

Applications of Inorganic Nanomaterials in Photothermal Therapy Based on Combinational Cancer Treatment

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Background: Cancer is one of the major causes of death and is difficult to cure using existing clinical therapies. Clinical cancer treatments [such as surgery, chemotherapy (CHT), radiotherapy (RT) and immunotherapy (IT)] are widely used but they have limited therapeutic effects and unavoidable side effects. Recently, the development of novel nanomaterials offers a platform for combinational therapy (meaning a combination of two or more therapeutic agents) which is a promising approach for cancer therapy. Recent studies have demonstrated several types of nanomaterials suitable for photothermal therapy (PTT) based on a near-infrared (NIR) light-responsive system. PTT possesses favorable properties such as being low in cost, and having high temporospatial control with minimal invasiveness. However, short NIR light penetration depth limits its functions.

Methods: In this review, due to their promise, we focus on inorganic nanomaterials [such as hollow mesoporous silica nanoparticles (HMSNs), tungsten sulfide quantum dots (WS₂QDs), and gold nanorods (AuNRs)] combining PTT with CHT, RT or IT in one treatment, aiming to provide a comprehensive understanding of PTT-based combinational cancer therapy.

Results: This review found much evidence for the use of inorganic nanoparticles for PTT-based combinational cancer therapy.

Conclusion: Under synergistic effects, inorganic nanomaterial-based combinational treatments exhibit enhanced therapeutic effects compared to PTT, CHT, RT, IT or PDT alone and should be further investigated in the cancer field.

Keywords: photothermal agents, hyperthermia, chemotherapy, radiotherapy, immunotherapy, photodynamic therapy

Introduction

As a leading cause of death, cancer is one of the most serious public health problems worldwide. According to current statistics, it is projected that more than 1.7 million new cases and 0.6 million cancer deaths will occur in the United States in 2019 alone.¹ Cancer is not a particular disease but a group of diseases and alarmingly there are more than one hundred different types of cancers. Moreover, cancer is hard to cure because of the high mutation rate and metastasis of cancer cells. Current main cancer treatments include surgery, CHT, RT and IT. It is common to ablate tumors as the first treatment, but it is difficult to remove tumor tissues completely through surgery. Even a single residual cancer stem cell can grow into a new tumor. The remaining cancer cells can be killed via CHT, however, patients have to suffer serious side effects caused by intrinsic off-target toxicity of CHT drugs.² RT can kill cancer cells and shrink tumors with high

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doses of radiation, but it can also damage nearby healthy cells. IT treats cancer by boosting the immune system against cancer cells, but it often happens that the immune system acts against healthy cells and tissues. Besides the above side effects, there is one more important problem – infection. Cancer patients are susceptible to infections due to their weakened immune systems. The problem can become worse after the immune system suffers more damage from cancer treatments such as surgery, CHT and RT. The use of antibiotics can solve infections, but it can also induce new problems like drug resistance bacteria.

Although the above therapies are not effective all the time and have unavoidable side effects, they still comprise the primary method of clinical cancer treatment. The development of nanotechnology has led to the development of new nanomaterials with several attractive properties providing a promising novel way for combining various cancer treatments together.³ Firstly, nanomaterials can be used as carriers to encapsulate drugs to prolong drug plasma circulation time and reduce contact with normal cells. In other words, nanomaterials can increase the efficiency of the drugs to target cancer cells and alleviate off-target toxicities.⁴ Secondly, nanoparticles can easily accumulate in tumors via the enhanced permeability and retention (EPR) effects caused by leaky tumor vasculature and dysfunctional lymphatic drainage.² This feature is the result of unintended coordination between solid tumors and nanoparticles, but it helps to improve drug deposition and target tumors.⁵

Thirdly, there is a wide range of diverse nanomaterials available today. Nanomaterials are roughly separated into

inorganic and organic materials. Inorganic nanomaterials include examples of gold nanoparticles (AuNP),⁶ mesoporous silica nanoparticles (MSNP),⁷ quantum dots (QD), carbon nanotubes (CNT),⁸ etc. Moreover, common organic nanomaterials include liposomes, polymeric micelles, dendrimers, etc. Due to their greater surface area, nanomaterials have unique properties that can play a role in cancer treatment regimes as enhanced photosensitizers for PDT. Fourthly, nanoparticles provide a platform for cancer treatment with unlimited possibilities according to each unique nanomaterial design. Besides the type of nanomaterial, the pharmacokinetics and biodistribution of nanoparticles can also be attributed to properties such as size, shape and surface modification.^{9,10} Nanoparticles with sizes in the range of 5~100 nm have a higher chance to survive renal clearance so that they have a great circulation time for accumulating in tumors.¹¹ As one of the most common nanoparticle surface modifications, PEGylation, improves nanoparticle pharmacokinetic properties by creating a hydrophilic layer resistant to protein adsorption and immune system clearance.¹² Finally, nanomaterials can possess excellent antibacterial activity to protect cancer patients from infections.¹³ Several nanoparticles have been proven to be effective to treat infectious diseases, even antibiotic resistant ones, in vitro and in vivo.¹⁴ Such studies highlight that the use of antibacterial nanomaterials can help reduce the abuse of antibiotics, and thus the emergence of antibiotic resistant bacteria.

