Recent advances in near-infrared-II hollow nanoplatforms for photothermal-based cancer treatment

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Abstract
Near-infrared-II (NIR-II, 1000–1700 nm) light-triggered photothermal therapy (PTT) has been regarded as a promising candidate for cancer treatment, but PTT alone often fails to achieve satisfactory curative outcomes. Hollow nanoplatforms prove to be attractive in the biomedical field owing to the merits including good biocompatibility, intrinsic physical-chemical nature and unique hollow structures, etc. On one hand, hollow nanoplatforms themselves can be NIR-II photothermal agents (PTAs), the cavities of which are able to carry diverse therapeutic units to realize multi-modal therapies. On the other hand, NIR-II PTAs are capable of decorating on the surface to combine with the functions of components encapsulated inside the hollow nanoplatforms for synergistic cancer treatment. Notably, PTAs generally can serve as good photoacoustic imaging (PAI) contrast agents (CAs), which means such kind of hollow nanoplatforms are also expected to be multifunctional all-in-one nanotheranostics. In this review, the recent advances of NIR-II hollow nanoplatforms for single-modal PTT, dual-modal PTT/photodynamic therapy (PDT), PTT/chemotherapy, PTT/catalytic therapy and PTT/gas therapy as well as multi-modal PTT/chemodynamic therapy (CDT)/chemotherapy, PTT/chemo/gene therapy and PTT/PDT/CDT/starvation therapy (ST)/immunotherapy are summarized for the first time. Before these, the typical synthetic strategies for hollow structures are presented, and lastly, potential challenges and perspectives related to these novel paradigms for future research and clinical translation are discussed.

Keywords: Near-infrared-II, Photothermal therapy, Hollow nanoplatforms, Synergistic cancer treatment, Nanotheranostics
Introduction
Cancer is known as the major public health issue globally and severely threatens human life with extremely high mortality rate [1–4]. Up to now, surgery, chemotherapy and radiotherapy have been widely applied in treating diverse tumors, but the curative outcomes are not that satisfied [5, 6]. For example, surgical resection is not able to realize complete removal of tumors because it is difficult to accurately distinguish the edge of tumorous tissues from the ambient tissues [7]. Moreover, these traditional therapeutic modalities tend to cause appendant damage to the normal tissues as the administrated small molecule drugs often suffer from non-specific biodistribution [8, 9]. The limited blood circulation time also results in poor tumor accumulation while high dose treatment regimens leads to systemic toxicities [10, 11]. Furthermore, the multidrug resistance and metastasis of tumors have always seriously restricted the therapeutic efficacy [12]. Therefore, the development of alternative treatment paradigms with superior merits is in urgent need [13–15].

Photothermal therapy (PTT) has received increasing attention in the past decade, which utilizes various photothermal agents (PTAs) to absorb near-infrared (NIR, 700–1700 nm) light and convert the light energy into hyperthermia for tumor ablation [16–18]. In contrast to the conventional treatment techniques, PTT is non-invasive and spatiotemporally controllable with higher therapeutic efficacy and low healthy-tissue damage, these advantages make PTT attractive and promising candidate for use in anti-cancer therapy [19, 20]. In short, PTAs exhibiting passive or active targeting capacities are capable of selectively accumulating in the tumor and then conducting accurate PTT with the help of localized NIR laser, since water, blood and other tissue components in body show insignificant NIR absorption [21, 22]. As we know, PTAs can be classified into two main categories, i.e. organic and inorganic nanomaterials. So far, small molecule dyes [23–25] and conjugated polymers [26–28] as the representatives of organic PTAs have been extensively explored for PTT. On the other hand, noble metal nanoparticles (NPs) [29, 30], metal chalcogenide NPs [31, 32] and 2D nanomaterials [33, 34] are popular inorganic PTAs. Each kind of PTAs possesses its own pros and pons, both organic and inorganic PTAs are very
attractive in cancer PTT. In general, organic PTAs display higher absorption coefficient and biocompatibility but worse water solubility and photostability than inorganic PTAs [18, 22, 35]. Besides, the particle size and morphology of inorganic PTAs are more readily tuned, and their surfaces also tend to be much easier to modify and functionalize [36, 37].

