian et al. developed a pH-responsive tumor therapeutic composed of bovine serum albumin (BSA) and PANI to enhance the PTT of the lesions (Fig.4).[228] The BSA-PANI developed is found able to overcome the limitations of low pH protonation and this assembly could convert the EB state to the ES state at pH < 7, accompanied by absorption redshift (from 570 to 800 nm). Both in vivo and in vitro results confirmed that TME could induce the enhancement of the photothermal performance of BSA-PANI. Furthermore, Wang et al. reported a novel core-shell biomaterial PANI formed using polyvinylpyrrolidone (PVP) to modify the surface of PANI nanoparticles for improving water solubility and biocompatibility.[229] PVP-PANI also possesses advanced stability and administrable morphology.

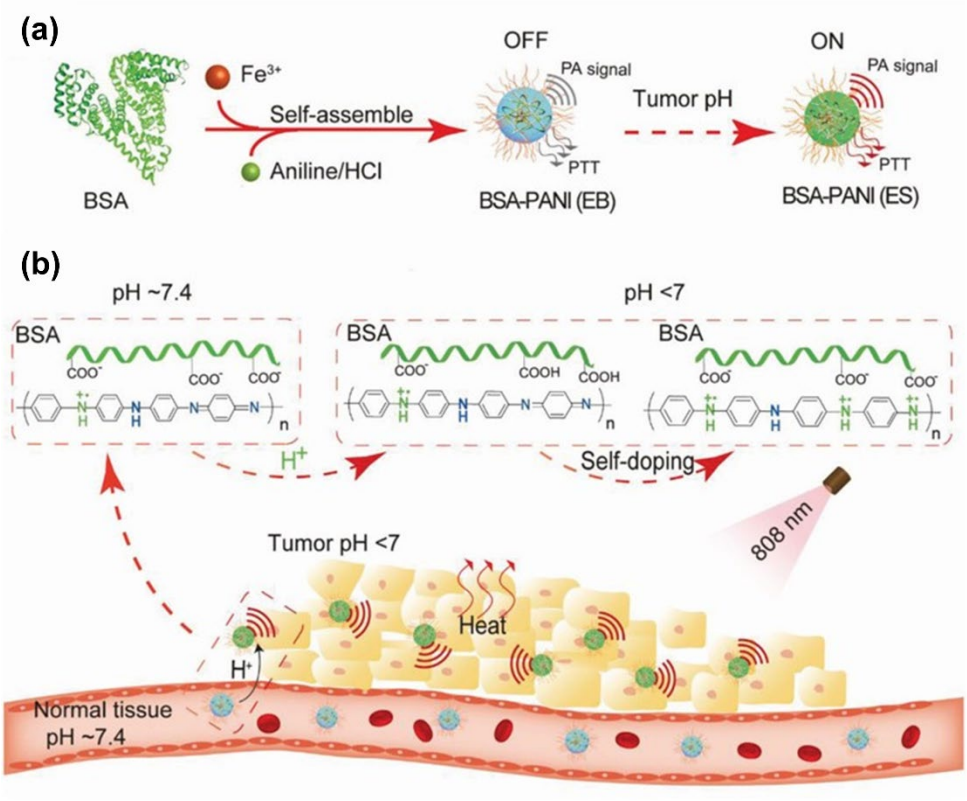


Figure 4. (a) Schematic illustration of the preparation process of tumor pH-responsive BSA-PANI

assemblies. (b) BSA-PANI assemblies for augmented PTT. The potential mechanism is based on intermolecular acid–base reactions between carboxyl groups of BSA and imine moieties of PANI. (Figures (a) and (b) adapted from ref. 228 with permission).

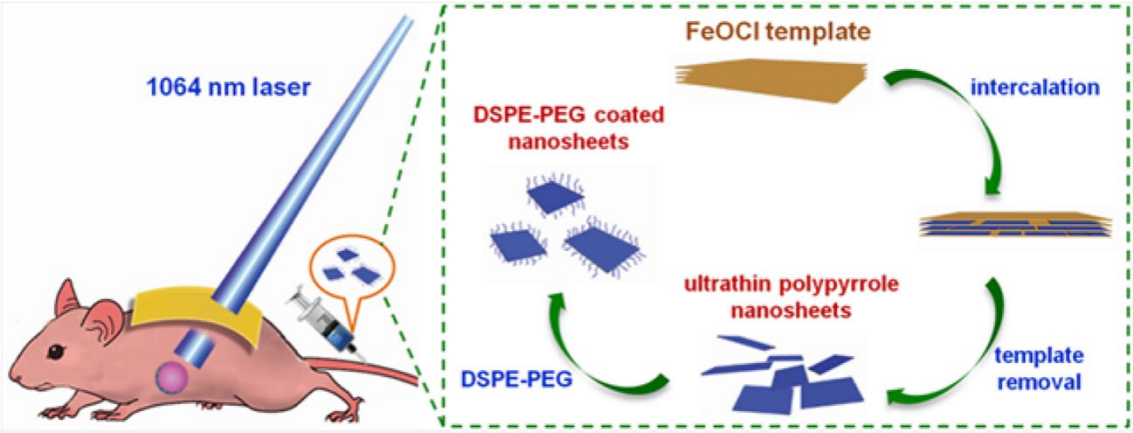


Figure 5. Schematic illustration of ultrathin polypyrrole nanosheets via space-confined synthesis for efficient photothermal therapy in the second near-infrared window.[232] Reproduced from Wang, X.; Ma, Y.; Sheng, X.; Wang, Y.; Xu, H. Ultrathin Polypyrrole Nanosheets Via Space-Confined Synthesis for Efficient Photothermal Therapy in the Second Near-Infrared Window. Nano Lett. 2018, 18, 2217-2225. Copyright 2018 American Chemical Society.

Currently, polypyrrole (PPy) has become a low-cost photothermal therapeutic agent with a great development potential due to its excellent biocompatibility, high photostability, low cytotoxicity and favorable photothermal conversion performance.[230] It is well-known that some spherical Au NPs have a strong SPR effect in the visible region (500-600 nm).[97,98] Nonetheless, without further modification, this SPR effect cannot exist in NIR window. It is thus severely limited the application of these Au

NPs in PTT. In order to adjust the response area of its NIR absorption, the structure of PPy-coated chainlike Au NPs was investigated.[231] Since the PPy-Au complex has larger PCE in the NIR region (650-1000 nm), therefore, it may has a significant effect on the inhibition of tumor growth. In addition, by controlling the doping process, the electronic structure of PPy and its related optical properties could be turned, resulting in the possibility of polarons and bipolar subbands in the band gap of PPy and then producing a strong absorption in the NIR-II zone (1100-2526 nm). For example, Wang et al. reported the preparation of two-dimensional ultra-thin PPy nanosheets through a novel space-constrained synthesis.[232] The PPy nanosheets exhibit distinct broadband absorption with a large extinction coefficient of 27.8 $Lg^{-1}cm^{-1}$ at 1000-1200 nm, which could be used as an effective photothermal agent in the NIR-II window (Fig.5). The distinctive optical feature is attributed to the formation of bipolaron bands in the highly doped PPy nanosheets. Both in vitro and in vivo studies indicated that these ultra-thin PPy nanosheets have ablation ability in the second zone of NIR (1000 -1200 nm). Besides, PEDOT:PSS is a composite product of conjugated polymer (poly (3,4-ethylenedioxythiophene) (PEDOT)), and a negatively charged polymer (poly (4-styrenesulfonate) (PSS)), PEDOT:PSS NPs show strong NIR absorption (830 nm) in aqueous solution. The application of these PEDOT:PSS NPs in the preparation of PTA has also been reported. In 2012, Liu et al. first synthesized PEDOT:PSS NPs via layer-by-layer self-assembly (LBL).[233] PEDOT:PSS NPs show strong physiological stability and long circulation time in vivo. The high accumulation also renders it eliminating lesions completely after 48 h of NIR light irradiation (808 nm). In addition, the small molecular drugs such as DOX and Ce6 can be loaded in PEDOT:PSS via π-π stacking and hydrophilic action.[234] The PEDOT:PSS-PEG NPs after loaded with other drugs are able to use in the combined

treatment of PTT (irradiated with 808 nm) and other tumor therapies to achieve synergistic treatment of lesions.

Polydopamine (PDA) is another polymer NIR absorbing material, which has attracted extensive attention. As an important component of melanin widely distributed in human body, PDA has obvious advantages in biosafety.[235,236] Many studies have shown that PDA may not interfere the activity and proliferation of a variety of mammalian cells, and that may not cause remarkable cytotoxicity even at a very high dose. More importantly, PDA has been proved completely degradable in vivo and has higher safety than other conjugated polymers.[237-239] In terms of their optical properties, PDA has similar light absorption properties to melanin. It has wide band absorption from ultraviolet to visible light. The light absorption could extend to the NIR region.[239] Li et al.[240] explored the feasibility of using PDA as photothermal therapeutic agent (irradiated with 808 nm). The experiments showed that the PCE of PDA nanoparticles reached 38.2%. Moreover, PDA can be functionalized by the regulation of their composition and surface property. Hu et al. adsorbed Fe^{3+} and ICG on the surface of PDA particles,[241] and the absorbance coefficient of PDA-Fe^{3+}-ICG particles in NIR region (800 nm) was improved. At the same time, the surface adsorbed Fe^{3+} ions make the particles exhibiting strong MRI contrast function (longitudinal relaxation R1 = 14 $mm^{-1}s^{-1}$). After injecting PDA-Fe^{3+}-ICG particles into tumor bearing mice, the temperature of tumor area can be rapidly increased to 57.6 °C by laser irradiation at lower dose (808 nm, 1 W/cm^2).

Taken together, by comparing with other photothermal nanomaterials, the polymer-based nanomaterials have the advantages of low preparation cost, easy scale regulation, single composition and high optical stability. Moreover, various synthesis strategies can be used to synthesize nanoscale

CPs-based NPs with the functionalized coating for improved PTT effects in cancer treatment. However, some polymers such as PPy are not readily to be biodegrade. Their distribution and metabolic pathways in animals are also required for further study.

