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REVIEW

Nanoparticle-Assisted Sonosensitizers and Their Biomedical Applications

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Abstract: As a non-invasive strategy, sonodynamic therapy (SDT) which utilizes sonosensitizers to generate reactive oxygen species (ROS) has received significant interest over recent years due to its ability to break depth barrier. However, intrinsic limitations of traditional sonosensitizers hinder the widespread application of SDT. With the development of nanotechnology, various nanoparticles (NPs) have been designed and used to assist sonosensitizers for SDT. This review first summarizes the possible mechanisms of SDT, then classifies the NPs-assisted sonosensitizers and discusses their biomedical applications in ultrasonography, drug delivery, high intensity focused ultrasound and SDT-based combination treatment. Finally, some challenges and future perspectives of NPs-assisted SDT has also been discussed.

Keywords: sonodynamic therapy, sonosensitizers, nanoparticles, combination therapy

Introduction

Non-invasive therapies have received increasing attention because of improved therapeutic efficacy, decreased side effects and excellent spatial/temporal resolution.[1,2] As a typical representative, photodynamic therapy (PDT), which utilizes photosensitizers to generate reactive oxygen species (ROS) for tumor cell apoptosis or necrosis, has been developed as a clinically therapeutic modality for superficial skin carcinoma.[3] However, the major challenge for PDT is the low penetration of light, which limits the application of PDT in deep tumor.[3]

Ultrasound (US), as a mechanical wave with a frequency higher than human hearing (>20 kHz), has many characteristics including deep tissue penetration, non-invasion and non-ionization.[4] Therefore, US has been developed for many biomedical applications such as ultrasonography, sonodynamic therapy (SDT), drug delivery, high intensity focused ultrasound (HIFU) and so on.[5] As an emerging treatment mode, SDT utilizes US to activate sonosensitizers for ROS production, which could overcome the depth limitation.[6] However, traditional organic sonosensitizers suffer from poor pharmacokinetics and tumor accumulation, which limit the efficacy of SDT.[7] Promoted by the rapid development of nanomedicine, various NPs have been developed to assist sonosensitizers for improving the efficacy of SDT.[8–10]

In this review, we have classified and discussed the NPs-assisted sonosensitizers, summarized their mechanisms and biomedical applications in SDT, imaging, drug delivery and HIFU. Furthermore, we highlighted the recent advances of SDT-based combination therapy. Finally, we discussed the challenges and future perspectives of NPs-assisted SDT.

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Mechanisms of Sonodynamic Therapy

Although extensive evidencess have demonstrated the therapeutic efficiency of SDT, the exact mechanism still remains unclear because of the complicated SDT processes.[8] Possible mechanisms could be summed up as generation of ROS, mechanical effects, and thermal effects.[8,11–13]

Generation of Reactive Oxygen Species

Up to now, the most recognized mechanism is the production of ROS induced by sonosensitizers during the US.[8] After absorbing the energy from US, the sonosensitizers could be activated to produce ROS including singlet oxygen ($^1O_2$), hydroxyl radicals ($^{\bullet}OH$), superoxide anion ($O_2^{\bullet-}$) or hydrogen peroxide (H_2O_2).[5,14] Different kinds of ROS are generated with the selection of different sonosensitizers. For example, hematoporphyrin could produce singlet oxygen to kill the tumor cells.[15] Meanwhile, titanium oxide TiO_2 NPs and bimetallic oxide MnWOx NPs are reported to generate both singlet oxygen and hydroxyl radicals for enhanced SDT efficiency.[16,17]

Mechanical Effects

Mechanical effects mainly include the cavitation effect and sonoporation effect.[11,13] Cavitation could be divided into stable cavitation and inertial cavitation according to how the bubbles collapse during US.[18] Under low sound pressure (<0.1 MPa), bubbles usually display stable cavitation (SC), which is a periodic shrink and expansion of gas bubbles.[11,13] Once the sound pressure is sufficiently high, the bubbles will collapse instantly, which is called as inertial cavitation (IC).[11] IC could produce acoustic emissions,[19] microstreaming,[19] jetting,[20] and shockwaves,[19] which lead to mechanical damage.[21] In addition, through thermal dissociation of water, the cavitation effect would also produce ROS.[8]

Sonoporation effect refers to formation of pores in the cell membrane under US irradiation.[13] These formed pores allow for the transfer of molecules and NPs into cells.[22] Thereby, sonoporation effect could be utilized to increase the uptake and accumulation of drug molecules, genes or NPs.[13]

Thermal Effects

Thermal effects are the rise of tissue temperature due to the absorption of US energy and converted into thermal energy.[23] The thermal conversion efficiency is connected with hemoperfusion and protein level.[11] For example, Barnett et al reported that the thermal conversion efficiency is positively related to protein level.[24] In addition, tissues with poor hemoperfusion could be dramatically heated under US irradiation due to the slow heat dissipation.[24]

Nanoparticles Used for Sonosensitizers

During the US process, ROS could be generated. However, the amount of produced ROS is not enough to exert treatment effect due to the limited generating rate and nonspecific distribution.[5] Hence, the addition of sonosensitizers is necessary to ensure adequate production of ROS in tumor tissues. Benefiting from the development of nanotechnology, a mass of sonosensitizers-based nanocarriers have been constructed to improve the therapeutic effect of SDT.[7] Those NPs could be broadly divided into organic NPs and inorganic NPs.

Organic Nanoparticles

The early used sonosensitizers in SDT are organic small molecules, which are inspired from photosensitizers for photodynamic therapy.[25] Similar to photosensitizers, the first generation of sonosensitizers are based on porphyrin derivatives, including hematoporphyrin monomethyl ether (HMME), protoporphyrin IX (PpIX) hematoporphyrin (Hp), photofrin and so on.[26] Furthermore, many other organic molecules have also been identified as sonosensitizers, such as chlorophyll, hypocrellin B (HB), curcumin and their derivatives.[27–34] However, the nonspecific distribution and poor pharmacokinetic property of organic small molecules have hindered their further clinical translation. These problems could be solved in a certain extent through loading the small molecules into organic NPs. Common organic NPs are including liposomes and self-assembled organic NPs.

Consisting of multiple phospholipids, liposomes are widely used for the sonosensitizer delivery because of their good biocompatibility and biodegradability. For example, porphyrin analogue (purpurin 18), as a sonosensitizer, was loaded into liposomes for the SDT of bacterial infections (Figure 1A).[35] Moreover, self-assembled organic NPs are also developed for the sonosensitizer encapsulation. For example, Zhai's group constructed chondroitin sulfate-adipic dihydrazide-chlorin e6-lipoic acid (CS-ADH-Ce6-LA) self-assemble NPs to load with docetaxel (DTX), named as DTX/X-NPs (Figure