Due to the deeper penetration depth, lower light absorption and scattering in tissues as well as higher maximum permissible exposure (MPE) intensity (1 W cm\(^{-2}\) for 1064 nm, 0.72 W cm\(^{-2}\) for 980 nm and 0.33 W cm\(^{-2}\) for 808 nm), NIR-II (1000–1700 nm) PTT appears to be more superior than NIR-I (700–1000 nm) PTT, and has become the research hotspot in recent years [38–40]. For example, a comparative in vivo study has been conducted by Zhou et al. [41] using hyperbranched gold plasmonic blackbodies (AuPBs). The as-prepared AuPB displayed a broadband absorption ranging from 400 to 1350 nm and possessed a superior photothermal conversion efficiency (PCE) over 80% at 1064 nm. Utilizing a 5 mm chicken tissue to cover tumors to simulate practical situation of treating buried tumors, the temperature of the covered tumor increased to higher than 50 °C within 3 min irradiation and successfully inhibited the tumor growth. However, the covered tumors treated with PTT at 808 nm reached the maximum temperature lower than the apoptotic threshold temperature (43 °C), thus showing a negligible inhibitory effect. Typically, NIR-II PTAs should exhibit good biocompatibility, low toxicity, strong photostability, NIR-II light absorption and desirable PCE [42]. Current researches demonstrate that size control and surface engineering can be used to regulate their cytotoxicity. Such as, various polymer biomolecules modified the surface of PTAs to prolong blood circulation time, satisfied tumor accumulation, easily excrete and achieve better biocompatibility [37]. Of note, optical absorption and photothermal conversion ability are the key parameters for ideal NIR-II PTAs. As for inorganic NIR-II PTAs, broadening NIR-II absorption is most commonly adopted to improve the photothermal effects. More specifically, inorganic materials with enough low energy charge carriers and localized surface plasmonic resonance (LSPR) effect are in favor of NIR-II PTAs. For example, carbon-based nanomaterials possessed delocalized π electrons can interact with NIR-II photons to enable absorption [43]. Transition metals have partially filled d sub-shells that are likely to have low-energy electrons for NIR-II absorption [40]. The collective resonant oscillation of conduction electrons induced LSPR effect of noble metals results in an easily tuned and broadened absorption [44]. Besides, special structure design, SPR effect, surfactant modification and elements doping are able to enhance the NIR-II harvesting for enhanced PTT [45]. Additionally, the photothermal performance seriously dependent on the transformation of light to heat. Doping different elements in the other PTAs will generate carrier traps or “hot centers” to boost the photothermal conversion, and adjusting the host matrix or components of different inorganic elements can also lead to a higher PCE [46, 47]. Meanwhile, precisely diagnosing tumor and monitoring the treatment process by diverse molecular imaging techniques are of significant importance [48–51]. Among the clinical diagnostic approaches, magnetic resonance imaging (MRI), computed tomography (CT) imaging and fluorescence imaging (FLI), etc. are extensively exerted with the assistance of contrast agents (CAs) [52–54]. However, several drawbacks still exist to restrict their further applications. For example, MRI suffers from low sensitivity and relatively long acquisition time; CT imaging is not able to achieve sufficient functional information and soft tissue contrast; FLI is often accompanied by poor spatial resolution and tissue penetration [55–58]. Interestingly, PTAs are intrinsic photoacoustic imaging (PAI) CAs, that is to say, PTAs themselves are able to be all-in-one theranostic nanoplatforms [18, 38]. It is noticeable that PAI as a hybrid imaging method integrates the merits of both optical and ultrasound imaging, providing non-destructive, high-spatial resolution and deep-tissue images for cancer diagnosis [59–61].

With the ever-increasing requirement of modern medicine, single-modal imaging or treatment cannot obtain sufficient diagnostic information and satisfied curative outcomes [62–65]. To address these issues, researchers have shifted their focuses to developing multifunctional nanotheranostics [66–68]. A promising way is to incorporate these diagnostic and therapeutic functions into one single nanoplatform especially hollow nanoplatform [69–71]. Hollow nanoplatforms are accompanied by mesoporous pore structures, thus it is not uncommon to see small molecule drugs encapsulated into the cavities [72, 73]. Such novel nanoplatforms are able to serve as smart drug delivery systems (DDSs) to enhance the therapeutic outcomes of conventional chemotherapy and radiotherapy with reduced side effects [74, 75]. Compared with the mesoporous nanocarriers, hollow nanoplatforms are more popular owing to the superior drug loading capabilities. For example, only 5.6% [76] and 9.09% [77] of doxorubicin (DOX) could be encapsulated into traditional mesoporous silica NPs, while the hollow mesoporous silica NPs showed a much higher DOX loading efficacy of 42.9% [78]. In general, the synthetic strategies for hollow nanoplatforms are divided into sacrificial-template-based method and self-templating method, the details of which will be discussed in the next section. Notably, the hollow nanoplatforms alone can be good PTAs or serve as the substrates to support the
deposition of PTAs [72, 79]. With other functional components combined, the hollow structured nanoplatforms are expected to allow imaging-guided PTT-based treatments. For example, Zheng et al. [80] loaded manganese carbonyl (MnCO) into the cavity of hollow mesoporous copper sulphide (CuS) NPs for MRI-guided combined PTT/gas therapy. Additionally, Wang et al. [69] reported a multifunctional macrophage-mediated nanotheranostics (denoted as MFe3O4-Cy5.5) based on fluorescent probe Cy5.5-conjugated Fe3O4 NPs, which could realize multi-modal diagnosis (PAI/MRI/NIR FLI), precise imaging-guided surgery and effective PTT of gliomas. By reasonable and optimal design, the hollow NIR-I nanoplatforms can also be extended to NIR-II nanosystems for synergistic diagnostic and therapeutic efficacy with enormous advantages [81, 82].