(VI) Two-Dimensional Nanomaterials

Two-dimensional (2D) nanomaterials are ultra-thin NPs with one dimension less than 100 nm.[242] Graphene prepared by mechanical stripping[243] is a milestone of 2D nanomaterials development and is a 2D sheet with honeycomb lattice structure,[244] which has a large specific surface area. Although graphene is a carbon-based nanomaterial, it also belongs to classical 2D nanomaterials. In 2011, a new 2D nanomaterial of Ti_3C_2 was discovered and named as MXenes[245], which refers to 2D transition metal carbides, carbides and nitrides. In 2014, black phosphorus (BP) nano flakes, also known as phosphorene, were stripped and found.[246] These 2D nanomaterials show the features of large specific surface area and long in vivo residence time. In recent years, 2D nanomaterials have been applied to PTT because of the plasma effect of NIR irradiation, which is conducive to the conversion of light energy into thermal energy. Compared with other class of nanomaterials, 2D nanomaterials usually possess two special characteristics: (i) The optical property of 2D nanomaterials can be adjusted by changing the number of layers or integrating with other plasma metals; (ii) After the surface modification, the 2D nano materials with large surface area can carry target molecules to achieve the synergistic treatment of tumors.[247-249]

Among many 2D nanomaterials reported, MXenes have attracted much attention because of their good medicinal properties and biocompatibility.[250,251] 2D MXenes also have unique planar nanostructures that make them have strong optical absorption and PCE in the NIR region. Moreover,

the high specific surface area of 2D MXenes can effectively load chemotherapeutic drugs and thus it could be is an efficient drug carrier.[250,252,253] Liu et al. prepared a Ti_3C_2 based MXene nanosheet added with Al and the loading rate of DOX is able to reach 84.2%.[254] Therefore, 2D MXenes may have great application potential in PTT. For example, based on zirconium carbide (ZrC) nanosheets can efficiently ablate tumors through the light and heat generated locally under NIR irradiation (1064 nm).[255] However, tissue absorption and laser scattering have a large negative impact on the PCE of 2D mxene for tumor thermal ablation. Compared with the commonly used NIR, NIR II has higher penetration depth and better maximum allowable irradiation dose, which are the outstanding advantages in phototherapy. Lin et al. developed the NIR II responsive MXenes photothermal nanomaterials,[256] which showed a major breakthrough in the construction of ultra-thin 2D Mo_2C MXenes and realizing an efficient photothermal ablation of tumors in response to NIR. Liu et al. used polyethylene glycol functionalized MoS_2 nano tablets as a multifunctional drug delivery system that was demonstrated for the first time to show high drug loading (about 239% for DOX).[257] This system acquires the advantage of the strong NIR absorption character of MoS_2. In addition, the combination of photothermal and chemotherapy for cancer treatment was realized in vivo and an excellent synergistic antitumor effect was achieved. In addition, Cai et al. used bovine serum albumin template gadolinium oxide (BSA-Gd_2O_3) nanoparticles as stripping agent and magnetic resonance imaging (MRI) T1 contrast agent to realize the stripping and in-situ functionalization of single-layer MoS_2. On this basis, the tumor targeting ligand HA was loaded on this nanosystem, and the tumor was thermally ablated under 808 nm laser irradiation.[258]

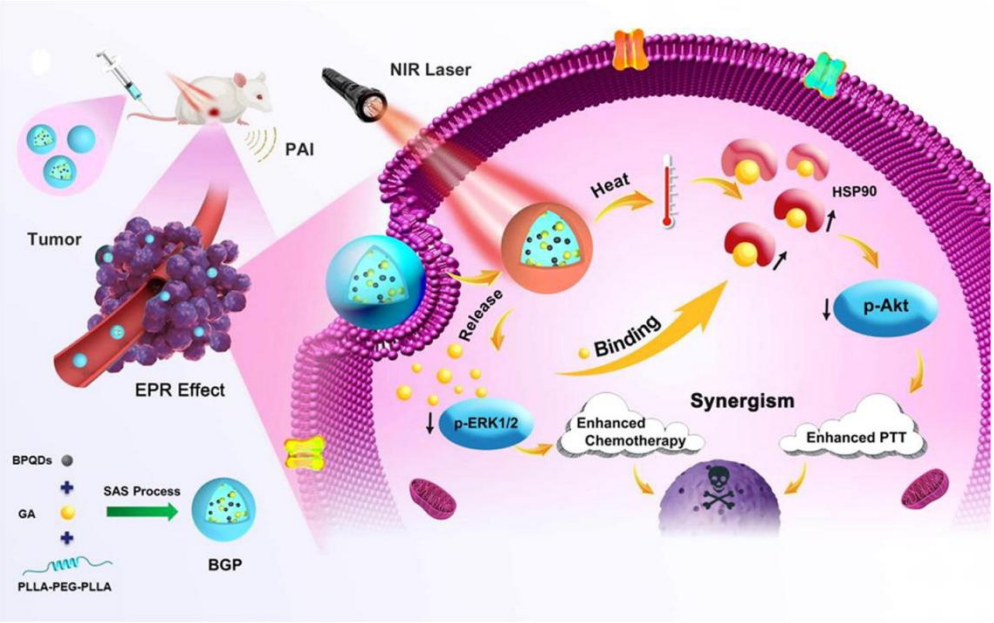


Figure 6. An illustration of different mechanisms of synergistic chemo-photothermal therapy of BPQDs (Figure adapted from ref. 267 with permission).

Black phosphorus (BP) is also one of the most popular 2D nanomaterials that display prominent physicochemical properties, biocompatibility and biodegradability, therefore, it is widely utilized in photothermal therapy development.[259-261] BP has a bilayer structure in the zigzag orientation. One phosphorous atom is connected to three adjacent phosphorus on two unequal planes.[262] BP also exhibits a large extinction coefficient (14.8 $Lg^{-1}cm^{-1}$) in the NIR region (at 808 nm), which offers good photothermal properties.[262-266] Chen et al. fabricated a black poly(L-lactide)-poly(ethylene glycol)-poly(L-lactide) triblock copolymer (PLLA-PEG-PLLA)[267] and then the (PLLA-PEG-PLLA)-based nanocomposites were co-loaded with BP quantum dots (BPQDs) and gambogic acid (GA) by employing supercritical carbon dioxide (SC-CO_2) technology to achieve imaging-guided PTT (Fig.6). The results show that BPQD displays NIR hyperthermia effects. The encapsulation of BPQDs

in polymers could significantly promote the early and late apoptosis. In addition, BP can be degraded into non-toxic intermediates such as phosphate and phosphate after the reaction with water and oxygen.[262,268] Cao et al. designed a BP-based hydrogel to achieve adjustable drug release by controlling the external laser stimulation.[269] Moreover, the entire hydrogel system was innoxious and degraded thoroughly in vivo.

In summary, it was found that the useful nanomaterials identified currently for PTT mainly included noble metals, carbon-based materials, semiconductors, conducting polymers and 2D nanomaterials (Table 1). The diversity of these functionalized materials renders them a great potential to be utilized for tailor-made photothermal composites to improve further PTT performance.

Table 1. Summary of photophysical properties and applications of various photothermal nanomaterials

Nanomaterials	Size (nm)	Types	Wavelength (nm)	Advantages	Disadvantages	Application	Ref.
Au-based nanoparticles	10-50	Nanospheres	400-600	Adjustable physiochemical and biochemical properties; Carrying cargoes and good biocompatibility	Poor biodegradability and light stability; Accurate control of size	Cervical carcinoma	102,103
		Nanoshells	815			Breast epithelial carcinoma	104,105
		Nanorods	804				106,107
		Nanocages	810			Breast cancer	108,109
		Nanoclusters	704			Oral epithelial cell carcinoma	110
Carbon-based nanomaterials	50-500	Chiral	808	Excellent photothermal stability; Carrying cargoes	Poor biodegradability and poor dispersion in water; Difficult to remove from the body	Ssquamous cell carcinoma	111
		Nanotubes	808			Breast cancer	129
		Nanodiamond	535			Cervical carcinoma	133
		Graphene	300-1000			Alveolar adenocarcinoma	130
		Graphene Oxides	808			Glioblastoma	131
		Carbon Dots	808			Cervical carcinoma	132
Semiconductor-based nanomaterials	10-800	Copper Chalcogenides	1064	Excellent photothermal stability and low cytotoxicity;	Poor biodegradability; Need to do surface modification	Cervical carcinoma	170,171
		Semiconductor Polymer	808	Superb optical properties; Large absorption coefficient; High photostability;	Unbeknown biodegradation behaviors; Poor aqueous solubility	Glioblastoma	195
Conducting polymer-based nanomaterials	40-150	PANI	808	Low preparation cost, easy scale regulation, single composition and high optical stability	Poor biodegradability; Unbeknown distribution and metabolic pathways	Epidermoid carcinoma	215-217
		PPy	808			Breast cancer	207, 230
		PEDOT:PSS	808				233, 234
		PDA	808			Glioma	235, 236
Two-Dimensional Nanomaterials	20-500	MXene	808	Good medicinal properties and biocompatibility; High PCE and efficient drug carrier	Need to do surface modification	Breast cancer	250-252
		Black Phosphorus	808				259-261

The integration of PTT with other technology to develop advanced synergic therapy

The traditional monotherapy may not be able to achieve a complete treatment for elimination of tumor cells. PTT is also no exception. Even though PTT has a prodigious therapeutic effect, it also has certain stints. For example, the insufficient depth of light penetrating the tissue leads to incomplete elimination of cancer cells, especially in the treatment of tumor cells at the edge. This may cause tumor recurrence and spreading.[32] However, the combination of PTT and other therapies most likely improve the overall therapeutic effects. The treatment consequent of combination therapy is not an ordinary summation of each treatment effect but is a synergistic effect. Many studies have shown that PTT promotes the cellular uptake of the nanodrug and followed triggers the irradiation region to facilitate the drug release of the nanomaterials, which is beneficial to the treatment involved in various drug delivery.[270-273] Moreover, PTT can increase oxygen perfusion and alter the tumor hypoxic microenvironment, which is good for the treatment of oxygen dependence such as PDT or radiotherapy.[274] Furthermore, thanks to the release of tumor-specific antigens, it probably stimulates the combination of PTT and immunotherapy.[275] Numerous studies indicate that PTT can directly kill cancer cells or enhance other treatments through a series of activities.[270-273] Therefore, PTT combined with other therapies may be able to improve the cancer treatment performance. At present, there are only few PTT combined therapeutic technologies reported.

(I) Synergic therapy with photothermal-chemotherapy technology

Chemotherapy is one of the main treatment strategies for malignant tumors. The commonly used chemotherapy drugs can inhibit the diffusion of tumor cells by interfering with the anabolism of nucleic acids, inhibiting mitosis and protein synthesis, and obstructing with deoxyribonucleic acid

(DNA) replication.[276] However, these chemotherapeutic drugs have many deficiencies, such as rapid clearance in the body, non-specific distribution and multiple drug resistance (MDR) of the tumor. As mentioned above, as a non-invasive tumor treatment tactics, PTT possesses the characteristics of high selectivity, non-toxicity, and easy operation.[277] Due to the problems of tumor heterogeneity and low efficiency of deep tissue PCE, the outcome of applying PTT alone to eradicate the tumor is thus not perfect. Some recent studies have shown that PTT may upregulate HSP in tumor cells and that may increase the heat stress tolerance of cancer cells, reduce the thermal effect and cause in insufficient heat to kill tumor cells.[278,279] Therefore, it may be more promising to combine multiple drugs to construct a multi-mode collaborative treatment system to improve the effectiveness and reduce the toxicity of chemotherapy drugs in cancer therapy.