There are several novel nanomaterial-based stimuli-responsive systems for cancer treatment (Table 1). According to tumor properties (such as type, size and

Table 1 Novel Nanomaterial-Based Stimuli-Responsive Systems for Cancer Treatment

Nanomaterial	Mechanism	Therapy	Ref
SCNs/Pt	pH-responsive size switching	CHT	[16]
DOX/CP-NI NPs	Light-triggered ROS generation; hypoxia-responsive chemo drug release	PDT/CHT	[17]
PhA/AuNPs	Light-triggered GSH-responsive ROS generation	PDT	[18]
TMPyP&DNM&Apt-gc34 @SPION	Light-triggered ROS generation; magnetic targeted pH-responsive chemo drug release	PDT/CHT	[21]
SPION/DOX/Microbubble	Ultrasound/magnetic targeted chemo drug delivery	CHT	[24]
BPQDs/PLGA nanospheres	Light-triggered hyperthermia	PTT	[25]
HPSN-Pax/PdPc	Light-triggered hyperthermia and chemo drug release	PTT/CHT	[26]
mPEG@HGPNs	Light-triggered hyperthermia; X-ray radiation	PTT/RT	[27]
HCuSNPs-CpG	Light-triggered hyperthermia; stimulating immune system	PTT/IT	[28]
UCNPs-NGO/ZnPc	Light-triggered hyperthermia and ROS generation	PTT/PDT	[29]

Abbreviations: SCNs, pH-sensitive cluster nanobombs; Pt, platinum; DOX, doxorubicin; CP-NI, 2-nitroimidazole-grafted conjugated polymer; ROS, reactive oxygen species; PhA, pheophorbide a; TMPyP, 5,10,15,20-tetrakis (1-methylpyridinium-4-yl) porphyrin; DMN, daunomycin; SPION, superparamagnetic iron oxide nanoparticles; BPQDs, black phosphorus quantum dots; PLGA, poly (lactic-co-glycolic acid); HPSN, hollow structured polymer-silica nanohybrid; Pax/PdPc, paclitaxel and palladium phthalocyanine; HGPNs, hollow gold nanoparticles; HCuSNPs, hollow CuS nanoparticles; CpG, cytosine-guanine; UCNPs, upconversion nanoparticles; NGO, nanographene oxide; ZnPc, zinc phthalocyanine.

location), various internal and external stimuli have been selected for site-specific therapy.¹⁵ Internal stimuli take advantage of tumor-specific microenvironments including low pH,¹⁶ hypoxia,¹⁷ high levels of glutathione (GSH)¹⁸ and over-expressed cancer-associated enzymes.¹⁹ For example, Li et al developed pH-responsive nanoparticles which can keep the nanoparticle size to 100 nm in normal pH conditions and change it to 5 nm at low pH conditions of the tumor microenvironment. The initial size prolongs plasma circulation time of the nanoparticle and the final size improves their tissue penetration and extravasation.¹⁵ However, it is difficult to precisely control an internal stimuli-responsive system because of complex microenvironments and individual variations in the body.²⁰

Compared to internal stimuli, external stimuli possess more advantages on the temporal and spatial control of nanoparticles with minimal invasiveness. Here, the nanoparticle system is not activated until the appearance of an external stimulus such as light, magnetic field irradiation and ultrasound.² Magnetic field technology has recently received much attention for magnetic hyperthermia, magnetic resonance imaging and a controlled drug release system. For example, Sun's team developed a multifunctional nanocarrier of super paramagnetic iron oxide nanoparticles (SPION) for delivering CHT agents and photosensitizer molecules to the tumor site. The delivery system displayed controlled drug release to cancer microenvironments.²¹ Ultrasound is also an excellent external stimulus due to efficient tissue penetration and non-invasiveness. Apart from established clinical ultrasound imaging, ultrasound induces apoptosis in the tumor through thermal effects like hyperthermia or nonthermal effects like cavitation.²² Light has common potentials with a magnetic field and ultrasound (such as safe, temporospatial accuracy and less invasiveness). Furthermore, light is tunable in terms of wavelength as there are many useful modalities such as UV light, visible light and NIR light. In the NIR region ranging from 650 to 900 nm, light displays deeper tissue penetration and less photo-damage than visible and UV light in vivo applications.²³ In this review, we outline inorganic nanomaterials used in NIR light-based stimuli-responsive system for PTT. In order to exert maximal therapeutic effects of PTT, we also focus this review on recent applications of inorganic nanomaterials in combinational cancer therapy of PTT and other treatments such as CHT, RT, IT and PDT, as well their antibacterial properties.

Photothermal Therapy in Cancer Treatment

Compared to UV and visible light, NIR light has photons of a longer wavelength and less energy. This characteristic helps NIR light penetrate deeper into living tissue but NIR photons cannot carry out many photochemical reactions without enough energy. This problem can be solved by mechanisms such as upconversion and two-photon absorption.³⁰ Upconversion nanoparticles (UCNP) can transform NIR to visible light and UV light by absorbing two or more photons then converting it into a high energy photon.³¹ Apart from these two mechanisms, the NIR light-responsive system also follows the photothermal effect mechanism which is at the core for PTT. In this case, light-sensitive nanomaterials can convert NIR light into heat which can be applied to a specific site for hyperthermia. When nanomaterials are applied as nanocarriers for drug delivery systems, heat-activated nanostructures change to release drugs. When nanomaterials are utilized as photothermal agents, heat can damage or ablate tumor cells directly. In order to design a qualified system for PTT, photothermal agents need to satisfy conditions like absorbing NIR light, efficiently converting light to heat and be biocompatible and biodegradable.² Examples of inorganic nanomaterials include AuNPs,²⁷ black phosphorus,²⁵ carbon nanomaterials and UCNPs.²⁹ Various organic nanomaterials also have excellent properties for PTT (such as polymeric materials including polypyrrole (PPy)³² and photothermal dyes including perylene diimide,³³ indocyanine green (ICG),³⁴ IR780³⁵ and IR825).³⁶