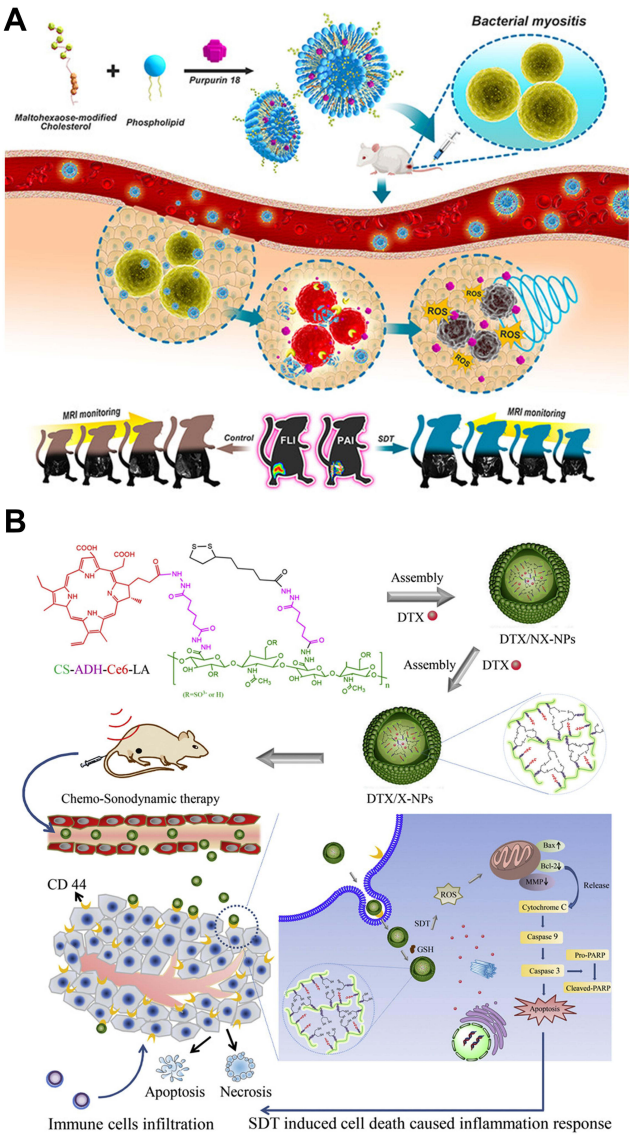

Figure 1 (**A**) Scheme illustration of purpurin 18 loaded liposomes for diagnosis and therapy of bacterial infection. Reprinted with permission from *ACS Nano*. Pang X, Xiao Q, Cheng Y et al. Bacteria-responsive nanoliposomes as smart sonotheranostics for multidrug resistant bacterial infections, pages 2427–2438. Copyright 2019 American Chemical Society.[35] (**B**) Illustration of the preparation, tumor accumulation, drug release and immune response mechanism of DTX/X-NPs. Reprinted from *Journal of Controlled Release*. Liu M, Khan A. R, Ji J et al. Crosslinked self-assembled nanoparticles for chemo-sonodynamic combination therapy favoring antitumor, antimetastasis management and immune responses, pages 150–164. Copyright 2018, with permission from Elsevier.[36]

1B).[36] Under low-intensity US irradiation, chemo-sonodynamic combination therapy can be achieved through these DTX/X-NPs.

Inorganic Nanoparticles

Inorganic sonosensitizers are also used to improve the efficacy of SDT, as they are usually made up of inorganic NPs. Compared with organic NPs, inorganic NPs exhibit superior chemical/physiological properties and multifunctionality.[7] Common inorganic sonosensitizers are including titanium dioxide (TiO_2) NPs, noble metal NPs, carbon-based and silica-based NPs.

TiO_2 Nanoparticles

Under US irradiation, TiO_2 NPs can produce electron−hole pairs for ROS generation.[37] However, the limited ROS generating rate due to the rapid electron−hole recombination and low stability in physiological conditions has hindered the application of TiO_2 NPs in SDT.[38] Through surface functionalization, these two challenges could be alleviated.

In order to improve the ROS-generating efficiency, functional materials could be integrated to the surface of TiO_2 NPs. For example, Deepagan et al reported hydrophilized Au-TiO_2 nano-composites (HAu-TiO_2 NCs) as sonosensitizers to increase the yield of ROS (Figure 2A).[38] Compared with HTiO_2 NPs, HAu-TiO_2 NCs were able to produce more ROS, which enhanced the efficacy of SDT.

For improving the stability, some molecules could be anchored on the surface of TiO_2 NPs. As a typical paradigm, You et al used hydrophilic carboxymethyl dextran (CMD) to modify the surface of TiO_2 NPs (Figure 2B).[39] After CMD coating, the stability and blood circulation time of TiO_2 NPs were increased.

Noble Metal Nanoparticles

Through preventing electron−hole recombination and increasing ROS generation, some noble metal materials like Au, Ag and Cu can be used to improve the efficacy of SDT.[8] Au NPs are eminently suitable for sonosensitizers due to the high biocompatibility and easy surface modification.[40,41] For example, Courrol et al reported gold NPs functionalized with polyethylene glycol (PEG) as sonosensitizers for SDT.[42] In addition, some other noble metal NPs could also enhance SDT. As a typical paradigm, Bernard et al developed AgCu bimetallic NPs to combine with US.[43] In vitro experimental results demonstrated that these bimetallic NPs could improve the SDT and significantly decrease the cell viability of human ovarian carcinoma cell A2780.

Carbon-Based and Silica-Based Nanoparticles

Carbon-based NPs such as fullerene and graphene have been developed for sonosensitizers because they can separate electrons and holes.[8] For example, Yumita et al investigated the US-induced antitumor effect of polyhydroxy

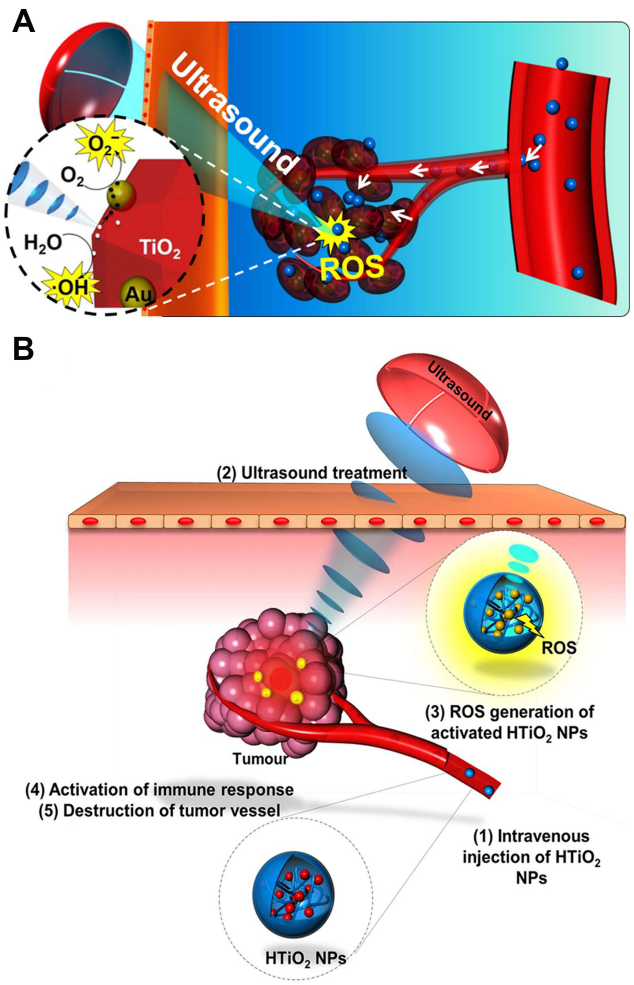

Figure 2 (**A**) Schematic illustration of passive accumulation and ROS generation by HAu-TiO_2 NCs. Reprinted with permission from *Nano letters*. Deepagan VG, You DG, Um W et al. Long-circulating Au-TiO_2 nanocomposite as a sonosensitizer for ROS-mediated eradication of cancer, 6257–6264. Copyright 2016, American Chemical Society.[38] (**B**) Schematic illustration of SDT induced by $HTiO_2$ NPs. Reprinted from *Scientific Reports*. You DG, Deepagan VG, Um W et al. ROS-generating TiO_2 nanoparticles for non-invasive sonodynamic therapy of cancer, article number 23200. Copyright 2016, with permission from Nature Publishing Group.[39]

fullerene (PHF) and proved that PHF is a potential sonosensitizer for SDT.[44]

Moreover, because the ability of absorbing US energy and inducing hyperthermia, silica-based NPs are also suitable for sonosensitizers.[45,46] For example, Osminkina et al prepared porous silicon NPs covered by dextran.[45] Upon US irradiation (1–3 MHz, 1–2 W/cm^2), these silicon NPs could inhibit the tumor growth both in vitro and in vivo through inducing hyperthermia.

