Nanoparticle-Assisted Sonosensitizers and Their Biomedical Applications

Pengxuan Zhao
Youbin Deng
Guangya Xiang
Yani Liu

Department of Medical Ultrasound, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, People's Republic of China; School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, People's Republic of China

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. 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. However, the major challenge for PDT is the low penetration of light, which limits the application of PDT in deep tumor.

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. 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. As an emerging treatment mode, SDT utilizes US to activate sonosensitizers for ROS production, which could overcome the depth limitation. However, traditional organic sonosensitizers suffer from poor pharmacokinetics and tumor accumulation, which limit the efficacy of SDT. Promoted by the rapid development of nanomedicine, various NPs have been developed to assist sonosensitizers for improving the efficacy of SDT.

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.
Mechanisms of Sonodynamic Therapy

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

Generation of Reactive Oxygen Species

Up to now, the most recognized mechanism is the production of ROS by sonosensitizers during the US. After absorbing the energy from US, the sonosensitizers could be activated to produce ROS including singlet oxygen (\(O_2^*\)), hydroxyl radicals (\(^{\cdot}\)OH), superoxide anion (\(O_2^{-}\)) or hydrogen peroxide (\(H_2O_2\)). Different kinds of ROS are generated with the selection of different sonosensitizers. For example, hematoporphyrin could produce singlet oxygen to kill the tumor cells. Meanwhile, titanium oxide TiO\(_2\) NPs and bimetallic oxide MnWO\(_x\) NPs are reported to generate both singlet oxygen and hydroxyl radicals for enhanced SDT efficiency.

Mechanical Effects

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

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

Thermal Effects

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

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. 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. These 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. 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. Furthermore, many other organic molecules have also been identified as sonosensitizers, such as chlorophyll, hypocrellin B (HB), curcumin and their derivatives. 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). 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 1B).
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. 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. 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. 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. 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. 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. Au NPs are eminently suitable for sonosensitizers due to the high biocompatibility and easy surface modification. For example, Courrol et al reported gold NPs functionalized with polyethylene glycol (PEG) as sonosensitizers for SDT. 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. 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. For example, Yumita et al investigated the US-induced antitumor effect of polyhydroxy

---

**Figure 1 (A)** Scheme illustration of purpurin 1B 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. **(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.
fullerene (PHF) and proved that PHF is a potential sono-sensitizer for SDT.\textsuperscript{44}

Moreover, because the ability of absorbing US energy and inducing hyperthermia, silica-based NPs are also suitable for sonosensitizers.\textsuperscript{45,46} For example, Osminkina et al prepared porous silicon NPs covered by dextran.\textsuperscript{45} Upon US irradiation (1–3 MHz, 1–2 W/cm\textsuperscript{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\textsubscript{2}, CO\textsubscript{2}, NO), the efficacy of SDT can also be improved.\textsuperscript{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,\textsuperscript{5,8} such as imaging,\textsuperscript{48} drug delivery,\textsuperscript{4,49} HIFU\textsuperscript{50} and SDT-based synergistic therapy.\textsuperscript{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.\textsuperscript{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.\textsuperscript{53}

The most common phase-changeable NPs are using NPs to load with liquid fluorocarbons.\textsuperscript{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).\textsuperscript{54} Through US irradiation (10 MHz, 0.0676 W/cm\textsuperscript{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\textsubscript{2}-PFP), which could enhance US/PA dual-modality imaging (Figure 3B).\textsuperscript{55} In another work, Chen’s group reported targeted theranostic NPs consisting of folic acid (FA), poly(lactic-co-glycolic acid) (PLGA), Fe\textsubscript{3}O\textsubscript{4} NPs, perfluorohexane (PFH) and doxorubicin (DOX) (PFH/DOX@PLGA/Fe\textsubscript{3}O\textsubscript{4}-FA), which were able to achieve US/MR dual-modality imaging and chemotherapy/HIFU synergistic therapy (Figure 3C).\textsuperscript{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,\textsuperscript{49} such as small molecules,\textsuperscript{57} DNA,\textsuperscript{58} small interfering RNA (siRNA)\textsuperscript{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.

(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.