For organic nanomaterials, Yang et al fabricated NIR-controlled drug-loaded nanoparticles for PTT-CHT. The heat generated from light-absorbable PPy made the nanoparticle size switchable. Upon continuous laser illumination, the nanoparticle swelled to release loaded camptothecin (CPT) and doxorubicin (DOX) and it shrank back to stop releasing CPT and DOX after switching the laser off.³² For inorganic nanomaterials, Betzer et al developed immunoconjugated gold nanorods (AuNRs) for selectively targeting and attaching to head and neck cancer (HNC) cells. AuNRs can absorb NIR light and induce hyperthermia to the cancer cells, and can do so in a greater manner than nano spherical particles or larger particles due to their greater surface areas. The results exhibited that PTT with AuNRs effectively decreased tumor size with minimal side effects.³⁷ Kang et al fabricated innovative gold nanoparticles/graphene oxide

(AuNP/GO) hybrid sheets that can attach to the surface of tumor-tropic mesenchymal stem cells (MSC) without being internalized so that cytotoxicity and exocytosis issues can be avoided. Compared to AuNP-internalized MSCs, AuNP/GO sheet-attached MSCs can convert more NIR light to heat in vivo in order to achieve therapeutic efficacy. Moreover, a strong plasmon coupling between AuNPs resulted from the tight packing of AuNPs on the GO sheets which also enhanced the photothermal effect.⁶ Multiple studies also demonstrated the antibacterial effects of inorganic nanomaterials such as AuNPs.¹³ Therefore, as an excellent photothermal agent, AuNPs also possess antibacterial properties.³⁸ As stated, due to their weakened immune system, cancer patients are strongly susceptible to infections. The combination of antibacterial and photothermal effects provides a promising method for applying inorganic nanomaterials for cancer treatment.

After converting NIR light to heat, the tumor microenvironment temperature increases. When the temperature is above 45 °C, cancer cells can be killed immediately. However, it inhibits other treatments because it often results in hemorrhage and stasis in tumor vessels. On the contrary, mild hyperthermia around 42–43 °C can induce cellular damage and increase tumor vessel permeability so that cancer cells are more vulnerable to allied treatments such as CHT or RT.³⁹ Because avoiding vascular occlusion can result from higher temperatures, mild hyperthermia can improve nanoparticle uptake by tumors.⁴⁰ An elevated microenvironment temperature improves tumor oxygenation, perfusion and the tendency of cancer cells towards apoptosis.³⁹ The above characteristics of mild hyperthermia via nanoparticles support the combination of PTT with other cancer treatments such as PDT, CHT, RT and IT. Furthermore, combination therapies enhance the therapeutic efficacy of individual treatments under synergistic effects which will be discussed in the following paragraphs.

Combination of PTT with CHT, RT, IT and PDT

PTT has so many advantages, such as high temporospatial control, low cost and minimal invasiveness, and it can also be used alone to eradicate the primary tumor or lymph metastasis in superficial tissues. However, light has a limitation on penetration depth. Even though NIR light can penetrate deeper than UV and visible light, it can only reach around a 3 cm deep in tissue.⁴¹ Due to the finite tissue penetration of NIR light in deep tissues, it is a great challenge for PTT alone

to eradicate metastatic cancer cells or metastatic nodules in distant organs.⁴² Accordingly, it is necessary to combine PTT with current available therapies for a desired efficacy on cancer metastasis (Figure 1).

Combination Therapy with PTT and CHT

Multiple studies demonstrated that CHT has several side effects such as drug resistance, intrinsic toxicity to normal cells, and individual behavioral differences in patients.⁴⁸ The problems can be alleviated or solved under the synergistic effect of a combination therapy with PTT. Photothermal agents combined with nanocarriers can deliver CHT drugs to tumors without exposure to normal cells and, thus, reduce the amount of drug needed potentially reducing toxic side effects and the development of chemotherapeutic resistant cancer cells. The release of drugs is limited without NIR irradiation and the drugs are rapidly released when photothermal agents are triggered by NIR irradiation so a lower dosage of drugs is required to achieve the ideal result.⁴⁹ Furthermore, if the release system is enough, intelligent drug-releasing nanoparticles can be immediately ceased when the NIR laser is switched off.⁵⁰ For example, Zhao et al developed an inorganic material-hollow structured polymer-silica nanohybrid (HPSN) as a nanocarrier to deliver the photothermal agent palladium phthalocyanine and chemotherapeutic drug paclitaxel. Due to a surface polyethylene glycol (PEG) ligand coating, most of the off-targeted HPSN could be excreted in 10 days through the hepatobiliary pathway. Fast clearance of nanocarriers efficiently reduced off-target toxicity of the anticancer drugs. The study also showed that the combination of PTT and CHT could inhibit tumor recurrence which could not be achieved by solely using PTT.²⁶