It is worth noting that the collapse of bubbles (namely inertial cavitation) can also generate ROS, even without the assistance of sonosensitizers. Therefore, thorough constructing gas-generating NPs and producing specific gas bubbles (such as O_2, CO_2, NO), the efficacy of SDT can also be improved.[47]

Biomedical Applications of Nanoparticles Assisted Sonosensitizers

Characterized by non-invasive and deep penetrative nature, US has been widely used in tumor diagnosis and treatment,[5,8] such as imaging,[48] drug delivery,[4,49] HIFU[50] and SDT-based synergistic therapy.[7–9]

Ultrasound Imaging

Effective ultrasonic imaging needs the particles size in the micron range, which are too large to penetrate through the intervals of vascular endothelial cells to cancer cells.[51,52] To solve this size challenge, many phase-changeable NPs have been designed, which could accumulate in tumor site through enhanced permeability and retention effect (EPR) and then generate micrometer-sized bubbles by phase-change.[53]

The most common phase-changeable NPs are using NPs to load with liquid fluorocarbons.[11] Under US irradiation, the liquid fluorocarbon changes to gas phase and microbubbles are formed, leading to enhanced ultrasonography. As a typical paradigm, Kim et al fabricated echogenic glycol chitosan NPs (named as Echo-CNPs) to encapsulate perfluoropentane (PFP) and anticancer drug (Figure 3A).[54] Through US irradiation (10 MHz, 0.0676 W/cm^2), liquid-phase PFP transformed to microbubbles and anticancer drugs were also released, which resulted in cancer theranostics.

Furthermore, US imaging can be used to combine with other imaging modalities, such as photoacoustic imaging (PAI) and magnetic resonance imaging (MRI). For example, Huang et al designed a mesoporous silica coated gold nanorod to fill with PFP (GNR@SiO_2-PFP), which could enhance US/PA dual-modality imaging (Figure 3B).[55] In another work, Chen's group reported targeted theranostic NPs consisting of folic acid (FA), poly(lactic-co-glycolic acid) (PLGA), Fe_3O_4 NPs, perfluorohexane (PFH) and doxorubicin (DOX) (PFH/DOX@PLGA/Fe_3O_4-FA), which were able to achieve US/MR dual-modality imaging and chemotherapy/HIFU synergistic therapy (Figure 3C).[56]

Ultrasound-Triggered Drug Delivery

Because of the sonoporation effect which can form pores in the cell membrane thus increased the drug transport, US has been widely used for drug delivery,[49] such as small molecules,[57] DNA,[58] small interfering RNA (siRNA)[59]

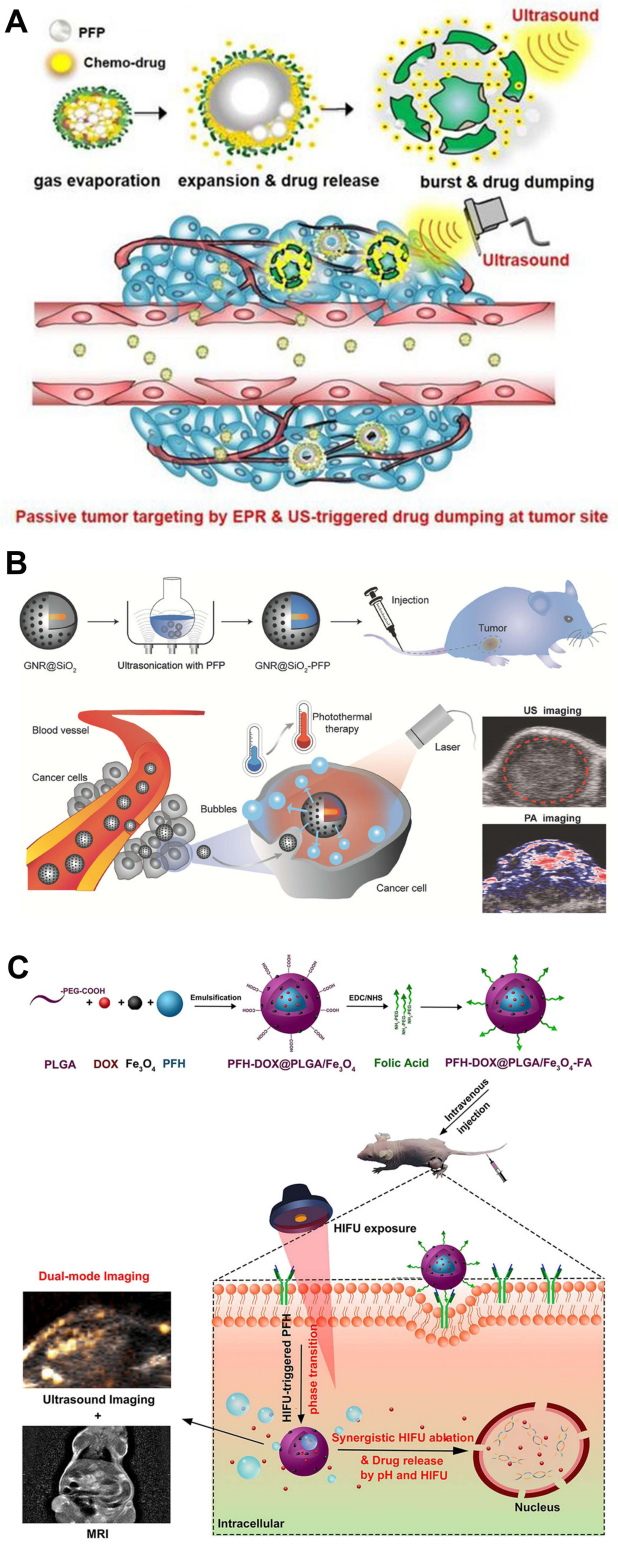

Figure 3 (**A**) Schematic illustration of Echo-CNPs. Reprinted from *Theranostics*. Min HS, You DG, Son S et al. Echogenic glycol chitosan nanoparticles for ultrasound-triggered cancer. *Theranostics*. 2015;5:1402–1418. Copyright 2015, with permission from Ivyspring International Publisher.[54] (**B**) Schematic illustration of GNR@SiO_2-PFP for US/PA dual-modality imaging. Reprinted from *Advanced Materials*. Li C, Zhang Y, Li Z et al. Light-responsive biodegradable nanorattles for cancer theranostics. © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[55] (**C**) Schematic illustration of PFH/DOX@PLGA/Fe_3O_4-FA NPs for US/MR dual-modality imaging and chemotherapy/HIFU synergistic therapy. Reprinted with permission from *ACS Applied Materials and Interfaces*. Tang H, Guo Y, Peng L et al. In vivo targeted, responsive, and synergistic cancer nanotheranostics by magnetic resonance imaging-guided synergistic high-intensity focused ultrasound ablation and chemotherapy, pages 15428–15441. Copyright 2018 American Chemical Society.[56]

and proteins.[60] For example, Shuai et al prepared a polymersome-based nanoprobe consisting of PFP, pentafluorobutane (PFB) and DOX for effective drug delivery into deep tissue through US (Figure 4A).[61] Once reaching the tumor site, the nanoprobes swelled and caused the reduction of the vaporization threshold of PFP/PFB, which resulted in the generation of nano/micro-bubbles for enhanced imaging and drug delivery. Moreover, under low-frequency US irradiation, the released DOX from nanoprobes could realize deep penetration.