(C) Schematic illustration of PFH/DOX@PLGA/Fe$_3$O$_4$-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.
and proteins. 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). 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), which is comprised
of endothelial cells and protects the brain from harmful substances. 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).

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. However, the relatively low curative effect has limited its further extensive application. 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 Fe₃O₄ and antitumor ruthenium complex (RuPOP) (Figure 5). 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 Fe₃O₄ 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. 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. However, the emergence of drug resistance always results in poor clinical prognosis. 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. 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.](https://doi.org/10.2147/IJN.S307885)
be achieved through combining SDT and chemotherapy. 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). 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/cm²), Ce6-PTX@IR783 can realize synergistic effect of SDT and chemotherapy.

Table I Sonodynamic Therapy-Based Combination Therapy

| Therapy Mode | NPs | In vitro US Parameters | In vivo US Parameters | Ref |
|--------------|-----|------------------------|----------------------|-----|
| SDT+Chemo    | Ce6-PTX@IR783 | 1 MHz, 1.5 W/cm², 50% duty cycle, 90 sec | 1 MHz, 1 W/cm², 50% duty cycle, 5 min | [69] |
|              | Hematoporphyrin-DOX-Pluronic F68 | 1 MHz, 1.5 W/cm², 30 s | 1 MHz, 3 W/cm², 5 min | [70] |
|              | Fe₃O₄@TiO₂-DOX | 1 W/cm², 3 min | 1 W/cm², 3 min | [71] |
|              | Fe₂O₃NaYF₄@TiO₂-DOX | 1 W/cm², 0.5–5 min | 1 W/cm², 3 min | [72] |
|              | Lipo-Ce6/TPZ@M₄ | 3 MHz, 1 W/cm², 40 s | 3 MHz, 1 W/cm², 40 s | [73] |
|              | CUR@PEI-FA-DSTN | 1 MHz, 2 W/cm², 30–120 s | | |
|              | DTX/CS-ADH-Ce6-LA | 1 MHz, 1 W/cm², 70% duty cycle, 1–3 min | 1 MHz, 1 W/cm², 70% duty cycle | [36] |
|              | ICG@PCH@Dox | 1 MHz, 2–6 W/cm², 5% duty cycle, 60 s | 1.2 MHz, 2–6 W/cm² | [75] |
|              | DOX@HMONs-PtIX-RGD | 1 MHz, 1 W/cm², 50% duty cycle, 1 min | 1 MHz, 1 W/cm², 50% duty cycle, 5 min | [76] |
|              | MTN@DTX-CD | 1 W/cm², 30 s | 1 W/cm², 40 s | [77] |
|              | PTX@FA-li-CD/H-MSN | 1 MHz, 0.4–1 W/cm², 80 s | 1 MHz, 0.8 W/cm², 3 min | [78] |
| SDT+CDT      | PrCu₄ | 35 kHz, 3 W/cm², 10 min | 35 kHz, 3 W/cm², 10 min | [80] |
|              | H₂O₂/Fe₃O₄-PLGA | 40 kHz, 40 MHz | | |
|              | PEG-TiO₂/P₄ | 40 kHz, 3.0 W/cm², 50% duty cycle, 5 min | 40 kHz, 3.0 W/cm², 50% duty cycle, 5 min | [82] |
|              | Au-MnO | 1 MHz, 2 W/cm², 10 min | 1 MHz, 2 W/cm², 10 min | [83] |
| SDT+Immunotherapy | Zn-tTCP/CpG | 40 kHz, 2 W/cm², 5 min | 40 kHz, 2 W/cm², 30 min | [86] |
|              | HMMEMR837@Lip | 1 MHz, 1.5 W/cm², 50% duty cycle, 1 min | 1 MHz, 1.5 W/cm², 50% duty cycle, 5 min | [87] |
|              | ANV⁺-TPPS | 1 MHz, 0.97 W/cm², 50% duty cycle, 8 min | 1 MHz, 0.97 W/cm², 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      | Pr-Cu₅-TAPP | 1 MHz, 0.5 W/cm², 60% duty cycle, 2 min | 1 MHz, 1 W/cm², 60% duty cycle, 5 min | [91] |
|              | B-TiO₂/P₄-PEG | 1 MHz, 1.5 W/cm², 50% duty cycle, 5 min | 1 MHz, 1.5 W/cm², 50% duty cycle, 5 min | [92] |
|              | MnOₓTiO₂-GR/PVP | 1 MHz, 1.5 W/cm², 50% duty cycle, 3 min | 1 MHz, 1 W/cm², 50% duty cycle, 5 min | [93] |
|              | Au NPL@TiO₂ | 3 MHz, 0.5 W/cm², 20 min | 3 MHz, 0.5 W/cm², 20 min | [94] |
|              | Ti₅-S-TiO₂/P₄ | 1 MHz, 1.5 W/cm², 50% duty cycle, 15 min | 1 MHz, 1.5 W/cm², 50% duty cycle, 15 min | [95] |
|              | D-ZnOxGd | 1 MHz, 0.7 W/cm², 50% duty cycle | 1 MHz, 1 W/cm², 50% duty cycle | [96] |
| SDT+PDT      | UCNP@SiO₂-RB/HMMEME | 2 W/cm², 10 min | | [98] |
|              | FA-NGO-SLux | 0.8 MHz, 3 W/cm², 3 min | | [99] |
|              | Fe@UCNP-HMMEME | 2 W/cm², 10 min | 2 W/cm², 10 min | [100] |
|              | HPI/ICG-PLGA | 1 MHz, 2.5 W/cm², 50% duty cycle, 30 s | 1 MHz, 3.5 W/cm², 50% duty cycle, 3.5 min | [101] |
|              | PARN | 1 MHz, 1 W/cm², 50% duty cycle, 3 min | 1 MHz, 1 W/cm², 50% duty cycle, 3 min | [102] |
Sonodynamic Therapy Combined with Chemodynamic Therapy