Meng et al designed an intelligent MEO₂MA@MEO₂MA-co-OEGMA-CuS-DOX composite (G-CuS-DOX). It was composed of CuS nanoparticles as photothermal agents, DOX as the CHT drug and MEO₂MA@MEO₂MA-co-OEGMA (G) as a thermosensitive nanogel. Under NIR irradiation, the nanocapsules induced hyperthermia which resulted in shrinkage of the nanogels to release DOX. When NIR irradiation was shut down, both the photothermal and chemotherapeutic effects were interrupted. It was demonstrated that synergistic PTT and CHT exhibited controllable and efficient advantages in in vivo experiments.⁵⁰ Zhang et al fabricated polymer-coated hollow mesoporous silica nanoparticles (HMSNs) encapsulating a photothermal

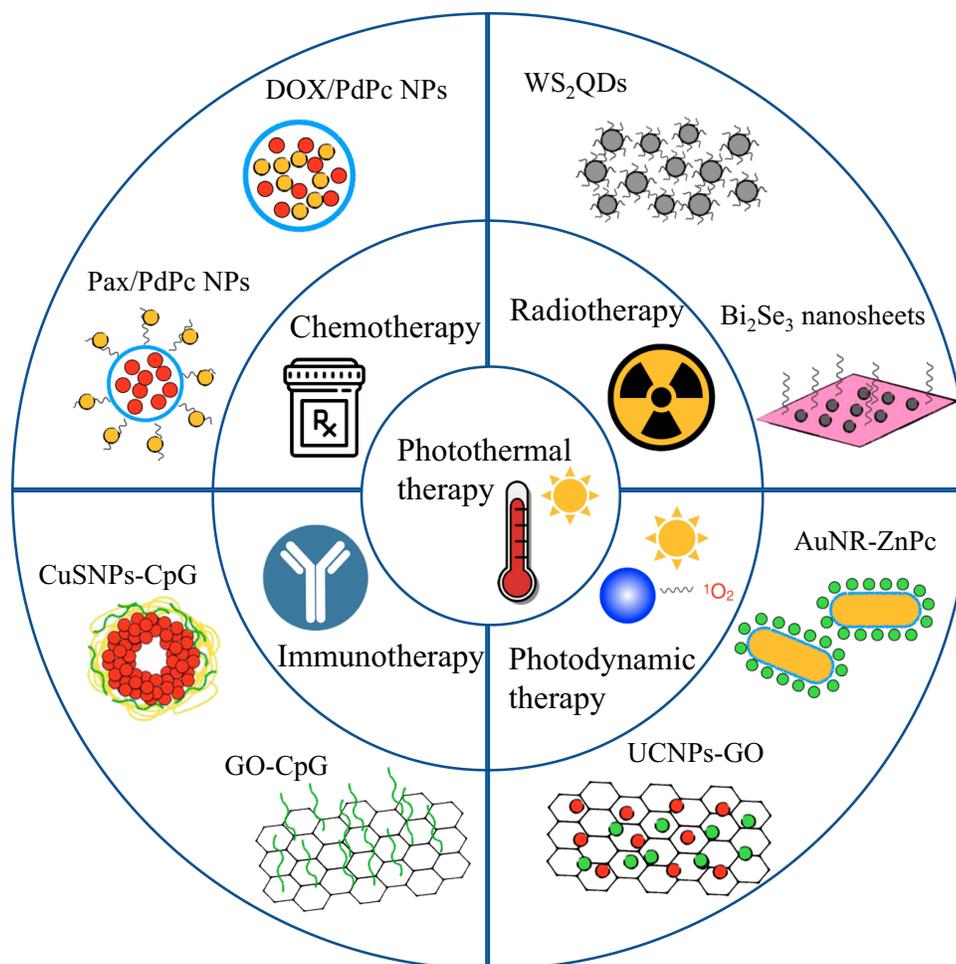


Figure 1 Schematic illustration for the combinational cancer therapy of photothermal therapy with chemotherapy, radiotherapy, immunotherapy and photodynamic therapy. The outside inorganic nanomaterials are examples of each combinational therapy.

Abbreviations: NPs, nanoparticles; Pax, paclitaxel; DOX, doxorubicin; WS₂QDs, tungsten sulfide quantum dots; CuSNPs, CuS nanoparticles; CpG, cytosine-guanine; GO, graphene oxide; AuNR, gold nanorod; ZnPc, zinc phthalocyanine; UCNPs, upconversion nanoparticles.

dye IR825 and covalently binding the anticancer drug DOX to the polymers on the outside. DOX was conjugated with a polymer via an acid-labile hydrazine bond which was cleaved in the low pH tumor microenvironment to release CHT drugs. HMSNs not only reduced the side effects of DOX but it also improved the stability of the organic dye IR825. Furthermore, the combination of DOX and IR825 exhibited therapeutic effects on DOX-resistant A2780/DOX^R cells.³⁶ This represents one of the few studies to combat chemotherapeutic resistant cancer cells. Further, Fang et al developed a multifunctional nanoplatform based on hollow mesoporous carbon nanoparticles (HMCN). HMCN were utilized not only as a nanocarrier to deliver DOX for CHT, but also as a photothermal agent to perform PTT. In addition, the pores from HMCN were capped by graphene quantum dots (GQDs) to prevent the early release

of DOX and the surface of HMCN was modified by hyaluronic acid (HA) to increase cancer cell uptake. The morphological changes caused by GQDs can be directly observed in the TEM images (Figure 2A and B). The nanocarrier HA-HMCN(DOX)@GQDs under NIR light exhibits excellent in vivo antitumor efficacy – showing an obvious inhibition of tumor growth in mice (Figure 2C and D).⁵¹ Both Liu et al and Wang et al fabricated nanoplatforms based on hydrogels for the synergistic tumor therapy of PTT and CHT. The solution was injected into the tumor at room temperature and the hydrogel instantaneously formed as the temperature increased to 37°C. The hydrogel matrix concurrently controlled the release of chemotherapeutic drugs and exhibited a photothermal effect. Their work proved that the designed composite hydrogel was a highly efficient platform for the treatment of tumors.^{52,53}