So far, serval works have reported diverse hollow nanoplatforms or NIR-II nanoagents for cancer theranostics [38, 42, 83–96]. In this review, we for the first time present the recent progress of NIR-II hollow nanoplatforms for PTT-based cancer therapies with several sections summarized according to the treatment modalities. First of all, the synthetic methods for hollow nanoplatforms are included. Subsequently, the basic introduction of each NIR-II hollow nanoplatforms is firstly given and then a detailed description of the applications including PAI, FLI, MRI and CT imaging as well as single-modal NIR-II PTT, dual-modal NIR-II PTT-based therapies and multi-modal NIR-II PTT-based therapies. More specifically, the categories can be divided into NIR-II PTT (e.g., HPP and Ag2S Ve), NIR-II PTT/PDT (e.g., AuHNRs-DTPP, AAM-Ce6 and TAT-Pd@Au/Ce6/PAH/H-MnO2), NIR-II PTT/chemotherapy (e.g., AuHNRs-DOX, DOX-NiP PHNPs and DSF@PEG-HCuS), NIR-II PTT/catalytic therapy (e.g., PEG-Cu5Se HNCs and HSC-2), NIR-II PTT/gas therapy(e.g., HC-AB), PTT/CDT/chemotherapy (e.g., DOX@H-Cu5Se/PEG and HMMNC), NIR-II PTT/chemo/gene therapy (e.g., CPT-RHNS-PGEA/p53) and NIR-II PTT/PDT/CDT/ST/immunotherapy (e.g., PEG-CMS@GOx). Figures were reproduced with permission from Ref. [97–111], respectively.

Scheme 1  Schematic illustration of various NIR-II hollow nanoplatforms for photothermal-based therapies. There are two representative NIR-II hollow nanoplatforms described in this work, i.e. (1) hollow nanoplatforms themselves serve as NIR-II PTAs and (2) hollow nanoplatforms are decorated with NIR-II PTAs. As for the outer circle, blue, green and orange background correspond to single-modal NIR-II PTT; dual-modal NIR-II PTT-based therapies and multi-modal NIR-II PTT-based therapies. More specifically, the categories can be divided into NIR-II PTT (e.g., HPP and Ag2S Ve), NIR-II PTT/PDT (e.g., AuHNRs-DTPP, AAM-Ce6 and TAT-Pd@Au/Ce6/PAH/H-MnO2), NIR-II PTT/chemotherapy (e.g., AuHNRs-DOX, DOX-NiP PHNPs and DSF@PEG-HCuS), NIR-II PTT/catalytic therapy (e.g., PEG-Cu5Se HNCs and HSC-2), NIR-II PTT/gas therapy(e.g., HC-AB), PTT/CDT/chemotherapy (e.g., DOX@H-Cu5Se/PEG and HMMNC), NIR-II PTT/chemo/gene therapy (e.g., CPT-RHNS-PGEA/p53) and NIR-II PTT/PDT/CDT/ST/immunotherapy (e.g., PEG-CMS@GOx). Figures were reproduced with permission from Ref. [97–111], respectively.
Synthetic methods for hollow nanoplatforms

Sacrificial-template-based method

Sacrificial-template-based method is regarded as the most commonly used strategy to synthesize hollow NPs, which exploits diverse removable NPs as hard and soft templates [112, 113]. Such templates are often prepared in advance and dissolved after growing the desired materials on their surface. The dissolution of the inner templates can be realized through chemical etching or thermal decomposition, leading to highly uniform hollow NPs [114–117]. By controlling the particle size of the templates and the reaction parameters of the outer shell, the diameter and shell thickness of the resultant hollow NPs are easily tuned [118, 119]. Inorganic solid silica (SiO2) NPs and organic polymeric NPs have been widely explored as hard templates. For example, Wu et al. [120] utilized the unreacted organosilica on the surface of SiO2 NPs to react with manganese permanganate (KMnO4) to in situ form a uniform mesoporous manganese dioxide (MnO2) layer. After sodium carbonate (Na2CO3) solution treatment, the SiO2 was dissolved and a hollow mesoporous structured MnO2 (denoted as H-MnO2) could be obtained for dual-modal MRI/FLI-guided synergistic PTT/PDT/chemotherapy with DOX and black phosphorus quantum dots (BPQDs) co-loaded (Fig. 1a). Besides, SiO2 NPs have also been applied to fabricate hollow polydopamine (PDA) NPs [121], hollow mesoporous silica NPs [122], hollow carbon NPs [123] and hollow mesoporous ferric oxide NPs [124], etc. Analogously, the reduction of KMnO4 by poly(lactic-co-glycolic acid) (PLGA) NPs also gave rise to H-MnO2 NPs after etching the inner PLGA by acetone [82]. In this nanosystem, Wang and co-workers used platelet membrane (PLTM) to coat the bufalin-loaded HMnO2 and investigated its feasibility for cancer-specific MRI-guided combined CDT/chemotherapy. Other polymeric NPs like polystyrene NPs are also popular template for the synthesis of hollow PDA NPs [70, 125, 126]. Additionally, zeolitic imidazolate framework-8 (ZIF-8) NPs as hard templates have been involved in preparing hollow PDA NPs [127] and hollow porphyrinic metal–organic framework [114]. As for soft templates, Wang et al. [117] converted the molybdenum disulfide (MoS2) nanodots to hollow MoSx NPs in the presence of ammonia (NH3) bubbles. With photosensitizer chloride aluminium phthalocyanine (AlPc) and O2 carrier perfluorohexane (PFH) incorporated, the resultant nanoplatform can be used for FLI/PAI/CT imaging and synergistic PTT/PDT (Fig. 1b). Lin et al. [116] adjusted the weight ratio between triblock copolymer Pluronic F127 and 1,3,5-trimethylbenzene (TMB) to fabricate hollow PDA nanospheres (H-PDANSs) and evaluated its potential as NIR laser- and acid pH-responsive DDSs. The formation mechanism of PDA NPs with different morphologies was shown in Fig. 1c. In the absence of TMB, F127 had no effect on the morphology and classical solid PDANs were obtained. After simultaneous addition of TMB and F127, oil-in-water emulsion droplet template was formed which could result in a small amount of H-PDANSs. When the amount of TMB was sufficient (TMB/F127 ≥ 0.6), some TMB and F127 also formed a number of columnar micelles that were vertically attached to the surface of the emulsion droplets. TMB could enter into the hydrophobic interior of columnar micelles and maintain a dynamic balance between emulsion droplets and columnar micelles. Subsequently, the added DA preferentially adsorbed on the hydrophilic surface of F127 and self-polymerized to form PDA small particles, which further gathered in large quantities on the surface of the hydrophilic F127. The size of the TMB oil droplets determined the size of the cavity, and the hydrophobic cavity of the F127/127 columnar micelles led to the mesoporous channels. When the amount of DA was sufficiently large, it could eventually cause the PDA particles to fill with the entire TMB droplet and give rise to a complete mesoporous structure with the cavity structure disappeared.