Chemodynamic therapy (CDT) is an ROS-based therapeutic modality, which utilize the acidity and overexpressed H$_2$O$_2$ of tumor microenvironment. Through Fenton or Fenton-like reactions, highly toxic •OH could be in situ produced by catalyzing H$_2$O$_2$ without external stimulation, thus avoiding the challenges of limited penetration and side effects. Investigators have doped the elements of CDT (such as Fe$^{3+}$/Fe$^{2+}$, Cu$^{2+}$/Cu$^{+}$, Mn$^{2+}$) into SDT to achieve the synergetic treatment, which leads to encouraging results. Most recently, Yang et al reported PtCu$_3$ nanocages as sonosensitizer with high ROS production under US irradiation (35 kHz, 3 W/cm$^2$). Under US irradiation (40 kHz, 2 W/cm$^2$), tumor-associated antigens were released through SDT; then, tumor-specific immune responses were triggered. 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. 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. Therefore, the combination of SDT and immunotherapy has been successively developed. 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). 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 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.
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. Recently, the combination of SDT and PTT has also been reported. 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). The deposition of Pt not only improved the photothermal performance, but also simulated nanozyme for catalyzing the decomposition of H$_2$O$_2$ 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. 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. Thereby, the combination of SDT and PDT is able to generate more ROS, which will increase the antitumor efficacy and decrease the sensitizer dose.
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).

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.
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.

**Acknowledgments**

This work was supported by Natural Science Foundation of China grants (No. 81371581).

**Disclosure**

The authors disclose no conflicts.

**References**

1. Trendowski M. The promise of sonodynamic therapy. *Cancer Metastasis Rev.* 2014;33:143–160.

2. Costley D, Mc Ewan C, Fowley C, et al. Treating cancer with sonodynamic therapy: a review. *Int J Hyperthermia.* 2015;31:107–117. doi:10.3109/02666736.2014.992484

3. Fan W, Huang P, Chen X. Overcoming the ‘achilles’ heel of photodynamic therapy. *Chem Soc Rev.* 2016;45:6488–6519. doi:10.1039/C5CS00616G

4. Mitragotri S. Healing sound: the use of ultrasound in drug delivery and other therapeutic applications. *Nat Rev Drug Discov.* 2005;4:255–260. doi:10.1038/nrd1662

5. Yang B, Chen Y, Shi J. Reactive Oxygen Species (ROS)-Based Nanomedicine. *Chem Rev.* 2019;119:4881–4985. doi:10.1021/acs.chemrev.8b00626

6. Yumita N, Nishigaki R, Umemura K, Umemura S. Hematoporphyrin as a Sensitizer of Cell-Damaging Effect of Ultrasound. *Japan J Cancer Res.* 1989;80:219–222. doi:10.1111/j.1349-7006.1989.tb02295.x

7. Qian X, Zheng Y, Chen Y. Micro/Nanoparticle-Augmented Sonodynamic Therapy (SDT): breaking the Depth Shallow of Photocactivation. *Adv Mater.* 2016;28:8097–8129.