In addition, US can be used to facilitate drug delivery across the blood-brain barrier (BBB),[9,62] which is comprised

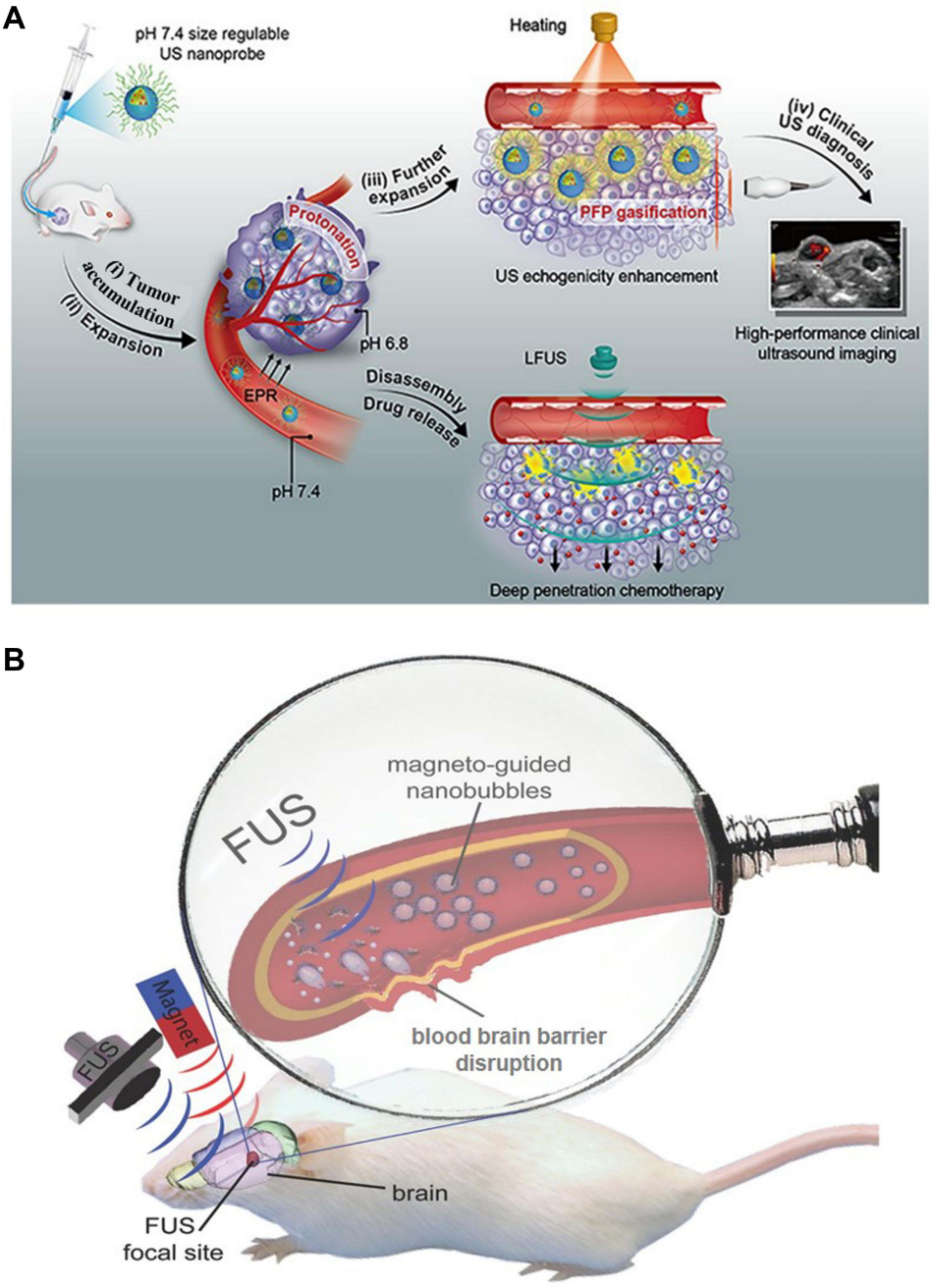

Figure 4 (**A**) Schematic illustration of theranostical nanoprobes showing tunable size and performance in vivo derived from multi-stimulation sensitivity. Reprinted with permission from *ACS Nano*. Zhang L, Yin T, Li B et al. Size-modulable nanoprobe for high-performance ultrasound imaging and drug delivery against cancer, pages 3449–3460. Copyright 2018 American Chemical Society.[61] (**B**) Schematic diagram of disrupting the BBB by magnetically guidable theranostic nanobubbles. Reprinted from *Advanced Materials*. Huang H, Liu H, Hsu P et al. A multitheragnostic nanobubble system to induce blood–brain barrier disruption with magnetically guided focused ultrasound. © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[64]

of endothelial cells and protects the brain from harmful substances.[63] As a typical paradigm, Chen's group designed a silica shell consisting of super-paramagnetic iron oxide and nanobubbles for magnetically guidable focused US-induced BBB disruption (Figure 4B).[64]

High Intensity Focused Ultrasound

HIFU, which uses the thermal effect for achieving ablation based on the high intensity, has been utilized for the cancer treatment.[50] However, the relatively low curative effect has limited its further extensive application.[65] With the help of NPs, the therapeutic efficacy of HIFU can be efficiently enhanced. Most recently, Chen et al designed silica-coated PLGA NPs encapsulating perfluorocarbon (PFOB), superparamagnetic Fe_3O_4 and antitumor ruthenium complex (RuPOP) (Figure 5).[66] Upon HIFU irradiation, the PFOB gasified and caused the collapse of silicon shell, which resulted in improved HIFU therapeutic effect. Furthermore, the blasting behavior also triggered the burst release of RuPOP in tumor tissue, which was contributed to maximize the synergistic effect of HIFU and chemotherapy. Furthermore, the addition of super-paramagnetic Fe_3O_4 can realize US/MR dual mode imaging.

Sonodynamic Therapy-Based Combination Therapy

Based on NPs, synergistic antitumor effect could be realized through combining SDT with other therapeutic strategies, such as chemotherapy, chemodynamic therapy (CDT), immunotherapy, photothermal therapy (PTT), photodynamic therapy (PDT) and so on.[9,10] In this section, we have listed and discussed several combined therapies based on SDT (Table 1).

Sonodynamic Therapy Combined with Chemotherapy

Chemotherapy is the most common and highly effective method for cancer therapy.[67] However, the emergence of drug resistance always results in poor clinical prognosis.[10,67] SDT is able to activate the caspase signaling pathway and downregulate the adenosine triphosphate-binding cassette (ABC) transporters, which is contributed to overcome the drug resistance.[68] Meanwhile, SDT can trigger the drug release in tumor site. Taken together, synergistic effect could