Self-templating method

On the other hand, self-templating method employing the transformation of self-generated internal solid NPs to hollow structures during chemical reactions, has also gained widespread attention in recent years [85, 128–131]. There are three main mechanisms involved in the self-templating method such as nanoscale Kirkendall effect, galvanic replacement reaction and Ostwald ripening process. For example, Ren et al. [132] reported a simple synthetic strategy to prepare monodisperse hollow manganese/cobalt oxide (MCO) NPs for tumor imaging and drug delivery. As shown in Fig. 2a, hollow MCO NPs were obtained from the oxidation of poly-acrylic acid (PAA)-covered cobalt (Co) by KMnO4, in which the formation of hollow cavities could be attributed to the Kirkendall effect, i.e. the different diffusion rates of MnO4− and Co atoms led to the pore generation. Jiang et al. [133] fabricated gold–silver@gold (denoted as Au–Ag@Au) hollow NPs with improved chemical stability and enhanced PCE of 36.5% at 808 nm by the replacement reaction for effective destruction of MCF-7 breast cancer cells (Fig. 2b). Meng et al. [134] developed hollow cuprous oxide@nitrogen-doped carbon (denoted as HCONC) with dual-shell structures via a one-step hydrothermal method based on cupric nitrate and dimethyl formamide for GSH-depletion boosted CDT (Fig. 2c). The preparation of HCONC mainly contained three stages including (1) the nucleation of cuprous oxide (Cu2O) nanocrystals under high temperature
and pressure as well as dissolved oxygen; (2) the formation of primary solid Cu₂O nanoclusters by aggregation with SCONC; (3) the further growth of outermost nanocrystals and consumption of small internal particles during Ostwald ripening gave rise to a hollow cavity and generated HCONC.

Fig. 1 a Schematic illustration of nanoprobe H-MnO₂/DOX/BPQDs synthesis route. Reproduced with permission from Ref. [120]. Copyright 2021, Wiley-VCH. b A scheme showing the synthesis and surface modification of HMoSₓ. Reproduced with permission from Ref. [117]. Copyright 2019, Ivyspring International Publisher. c Schematic illustration of the formation of PDA nanospheres (PDANSs, H-MPDANSs and MPDANSs) with different morphology (the lower left corner in the green dotted box is the longitudinal section of the columnar micelle, and the lower right corner is the cross section of the columnar micelle). Reproduced with permission from Ref. [116]. Copyright 2021, IOP Publishing Ltd
Though the sacrificial-template-based approach can form various hollow NPs with uniform morphology, tunable diameter and shell thickness, it often requires strong acid and alkali as well as harmful organic solvents [135, 136]. As a contrast, the self-templating method possesses simplified synthetic procedures and reduced chemical waste formation [137–141]. Both of the two strategies have been widely explored for constructing hollow nanoplatforms for highly efficient NIR-II PTT. Such nanoplatforms themselves can be promising NIR-II PTAs or facilitate the growth of NIR-II PTAs on their surfaces [97, 101]. More importantly, the hollow cavity is able to encapsulate various diagnostic and therapeutic components, displaying tremendous promise in bioimaging.

![Fig. 2](image_url)
drug delivery and tumor therapy [118, 142]. In the following sections, diverse nanoplatforms are introduced for single NIR-II PTT, NIR-II PTT-based dual-modal therapies including PTT/PDT, PTT/chemotherapy, PTT/catalytic therapy and PTT/gas therapy as well as NIR-II PTT-based multi-modal therapies such as PTT/CDT/chemotherapy, PTT/chemo/gene therapy and PTT/PDT/CDT/ST/immunotherapy. At the meanwhile, their capacities in FLI, MRI, PAI and CT imaging are also incorporated.

**Hollow nanoplatforms for single NIR-II PTT**

Thanks to the merits of non-invasiveness, efficient tumor ablation and low systemic toxicity, PTT excited and controlled by NIR light has been regarded as a promising candidate for the treatment of different types of cancers [143–145]. Currently, most of the PTT are conducted under an 808 nm laser irradiation, in which the low MPE value and limited penetration depth still hinder their further applications. Therefore, the development of NIR-II PTAs has become more and more popular [44, 90, 93, 146, 147]. Though organic nanomaterials especially conjugated polymers prove to be excellent NIR-II PTAs, the corresponding hollow structures are seldom reported [86]. So past studies have focused mainly on the design of various inorganic NIR-II hollow nanoplatforms including carbon-based, Au-based and metal chalcogenide materials, etc. [99, 100, 102, 105–107, 148].