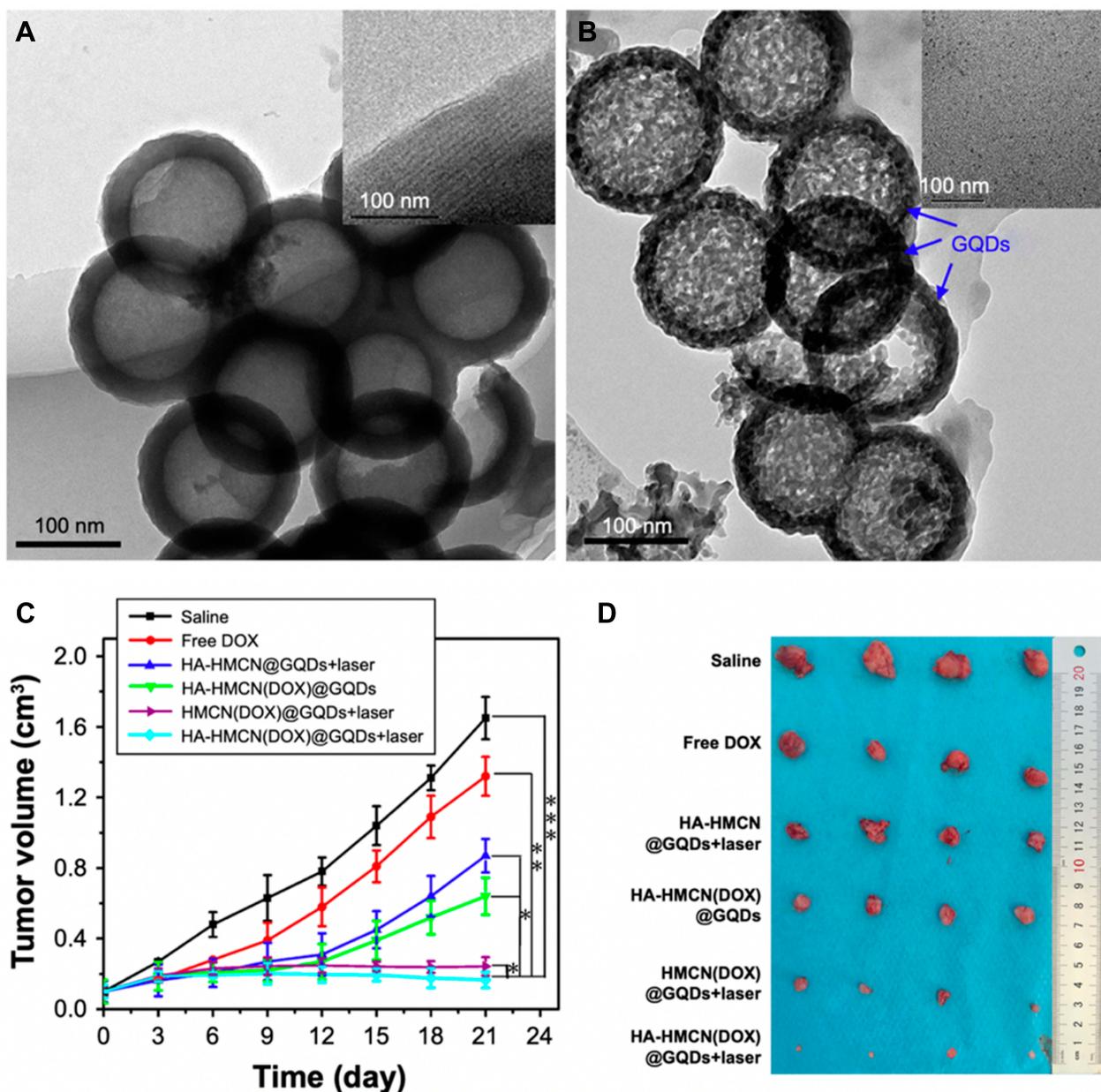


Figure 2 The morphology and in vivo antitumor activity of HA-HMCN(DOX)@GQDs.

Notes: (A) TEM images of HMCN and the mesoporous shell of HMCN (inset). (B) TEM images of HA-HMCN(DOX)@GQDs and GQDs (inset). (C) Relative tumor volume after various treatments (n=4). (D) The photographs of the tumors from each group of mice at the end of therapy on day 21. *p < 0.01, **p < 0.05, and ***p < 0.01. Adapted from Fang J, Liu Y, Chen Y, Ouyang D, Yang G, Yu T. Graphene quantum dots-gated hollow mesoporous carbon nanoplatfor for targeting drug delivery and synergistic chemo-photothermal therapy. *Int J Nanomedicine*. 2018;13:5991–6007. © 2018 Fang et al.⁵¹

Abbreviations: TEM, transmission electron microscopy; HA, hyaluronic acid; HMCN, hollow mesoporous carbon nanoparticle; DOX, doxorubicin; GQDs, graphene quantum dots.