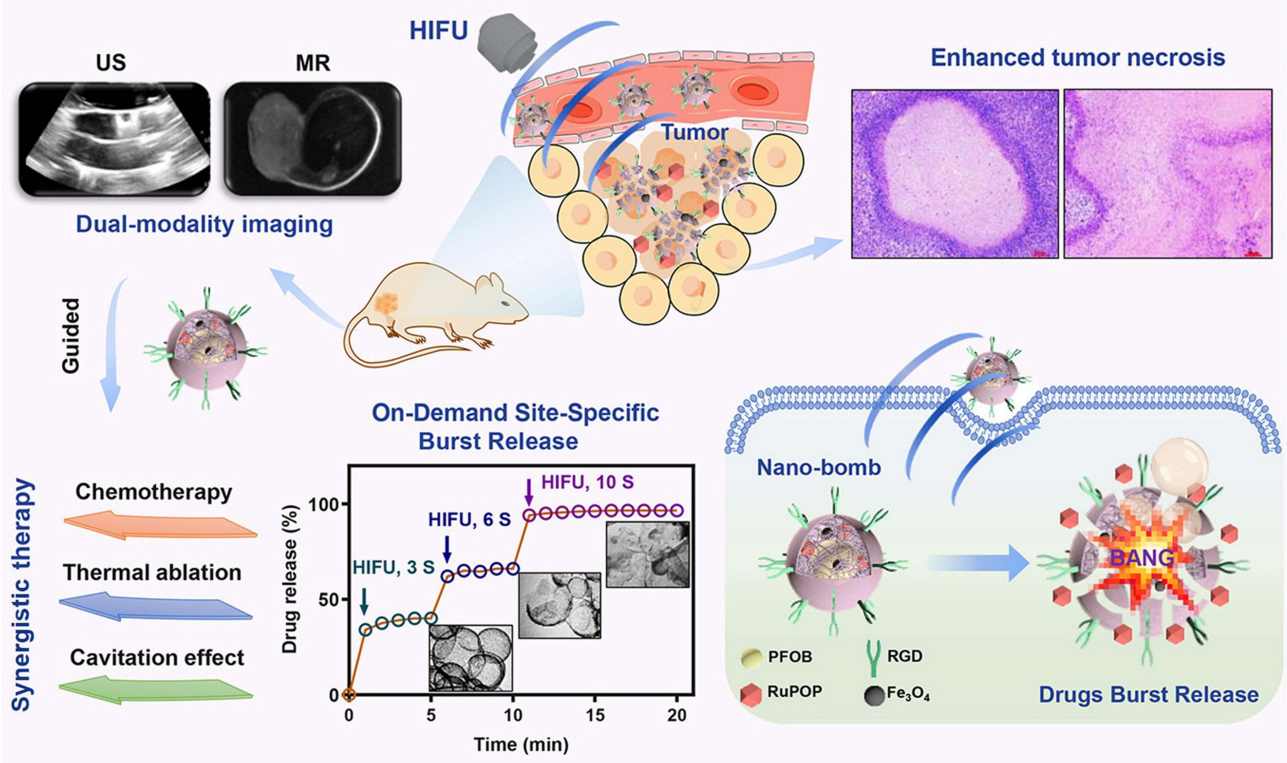

Figure 5 Schematic illustration of nano-bomb with site-specific drug burst release to achieve HIFU/chemotherapy synergistic therapy under the US/MR-guided imaging. Reprinted from *Journal of Controlled Release*. Mai X, Chang Y, You Y et al. Designing intelligent nano-bomb with on-demand site-specific drug burst release to synergize with high-intensity focused ultrasound cancer ablation, pages 270–281. Copyright 2020, with permission from Elsevier.[66]

Table 1 Sonodynamic Therapy-Based Combination Therapy

Therapy Mode	NPs	In vitro US Parameters	In vivo US Parameters	Ref
SDT+Chemo	Ce6-PTX@IR783	1 MHz, 1.5W/cm^2, 50% duty cycle, 90 sec	1 MHz,1 W/cm^2, 50% duty cycle, 5 min	[69]
	Hematoporphyrin-DOX-Pluronic F68	1 MHz, 1.5 W/cm^2, 30 s	1 MHz, 3 W/cm^2, 5 min	[70]
	Fe_3O_4@TiO_2-DOX	1 W/cm^2, 3 min	1 W/cm^2, 3 min	[71]
	Fe_3O_4-$NaYF_4$@TiO_2-DOX	1 W/cm^2, 0.5–5 min	1 W/cm^2, 3 min	[72]
	Lipo-Ce6/TPZ@M_H	3 MHz, 1 W/cm^2, 40 s	3 MHz, 1 W/cm^2, 40 s	[73]
	CUR@PEI-FA-DSTN	1 MHz, 2 W/cm^2, 30–120 s		[74]
	DTX/CS-ADH-Ce6-LA	1 MHz, 1 W/cm^2, 70% duty cycle, 1–3 min	1 MHz, 1 W/cm^2, 70% duty cycle	[36]
	ICG@PCH@Dox	1 MHz, 2–6 W/cm^2, 5% duty cycle, 60 s	1.2 MHz, 2–6 W/cm^2	[75]
	DOX@HMONs-PpIX-RGD	1 MHz, 1 W/cm^2, 50% duty cycle, 1 min	1 MHz, 1 W/cm^2, 50% duty cycle, 5 min	[76]
	MTN@DTX-CD	1 W/cm^2, 30 s	1 W/cm^2, 40 s	[77]
	PTX@FA-β-CD/H-MSN	1 MHz, 0.4–1 W/cm^2, 80 s	1 MHz, 0.8 W/cm^2, 3 min	[78]
SDT+CDT	$PtCu_3$	35 kHz, 3 W/cm^2, 10 min	35 kHz, 3 W/cm^2, 10 min	[80]
	H_2O_2/Fe_3O_4-PLGA	40 MHz	40 MHz	[81]
	PEG−TiO_{1+x}	40 kHz, 3.0 W/cm^2, 50% duty cycle, 5 min	40 kHz, 3.0 W/cm^2, 50% duty cycle, 5 min	[82]
	Au-MnO	1 MHz, 2 W/cm^2, 10 min	1 MHz, 2 W/cm^2, 10 min	[83]
SDT+Immunotherapy	Zn-TCPP/CpG	40 kHz, 2 W/cm^2, 5 min	40 kHz, 2 W/cm^2, 30 min	[86]
	HMME/R837@Lip	1 MHz, 1.5 W/cm^2, 50% duty cycle, 1 min	1 MHz, 1.5 W/cm^2, 50% duty cycle, 5 min	[87]
	ANVs-TPPS	1 MHz, 0.97 W/cm^2, 50% duty cycle, 8 min	1 MHz, 0.97 W/cm^2, 50% duty cycle, 8 min	[88]
	PFP@PEG-CMD-Ce6	1 MHz, 30 W, 20% duty cycle, 5 min	1 MHz, 10 W, 20% duty cycle, 10 min	[89]
SDT+PTT	Pt-CuS-TAPP	1 MHz, 0.5 W/cm^2, 60% duty cycle, 2 min	1 MHz, 1 W/cm^2, 60% duty cycle, 5 min	[91]
	B-TiO_{2-x}-PEG	1 MHz, 1.5 W/cm^2, 50% duty cycle, 5 min	1 MHz, 1.5 W/cm^2, 50% duty cycle, 5 min	[92]
	MnOx/TiO_2-GR-PVP	1 MHz, 1.5 W/cm^2, 50% duty cycle, 3 min	1 MHz, 1 W/cm^2, 50% duty cycle, 5 min	[93]
	Au NPL@TiO_2	3 MHz, 0.5 W/cm^2, 20 min	3 MHz, 0.5 W/cm^2, 20 min	[94]
	Ti−S−TiO_{2-x}	1 MHz, 1.5 W/cm^2, 50% duty cycle, 15 min	1 MHz, 1.5 W/cm^2, 50% duty cycle, 15 min	[95]
	D-ZnOx:Gd	1 MHz, 0.7 W/cm^2, 50% duty cycle	1 MHz, 1 W/cm^2, 50% duty cycle	[96]
SDT+PDT	UCNP@SiO_2-RB/HMME	2 W/cm^2, 10 min		[98]
	FA-NGO-SLux		0.8 MHz, 3 W/cm^2, 3 min	[99]
	Fe@UCNP-HMME	2 W/cm^2, 10 min	2 W/cm^2, 10 min	[100]
	HP/ICG-PLGA	1 MHz, 2.5 W/cm^2, 50% duty cycle, 30 s	1 MHz, 3.5 W/cm^2, 50% duty cycle, 3.5 min	[101]
	PARN	1 MHz, 1 W/cm^2, 50% duty cycle, 3 min	1 MHz, 1 W/cm^2, 50% duty cycle, 3 min	[102]

be achieved through combining SDT and chemotherapy.[36,69–78] Recently, Chen et al fabricated a self-assemble sonosensitizer composed of hydrophobic fluorescent dye chlorin e6 (Ce6), hydrophobic antitumor drug paclitaxel (PTX) and hydrophilic cyanine dye IR783 (named as Ce6-PTX@IR783, Figure 6).[69] Among these three parts, Ce6 can improve the efficacy of SDT, PTX was used for chemotherapy, and IR783 was applied for tumor-targeting and PAI. Upon US irradiation (1.0 MHz, 1.0–1.5 W/cm^2), Ce6-PTX@IR783 can realize synergistic effect of SDT and chemotherapy.