8. Lin X, Song J, Chen X, Yang H. Ultrasound Activated Sensitzers and Applications. *Angewandte Chemie Int Edition.* 2020;59:14212–14233. doi:10.1002/anie.201906823

9. Liang S, Deng X, Ma P, Cheng Z, Lin J. Recent Advances in Nanomaterial-Assisted Combinational Sonodynamic Cancer Therapy. *Adv Mater.* 2020;32:2003214. doi:10.1002/adma.202003214

10. Son S, Kim JH, Wang X, et al. Multifunctional Sonosensitizers in Sonodynamic Cancer Therapy. *Chem Soc Rev.* 2020;49:3244–3261. doi:10.1039/C9CS00648F

11. Duan L, Yang L, Jin J, Yang F, Gu N. Micro/Nano-Bubble-Assisted Ultrasound to Enhance the EPR Effect and Potential Theranostic Applications. *Theranostics.* 2020;10:462–483. doi:10.7150/thno.37593

12. Rosenthal I, Sostaric JZ, Riesz P. Sonodynamic Therapy—a Review of the Synergistic Effects of Drugs and Ultrasound. *Ultrasound Sonochem.* 2004;11:349–363. doi:10.1016/S0304-385X(03)00404

13. Tharkar P, Varanasi R, Wong WSF, Jin CT, Chrzanoski W. Nano-enhanced drug delivery and therapeutic ultrasound for cancer treatment and beyond. *Front Bioeng Biotechnol.* 2019;7:324. doi:10.3389/fbioe.2019.00324

14. Li H, Shi W, Huang W, et al. Carbon Quantum Dots/TiOx Electron Transport Layer Boosts Efficiency of Planar Heterojunction Perovskite Solar Cells to 19%. *Nanotechnology.* 2017;17:2328–2335. doi:10.1088/1361-6528/6005177

15. Zhang H, Chen J, Zhu X, et al. Ultrasound induced phase-transition and invisible nanobomb for imaging-guided tumor sonodynamic therapy. *J Mater Chem B.* 2018;6:6108–6121. doi:10.1039/C8TB01788C

16. Gong F, Cheng L, Yang N, et al. Ultrasmall Oxygen-Deficient Bimetallic Oxide MnWOX Nanoparticles for Depletion of Endogenous GSH and Enhanced Sonodynamic Cancer Therapy. *Adv Mater.* 2019;31:1900730. doi:10.1002/adma.201900730

17. Han X, Huang J, Jing X, et al. Oxygen-deficient black titania for synergetic/enhanced sonodynamic and photoinduced cancer therapy at near infrared-ii biowindow. *ACS Nano.* 2018;12:4545. doi:10.1021/acsnano.8b00899

18. Greillier P, Bawiec C, Bessière F, Lafon C. Therapeutic Ultrasound for the Heart: state of the Art. *IRBM.* 2018;39:227–235. doi:10.1016/j.irbm.2017.11.004

19. Coussios CC, Roy RA. Applications of Acoustics and Caviation to Noninvasive Therapy and Drug Delivery. *Annu Rev Fluid Mech.* 2008;40:395–420. doi:10.1146/annurev.fluid.40.111407.102116

20. Sankin GN, Simmons WN, Zhu SL, Zhong P. Shock wave interaction with laser-generated single bubbles. *Phys Rev Lett.* 2005;95:034051. doi:10.1103/PhysRevLett.95.034501

21. Pang X, Xiao Q, Cheng Y, et al. Bacteria-responsive nanoliposomes as smart sonotheranostics for multidrug resistant bacterial infections. *ACS Nano.* 2019;13:2427–2438. doi:10.1021/acs.nanolett.8b00936