Combination Therapy of PTT and RT

The abnormal microenvironment of tumors forms transport barriers limiting the distribution of antitumor agents, from small-molecule anticancer drugs to therapeutic nanoparticles. In order to be delivered into the tumor site, nanoparticles have to overcome transport barriers such as growth-induced solid stress, complex tumor vascular

networks, increased interstitial fluid pressure and tortuous interstitial structures.⁵⁴ It has been demonstrated that radiation-treated tumors have increased vessel perfusion, elevated vascular permeability and alleviated interstitial fluid pressure.⁵⁵ Mild hyperthermia induced by PTT also has similar effects including increasing tumor perfusion, vessel permeability and nanoparticle uptake.³⁹

Furthermore, low-energy long-wavelength NIR light and high-energy short-wavelength radiation compete with each other for further advantages. NIR light has a limited penetration depth while X-ray and γ -ray radiation do not have depth restrictions. RT displays low therapeutic efficacy for hypoxic cancer cells while PTT efficiently kills this type of cancer cell because hyperthermia can enhance oxygenation status in the tumor.⁵⁶ Thus, the combination treatment of PTT and RT can strengthen the therapeutic efficacy of each alone.

Yong et al designed a multifunctional nanomedicine based on tungsten sulfide quantum dots (WS_2 QDs) as

both radiosensitizers and photothermal agents. Furthermore, WS_2 QDs can also be used for dual-modal imaging including X-ray computed tomography (CT) and photoacoustic (PA) imaging because of its high X-ray attenuation ability and strong NIR optical absorbance. The tumor could be precisely located via simultaneous CT/PA imaging and be eradicated by PTT/RT therapy. Besides excellent CT/PA imaging capacity and a PTT/RT synergistic effect, WS_2 QDs exhibited remarkable biocompatibility.⁴³ Cheng et al fabricated PEG-modified $FeSe_2/Bi_2Se_3$ nanosheets for combined PTT and RT treatment (Figure 3A and B). $FeSe_2/Bi_2Se_3$ -PEG possessed intrinsic properties (such as strong

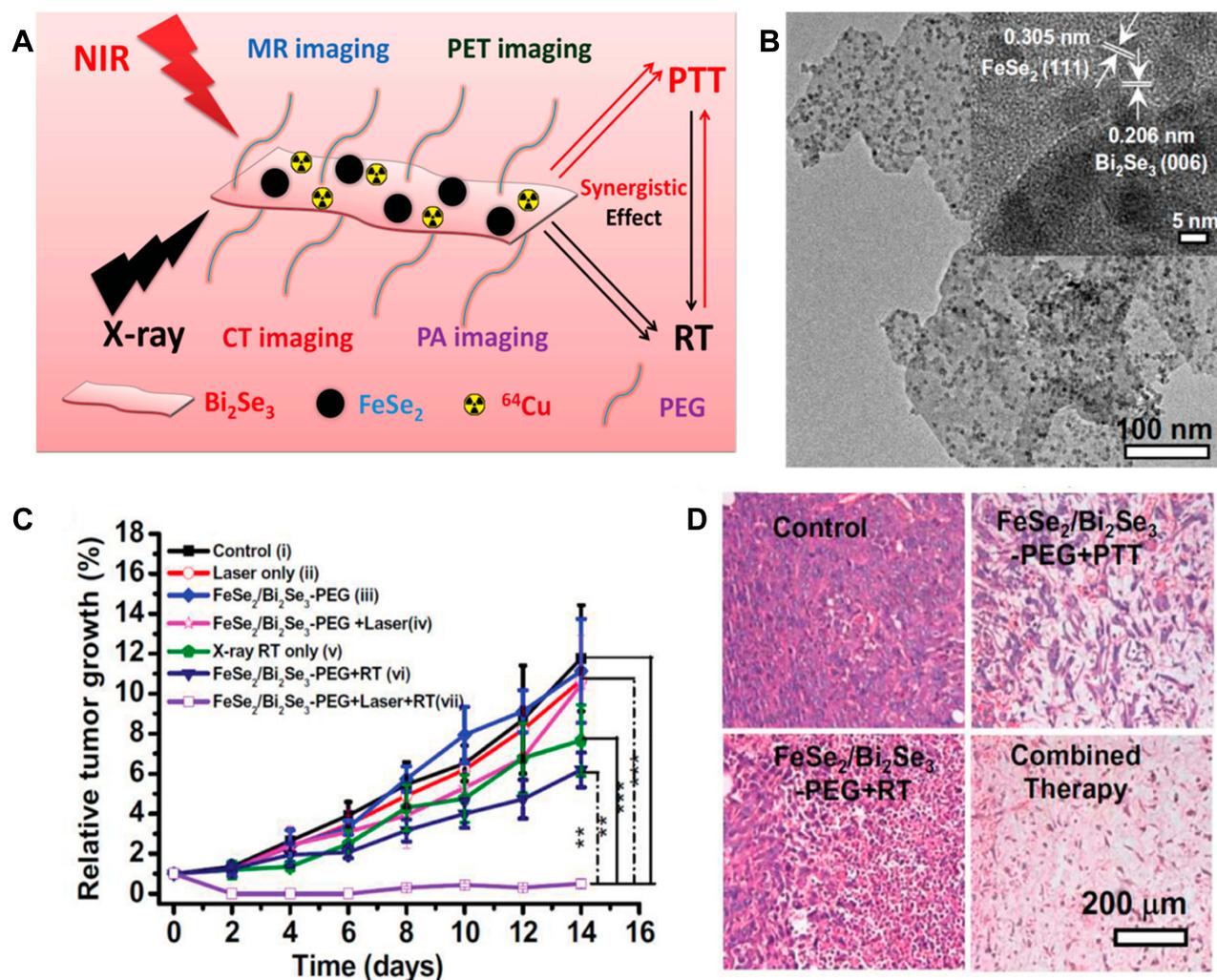


Figure 3 The morphology and in vivo antitumor activity of $FeSe_2/Bi_2Se_3$ -PEG.