For example, Xu et al. [97] successfully prepared a polyethylene glycol-graft-polyethylenimine (PEG-g-PEI) modified hollow carbon nanosphere (denoted as HPP) using SiO2 NPs as the templates. The uniform HPP (~215 nm) possessed a high PCE of 45.1% at 1064 nm due to the excellent optical absorbance in the NIR-II biowindow, and the outer PEG-g-PEI functionalization guaranteed its aqueous dispersity and biocompatibility. In vitro and in vivo therapeutic outcomes were evaluated with a safe laser power density (1064 nm, 0.6 W/cm²), showing that the HPP exhibited remarkable photocytotoxicity towards 4T1 cells and tumors. Only 10% of the cells survived when the concentration was 80 µg/mL and the tumor sizes were dramatically diminished with three groups completely eradicated after HPP + 1064 nm laser treatment.

Liu et al. [98] fabricated a smart tumor microenvironment (TME)-activatable hollow silver sulfide vesicle (denoted as Ag2S Ve) for NIR-II FLI-guided NIR-II PTT. In this design, ultrasmall Ag2S QDs (~8 nm) were first synthesized in dimethyl formamide (DMF) with pH-sensitive thiolated polystyrene-co-poly(4-vinylpyridine) (HS-PS-P4VP) and hydrophilic poly(ethylene glycol)-thiol (PEG–SH) polymers modified and subsequently dispersed in chloroform after discarding DMF. When sodium aqueous dodecyl sulfate (SDS) solution was added, the Ag2S QDs could be transformed to Ag2S Ve via a self-assembly procedure under sonication. With the removal of chloroform, the final Ag2S Ve aqueous dispersion was obtained. Interestingly, the larger particle size (160 nm) of Ag2S Ve gave rise to enhanced tumor accumulation. Due to the responsiveness of PS-P4VP at acidic TME, the hydrophilic copolymer was changed to hydrophilic to allow the release of PEG-SH modified Ag2S QDs, turning on the remarkable NIR-II fluorescence. Meanwhile, the NIR absorption enabled the Ag2S QDs to be a good NIR-II PTA. Such novel TME-activated theranostic features were further investigated in vivo for efficient and accurate NIR-II FLI-guided PTT of subcutaneous 4T1 tumors, displaying enormous potential for avoiding health tissues from photothermal damage as well (Fig. 3).

**Hollow nanoplatforms for NIR-II PTT-based dual-modal therapies**

Although tremendous progress has been made, it is still quite difficult to realize a complete cure via single-modal NIR-II PTT as the unique TME promotes the proliferation and metastasis of cancers [149–151]. Besides, PTT has been demonstrated to be restricted by the overexpressed heat shock proteins (HSPs) found in serval types of cancers [35, 152, 153]. To this end, synergistic treatment as a new paradigm proves to be the hotspot not only in clinical judgment but also scientific research, aiming at significantly improving the antitumor efficacy [14, 84, 154]. Most notably, reactive oxygen species (ROS) accumulation is able to reduce the HSPs expression and in turn, hyperthermia generated from PTT can boost tumor blood flow, which is beneficial for O2-dependent cancer therapies [155–157]. This means that the combination of NIR-II PTT and ROS-mediated treatment modalities such as PDT, chemotherapy and catalytic therapy can realize super-additive effects. In addition, gas therapy with different kinds of gaseous signaling molecules included is also capable of inhibiting the inflammation during PTT to greatly enhance the therapeutic outcomes [158, 159]. In this section, we will introduce these dual-modal treatment strategies in detail.

**PTT/PDT**

As another kind of phototherapy, PDT integrating the merits including noninvasiveness, ideal tumor-destroying selectivity, low side effects and insignificant drug resistance has also been widely investigated and demonstrated to be a promising candidate for cancer therapy [160, 161]. Briefly, PDT kills cancer cells by generating cytotoxic ROS through laser irradiating diverse photosensitizers in the presence of O2 [162, 163]. Nowadays, the majority of photosensitizers involved in PDT are small organic
molecules (e.g., chlorin e6 (Ce6) [164], indocyanine green (ICG) [165] and methylene blue (MB) [166], etc.), which exhibit the drawbacks of non-specific biodistribution and damage to skin as well as other normal tissues after administration. In light of these, hollow NIR-II PTAs can serve as smart nanocarriers to load photosensitizers and control their functions on demand.