22. Feng Y, Tian Z, Wan M. Bioeffects of Low-Intensity Ultrasound in vitro: apoptosis, Protein Profile Alteration, and Potential Molecular Mechanism. *J Ultrasound Med.* 2010;29:963–974. doi:10.7863/jum.2010.29.6.963

23. Sirsi SR, Borden MA. State-of-the-Art Materials for Ultrasound-Triggered Drug Delivery. *Adv Drug Deliv Rev.* 2014;72:3–14. doi:10.1016/j.addr.2013.12.010

24. Barnett SB, Rott HD, Haar GRT, Ziskin MC, Maeda K. The sensitivity of biological tissue to ultrasound. *Ultrasound Med Biol.* 1997;23:805–812. doi:10.1016/S0301-5629(97)90002-6

25. Umemura S, Kawabata K, Sasaki K. Recent advances in sonodynamic approach to cancer therapy. *Ultrason Sonochem.* 1996;3:187–191. doi:10.1016/S1350-4487(96)90002-7

26. Chen H, Zhou X. Recent Progress in Development of New Sonosensitizers for Sonodynamic Cancer Therapy. *Drug Discov Today.* 2014;19:502–509. doi:10.1016/j.drudis.2014.01.010

27. Umemura K, Yumita N, Nishigaki R, Umemura S. Sonodynamically Induced Antitumor Effect of Photophorbide a. *Cancer Lett.* 1996;102(1–2):151–157. doi:10.1016/0304-385X(96)00474-2

28. Shi H, Liu Q, Qin X, Wang P, Wang X. Pharmacokinetic Study of a Novel Sonosensitizer Chlorin-e6 and its Sonodynamic Anti-Cancer Activity in Hepatoma-22 Tumor-Bearing Mice. *Biopharm Drug Dispos.* 2011;32:319–332. doi:10.1007/bdd.761

29. Wang H, Liu Q, Zhang K, et al. Comparison Between Sonodynamic and Photodynamic Effect on MDA-MB-231 Cells. *J Photochem Photobiol B.* 2015;127:182–191. doi:10.1016/j.jphotobiol.2013.08.015

30. Wang P, Xu CS, Xu J, Wang X, Leung AW. Hypocrellin B Enhances Ultrasound-Induced Cell Death of Nasopharyngeal Carcinoma Cells. *Ultrasound Med Biol.* 2010;36:336–342. doi:10.1016/j.ultrasmedbio.2009.09.007

31. El-Sikhy HE, Miller GG, Madiyalakan MR, Seubert JM. Sonodynamic and Photodynamic Mechanisms of Action of The Novel Hypocrellin Sonosensitizer, SL017: mitochondrial Cell Death is Attenuated by 11, 12-Epoxycis-tetraenoic Acid. *Invest New Drugs.* 2011;29:1328–1336. doi:10.1007/s10637-010-9495-2

32. Ai X, Lyu L, Zhang Y, et al. Remote Regulation of Membrane Channel Activity by Site-Specific Localization of Lanthanide-Doped Upconversion Nanocrystals. *Angewandte Chemie Int Edition.* 2017;56:3031–3035. doi:10.1002/anie.201612142

33. Qian J, Gao Q. Sonodynamic Therapy Mediated by Emodin Induces the Oxidation of Microtubules to Facilitate the Sonodynamic Effect. *Ultrasound Med Biol.* 2018;44:853–860. doi:10.1016/j.ultrasmedbio.2017.12.016
34. Wang F, Gao Q, Guo S, et al. The Sonodynamic Effect of Curcumin on THP-1 Cell-Derived Macrophages. *Biomed Res Int.* 2013;2013:737264.

35. Pang X, Xiao Q, Cheng Y, et al. Bacteria-Responsive Nanoliposomes as Smart Sonotheranostics for Multidrug Resistant Bacterial Infections. *ACS Nano.* 2019;13:2438.

36. Liu M, Khan AR, Ji J, Lin G, Zhao X, Zhai G. Crosslinked Self-Assembled Nanoparticles for Chemo-Sonodynamic Combination Therapy Favoring Antitumor, Antimetastasis Management and Immune Responses. *J Controlled Release.* 2018;290:150–164. doi:10.1016/j.jconrel.2018.10.007.