During the PTT process, due to the thermal conversion effect of PTA, the local tissues temperature could exceed 40 °C and that temperature promotes the denaturation of tumor cell proteins. The heat generated strengthens the rate of crosslinking and chemical reactions between the drug and tumor cell DNA, depresses the activity of DNA repair enzymes in lesions after chemotherapy, disrupts DNA synthesis and repair in cells, and leads to cancer cell death.[280] In addition, the elevated temperature produced by PTT not only boosts the concentration of nano-medicines in tumor tissues through the EPR effect, heightens the permeability of cell membranes, and accelerates the uptake of nanometer preparations by cancer cells to augment the accumulation of chemotherapeutic drugs in lesions, but also improves the chemotherapeutics drugs solubility in TME and accelerates their thermal motion to further accelerate the release of drugs to enhance the efficiency of chemotherapy.[37-39]

Zhang et al. designed a graphene oxide nanosystem containing a prodrug hyaluronic acid-methotrexate conjugate to achieve the combination of PTT and chemotherapy.[281] The results showed that the co-administration group offered the strongest inhibitory effect on HeLa cells proliferation after irradiation with a 808 nm laser. The combined treatment also provided an efficient and synergistic inhibitory effect on the growth of Balb/c nude mouse tumor tissues modeled by HeLa tumor inoculation. Liu et al. developed a multifunctional calcium phosphate nano-formulation (ICG-DOX/DNA@CaP).[282] This nanocomposite uses DNA as a DOX carrier, which was conducive in loading DOX into the CaP matrix to reduce DOX leakage (Fig.7). After irradiating with a NIR laser (808 nm, 1.5W/cm^2) for 5 min, DOX was explosively released in MCF-7 cells and the high concentrations of DOX entered the nucleus in large quantities to enhance cytotoxicity. The effect may possibly attribute to the high temperature generated by the PTA that destroys the biological integrity of the membrane structure. Thus, it enhances the drug permeability and increases the high accumulation of chemotherapy drugs in the nucleus of cells.

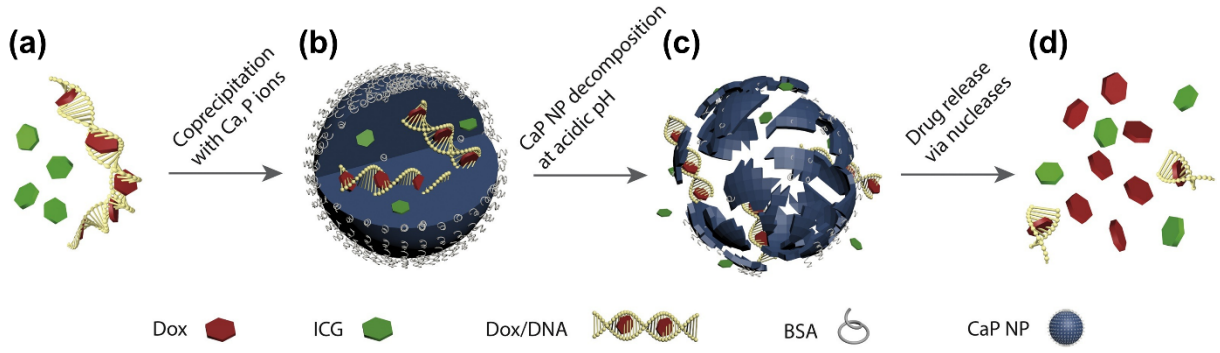


Figure 7. The schematic diagram briefly illuminates the preparation of ICG-DOX/DNA@CaP nanocomposites and the delivery, and release mechanism of loaded therapeutic agents. (a) Dox/DNA and ICG. (b) The nanocomposite (ICG-Dox/DNA@CaP) was an elegant co-precipitate of Dox/DNA complexes and ICG molecules in the CaP matrix with bovine serum albumin encapsulated both inside and on the surface (for colloidal stability). (c) CaP NP decomposition at acidic pH. (d) Drug release

via nucleases.

(Figures adapted from ref. 282 with permission).

In addition, the high heat energy generated by PTT can effectively alter the activity of chemotherapeutic drugs by changing the metabolic methods and pathways of drugs in the body. Ultimately, it may improve the susceptibility of cancer cells to chemotherapeutic drugs. Some chemotherapeutic drugs hardly reveal cytotoxicity at 37 °C. When under the action of heat, the transform the chemical structure of the chemotherapeutic drugs produces toxic effects on the cells. For example, benzaldehyde has almost no antitumor effect at 37 °C, yet, when it is heated at 42 or 43 °C, it will hinder the activity of biofilm and the permeability of lactic acid. In addition, it further decreases the pH value of cancer cells, thereby improving the antitumor activity of benzaldehyde.[283] Surprisingly, the local high temperature engendered by PTT may directly enhance the cytotoxicity of some commonly used chemotherapy drugs. More specifically, when chemotherapy drugs such as cyclophosphamide, cisplatin, carboplatin, carmustine combined with PTT act on lesions, as the local tumor temperature increases from 37 to 40 °C, the cytotoxicity of these drugs is linearly enhanced.[283] The study reported by Urano et al. further indicated that when the local temperature increased to 40.5 - 43.0 °C, the toxicity of chemotherapy drugs could be enhanced to the greatest extent.[284] Furthermore, the elevated temperature can also strengthen the body's innate immunity and acquired immunologic function.

PTT combined with chemotherapy drugs can alleviate the immune suppression state caused by chemotherapy drugs and improve the body's anti-tumor ability. Some studies have found that the immunologic function of patients with malignant tumors is low-graded, partly because tumor cells

secrete soluble immunosuppressive factors,[285] such as IL-10, TGF-b and BAY 11-7082, which inhibit immune cells from exerting normal functions. Eventually, it causes the collapse of the immune system. Li et al. constructed a biomimetic albumin-modified gold nanorod combined with photothermal-chemotherapy for the macrophage polarization regulation.[286] By irradiating with NIR laser (808 nm), the photothermal-chemotherapy could inhibit tumor tissues M1 type macrophages transforming into M2 macrophages, prompt M1 macrophages to secrete anti-tumor cytokines or directly "engulf" tumor cells, down-regulate the number of M2 tumor-associated macrophages in lesions, and produce more anti-tumor cytokines. Ultimately, the cooperative chemotherapy promotes tumor cells apoptosis.

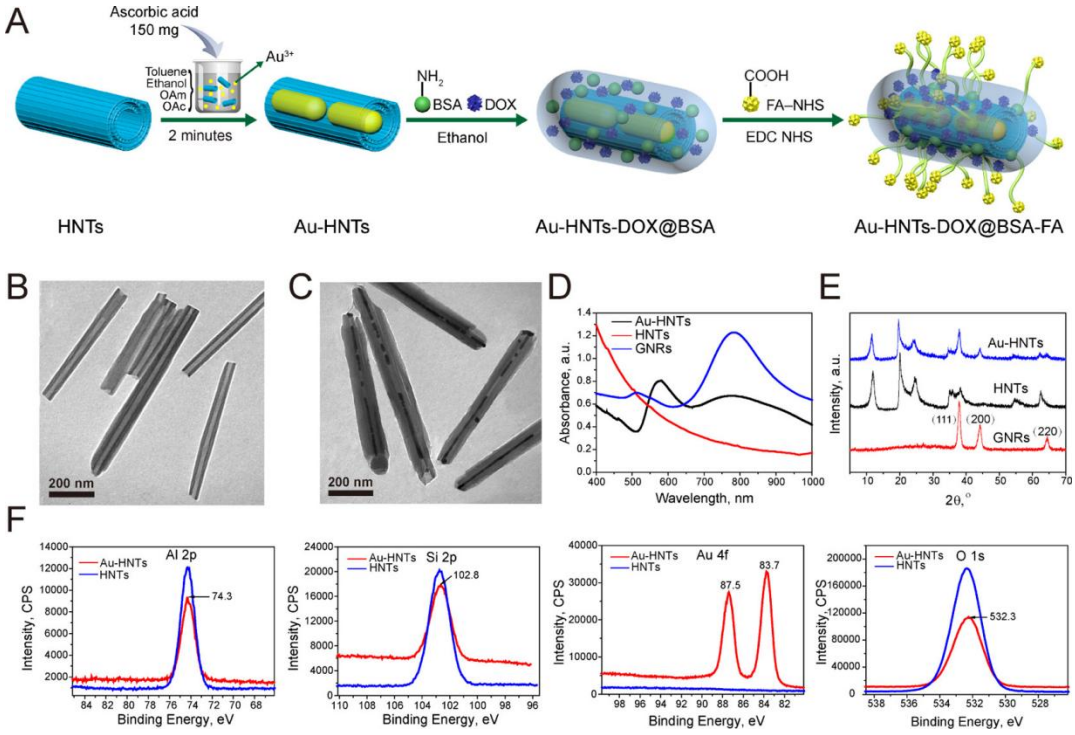


Figure 8. (A) Synthesis process of Au-HNT-DOX@BSA-FA. TEM images of (B) HNTs and (C) Au-HNTs. (D) UV−vis absorption spectra of different samples. (E) XRD patterns of different samples. (F) High-resolution scanning of Al, Si, Au, and O elements of HNTs and Au-HNTs.[288]

Reproduced from Zhang, J.; Luo, X.; Wu, Y. P.; Wu, F.; Li, Y. F.; He, R. R.; Liu, M. Rod in Tube: a Novel Nanoplatform for Highly Effective Chemo-Photothermal Combination Therapy Toward Breast Cancer. ACS Appl. Mater. Interfaces 2019, 11, 3690-3703. Copyright 2019 American Chemical Society.

MDR is one of the critical reasons for chemotherapy failure. Researchers have found that restraining ATP production and releasing therapeutic drugs through mitochondrial dysfunction caused by hyperthermia may be an effective strategy to surmount MDR. Tu et al. used triazine as a raw material to synthesize pH-triggered nano-graphite flake (NG) with co-loaded DOX.[287] It was further modified with hyperbranched polyglycerolamine ($HPGNH_2$) to couple the mitochondrial-targeted ligand (triphenylphosphine (TPP)) to the surface of the nanomaterial. The hyperthermia under the irradiation of NIR laser disrupted mitochondrial function and inhibited the production of ATP, which in turn bates the expression of multidrug resistance genes and multidrug resistance-related proteins, effectively reversing the tumor MDR to improve chemotherapy effect. Moreover, Zhang et al. loaded GNRs and DOX into the lumen of halloysite nanotubes (HNTs) and conjugated FA with HNTs by the reaction with bovine serum albumin (BSA) (Fig.8).[288] After the nanocomposite was irradiated with an 808 nm laser for 8 min at a power density of $0.8 W/cm^{-2}$, the temperature was increased by 26.8 °C. The functionalized HNTs exhibited a strong chemotherapy effect under laser irradiation due to the laser promoting the release of DOX. The survival rate of the MCF-7 cells treated with Au-HNT-DOX@BSA-FA and irradiated by the laser is only 7.4%.

To summarize briefly for the approach of combining PTT and chemotherapy, it may directly

ablate some cancer cells, accelerate the uptake of oncology drugs by cancer cells, reverse significantly the multi-drug resistance of lesions, reduce the adverse reactions of chemotherapy drugs, and eliminate tumor tissues more efficiently. From a long-term perspective, it can also activate the body's immune system and exert a sustained anti-tumor effect. However, the PTT allied chemotherapy strategy has achieved some success in animals but it encounters many challenges in clinical applications for human. We believe that with continuous improvements and the optimization of PTT and nanotechnology, the combined strategy may play a graver role in cancer treatment.