Notes: (A) Schematic illustration of the $FeSe_2/Bi_2Se_3$ composite-nanostructure for multimodal imaging and photothermal-radiation combined tumor therapy. (B) The TEM images of $FeSe_2/Bi_2Se_3$ nanostructures and the respective high-resolution TEM images (inset). (C) Relative tumor growth after various treatments (n=5). (D) The images of H&E stained tumor slices from different groups of mice treated with PBS, $FeSe_2/Bi_2Se_3$ -PEG+NIR, $FeSe_2/Bi_2Se_3$ -PEG+RT, and $FeSe_2/Bi_2Se_3$ -PEG+RT+NIR. The tumors were harvested 2d after the treatments were conducted. **p < 0.05 and ***p < 0.01. Reproduced with permission from Cheng L, Shen S, Shi S et al. $FeSe_2$ -decorated Bi_2Se_3 nanosheets fabricated via cation exchange for chelator-free ^{64}Cu -labeling and multimodal image-guided photothermal-radiation therapy. *Advanced functional materials*. 2016;26(13):2185–97. © 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.⁴⁴

Abbreviations: TEM, transmission electron microscopy; PEG, polyethylene glycol; H&E, hematoxylin and eosin; PBS, phosphate-buffered saline; NIR, near infrared; RT, radiation therapy.

X-ray attenuation and high NIR absorption) which are fundamental for RT and PTT, respectively. In addition to being labeled with a radioisotope ^{64}Cu , the whole composite nanostructure could be used as a contrast agent for in vivo computer tomography, magnetic resonance (MR), photoacoustic (PA), and positron emission tomography (PET) tetra-modal imaging. $\text{FeSe}_2/\text{Bi}_2\text{Se}_3$ -PEG displayed remarkable therapeutic effects on tumor destruction and excellent inhibition on tumor growth (Figure 3C and D).⁴⁴ Yi et al developed PEG-modified iodine-131-doped copper sulfide ($\text{CuS}/[^{131}\text{I}]\text{I}$ -PEG) nanoparticles for PTT and RT. The nanomaterial took advantage of high NIR optical absorbance for PTT, but it utilized the doped ^{131}I -radioactivity for internal CT which is different from external CT used by the above two nanomaterials. Yi's studies demonstrated that $\text{CuS}/[^{131}\text{I}]\text{I}$ -PEG offered great synergistic therapeutic efficacy in both in vitro and in vivo experiments. Importantly, the combined PTT and RT could inhibit cancer metastasis and prolong animal survival when applied to lymph nodes for assisting in the surgical removal of primary tumors.⁵⁷

Combination Therapy of PTT and IT

Compared to gold-standard cancer treatments such as surgery, CHT and RT, IT is an emerging treatment through training or stimulating the host immunological systems to kill tumor cells.⁵⁸ IT has shown remarkable promises, but it still has many limitations like high cost, immunotoxicity and large individual variations.⁵⁹ Some nanomaterial-based therapies (such as PTT) could strengthen the immune response in IT. Hyperthermia triggered by PTT can not only kill cancer cells directly but can also induce the release of tumor-associated antigens which are essential for antigen processing and presentation. If IT and PTT are combined into one treatment, IT could perform a more therapeutic efficiency against tumors with the help of the released antigens and immunoadjuvants.⁶⁰

Guo et al designed chitosan-coated hollow CuS nanoparticles (HCuSNPs) with oligodeoxynucleotides (ODNs) containing cytosine-guanine (CpG) motifs as the immunoadjuvants. CpG ODNs are efficient immunological modulators. Nanoparticles can enhance their in vivo stability, pharmacokinetic and biodistribution properties and intracellular uptake for being recognized by TLR9.²⁸ NIR irradiation triggers the disintegration and reassembly of nanoparticles to form chitosan-CpG nanocomplexes with high tumor retention and intracellular uptake. It was demonstrated that HCuSNPs -CpG exhibited more potent immune responses and remarkable synergistic anticancer

effects than IT or PTT alone. After NIR irradiation, nanoparticles can be quickly eliminated from the body because of their biodegradability.⁴⁵ Tao et al utilized PEG and polyethyleneimine (PEI) dual-polymer-functionalized graphene oxide (GO) as the carrier for delivering CpG. GO-PEG-PEI-CpG nanocomplexes can remarkably improve the production of proinflammatory cytokines and strengthen the immunostimulatory activity under NIR irradiation. Moreover, immune responses are efficiently improved because the photothermal effect of GO accelerates intracellular transportation of CpG ODNs.⁴⁶