37. Qian X, Han X, Chen Y. Insights into The Unique Functionality of Inorganic Micro/Nanoparticles for Versatile Ultrasound Theranostics. *Biomaterials.* 2017;142:33–30. doi:10.1016/j.biomaterials.2017.07.016.

38. Deepagan VG, You DG, Um W, et al. Long-Circulating Au-TiO₂ Nanocomposite as a Sonosensitizer for ROS-Mediated Eradiation of Cancer. *Nano Lett.* 2016;16:6257–6264. doi:10.1021/acs.nanolett.6b02547.

39. You DG, Deepagan VG, Um W, et al. ROS-Generating TiO₂ Nanoparticles for Non-Invasive Sonodynamic Therapy of Cancer. *Sci Rep.* 2016;6:23200. doi:10.1038/srep23200.

40. Chen H, Shao L, Li Q, Wang J. Gold Nanorods and Their Plasmonic Properties. *Chem Soc Rev.* 2013;42:2679–2724. doi:10.1039/C3CS35367A.

41. Zhou LQ, Li P, Cui XW, Dietrich CF. Ultrasound Nanotheranostics in Fighting Cancer: advances and Prospects. *Cancer Lett.* 2020;470:204–219. doi:10.1016/j.canlet.2019.11.034.

42. Karina DOGA, Vieira DP, Courrol LC. Synthesis and Characterization of Aminoolevulinic Acid Gold Nanoparticles: photo and Sonosensitizer Agent for Atherosclerosis. *J Lumin.* 2018;197:317–323. doi:10.1016/j.jlumin.2018.01.057.

43. Bernard V, Zobac O, Sopousek J, Mornstein V. AgCu Bimetallic Nanoparticles under Effect of Low Intensity Ultrasound: the Cell Viability Study *In Vitro.* *J Cancer Res.* 2014;2014:971769. doi:10.1155/2014/971769.

44. Yumita N, Iwase Y, Imaizumi T, et al. Sonodynamically-Induced Anticancer Effects by Functionalized Fullerene. *Anticancer Res.* 2013;33:3145–3151.

45. Osminkina LA, Nikolaev AL, Svidirov AP, Andronova NV, Tamarov KP. Porous Silicon Nanoparticles as Efficient Sensitizers for Sonodynamic Therapy of Cancer. *Microporous Mesoporous Materials.* 2015;210:169–175. doi:10.1016/j.micromeso.2015.02.037.

46. Svidirov AP, Andreev VG, Ivanova EM, Osminkina LA, Tamarov KP, Timoshenko VY. Porous Silicon Nanoparticles as Sensitizers for Ultrasonic Hyperthermia. *Appl Phys Lett.* 2013;103:2873. doi:10.1063/1.4829148.

47. Yu L, Hu P, Chen Y. Gas-Generating Nanoplatforms: material Chemistry, Multifunctionality, and Gas Therapy. *Adv Mater.* 2018;30:1801964.

48. Park SM, Aalipour A, Vermesh O, Yu JH, Gambhir SS. Towards Clinically Translatable *in vivo* Nanodiagnostics. *Nature Rev Materials.* 2017;2:17014. doi:10.1038/natrevmats.2017.14.

49. Sirsi SR, Borden MA. State-of-the-Art Materials for Ultrasound-Triggered Drug Delivery. *Adv Drug Deliv Rev.* 2014;72:14.

50. Kennedy JE. High-Intensity Focused Ultrasound in the Treatment of Solid Tumours. *Nat Rev Cancer.* 2005;5:321–327. doi:10.1038/nrc1591.

51. Oeffering BE, Wheatley MA. Development and Characterization of a Nano-Scale Contrast Agent. *Ultronics.* 2004;42:343–347. doi:10.1016/S0169-409X(02)00044-3.