(II) Synergic therapy with photothermal-photodynamic technology

Both PTT and PDT are treated with photo-induced drugs. PDT reagents can be activated under light irradiation to form singlet oxygen, which is cytotoxic to adjacent cells owing to oxidative stress.[289-291] Moreover, the NIR region of PDT is ideal in terms of penetration,[292-294] similar to PTT. Furthermore, regarding PTT, regardless of the oxygen content, its therapeutic effect is not affected and the modified oxygen perfusion of PTT can amplify the therapeutic effect of PDT. Moreover, it can produce a synergistic effect even in solid tumors with severe hypoxia. Therefore, PTT combined with PDT is an effective tumor therapy. Since the binding of porphyrin PS (Ce6) to GO NPs was first reported by Liu et al. and a good synergistic effect of PTT and PDT was observed.[295] Subsequently, a large number of PTT and PDT nanomaterials have been developed and their therapeutic effects were verified in vitro and in vivo.[296-298]

Nano-systems for PTT-PDT synergistic therapy have also been proposed. Currently, Co_3O_4 as a potential PTT reagent has received extensive attention, such as $CoFe_2O_4$,[299] CoP,[300] CoPt,[301] CoS[302] and $CuCo_2S_4$.[303] The study of Co_3O_4 in the therapeutic application of biomedicine is ongoing

worldwide. Yuan et al. fabricated porous Co_3O_4 nanoplates (pCo_3O_4 NPs) by hydrothermal method and calcination treatment.[304] It was demonstrated that pCo_3O_4 nanoplates are a kind of tumor photothermal agent that may trigger both PTT and PDT by NIR laser irradiation without significant side effects. The pCo_3O_4 NPs are black in appearance and exhibit strong absorbance in NIR region (Fig.9a). By regulating the concentration, the temperature could be increased from 0.8 to 28 °C (Fig.9b). In addition, to irradiate pCo_3O_4 NPs at the concentration of 1 mg/ml, the power density is transformed from 0.4 to 2 W/cm^2 (Fig.9c). The temperature range indicated that the NPs have an excellent photothermal stability (Fig.9d). The PCE was estimated to be 66.9% (Fig.9e), which is better than the commercial photothermal agents (ICG). In addition, the combination of pCo_3O_4 NPs and NIR allows the sample to generate ROS even stored on ice (Fig.9f). Therefore, pCo_3O_4 is a good photothermal reagent with great application potential to integrate PTT and PDT. This excellent photothermal conversion performance makes pCo_3O_4 NPs a photothermal sensor for PA imaging (Fig.9g). The PA signal is linearly enhanced in the presence of pCo_3O_4 NPs. In order to study further the PA imaging effect of pCo_3O_4 NPs in vivo, a tumor-bearing mouse was scanned (Fig.9h). The results showed that the PA signal was significantly enhanced after intratumoral administration. The in vivo MRI performance of pCo_3O_4 NPs was evaluated (Fig.9i). Similar to the PA imaging results, the T2-weighted signal is improved with the increase of pCo_3O_4 NPs concentration. Finally, it was proved that pCo_3O_4 NPs enhanced the T2-weighted signal of tumor in vivo (Fig.9j). These results may confirm that pCo_3O_4 NPs could be a promising multimodal imaging agent.

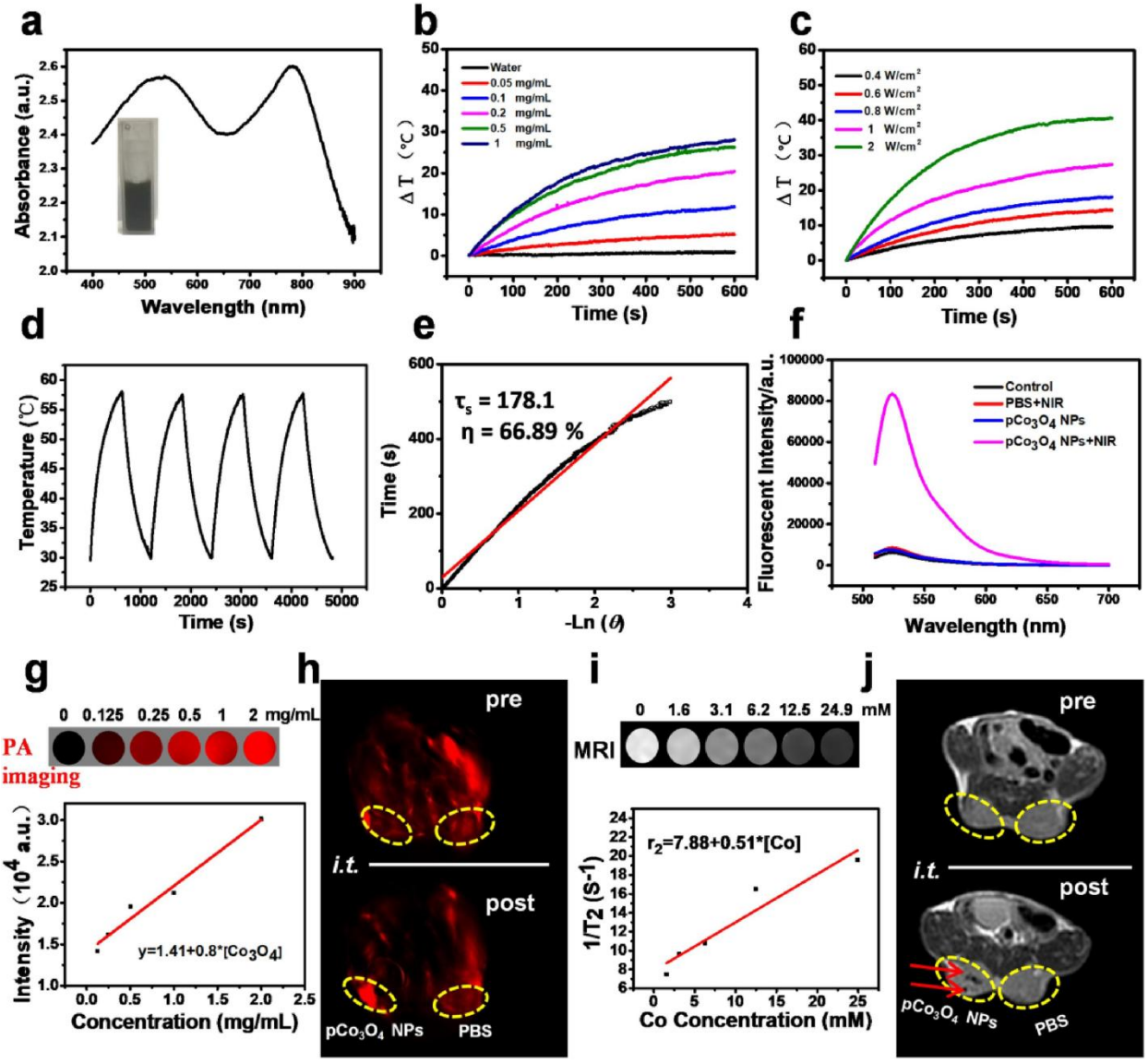


Figure 9. The evaluation of the physical properties of Co_3O_4 NPs. (a) pCo_3O_4 NPs exhibits strong absorbance in the NIR region. The UV–vis–NIR absorbance spectrum of pCo_3O_4 NPs suspension (1 mg/mL) is shown. The inset is a digital photo of pCo_3O_4 NP aqueous suspension. (b) The photothermal conversion of pCo_3O_4 NPs are dependent on their concentrations. The photothermal heating curves of pCo_3O_4 NPs aqueous suspension are shown. (c) pCo_3O_4 NPs display strong dependence on irradiation-energy. The photothermal heating curves of pCo_3O_4 NP aqueous suspension (1 mg/mL) at different power densities (0.4–2 W/cm^2) are shown. (d) pCo_3O_4 NPs have

an excellent photothermal stability. Temperature variation of pCo_3O_4 NP aqueous dispersion (1 mg/mL) over four heating–cooling cycles of continuous irradiation (1 W/cm^2) is shown. (e) The η of pCo_3O_4 NPs is estimated to be about 66.89%. (f) pCo_3O_4 NPs + NIR induced ROS production. Fluorescence spectra of DCFH-DA mixed with PBS or pCo_3O_4 NPs aqueous suspension with or without 808 nm laser irradiation (2 W/cm^2) are shown. (g, h) pCo_3O_4 NPs have an outstanding potential for PA imaging. In vitro PA intensity of different pCo_3O_4 NP concentrations are shown; In vivo PA images of mice before and after intratumoral (i.t) injection with pCo_3O_4 NPs (5 mg/kg) or PBS are shown. (i, j) pCo_3O_4 NPs have an excellent potential for MRI. In vitro T2-weighted MRI using different concentrations of pCo_3O_4 NP is shown; In vivo T2-weighted MRI and signal intensity of mice collected pre- and post intratumoral injection of pCo_3O_4 NPs (5 mg/kg) or PBS are shown. (Figures (a)-(j) adapted from ref. 304 with permission).

In addition, Luo et al. conjugated a scintillator complex and gold nanosensitizer for PTT and X-ray-induced PDT (Fig.10a).[305] Lanthanide complexes can also be conjugated to provide luminescence for PDT effects. The investigation conducted in vitro and in vivo indicated that the nanosystem may offer outstanding dual-modal imaging capability to guide PTT-PDT synergic therapy and inhibit tumor growth under NIR irradiation. Recently, Wang et al. developed a new kind of manganese phthalocyanine ($MnPcE_4$) photosensitizer with strong NIR absorption (Fig.10b).[306] $MnPcE_4$ was applied to modify the pure Bi nanomaterials to obtain intelligent multifunctional nanocomposite materials ($Bi/MnPcE_4$). The Mn^{2+} in the nanocomposite material could catalyze the over-expressed H_2O_2 in the TME to generate oxygen (O_2). It is thus able to overcome the tumor's hypoxia and

improve the efficacy of PDT.[306]

The bimetallic nanoparticles have also attracted great attention due to their synergistic effects and versatility. Recently, Zhang et al. reported a new multi-functional Pd@Au bimetallic nanoplate modified hollow mesoporous MnO_2 nanoplates (Fig.10c),[307] which not only achieve target nuclear NIR-II PTT but also relieve TME hypoxia to enhance PDT. Aiming at the problem of severe hypoxia at the tumor site, Zhang et al. synthesized a natural product, hypocrellin derivative (AETHB),[308] with a singlet oxygen quantum yield of 0.64, indicating a highly efficient photosensitizer. AETHB and human serum albumin were further assembled to form nanoparticles (HSA-AETHB-NPs) with PCE at about 50 % (Fig.10d). The nanoparticle also has favorable water solubility and biocompatibility, pH and light stability, broad absorption (400-750 nm) and NIR emission at 710 nm. In addition, HSA-AETHB nanoparticles could be used for fluorescence and photoacoustic dual-model imaging and are applicable for the combined PDT and PTT therapies of hypoxic solid tumors with high-efficiency.

Despite PTT and PDT can be excited by NIR laser at the same time, there are still some unresolved problems in theory. First, the maximum absorption wavelength of PTT agents and PDT agents in NIR region may be not exactly the same. Single-wavelength NIR light cannot simultaneously induce photothermal and photodynamic effects at the same time, while the broadband NIR light may cause accidental negative influences. The combined application of PTT and PDT is expected to obtain better therapeutic effects; however, since both the NIR-induced and NIR light will be reduced in the process of penetrating tissues, these two therapies are difficult for the drug to target deep tumor lesions. Therefore, in this case, these synergistic therapies may become failed under inefficient NIR radiation.