For example, Zhang et al. [99] developed a hollow Au nanorods-based nanoplatform (denoted as AuHNRs-DTPP) for NIR-II PTT, supplementary PDT and real-time apoptosis FLI. The nanoplatform was consisted of Au hollow nanorods (AuHNRs) and photosensitizer containing chimeric peptide PpIX-PEG8-GGK(TPP) GRDEVDGDC (abbreviated as DTPP, PpIX was short for protoporphyrin), in which the AuHNRs were obtained using tellurium (Te) nanorods as the template and the DTPP was prepared via a solid-phase peptide synthesis method. As shown in Fig. 4a, b, the AuHNRs displayed typical hollow structure and the length/width ratio was calculated to be 3 : 1. After loading DTPP onto the AuHNRs, the plasmon resonances peaks (614 and 990 nm) of AuHNRs showed obvious red-shift while the absorption peaks of DTPP were quenched (Fig. 4c). The intensive NIR-II absorption provided excellent photothermal conversion capacity for AuHNRs-DTPP as NIR-II PTA. As shown in Fig. 4d, e, the temperature of the AuHNRs-DTPP dispersion went up with the increase of laser power density, time and concentration. The quenched fluorescence and inhibited ROS production of AuHNRs-DTPP were capable of protecting the non-tumoral tissues from photodynamic toxicity. Interestingly, the presence of human recombinant caspase-3 could cleave the linkage between AuHNRs and DTPP, leading to the release of DTPP and thus the recovery of fluorescence as well as the ROS-generating ability upon a 633 nm laser irradiation (Fig. 4f, g). Similar trends were found at the cellular level and the vivid green fluorescence confirmed the potent PDT effects.
(Fig. 4 h). For in vivo experiments, the AuHNRs-DTPP could accumulate at the tumor site via enhanced permeability and retention (EPR) effect after intravenous injection. Compared to the non-specific distribution of free DTPP, the AuHNRs-DTPP treatment gave limited fluorescence at 8 h post-injection but the fluorescence signal was significantly strengthened with the assistance of 1064 nm laser irradiation. These data evidenced that the NIR-II PTT could facilitate the PDT and remarkable tumor suppression was achieved owing to the well-integrated PTT/PDT (Fig. 4i, j).

It is known that PDT relies greatly on the O2 level, but TME is often hypoxic [163, 167]. Nowadays, two main methods (1) direct transportation of O2 by perfluorocarbon nanodroplets or oxygenated hemoglobin, etc. and (2) in situ catalytic generation of O2 using catalase and catalase-mimicking nanozymes are applied to improve the intratumoral O2 concentration [168, 169]. The latter...
one becomes more popular on account of the overproduced endogenous hydrogen peroxide (H$_2$O$_2$), and MnO$_2$ is one of the most appealing catalase-mimicking nanozymes [170, 171]. For example, Wu et al. [100] fabricated a novel multifunctional Au/Ag-MnO$_2$-Ce6 hollow nanospheres (denoted as AAM-Ce6 HNSs) for PAI/FLI/MRI-guided PTT/PDT. The hollow structured Au/Ag alloy was first prepared via a galvanic replacement reaction, followed by in situ growth of MnO$_2$ NPs on the surface with KMnO$_4$ added. After Ce6 loading and SH-PEG modification, the final AAM HNSs were obtained. The AAM-Ce6 HNSs displayed broad absorption in the NIR region and outstanding NIR-II photothermal effects (PCE = 52.5% at 1064 nm), which could allow excellent PAI and PTT. The outer MnO$_2$ NPs showed rapid responsiveness towards TME, decomposing endogenous H$_2$O$_2$ to produce O$_2$ for hypoxia-relieved PDT and simultaneously releasing abundant Mn$^{2+}$ ions as MRI CAs. With the FLI performance of Ce6 integrated, triple-modal imaging was realized to guide the combined PTT/PDT. In vitro and in vivo experiments revealed that the synergistic therapeutic efficacy was much better than any single-modal treatment, showing bright prospect for cancer theranostics.

In other work, Zhang et al. [101] constructed a multifunctional nanoplatform (denoted as TAT-Pd@Au/Ce6/PAH/H-MnO$_2$, Pd was short for palladium) by decorating transactivator of transcription (TAT)-Pd@Au nanoparticles onto hollow mesoporous MnO$_2$ (H-MnO$_2$), in which the H-MnO$_2$ was loaded with Ce6 and modified
with a cationic polymer poly allylamine hydrochloride (PAH) layer (Fig. 5). The PEG-TAT functionalization endowed the nanoplatform with long blood circulation time and nuclear targeting ability. Once reaching the tumor site, the inner H-MnO$_2$ could be degraded by the acidic H$_2$O$_2$ to produce Mn$^{2+}$ for MRI and O$_2$ to alleviate the hypoxic atmosphere for enhanced PDT, respectively. At the meanwhile, the released small TAT-Pd@Au nanoplates were able to effectively enter into the nucleus to conduct NIR-II PTT with an outstanding PCE up to 56.9%. Consequently, significant therapeutic effects could be achieved due to the synergistic PTT/PDT. This novel nanotheranostics inspires a new strategy for subcellular targeting cancer diagnosis and therapy.

**PTT/chemotherapy**

Chemotherapy using different kinds of chemotherapeutic drugs has been an essential part for clinical cancer treatment over the past decades [172–174]. However, the deficient tumor accumulation and overdose of drugs in current chemotherapy often lead to poor curative outcomes and severe side effects [175–177]. Therefore, a large number of smart DDSs including polymeric NPs [178], SiO$_2$ NPs [179] and metal-based NPs [5, 180], etc. are developed, which can response to the unique TME such as low pH [181], high glutathione (GSH) [182] and enzyme [183], etc., as well external triggers like photo [184] and ultrasound [185], etc. for site-specific drug release with higher tumor accumulation and reduced systemic toxicities. Among the reported chemotherapeutic drugs, DOX is one of the most commonly explored model drugs and demonstrated to effectively treat breast carcinoma and ovarian carcinoma, etc. [186, 187].