Combination Therapy of PTT and PDT

Both PTT and PDT are treatments as a result of light-responsive nanomaterials, but PTT depends on hyperthermia to kill cancer cells while PDT depends on reactive oxygen species (ROS) to kill tumor cells. Even though their therapeutic mechanisms are different, PTT and PDT have similar light triggering conditions.⁶¹ Thus, PTT and PDT can work independently and complementarily under the same NIR laser irradiation.⁶² For example, Wang et al fabricated an ICG-based cisplatin polyprodrug nanoplatfom in which the concurrent photodynamic and photothermal therapy exhibited excellent performance. Upon cellular uptake in lysosomes, ICG could induce local hyperthermia and ROS under NIR light irradiation and it could also assist the escape of cisplatin prodrugs into the reductive cytosol by damaging lysosomes.³⁴ In addition, the combination treatment of PDT can benefit from pathogen inhibition. Liu et al developed azonia-containing polyelectrolytes with extraordinary performance for ROS generation for antibacterial applications.⁶³

But back to inorganic nanomaterials, Tham et al reported novel nanomaterial-zinc phthalocyanine (ZnPc) anchored silica-coated gold nanorods (AuNRs) for combination PDT and PTT. Anchored ZnPc is a PDT precursor used to produce singlet oxygen. AuNR is a photothermal agent exhibiting localized surface plasmon resonance (LSPR), which then, hyperthermia induced by AuNRs can improve blood flow and oxygenation to and in the tumor, further improving PDT.⁶⁴ In Tham's study, both ZnPc and AuNR were excited by NIR light leading to hyperthermia and ROS at the tumor site for synergistic PTT and PDT.⁴⁷ Kalluru et al fabricated a GO-PEG-folate nanocomposite to exert photothermal and photodynamic therapeutic effects on tumors. GO (as the core of the nanomaterial) possesses intrinsic photothermal properties and can generate

a singlet oxygen for PDT. Kalluru's team showed that cellular death was caused by PDT and PTT in vitro experiments and they confirmed that the combination treatment was more effective than PDD or PTT alone using in vivo experiments.⁶⁵ Wang et al developed a multifunctional nanoplatform through covalently grafting upconversion nanoparticles (UCNPs) with nanographene oxide (NGO) and loading ZnPc on the surface of NGO. In UCNPs-NGO/ZnPc, ZnPc was used as a photosensitizer for PDT and UCNPs were utilized as photothermal agents for PTT. Then, NGO worked as a carrier for ZnPc and UCNPs because of its high NIR absorption and large surface area. According to this study, the combined treatment showed significantly greater performance on cancer therapy.²⁹ In addition, both Wang et al and Zhang et al also utilized UCNPs for enhancing the efficacy of PDT. Under NIR light excitation, UCNPs can emit UV-vis light then further excite photosensitizers to generate ROS.^{31,66}

Conclusion

In summary, several inorganic nanomaterial-based combinational cancer therapies are discussed in this review combining PTT/CHT, PTT/RT, PTT/IT and PTT/PDT. The most important advantages that such inorganic nanoparticle provide are improved therapeutic efficacy and safety. In each combinational therapy, two cancer treatments work independently and complementarily and the synergistic effects due to each is unique. For combined PTT/CHT, nanomaterials lower the dosage of anticancer drugs and protect normal cells from the intrinsic toxicity of the drugs. It also makes the drug release system more controllable and efficient. For the combined PTT/RT, both hyperthermia and radiation can change the tumor microenvironment to correspond to each other's treatment. PTT exerts better performance on radiation-treated tumors and RT works better on hypoxic cancer cells with hyperthermia-induced oxygenation. For combined PTT and IT, tumor-associated antigens induced by PTT and immunoadjuvants coupled on nanomaterials result in strengthening of the immune system. For combined PTT and PDT, the same NIR light irradiation can simultaneously activate PTT and PDT to produce heat and ROS. Besides the above combinational therapies, the combination with chemodynamic therapy is also a promising approach. Due to the high level of intracellular H_2O_2 in tumor cells, it is possible to produce cytotoxic hydroxyl radicals ($\cdot OH$) by the catalysis of metal ions provided by nanoplatforms. Because the nanoplatform is specific to the tumor

microenvironment, the efficiency of the combination therapy can be enhanced.⁶⁷

Despite the fact that inorganic nanoparticle combinational therapies have favorable properties, they still need further investigation. Recent studies in this review demonstrated the application of nanomaterials for such purposes using in vitro and in vivo experiments. However, it is a long way for them to be used in clinical trials and preclinical data should be further optimized. Furthermore, combinational therapies exhibit enhanced therapeutic effects, but the underlying mechanisms of synergistic effects (and how they can be further optimized) require further investigation, such as combined PDT and IT properties. The therapeutic efficacy of inorganic nanomaterials can be further enhanced by utilizing their antibacterial effects. It is a promising way to protect cancer patients from infections during cancer treatments. The development of nanomaterials makes the multifunctional platform possible. In the future, antibacterial effects could be set further as an intrinsic property requirement for developing nanomaterials for cancer treatment.

Although this review presents some promise aspects for nanoparticles to simultaneously treat cancer cells and bacteria, much more work is needed especially on the antibacterial side. Furthermore, it is also possible to combine PTT with other cancer treatments (such as chemodynamic therapy⁶⁷ and nanoCRISPR⁶⁸) together to promote the synergistic effects necessary for treating cancer. Inorganic nanomaterials have demonstrated exceptional accomplishments in biomedical research. The application of such materials in biomedicine requires more actuation and stability due to the complex environment of living organisms. Tumor targeting and biodegradability of the inorganic nanomaterial cannot be ignored in the case of toxicity caused by the material. Clearly, although showing much promise, more efforts are required for achieving additional advances in the development of inorganic nanomaterials for anti-cancer biomedicine.

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Disclosure

The authors report no conflicts of interest in this work.

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