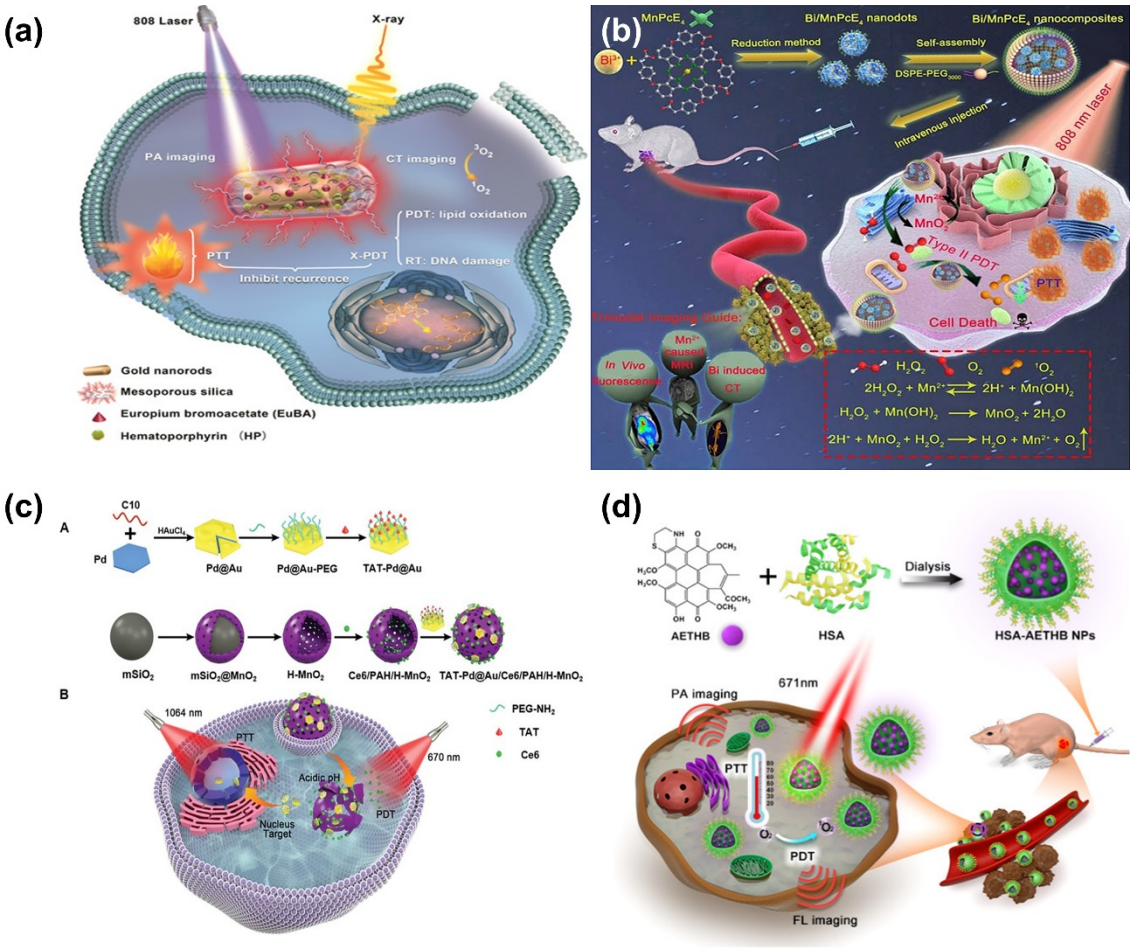


Figure 10. (a) Illustration of conjugation of a Scintillator complex and GNRs for PTT-PDT synergic therapy of Tumors.[305] Reproduced from Luo, L.; Sun, W.; Feng, Y.; Qin, R.; Zhang, J.; Ding, D.; Shi, T.; Liu, X.; Chen, X.; Chen, H. Conjugation of a Scintillator Complex and Gold Nanorods for Dual-Modal Image-Guided Photothermal and X-Ray-Induced Photodynamic Therapy of Tumors. ACS Appl. Mater. Interfaces 2020, 12, 12591-12599. Copyright 2020 American Chemical Society. (b) Schematic illustration of the synthesis and antitumor performance of Bi/MnPcE$_4$ nanocomposites upon 808 nm laser irradiation (Figures adapted from ref. 306 with permission). (c) Schematic illustration of preparation procedure of TAT-Pd@Au/Ce$_6$/H-MnO$_2$ for nucleus-targeted photothermal and hypoxia-relieved photodynamic therapy (Figures adapted from ref. 307 with permission). (d)

Schematic illustration of preparation of HSA-AETHB NPs and PTT-PDT synergic therapy of tumors.[308] Reproduced from Zhang, C.; Wu, J.; Liu, W.; Zheng, X.; Wang, P. Natural-Origin Hypocrellin-HSA Assembly for Highly Efficient NIR Light-Responsive Phototheranostics Against Hypoxic Tumors. ACS Appl. Mater. Interfaces 2019, 11, 44989-44998. Copyright 2019 American Chemical Society.

(III) Synergic therapy wi**th photothermal-gene therapy technology**

Gene therapy (GT) may down-regulate or replace mutant genes with plasmid DNA, or weaken the expression of certain proteins through RNA interference.[309] In cancer therapy, GT can trigger apoptosis of tumor cells, down-regulate the expression of heat shock proteins (HSPs) that preserve cells from light and heat, or up-regulate cytotoxic immune cytokines. GT combined with PTT can employ low-intensity lasers to achieve excellent therapeutic effects. In addition, DNA or RNA is hard to be internalized by cells and is severely degraded by enzymes in the body. The delivery of DNA or RNA through PTA can increase cell uptake and in vivo stability.[310-314] It is also reported that PTT can induce endoplasmic escape of gene delivery vectors and promote the release of genes in the cytoplasm.[315] Therefore, the combination of PTT and GT may obtain a desirable effect of synergistic therapy.[316,317]

Wang et al. developed a nanosystem that is constructed with the hybrid mesoporous polydopamine nanoparticles (MPDA).[318] The particle size is less than 100 nm and PCE of MPDA is 37% (Fig.11a). Through the Michael addition reaction of PDA, the surface of the particles can be embellished with tertiary amine to achieve high siRNA loading (10 wt%). In addition, a calcium

phosphate (CaP) coating was successfully constructed on the cationic nanoparticles through bio-mineralization to prevent the premature release of siRNA. Since the lysosomal membrane has sufficient permeability, high lysosomal escape efficiency is achievable. Therefore, siRNA could be delivered enough through cytoplasm to achieve high gene silencing efficiency. When survivin (an inhibitor of apoptosis protein) was effectively knocked out and combined with a subsequent photothermal ablation, the efficacy of in vitro and in vivo observation was significantly higher than that of monotherapy. In addition, Feng et al. demonstrated that the photothermal agent MnPDA for PTT could also be used as an effective carrier for DNA enzyme transmission and an autogenous source of DNA enzyme cofactors that catalyze mRNA cleavage, and thus realizing the synergistic therapy of PTT and gene therapy (Fig.11b).[319] This nanosystem is able to protect the deoxyribozyme from being degraded, and improves the cell absorption efficiency. In the presence of intracellular glutathione, nanoparticles could generate free Mn^{2+} in situ as a cofactor of DNAzyme; thereby, it effectively triggers the catalytic cleavage of mRNA to achieve gene silencing.

Reducing PTT dose can lessen accidental injury to healthy tissues in the irradiated area and the patient discomfort caused by heat exposure can be minimized. However, applying low dose may reduce the efficiency of PTT in the treatment of HSPs, which requires a strong laser power density to surmount thermal resistance. To solve this bottleneck and to achieve the purpose of inhibiting the heat shock response, siRNA is used to block the expression of HSPs such as HSP70 and BAG3.[312,320] Liu et al. designed a multifunctional Prussian blue (PB) nano-diagnostic platform and loaded with the therapeutic plasmid DNA (HSP70-p53-GFP).[321] A NIR laser is applied to trigger the temperature-controlled GT-PTT co-therapy (Fig.11c). Based on the distinct structure of the PB nanocube, the

nanoparticles have good photothermal characteristics and significant tumor contrast in T_1/T_2-weighted magnetic resonance imaging. Moreover, it could stimulate the HSP70 promoter and facilitate tumor suppressor p53-dependent apoptosis under mild NIR laser irradiation (about 41 °C), while strong NIR laser irradiation (about 50 °C) could induce PA to cause cells disorders and necrosis.

In the treatment of tumors, accurate in situ demarcation of tumor margins has always been an important challenge. Yan et al. discovered a strategy of spherical nucleic acid technology.[322] By transforming and amplifying the pathophysiological redox signal in the tumor microenvironment, the tumor edge can be delineated in situ. The technology involves the design of gold nanostar (AuNS)-based nanoflares (AuNS-ASON) and then the material was coated with a dense disulfide bridged insertion layer and the cyanine dye-labeled antisense oligonucleotides (ASON) that targeted survivin mRNA (Fig.11d). AuNS-ASON could quickly distinguish tumor cells by activated fluorescence signals within 2 h, which realizes the cooperative ablation of gene/photothermal tumor cells under NIR laser irradiation. Interestingly, based on the AuNS-ASON technology, the high precision and high-spatial resolution (< 100 μm) tumor edge depiction could be obtained in situ to provide intraoperative guidance for tumor resection. The examples demonstrated that GT-induced apoptosis combined with PTT hyperthermia could make overall therapeutic effects better.

Despite GT combined with PTT is promising for the next generation of therapeutics, it has not been studied clinically. In addition, several critical limitations have to be addressed before clinical applications become possible. The active PAs applied in GT-PTT treatment are usually composed of inorganic materials. This may imply that bioavailability of PAs is one of the major bottlenecks. Moreover, large-sized PAs are beneficial to promote passive targeting and high photothermal effects

but they may cause long-term toxicity. Another bottleneck is the biocompatibility of gene delivery agents. The cytotoxic cationic and non-biodegradable polymers commonly are used in gene delivery, which is a potential safety problem that cannot be ignored in the combination therapy of GT and PTT.