52. Brigger I, Dubernet C, Couvreur P. Nanoparticles in Cancer Therapy and Diagnosis. *Adv Drug Deliv Rev.* 2002;54:631–651. doi:10.1016/S0169-409X(02)00044-3.
72. Shen S, Guo X, Wu L, et al. Dual-Core/Shell-Structured Fe3O4-NaYF4@TiO2 Nanocomposites as a Magnetic Targeting Drug Carrier for Bioimaging and Combined Chemo-Sonodynamic Therapy. *J Mater Chem B*. 2014;2:5755–5784. doi:10.1039/C4TB00841C
73. Zhao H, Zhao B, Li L, et al. Biomimetic decoy inhibits tumor growth and lung metastasis by reversing the drawbacks of sonodynamic therapy. *Adv Healthcare Mater*. 2020;9:1901335. doi:10.1002/adhm.201901335
74. Malekmohammadi S, Hadadzadeh H, Rezakhani S, Amirghofran Z. Design and synthesis of gatekeeper coated dendritic silica/titania mesoporous nanoparticles with sustained and controlled drug release properties for targeted synergetic chemo-sonodynamic therapy. *ACS Biomaterials Sci Eng*. 2019;5:4405–4415. doi:10.1021/acsbiomaterials.9b00237
75. Wu P, Sun Y, Dong W, et al. Enhanced Anti-Tumor Efficacy of Hyaluronic Acid Modified Nanocomposites Combined with Sonochemotherapy Against Subcutaneous and Metastatic Breast Tumors. *Nanoscale*. 2019;11:11470–11483. doi:10.1039/C9NR01691K
76. Li Z, Han J, Yu L, et al. Synergistic Sonodynamic/Chemotherapeutic Suppression of Hepatocellular Carcinoma by Targeted Biodegradable Mesoporous Nanosonosensitizers. *Adv Funct Mater*. 2018;28:1800145. doi:10.1002/adfm.201800145
77. Shi J, Chen Z, Wang B, Wang L, Lu T, Zhang Z. Reactive oxygen species-manipulated drug release from a smart envelope-type mesoporous titanium nanovehicle for tumor sonodynamic-chemotherapy. *ACS Appl Mater Interfaces*. 2015;7:28554–28565. doi:10.1021/acsami.5b09937
78. Wang J, Jiao Y, Shao Y. Mesoporous silica nanoparticles for dual-mode chemo-sonodynamic therapy by low-energy ultrasound. *Materials*. 2018;11:2041. doi:10.3390/ma11102041
79. Tang Z, Liu Y, He M, Bu W. Chemodynamic therapy: tumor microenvironment-mediated fenton and fenton-like reactions. *Angewandte Chemie Int Edition*. 2019;58:946–956. doi:10.1002/anie.201805664
80. Zhong X, Wang X, Cheng L, Tang Y. GSH-Depleted PtCu Nanocages for chemodynamic-enhanced sonodynamic cancer therapy. *Adv Funct Mater*. 2020;30:1907954. doi:10.1002/adfm.201907954
81. Li WP, Su CH, Chang YC, Lin YJ, Yeh CS. Ultrasound-Induced Reactive Oxygen Species Mediated Therapy and Imaging Using a Fenton Reaction Activable Polymersome. *ACS Nano*. 2016;10:2017–2027. doi:10.1021/acsnano.5b06175
82. Wang X, Zhong X, Bai L, et al. Ultrafine Titanium Monoxide (TiO2-x) Nanorods for Enhanced Sonodynamic Therapy. *J Am Chem Soc*. 2020;142:6527–6537. doi:10.1021/jacs.9b10228
83. Lin X, Liu S, Zhang X, et al. An Ultrasound Activated Vesicle of Janus Au-MoO3 Nanoparticles for Promoted Tumor Penetration and Sono-Chemodynamic Therapy of Orthotopic Liver Cancer. *Angewandte Chemie Int Edition*. 2020;59:1682–1688. doi:10.1002/anie.201912768
84. Nam J, Son S, Park KS, Zou W, Shea LD, Moon JJ. Cancer Nanomedicine for Combination Cancer Immunotherapy. *Nature Reviews Materials*. 2019;4:398–414. doi:10.1038/s41578-019-0108-1
85. Liu M, Khan AR, Ji J, Lin G, Zhao X, Zhai G. Crosslinked self-assembled nanoparticles for chemo-sonodynamic combination therapy favoring antitumor, antimetastasis management and immune responses. *J Controlled Release*. 2018;290:150.
86. Zhu W, Chen Q, Jin Q, et al. Sonodynamic therapy with immune modulatable two-dimensional coordination nanosheets for enhanced anti-tumor immunotherapy. *Nano Res*. 2020;14:1–10.