By utilizing a selenium (Se)-doped Te nanorod as the template, Cai et al. [102] synthesized anisotropic AuHNRs with tunable aspect ratios. The AuHNRs displayed an LSPR peak in the NIR-II area when the aspect ratio was ~3, which was much less than that of the conventional Au nanorods. Upon a 1064 nm laser irradiation for 10 min, the temperature of the AuHNRs aqueous dispersion (0.15 mg mL$^{-1}$) increased by about 35 °C and the PCE was calculated to be 33%. Moreover, AuHNRs proved to be nontoxic and able to encapsulate DOX, in which the loading efficiency went up with the elevation of feeding amount. Based on these features, the AuHNRs could serve as ideal nanoagents for combined PTT/chemotherapy. Furthermore, the feasibility of AuHNRs as multifunctional CAs in PAI and CT imaging were also evidenced.

In order to resolve the nonbiodegradability and potential long-term toxicities of inorganic PTAs, Liu et al. [103] successfully fabricated acidic/oxidative double switch degradable and clearable bovine serum albumin (BSA)-modified trinickel monophosphide (NiP) porous hollow nanospheres (denoted as NiP PHNPs). On account of the excellent NIR-II absorption, the NiP PHNPs possessed a remarkable PCE of 56.8% and high molar extinction coefficient (1.577 × 10$^{10}$ M$^{-1}$ cm$^{-1}$) at 1064 nm. Such superior photothermal effect led to highly effective PTT with the tumors being completely eliminated. Interestingly, the hollow structure provided the capacity of NiP PHNPs for DOX delivery, while the acidic and oxidative degradation behaviors could trigger the on-demand release of loaded DOX in TME. Benefiting from the PTT/chemotherapy, the tumors were fully eradicated without recurrence. Additionally, the good paramagnetic and high molar extinction coefficient properties enabled the NiP PHNPs to be T$_1$-weighted MRI and PAI CAs for diagnosis of tumors and guiding the therapeutic process. This work inspires the researchers to broaden the biomedical applications of transition metal phosphides.

In addition, Shi group revealed that disulfiram (DSF) could be an efficient chemotherapeutic agent after chelation with Cu$^{2+}$ ions (denoted as Cu(DTC)$_2$). Actually, DSF is a U.S. Food and Drug Administration (FDA)-approved drug for chronic alcoholism treatment, this method tends to be quite appealing because it in situ converts the nontoxic DSF to toxic Cu(DTC)$_2$ in the tumor site. Based on that, Liu et al. [104] loaded DSF into NH$_2$–PEG$_{2000}$-modified hollow CuS NPs (denoted as DSF@PEG-HCuS NPs) for NIR-II PTT and chemotherapy (Fig. 6a, b). As shown in Fig. 6c, the HCuS NPs were hollow and spherical in morphology, possessing an average particle size of 220 nm. UV–vis–NIR spectra evidenced the strong optical absorption of HCuS NPs especially in the NIR-II area with an extinction coefficient calculated to be 15.69 L g$^{-1}$ cm$^{-1}$ at 1064 nm (Fig. 6d). Besides, the growing absorbance from 250 to 325 nm in the green curve suggested that the DSF was successfully loaded as DSF exhibited pronounced absorption within this range (Fig. 6e). Upon a 1064 nm laser irradiation, the DSF@PEG-HCuS NPs dispersions showed obvious temperature elevation. Specifically, the temperature increased from 27.9 to 53.5 °C at a concentration of 400 ppm after irradiation for 10 min, demonstrating that the DSF@PEG-HCuS NPs could be a good NIR-II PTA (PCE = 23.8%) (Fig. 6f, g). After internalization by 4T1 cells, the DSF@PEG-HCuS NPs underwent low pH-triggered degradation that rapidly promoted the DSF and Cu$^{2+}$ ions release, resulting in the generation of cytotoxic Cu(DTC)$_2$. The DSF-based chemotherapy was evidenced by the high percentage (55.3%) of cell death that could be further enhanced by the NIR-II PTT, and the synergistic NIR-II PTT/chemotherapy led to more efficient cell-killing effects (89.3%) (Fig. 6 h). Owing to the good
photothermal capability, the DSF@PEG-HCuS NPs also served as the PA CAs to guide the treatment process. As shown in Fig. 6i, the PA signal at the tumor site amplified over time and reached the maximum at 24 h post-injection. In vivo curative effects were in line with the in vitro results as expected, the DSF@PEG-HCuS NPs + 1064 nm laser treatment induced an inhibition rate of 100%, in which the 4T1 tumors were totally eliminated and no further recurrence and significant body weight changes were found throughout the 24-day period (Fig. 6j, k). This work presents a distinctive strategy of Cu$^{2+}$ complexation-triggered nontoxicity to toxicity conversion for photothermal/DSF-based chemotherapy.