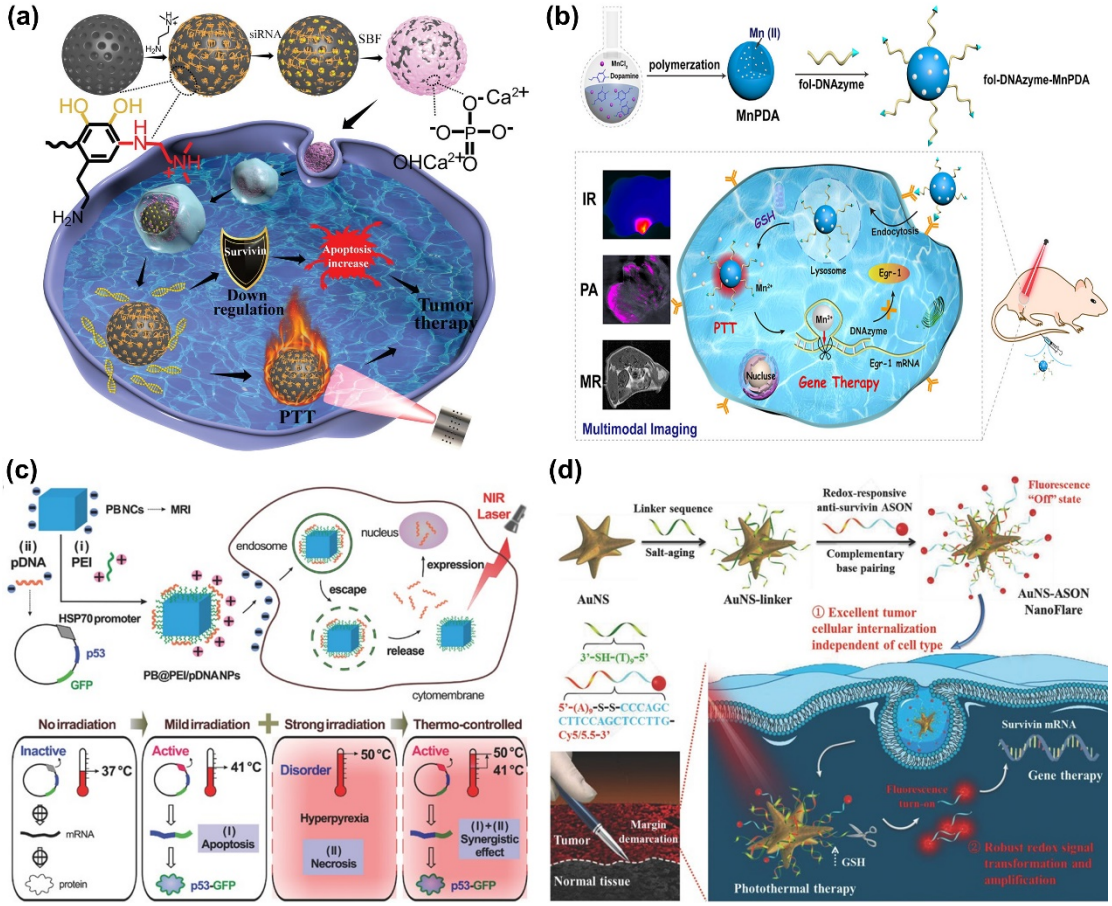


Figure 11. (a) Schematic illustration on the preparation of hybrid mesoporous nanoparticles (MPDA) integrating functions of PTCA, biomimetic wet-adhesion, and biomineralization encapsulation for combined photothermal and gene therapy (Figures adapted from ref. 318 with permission). (b) Illustration of fol-DNAzyme-MnPDA nanoplatform as a versatile vehicle for multimodal imaging-guided therapy.[319] Reproduced from Feng, J.; Xu, Z.; Liu, F.; Zhao, Y.; Yu, W.; Pan, M.; Wang, F.; Liu, X. Versatile Catalytic Deoxyribozyme Vehicles for Multimodal Imaging-Guided Efficient Gene Regulation and Photothermal Therapy. ACS Nano 2018, 12, 12888-12901. Copyright 2018 American

Chemical Society. (c) Illustration of the human HSP70 promoter-based Prussian blue nanotheranostic platform for thermo-controlled synergistic GT/PTT (Figures adapted from ref. 321 with permission). (d) Conceptual illustration of the AuNS-ASON NanoFlare-based strategy for in situ tumor margin demarcation and neoadjuvant gene/photo-thermal therapy (Figures adapted from ref. 322 with permission).

(IV) Synergic therapy with photothermal-immunotherapy technology

Immunotherapy is derived from patient's own immune system and is expected to be a safer and effective treatment similar to PTT. Compared with radiotherapy and chemotherapy, immunotherapy does not require severe external stimulation because it depends on the immune system of patient.[323,324] For example, cancer cells reduce the stimulation of T cells to suppress the immune system.[325,326] Therefore, the patient's immune system is not able to carry out an effective defense response. The purpose of immunotherapy is to provide vaccines or adjuvants and induce immune anti-cancer response.

Tumor immunotherapy is a method that utilizes the host immune system to struggle with cancer,[327] in which the induction of tumor antigen-specific adaptive immune response is the key to tumor immunotherapy.[328,329] When a variety of immune cells including dendritic cells (DC) and T cells infiltrate the lesions, the activation of this antigen-specific immune response is mostly suppressed due to the immunosuppressive effect of the TME.[330,331] Since cancer cells in the tumor site release cancer antigens, to activate tumor-infiltrating immune cells is a reasonable mean to trigger antigen-specific immune responses in tumor therapy. Ong et al. proposed that mesoporous silica NPs

(Au@XL-MSNs) modified with Au NPs deliver CpG-ODNs to lesions to stimulate DCs infiltrating tumors and induce antigen-specific adaptive immune responses (Fig.12).[332] Compared with the soluble CpG-ODNs modified with Au@XL-MSNs, bone marrow-derived dendritic cells (BMDCs) can be internalized effectively. BMDCs can also increase the expression of costimulatory molecules and enhance the secretion of pro-inflammatory cytokines. Moreover, by inducing the PTT based on assembled AuNPs on XL-MSNs, a cancer antigen that could be processed by tumor-infiltrating DC can be generated at the tumor site, and thus enhancing the tumor immunotherapy effectiveness.

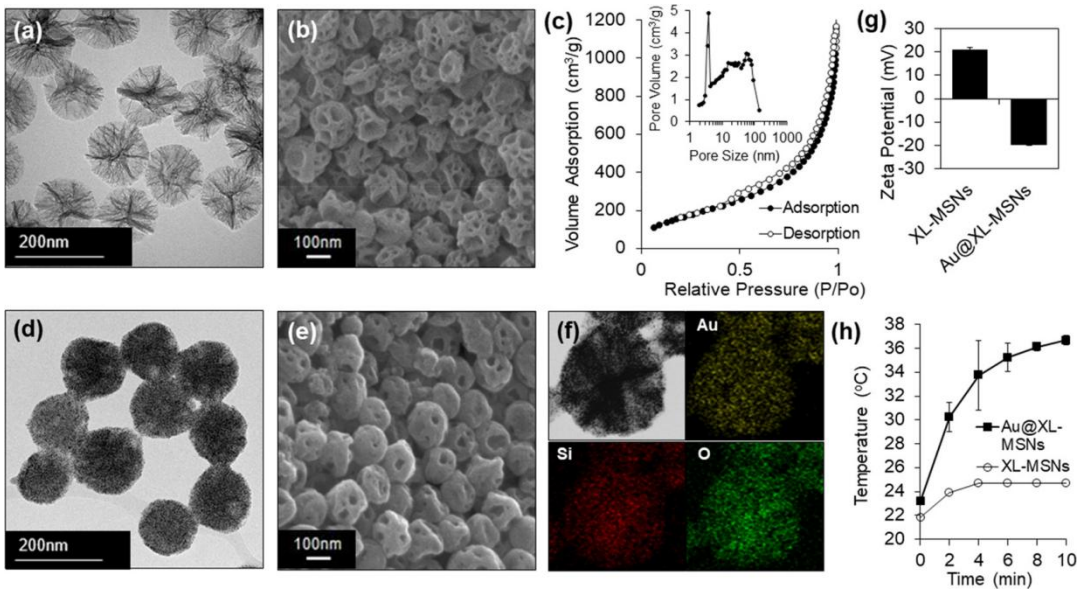


Figure 12. Mesoporous silica nanoparticles (XL-MSNs) and gold nanoparticle decorated mesoporous silica nanoparticles (Au@XL-MSNs). TEM images of (a) XL-MSNs and (d) Au@XL-MSNs. SEM images of (b) XL-MSNs and (e) Au@XL-MSNs. (c) N2sorption analysis of XL-MSNs. (f) Energy-dispersive X-ray spectroscopy (EDS) of Au@XL-MSNs. (g) ζ potential of XL-MSNs and Au@XL-MSNs dispersed in PBS. (h) Photothermal conversion of XL-MSNs and Au@XL-MSNs.[332] Reproduced from Ong, C.; Cha, B. G.; Geun, B. Mesoporous Silica Nanoparticles Doped with Gold

Nanoparticles for Combined Cancer Immunotherapy and Photothermal Therapy. ACS Appl. Energy Mater. 2019, 2, 3630-3638. Copyright 2019 American Chemical Society.

Most cancer vaccines under development are related to defined peptide/protein antigens rather than all potential antigens isolated from whole tumor cells and these cancer vaccines can generate a powerful anti-tumor immune memory.[333-335] Chen et al. designed an immunomodulator (R848) loaded nanoparticle system (R848@NPs),[336] which could absorb NIR laser (808 nm) to produce low-temperature hyperthermia and then it can be cooperated with the loaded R848 to produce a powerful anti-tumor memory immunity (Fig.13a). R848@NPs could be internalized by dendritic cells to mature and followed to regulate their anti-tumor immune response. Zhang et al. reported a PTA with a 2D structure formed by the coordination of tetrahydroxyanthraquinone with Mn^{2+} ions for immunotherapy of hepatocellular carcinoma (HCC) (Fig.13b).[337] In addition, the engineered NK cells with HCC-specific targeting TLS11a-aptamer modification were constructed to eliminate specifically the tumor cells that may remain after PTT and thus improving the PTT therapeutic effectiveness. The combination of A-NK cells with anti-heat tolerance could potentially develop an effective strategy that enhances the immunity of solid tumors and strengthens the efficiency of PTT. This treatment tactic is worthy to be highlighted and developed further.

Recently, Deng et al. explored NPs extracted from cuttlefish ink with anti-tumor effects.[338] These CINPs are spherical with good dispersion ability and rich in melanin and containing a variety of amino acids and monosaccharides. By activating the mitogen-activated protein kinase (MAPK) signaling pathway, CINPs could reprogram tumor-associated macrophages (TAM) from an

immunosuppressive M2-like phenotype to an anti-tumor M1-like phenotype. In addition, CINPs are able to increase the proportion of M1 macrophages and promote the recruitment of cytotoxic T lymphocytes (CTLs) to tumors, thereby reducing the primary tumor growth and lung metastasis (Fig.13c). Combined with PTT, CINPs could almost completely inhibit tumor growth by stimulating a more active immune response.

Despite the combination of PTT and immunotherapy has achieved significant effects in the therapy of cancer, even against the advanced/metastatic cancers, there is still no clear description of the immune mechanism involved in this combination therapy. If we could understand more about the process of laser immunotherapy and identify which immune cells participated, what kind of immune response occurred, what roles of these changes have been taken place, it may provide a great breakthrough in the development of laser immunotherapy.