87. Yue W, Chen L, Yu L, et al. Checkpoint Blockade and Nanosonosensitizer-Augmented Noninvasive Sonodynamic Therapy Combination Reduces Tumour Growth and Metastases in Mice. *Nat Commun*. 2019;10:2025. doi:10.1038/s41467-019-09760-3
88. Pang X, Liu X, Cheng Y, et al. Sono-Immunotherapeutic Nanocaptor to Combat Multidrug-Resistant Bacterial Infections. *Adv Mater*. 2019;31:1902530. doi:10.1002/adma.201902530
89. Um W, Ko H, You DG, et al. Necroptosis-inducible polymeric nanobubbles for enhanced cancer sonoimmunotherapy. *Adv Mater*. 2020;32:1907953. doi:10.1002/adma.201907953
90. Huang X, El-Sayed IH, Qian W, El-Sayed MA. Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. *J Am Chem Soc*. 2006;128:2115–2120. doi:10.1021/ja057254a
91. Liang S, Deng X, Chang Y, et al. Intelligent hollow pt-Cus janus architecture for synergistic catalysis-enhanced sonodynamic and photothermal cancer therapy. *Nano Lett*. 2019;19:4134–4145. doi:10.1021/acs.nanolett.9b01595
92. Han X, Huang J, Jing X, et al. Oxygen-deficient black titania for synergetic/enhanced sonodynamic and photoinduced cancer therapy at near infrared-II biowindow. *ACS Nano*. 2018;12:4545–4555.
93. Dai C, Zhang S, Liu Z, Wu R, Chen Y. Two-dimensional graphene augments nanosonosensitized nanocatalytic tumor eradication. *ACS Nano*. 2017;11:9467–9480. doi:10.1021/acsnano.7b05215
94. Gao F, He G, Yin H, et al. Titania-Coated 2D gold nanoparticles as nanoagents for synergistic photothermal/sonodynamic therapy in the second near-infrared window. *Nanoscale*. 2019;11:2374–2384. doi:10.1039/C8NR07188H
95. Su K, Tan L, Liu X, et al. Rapid photo-sonotherapy for clinical treatment of bacterial infected bone implants by creating oxygen deficiency using sulfur doping. *ACS Nano*. 2020;14:2077–2089. doi:10.1021/acs.nanolett.9b08686
96. Liu Y, Wang Y, Zhen W, et al. Defect modified zinc oxide with augmenting sonodynamic reactive oxygen species generation. *Biomaterials*. 2020;251:120075. doi:10.1016/j.biomaterials.2020.120075
97. Dolmans DE, Fukumura D, Jain RK. Photodynamic Therapy for Cancer. *Nat Rev Cancer*. 2003;3:380–387. doi:10.1038/nrc1071
98. Xu F, Hu M, Liu C, Choi SK. Yolk-structured multifunctional up-conversion nanoparticles for synergistic photodynamic-sonodynamic antibacterial resistance therapy. *Biomater Sci*. 2017;5:678–685. doi:10.1039/C7BM00030H
99. Abd El-Kareem SA, Abd Elsamie GH, Abd-Alkareem AS. Sonophotodynamic modality for cancer treatment using bio-degradable bio-conjugated sonellex nanocomposite in tumor-bearing mice: activated cancer therapy using light and ultrasound. *Biochem Biophys Res Commun*. 2018;530:1075–1086. doi:10.1016/j.bbrc.2018.06.119
100. Wang Z, Liu C, Zhao Y, et al. Photomagnetic nanoparticles in dual-modality imaging and photo-sonodynamic activity against bacteria. *Chem Eng J*. 2019;356:811–818. doi:10.1016/j.cej.2018.09.077
101. Nomikou N, Curtis K, McEwan C, et al. Stimulus-responsive nanoparticle-based platform for use in both sonodynamic and photodynamic cancer therapy. *Acta Biomaterialia*. 2017;49:414–421. doi:10.1016/j.actbio.2016.11.031
102. Liu Z, Li J, Jiang Y, Wang D. Multifunctional nanocapsules on a seesaw balancing sonodynamic and photodynamic therapies against superficial malignant tumors by effective immune-enhancement. *Biomaterials*. 2019;218:119251. doi:10.1016/j.biomaterials.2019.119251