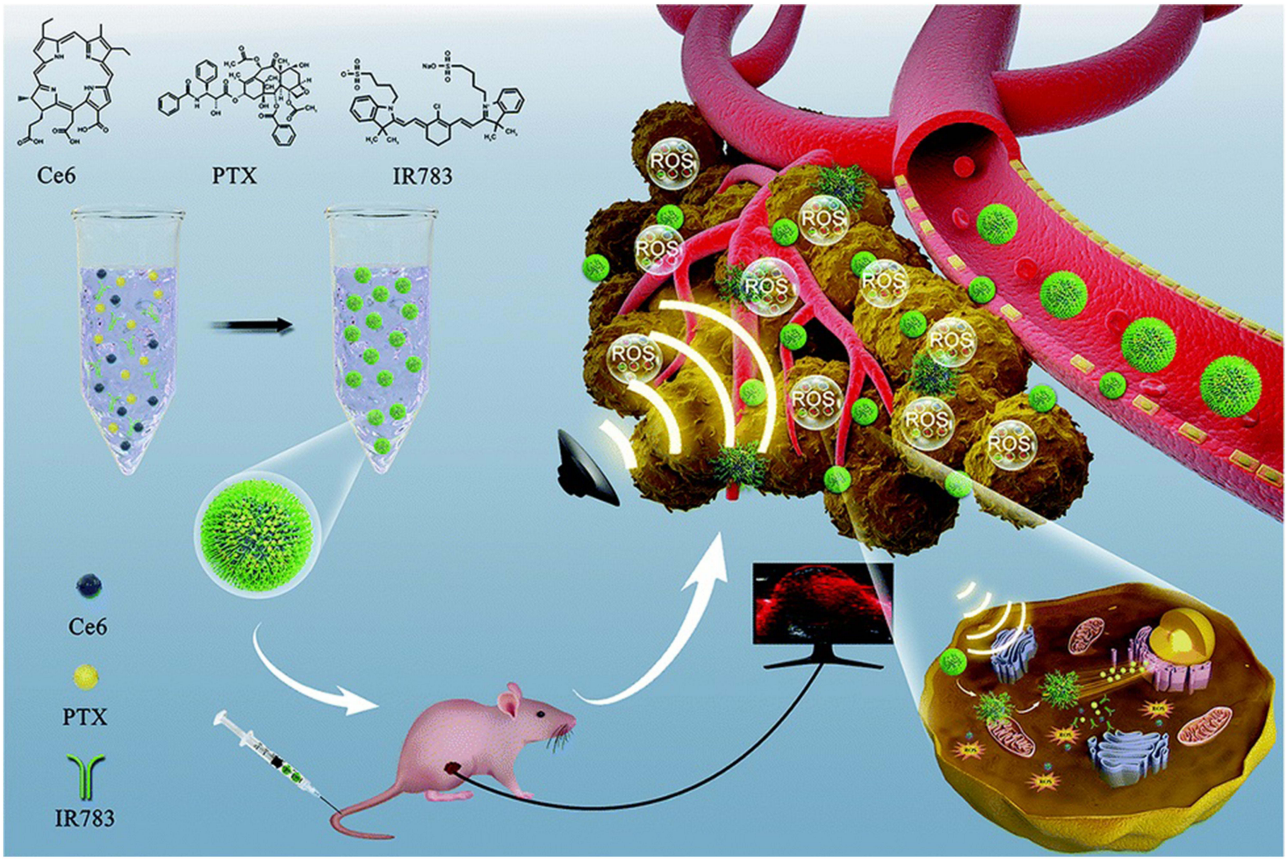

Figure 6 Schematic illustration of SDT-chemo combination therapy based on Ce6-PTX@IR783, including transportation in blood vessels, tumor accumulation, PA image, drug release and US-triggered synergistic effect. Reprinted from *Nanoscale*. Dong C, Jiang Q, Qian X et al. A self-assembled carrier-free nanosonosensitizer for photoacoustic imaging-guided synergistic chemo-sonodynamic cancer therapy, pages 5587–5600. Copyright 2020, with permission from Royal Society of Chemistry.[69]

Sonodynamic Therapy Combined with Chemodynamic Therapy

Chemodynamic therapy (CDT) is an ROS-based therapeutic modality, which utilize the acidity and overexpressed H_2O_2 of tumor microenvironment. Through Fenton or Fenton-like reactions, highly toxic $^{\bullet}OH$ could be in situ produced by catalyzing H_2O_2 without external stimulation, thus avoiding the challenges of limited penetration and side effects.[79] Investigators have doped the elements of CDT (such as Fe^{3+}/Fe^{2+}, Cu^{2+}/Cu^{+}, Mn^{2+}) into SDT to achieve the synergistic treatment, which leads to encouraging results.[80–83] Most recently, Yang et al reported $PtCu_3$ nanocages as sonosensitizer with high ROS production under US irradiation (35 kHz, 3 W/cm^2, Figure 7).[80] Meanwhile, these nanocages can act as Fenton-like nanozymes to catalyze the decomposition of H_2O_2 into $^{\bullet}OH$ under the acidic tumor microenvironment for CDT. Moreover, $PtCu_3$ nanocages were able to mimic glutathione peroxidase to accelerate glutathione (GSH) depletion. Taken together, $PtCu_3$ nanocages can realize effective CDT-enhanced SDT.

Sonodynamic Therapy Combined with Immunotherapy

Immunotherapy aims to active the immune system to search and destroy tumor cells.[84] An activated immune response is able to facilitate systemic immune surveillance, eliminate local and metastatic tumor. Moreover, immunotherapy could generate long-term immune memory to prevent cancer recurrence. Meanwhile, SDT has been confirmed to produce tumor cell fragments, which can act as tumor antigens for inducing the antitumor immune effect.[85] Therefore, the combination of SDT and immunotherapy has been successively developed.[86–89] For example, Liu's group fabricated two-dimensional (2D) nanosheets consisting of Zn^{2+}, sonosensitizer tetrakis (4-carboxyphenyl) porphyrin (TCPP) and immune adjuvant cytosine–phosphorothioate–guanine (CpG) (Zn-TCPP/CpG nanosheets, Figure 8).[86] Under US irradiation (40 kHz, 2 W/cm^2), tumor-associated antigens were released through SDT; then, tumor-specific immune responses were triggered. Thereby, through the assist of