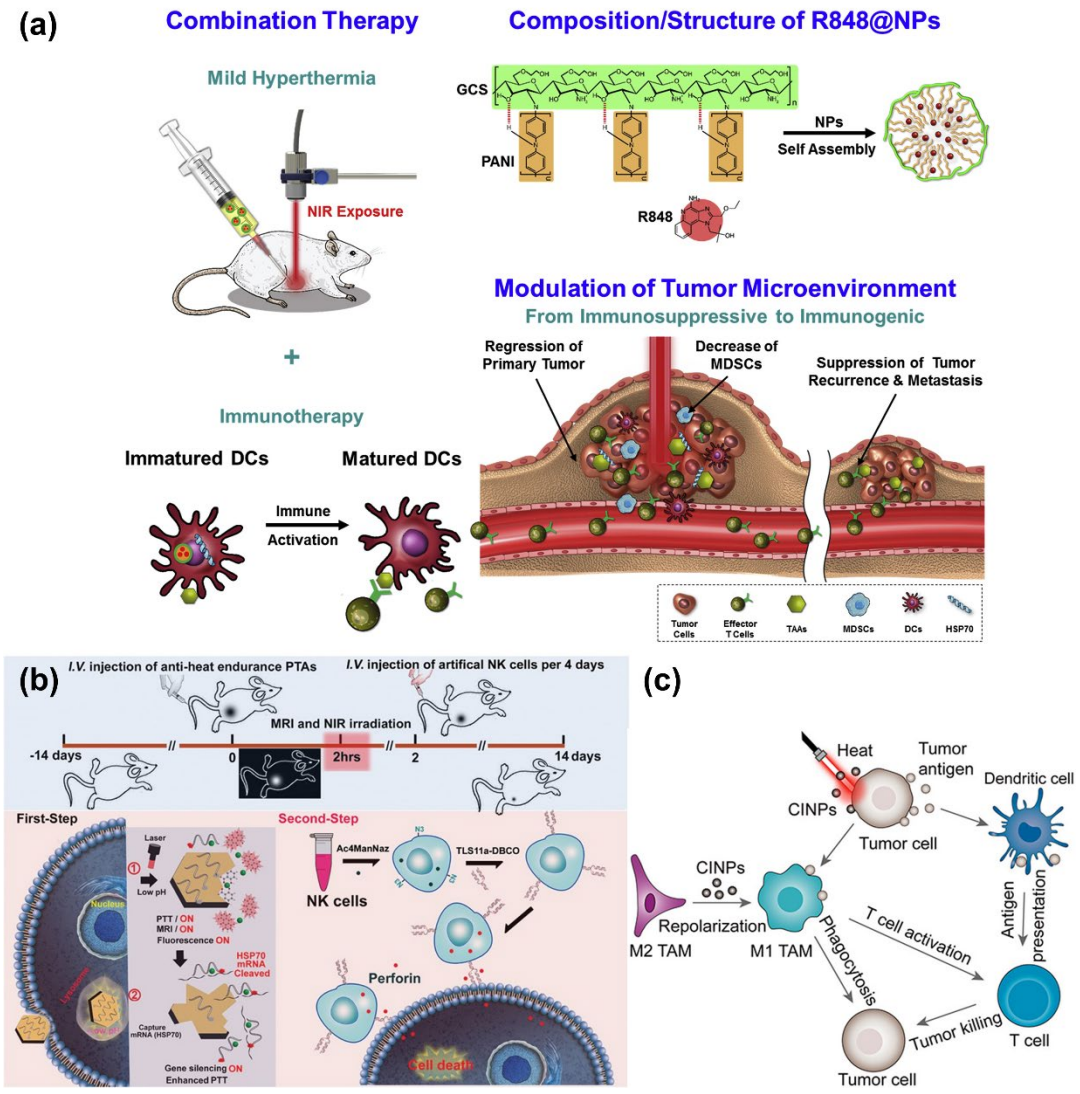


Figure 13. (a) Composition/structure of R848@NPs and mechanisms by which they activate immune cells in tumor microenvironment (Figures adapted from ref. 336 with permission). (b) Schematic illustration of artificial engineered NK cells combined with antiheat endurance strategy for improving the therapeutic efficiency of PTT. A simple strategy to engineer NK cells by aptamers has been developed, and it has been further combined with antiheat endurance of DNAzyme to act as powerful strategy for immuno-enhancing the therapeutic efficiency of T1-MRI-guided PTT. After 808 nm NIR laser irradiation, the DNAzyme@Mn-CONASHs with effective photothermal conversion ability

could damage tumors and subsequently release Mn^{2+} by tumor acidic-cleaving the coordination bonds between Mn^{2+} and THAQ, serving as cofactors to DNAzyme for HSP70 gene silencing to overcome heat resistance of tumor cells during PTT. Finally, the TLS11a aptamer decorated artificial NK cells could actively target and effectively kill the residual unkilled or resistant tumor cells after PTT to improve the completeness of tumor removal (Figures adapted from ref. 337 with permission). (c) Schematic illustration of cinps for inhibiting tumor growth by inducting macrophage repolarization and synergizing photothermal therapy.[338] Reproduced from Deng, R. H.; Zou, M. Z.; Zheng, D.; Peng, S. Y.; Liu, W.; Bai, X. F.; Chen, H. S.; Sun, Y.; Zhou, P. H.; Zhang, X. Z. Nanoparticles from Cuttlefish Ink Inhibit Tumor Growth by Synergizing Immunotherapy and Photothermal Therapy. ACS Nano 2019, 13, 8618-8629. Copyright 2019 American Chemical Society.

(V) Synergic therapy with photothermal-radiotherapy technology

Radiotherapy (RT) is a clinical radiotherapy for cancer treatment. It kills cancer cells in a variety of ways without any depth limitation. The direct damage to DNA and induction of ROS indirectly injury are the most important methods.[339,340] Although RT has high linear energy transfer (LET) radiation, tumor hypoxia is a common reason for the failure of clinical application of low LET radiotherapy because of linear energy transfer (LET) radiation.[341] The photon/electron beam produced by the accelerator usually has a very low LET and cannot effectively kill the hypoxic cancer cells[342] as the oxygen level is crucial for promoting DNA damage by ROS.[343-346]

Tumor-specific oxygen delivery is an ideal radiotherapy sensitization strategy due to the irreplaceable role of oxygen in radiotherapy both enhancing and blocking DNA self-repair.[347] Peng

et al. constructed an oxygen-carrying nanoplatform based on PEGylated TaOx for triple sensitization of tumor radiotherapy.[348] Based on the in-situ growth of ultra-small sized CuS nanocrystals, high-Z element-based hollow mesoporous TaOx nanospheres were prepared and packaged with the O_2 saturated perfluoropentane (PFP). Gentle hyperthermia triggered by a NIR laser could increase the blood flow in the tumor and release oxygen, which is able to improve the efficiency of radiation therapy. On the other hand, Ta element deposited radiation energy inside the tumor could also achieve triple sensitization of radiotherapy. In vivo studies showed that the nanospheres could almost thoroughly inhibit tumor growth without obvious side effects (Fig.14).[348]

In addition, the small difference between the tumor and normal tissues response to ionizing radiation is an important issue in tumor radiotherapy. Huang et al. reported that dumbbell-shaped heterogeneous copper-gold selenide nanocrystals could be used as an effective radiosensitizer.[349] The average lethal dose of X-rays to 4T1 tumor cells can be reduced by about 40%. Due to the synergistic effect of the hetero-structure, the dose of X-rays required is much lower than $Cu_{2-x}Se$+Au nanoparticles (1.78Gy), $Cu_{2-x}Se$ nanoparticles (1.72Gy) and Au nanoparticles (1.50Gy). Moreover, because of the synergy of local surface plasmon resonance, heterogeneous nanocrystals showed higher light-to-heat conversion efficiency and better therapeutic effects (Fig.15).[349]

In general, RT combined with PTT is an attractive treatment for cancers. Many recent studies of PTT combined with RT have successfully demonstrated the good anti-tumor effects.[339-341] However, how to find a suitable medicament is still a challenging problem because ideal medicament controls not only the effectiveness of two treatment modes but also the target specificity and sensitivity of radiotherapy.

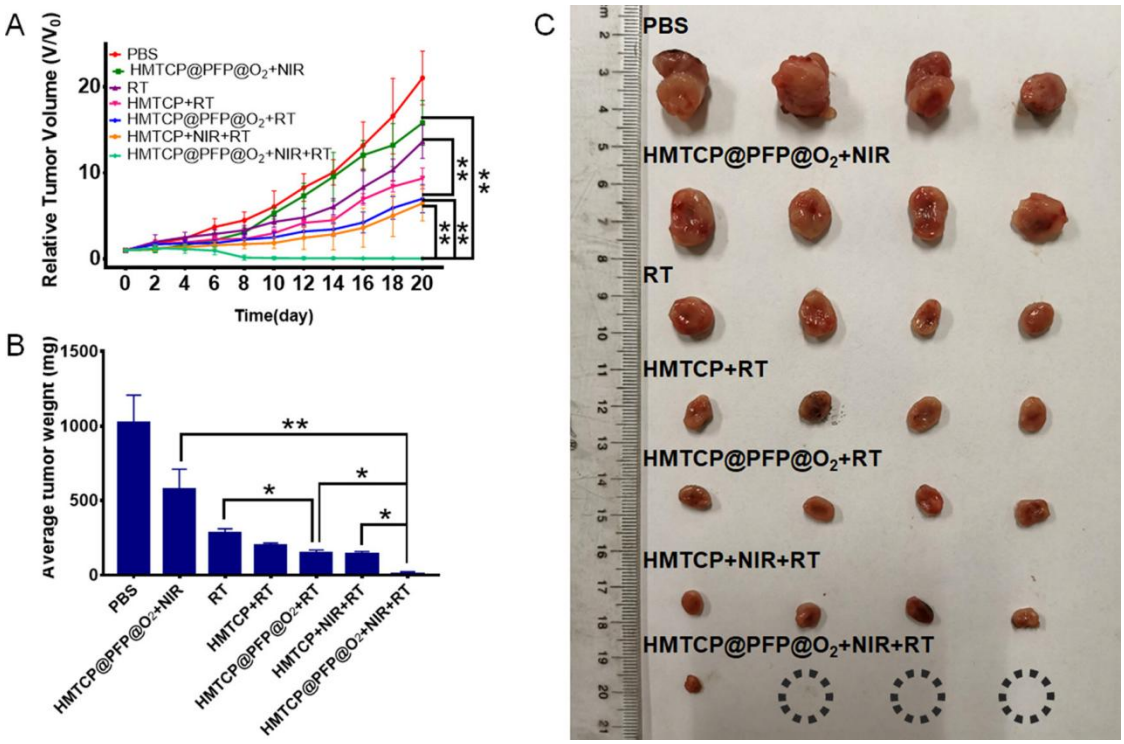


Figure 14. In vivo triple sensitization of radiotherapy by HMTCP nanospheres. (A) Tumor growth curves of mice post-treatment during 20 days (n=4). (B) Average weight of tumor from different groups 20 days post-treatments. (C) Digital graphs of tumor tissues in the different groups 20 days post-treatments.[348] Reproduced from Peng, C.; Liang, Y.; Chen, Y.; Qian, X.; Luo, W.; Chen, S.; Zhang, S.; Dan, Q.; Zhang, L.; Li, M.; Yuan, M.; Zhao, B.; Li, Y. Hollow Mesoporous Tantalum Oxide Based Nanospheres for Triple Sensitization of Radiotherapy. ACS Appl. Mater. Interfaces 2020, 12, 5520-5530. Copyright 2020 American Chemical Society.