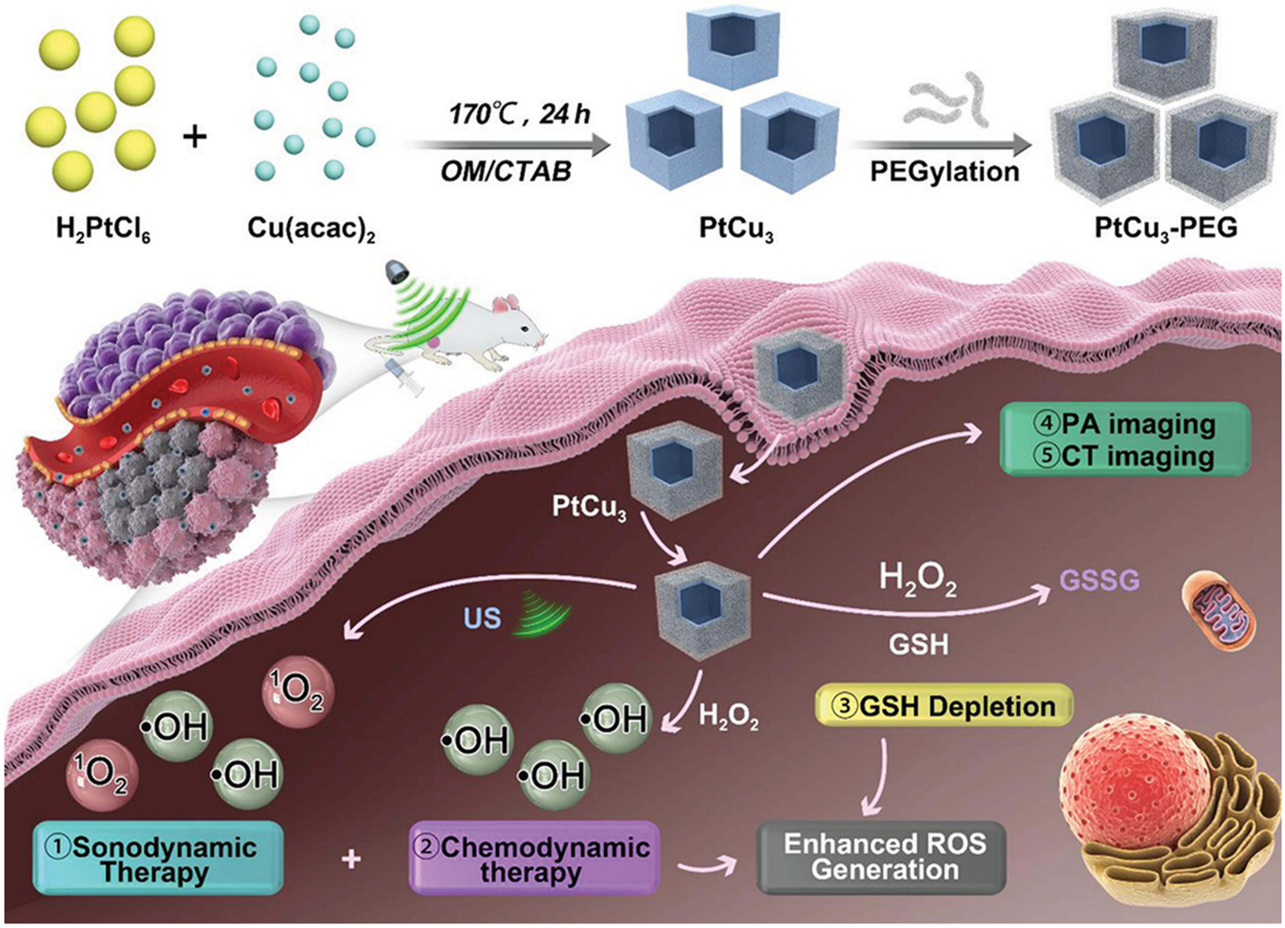

Figure 7 Schematic image of photoacoustic (PA)/computed tomography (CT) dual-modal imaging guided CDT/SDT combination therapy by $PtCu_3$ nanocages. The $PtCu_3$ nanocages can generate $^1O_2$ and $^{\bullet}OH$ upon the US irradiation. Furthermore, $PtCu_3$ nanocages as horseradish peroxidase (HRP) mimic could also generate $^{\bullet}OH$ via Fenton-like reaction for CDT. Interestingly, $PtCu_3$ nanocages as another glutathione peroxidase (GSH-Px)-like nanozyme can accelerate the depletion of GSH. Reprinted from *Advanced Functional Materials*. Zhong X, Wang X, Cheng L et al. GSH-depleted $PtCu_3$ nanocages for chemodynamic-enhanced sonodynamic cancer therapy. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[80]

Zn-TCPP/CpG nanosheets, SDT can not only destruct primary tumors, but also induce effective immune responses and memory to inhibit distant tumors and cancer recurrence.

Sonodynamic Therapy Combined with Photothermal Therapy

Photothermal therapy (PTT), providing thermal energy under light irradiation for tumor damage, has become a promising antitumor approach.[90] Recently, the combination of SDT and PTT has also been reported.[91–96] For example, Lin and co-workers synthesized a novel Pt-CuS Janus consisting of hollow semiconductor CuS, sonosensitizer tetra-(4-aminophenyl) porphyrin (TAPP) and noble metallic Pt (Figure 9).[91] The deposition of Pt not only improved the photothermal performance, but also simulated nanozyme for catalyzing the decomposition of H_2O_2 to generate O_2 that could overcome tumor hypoxia and enhance the ROS production. Under US (1 MHz,1.0 W/cm^2) and laser (808 nm) irradiation, the synergistic antitumor effect of SDT and PTT can be realized.

Sonodynamic Therapy Combined with Photodynamic Therapy

Photodynamic therapy (PDT), which utilizes photosensitizers to generate ROS for directly or indirectly perishing cancer cells, has served as an effective modality for cancer therapy.[97] However, the limited tissue penetration of light has hindered the widespread application of PDT. SDT can provide deeper penetration depth; meanwhile, most of sonosensitizers are from photosensitizers, which makes these sensitizers could be activated by both US and light irradiation.[25] Thereby, the combination of SDT and PDT is able to generate more ROS, which will increase the antitumor efficacy and decrease the sensitizer dose.[98–102] For

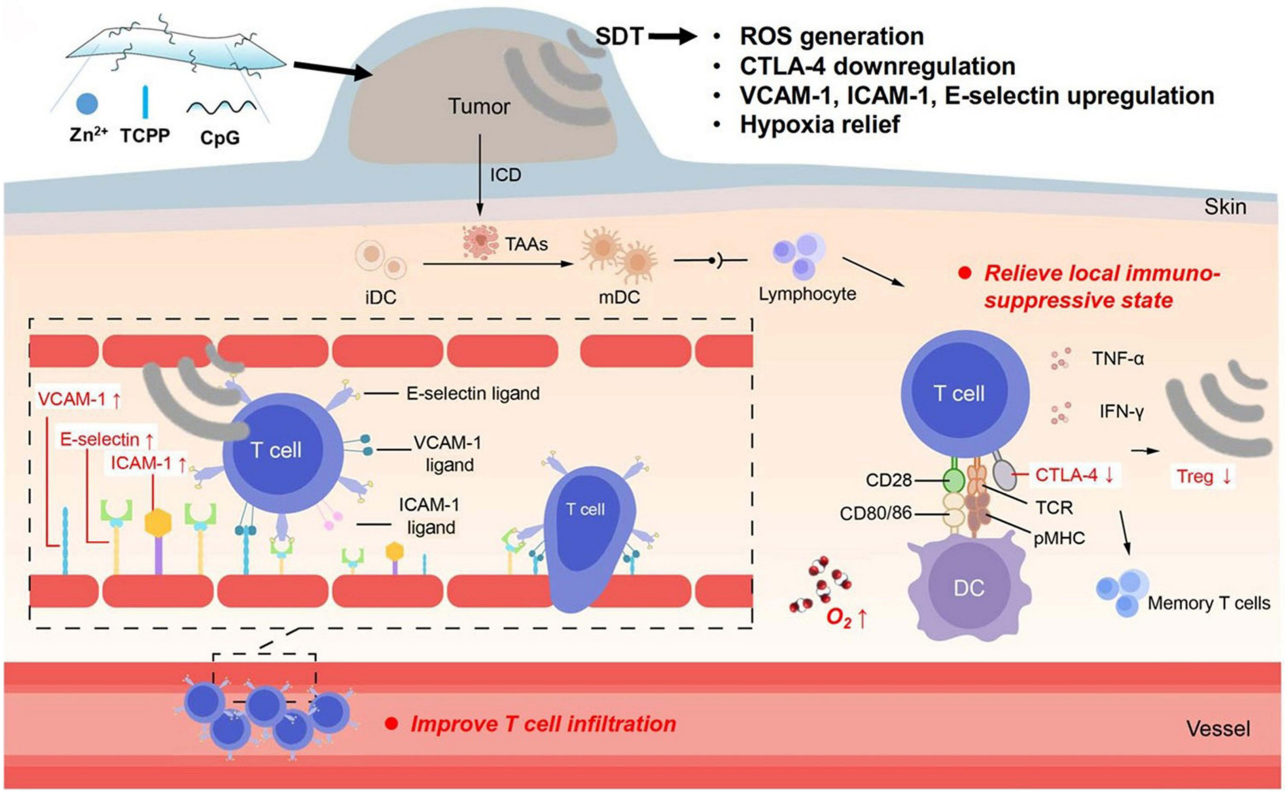

Figure 8 Schematic illustration of the immune response mechanism induced by Zn-TCPP/CpG nanosheets-based SDT. First, SDT could induce immunogenic cell death (ICD) and release tumor-associated antigens (TAAs), which could be presented by dendritic cells (DCs). Then, the immune system could be activated to inhibit tumor metastasis due to the antigen presentation by matured DCs. In addition, US itself can enhance anti-tumor immune responses through improving T cells infiltration and decreasing regulatory T cells in the tumor microenvironment. Reprinted with permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Nano Research* https://www.springer.com/journal/12274. Zhu W, Chen Q, Jin Q et al. Sonodynamic therapy with immune modulatable two-dimensional coordination nanosheets for enhanced anti-tumor immunotherapy. Copyright 2020.[86]

example, Liu et al developed core-shell up-conversion NPs (UCNPs), which loading HMME into up-conversion core and covalently linking rose bengal (RB) on silica (SiO_2) shell, for SDT and PDT synergistic antibacterial treatment (Figure 10).[98]

It is worth noting that both SDT and PDT are heavily dependent on O_2; hence, O_2 could be a breakthrough point for improving the synergistic efficacy. Furthermore, SDT can also combine with some other therapy modalities such as gas therapy, starvation therapy, HIFU and so on.