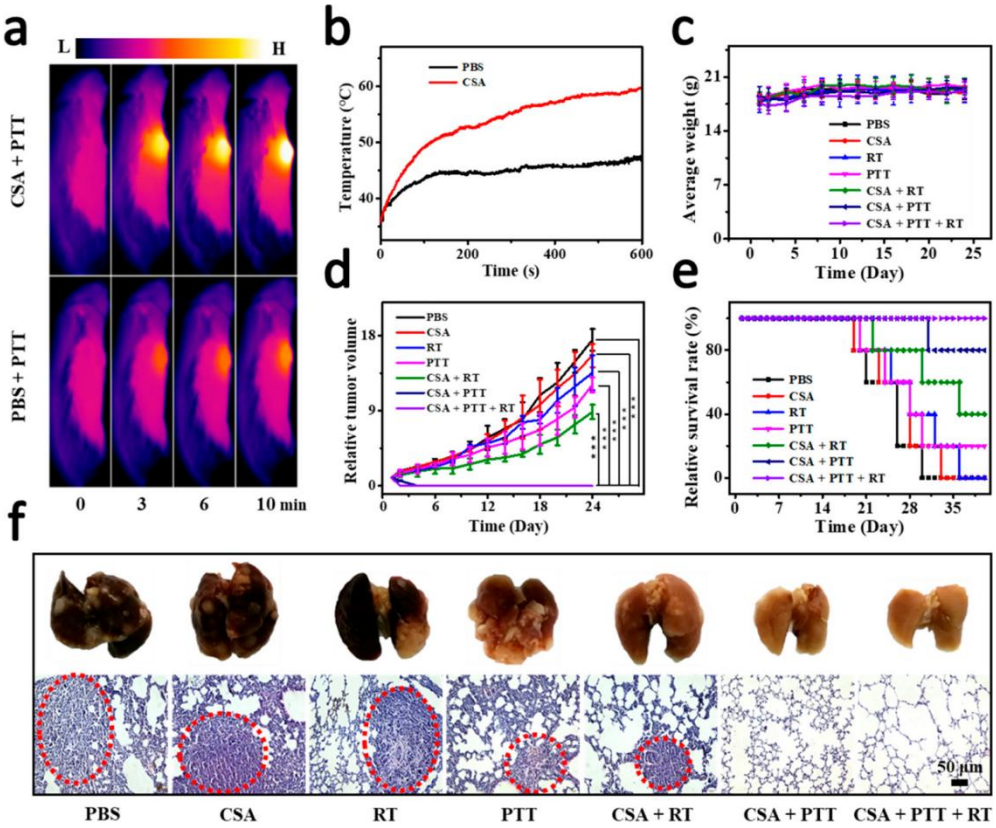


Figure 15. (a) Infrared thermal images of tumor-bearing mice and (b) the temperature curves of the tumor site after they were intravenously injected with CSA nanoparticles (dose 2.5 mg mL^{-1}, 200 μL) and PBS, respectively, and then exposed to an 808 nm NIR laser (1.5 W cm^{-2}, 10 min). The variations in (c) weight, (d) relative tumor volume, and (e) survival rates of mice from the different groups treated under different conditions. (f) Images of whole lungs of mice collected from different groups at the end of treatment (top) and the corresponding lung slices stained with hematoxylin and eosin (H&E) (bottom) (*$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$).[349] Reproduced from Huang, Q.; Zhang, S.; Zhang, H.; Han, Y.; Liu, H.; Ren, F.; Sun, Q.; Li, Z.; Gao, M. Boosting the Radiosensitizing and Photothermal Performance of $Cu_{2-x}Se$ Nanocrystals for Synergetic Radiophotothermal Therapy of Orthotopic Breast Cancer. ACS Nano 2019, 13, 1342-1353. Copyright 2019 American Chemical Society.

The clinical study of nanomaterials in photothermal therapy

The clinical development of PTT is enhanced by the photothermal contrast of PAs. Thermal ablation can be also achieved by stimulating endogenous chromophores in human tissues.[350] Therefore, the focus of preclinical research and clinical research of PTT is different. Preclinical researches mainly center at the characteristics of various photothermal nanomaterials. When the nanomaterial entering the clinical research, it concentrates on the development of laser ablation system rather than relying on PAs. The different focus reflects that the tumor ablation of PTT can be easily confirmed in preclinical tumor models. Therefore, various new photothermal nanomaterials may be tested quickly and repeatedly.[350]

As mentioned above, despite most studies are only limited to preclinical models, the use of Au nanoshells and related nanomaterials with photothermal conversion properties as PAs has attracted great attention currently.[351] In 2019, the results of a phase I trial proved the feasibility of employing silicon core and Au shell for photothermal ablation of prostate tumors (NCT04240639). In the study, 16 patients received a single infusion of Au nanoshell, followed by 21 optical fiber interstitial laser placement (1.8 cm long) in the tumor, and then irradiated with an 808 nm laser. The results showed that 94% of patients' tumors were thermally ablated and no serious complications were observed after treatment.[352] In addition, a pilot study of PTT platform was also investigated in patients with head and neck cancer (NCT00848042). However, this PAs dependent laser ablation has not been tested in large clinical trials. The laser ablation without PTT drugs has been used clinically, such as Nd:YAG and other lasers can be used for endoscopic irradiation of obstructive endobronchial cancers and to ablate the tumor by photocoagulation.[353]

Taken together, contrast enhanced PTT is an emerging research field and its potential in clinical applications remains to be established further in the future. The ongoing clinical trials, for example, prostate cancer ablation with the Au nanoshell, indicate that this field may have great research prospects. Moreover, the cancer mechanism is complicated and diverse. Monotherapy may not be effective and produce obvious side effects.[1,2] Clinical research on this area has to be advanced from single treatment to combined treatment to produce desirable synergistic therapeutic effects.[354]

Summary and outlook

The rapid development of nanotechnology has promoted the significant application of PTT in cancer diagnosis and treatment. PTT is an effective, non-invasive and target specific therapy for cancer. Many nanomaterials have been tailor-made and introduced into PTT. The functionalized nanomaterials show a great prospect in the development of selective and non-invasive cancer treatment technology. Although the current research is only a drop in the bucket, some biological studies on PTT have achieved exciting results and progress. Besides, it is found that the mechanism of action of these photothermal agents is diverse and the photothermal effect can be improved by adjusting the characters of the nanoparticles such as shape and size. On the one hand, at present, numerous potential PTT candidates such as gold nanorods, carbon nanotubes and small organic molecules have been reported and well characterized. We therefore can utilize the nano-controllable technology to synthesize ideal nanomaterials with excellent PCE. The potential or underestimated negative effects of nanomaterials on cancer treatment need to be addressed and further evaluated. It is definitely critical regarding the safety of nanomaterials employed in PTT, although scientists have

adopted different means such as PEG coating to reduce cytotoxicity of the nanomaterials. In addition, the in vivo environment is also very complicated and unpredictable. It is hard to determine the solubility, hydrophilicity and aggregation of nanomaterials after entering human body. It is therefore a great challenge for making use of nanomaterials in PTT and its combined technology practically or clinically, despite they are known to possess excellent biocompatibility and high PCE. Similar to other related medical research on nanomaterials, tracking nanomaterials after therapy is also extraordinary challenging. Therefore, an advanced technology is required for long-term tracking of nanomaterials in patients. In addition, it is noteworthy that not all of the photothermal nanomaterials described in this review irritated by NIR laser meet the safety limits of the national standard of the United States. Improper light stimulation may lead to serious absorption of water, thus reducing the efficiency of PTT and then affecting the treatment of tumors.

Currently, PTT shows great development prospects but obviously further development is required to achieve goal for clinical applications. We expect that safety issues of PTT can be addressed and PTT may meet the need for antitumor therapy in the future. Furthermore, to enhance further the therapeutic effects against tumors, it is worthy to focus the work on the integration of PTT and collaborative therapy as prior arts have given a hint that a single treatment is not likely to achieve a complete cure of tumor. The nanomaterials for PTT collaborative treatment require being multifunctional. Certain PTAs have the potency for being applied as contrast agents or drug carriers, so that real-time imaging of PTT or PTT combined with other therapies can be realized. More importantly, the collaborative treatment may be implemented for achieving better anti-tumor effects. So far, the application of photothermal nanomaterials is generally favored by a wide range of

scientists and many these significant works contributed to field of synergistic therapy with PTT have been recognized and highlighted.

Despite the NIR light driven photothermal ablation technology provides a new direction for cancer treatment with its minimally invasive and high efficiency, to explore better photothermal conversion nanomaterials, it definitely needs more in-depth studies in the following aspects: (i) Design and synthesis of materials with high PCE, which can be improved based on the existing nanomaterials, or looking for new nanomaterials with high PCE because PAs are the core elements of PTT. (ii) Improve the biocompatibility and tumor targeting of PAs. The surface functionalization treatment of PAs can improve the in vivo stability and half-life cycle of PAs. To realize photothermal targeted treatment of cancer, the immobilization of some targeting reagents to the surface of PAs may be required to guide the photothermal conversion materials to accumulate in the cancer cells or tumor site. (iii) Study and analyze the ablation mechanism of nanomaterials on cancer cells, side effects on normal cells and the in vivo metabolism. (iv) Develop new "all in one" photothermal reagents to make nanomaterials have the synergistic therapeutic effect of photothermal, chemotherapy and radiotherapy at the same time, and have the function of multi-mode imaging, so as to achieve the optimal effect of diagnosis and treatment and to minimize patients' pain and discomfort. At present, the clinical application of PTT is still very limited; however, by overcoming the bottleneck of the current nanotechnology, PTT combined with other therapy may be able to realize the practical and clinical utilization for anti-tumor therapy or other diseases in the near future.

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ABBREVIATIONS

5-Fluorouracil (5Fu)
Magnetic Resonance Imaging (MRI)
Black Phosphorus (BP)
Bovine Serum Albumin (BSA)
BP Quantum Dots (BPQDs)
Carbon Dots (CDs)
Carbon Nanotubes (CNTs)
Carbon Nanotubes (SWNTs)
Chitosan (CS)
Conductive Polymers (CPs)
Cytotoxic T Lymphocytes (CTLs)
Dendritic Cells (DC)
Deoxyribonucleic acid (DNA)
Doxorubicin (DOX)
Emeraldine base (EB)
Emeraldine salt (ES)
Folic Acid (FA)
Gambogic Acid (GA)
Gene Therapy (GT)
Gold Nanobipyramids (GNBs)
Gold-based Nanoparticles (Au NPs)
Graphene Oxides (GO)
Halloysite Nanotubes (HNTs)
Heat Shock Protein 90 (HSP90)
Heat Shock Proteins (HSPs)
Hepatocellular Carcinoma (HCC)
Hyaluronic Acid (HA)
Hydrogen Peroxide (H_2O_2)

Hyperbranched polyglycerolamine (HPGNH2)
Indocyanine Green (ICG)
Linear Energy Transfer (LET)
Low-temperature PTT (LTPTT)
Manganese Dioxide (MnO_2)
Manganese Phthalocyanine ($MnPcE_4$)
Marrow-derived Dendritic Cells (BMDCs)
Matrix Metalloproteinase (MMP)
Mesoporous Polydopamine Nanoparticles (MPDA)
Mitogen-activated Protein Kinase (MAPK)
Multiple drug resistance (MDR)
Nano-graphite (NG)
Nanoparticles (NPs)
Near-Infrared (NIR)
Oxygen (O_2)
Perfluoropentane (PFP)
Permeability and Rretention Effects (EPR)
Photodynamic Therapy (PDT)
Photothermal Agents (PTAs)
Photothermal Conversion Efficiency (PCE)
Photothermal Therapy (PTT)
Polyaniline (PANI)
Polyethylene Glycol (PEG)
Poly (3,4-ethylenedioxythiophene) (PEDOT)
Poly (4-styrenesulfonate) (PSS)
Polypyrrole (PPy)
Polyvinylpyrrolidone (PVP)
Prussian Blue (PB)
Reactive Oxygen Species (ROS)
Supercritical Carbon Dioxide (SC-CO_2)
Surface Plasmon Resonance (SPR)
Transmission Electron Microscopy (TEM)
Triphenylphosphine (TPP)
Tumor Environment (TME)
Tumor-associated Macrophages (TAM)

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