Challenges and Future Perspectives

NPs-based sonosensitizers have been successfully assisted US applications, especially in SDT. Although clinical trials are still awaited, the pre-clinical data have evidently demonstrated the efficacy of NPs-assisted sonosensitizers in SDT. In order to realize the clinical translation of SDT, there are still several challenges which need to be addressed.

First, the exact mechanism of SDT still remains unclear so far. Future studies ought to confirm the SDT mechanism, including the role of NPs-assisted sonosensitizers and the process of synergistic treatment.

Second, current sonosensitizers suffer from skin sensitivity, low specificity and poor pharmacokinetics, which limit the therapeutic effect of SDT. Further research should focus on exploring novel sonosensitizers with high efficacy and less toxicity through optimizing the structural and acoustic capabilities.

Third, although plenty of studies have proved the short-term safety of involved NPs, long-term toxicity studies are needed to ensure the biosafety of NPs-assisted sonosensitizers. In next step research, NPs with improved biocompatibility and biodegradability need to be developed.

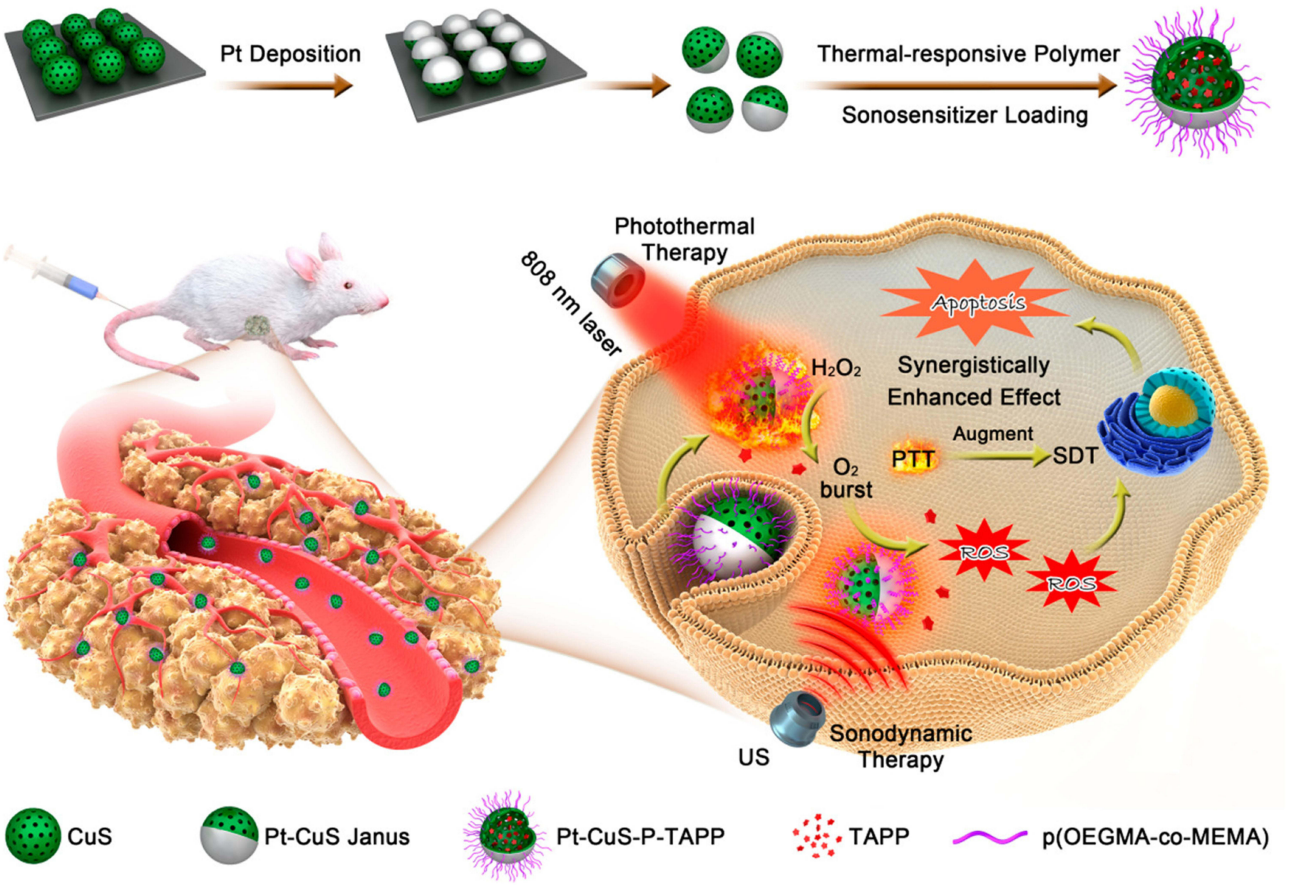

Figure 9 Schematic diagram of preparation and synergistic mechanism of Pt-CuS-P-TAPP. Reprinted with permission from *Nano Letters*. Liang S, Deng X, Chang Y et al. Intelligent hollow Pt-CuS janus architecture for synergistic catalysis-enhanced sonodynamic and photothermal cancer therapy, pages 4134–4145. Copyright 2019 American Chemical Society.[91]

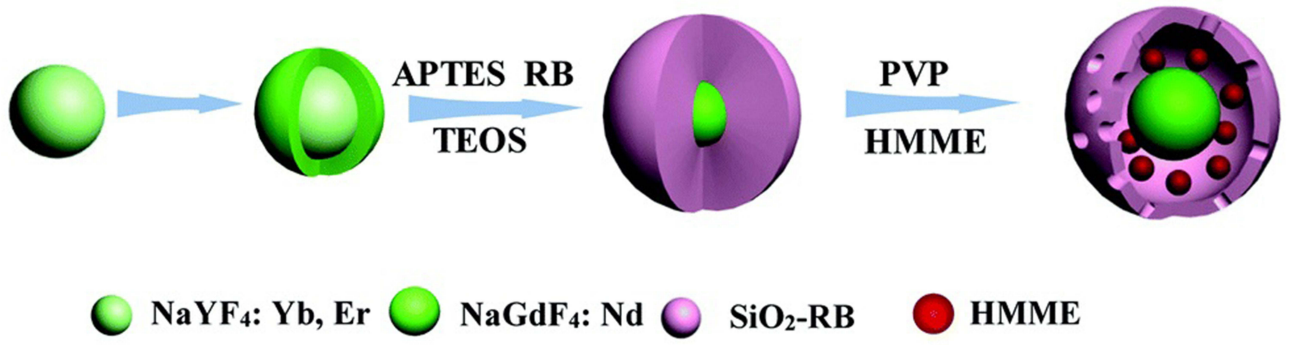

Figure 10 Schematic illustration of the construction of UCNP@SiO_2-RB/HMME NPs. Reprinted from *Biomaterials Science*. Xu F, Hu M, Liu C et al. Yolk-structured multifunctional up-conversion nanoparticles for synergistic photodynamic-sonodynamic antibacterial resistance therapy, pages 678–685. Copyright 2017, with permission from Royal Society of Chemistry.[98]

Fourth, the US parameters used in different studies lack of consistency. Hence, further research is needed to optimize US parameters such as frequency, intensity, treatment duration and mechanical index.

So far, NPs-assisted sonosensitizers in biomedical applications are mostly focused on tumor therapy. Future potential prospect could include BBB opening for central nervous system therapy, anti-microbial and bacterial therapy. Although

there remain many obstacles to overcome, the development of NPs-assisted SDT will provide more benefits for patients.

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Disclosure

The authors disclose no conflicts.

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