**PTT/catalytic therapy**

Catalytic therapy is an emerging treatment paradigm that attracts great attention in recent years [188–191]. It utilizes typical endogenous substances to realize tumor-specific therapy with high catalytic activity and negligible side effects [192, 193]. Up to now, CDT [194–196], glucose oxidase (GOx)-based therapy [197–199] and various nanozymes-instructed therapies have been widely investigated in cancer catalytic treatments. Among them, CDT
based on Fenton or Fenton-like reactions is most popular, which employs diverse transition metal ions (e.g., Fe$^{2+}$, Co$^{2+}$, Cu$^+$, and Mn$^{2+}$, etc.) to catalyze intracellular H$_2$O$_2$ to produce toxic hydroxyl radical (•OH) [200, 201]. However, the CDT efficacy is limited due to the mild pH and deficient amount of H$_2$O$_2$ [202, 203]. In light of this, PTT is commonly bundled with CDT since the hyperthermia can promote the Fenton/Fenton-like reaction rates, while the •OH also can attack HSPs to overcome the heat-resistance during PTT, leading to remarkably enhanced therapeutic effects [194, 204, 205].

For example, Wang et al. [105] proposed an anion exchange method using Cu$_2$O nanocubes (NCs) as the template to prepare cuprous selenide (Cu$_2$Se) hollow HNCs for synergistic PTT/CDT (Fig. 7a, b). It was noticeable that the NIR-II absorption of the system gradually strengthened but the Fenton-like performance gradually weakened during the transforming process from Cu$_2$O NCs to Cu$_2$Se HNCs. After reaction for 1.5 h, the optimized Cu$_2$Se HNCs exhibited both outstanding PCE (50.89% at 1064 nm) in the NIR-II biowindow and satisfied Fenton-like property. Subsequent SH-PEG modification enabled the final PEG-Cu$_2$Se HNCs to possess good water dispersibility, stability and biocompatibility. In vitro experiments indicated that PEG-Cu$_2$Se HNCs were able to catalyze H$_2$O$_2$ to generate abundant •OH via Fenton-like reaction for effective cancer cells apoptosis. Under a 1064 nm laser irradiation, the cancer cells could be completely eliminated due to the fact that the mild hyperthermia generated from the photothermal process was capable of accelerating the Fenton-like reaction to realize a synergistic manner. In vivo investigations also demonstrated the remarkable antitumor efficiency of combined PTT/CDT, which was more prominent than that of single PTT or CDT. This study offers a new method for designing copper-based CDT agents as well as evidences the tremendous potential of such multifunctional nanoagent with photothermal-boosted CDT efficacy for cancer theranostics.

Benefiting from the high stability, low cost and ease of preparation, nanozymes that mimic both the unique physicochemical performances of nanomaterials and catalytic properties of natural enzymes have also become the research focus in cancer theranostics [206–209]. In recent years, MnO$_2$ as a catalase-like nanozyme is involved in numerous nanotheranostics to overcome hypoxia via decomposing endogenous H$_2$O$_2$ [210, 211]. Besides, Au NPs prove to be good GOx-like nanozyme that deplete intratumoral glucose for ST [212, 213]. Nowadays, it is found that one single nanozyme can be equipped with multifunctionality to amplify the curative effects [153, 214]. For example, Zheng et al. [106] designed and constructed a NIR-II PAI/NIR-II FLI-tunable zeolite–carbon-based nanozyme (denoted as HSC-2) for precisely dual-modal imaging-guided synergistic photothermal-catalytic therapy (Fig. 7c). Zeolite nano-Beta with three dimensional 12-ring pore system and large surface area was first selected as the matrix, the electronic structure of which could be transformed from the indirect to direct band gap by carbon doping due to the adsorption capability of ionic liquids, resulting in excellent NIR-II FLI performance. Interestingly, the etching process of silicon gave rise to remarkable dual-modal NIR-II PAI/NIR-II FLI properties that was facilitated by optimizing silicon/carbon ratio, concurrently guaranteeing effective PTT in the NIR-II biowindow. The PCE and extinction coefficient of HSC-2 were about 41.41% and 2.01 L g$^{-1}$ cm$^{-1}$, respectively, while the quantum yield (QY) of HSC-2 in water was calculated to be 0.412% using IR-1061 in dichloromethane (QY = 1.7%) as a reference. More importantly, the HSC-2 exhibited typical peroxidase-mimicking activity in TME, which was able to produce •OH and superoxide anion (•O$_2^-$) by catalyzing intratumoral H$_2$O$_2$ to increase the oxidative stress for cancer treatment. Moreover, the catalytic process could be further significantly promoted by the photothermal effect, leading to prominent antitumor efficacy under NIR-II PAI/FLI guidance. Additionally, the catalase-like property of HSC-2 was capable of eliminating excessive ROS in the normal cells to protect them from oxidative damage. Such all-in-one nanozymes provides a new dimension for accurate and efficient cancer theranostics.

**PTT/gas therapy**

Gas therapy has been considered as a green and promising therapeutic modality via applying high concentration of gaseous drugs such as hydrogen (H$_2$), nitric oxide (NO) and carbon monoxide (CO), etc.) [215–217]. Though excess gaseous drugs are beneficial for treating cancers, the release manners of them should be precisely controlled to reduce the harm to healthy tissues [218, 219]. Previous studies have evidenced that PTT is able to destroy the integrity of cell membrane to trigger the leakage of intracellular ROS and induce proinflammatory reactions, leading to tumor regeneration and spread [220]. Therefore, inhibiting inflammation appears to be a potent choice to greatly improve the PTT efficacy. Among these gasotransmitters, H$_2$ shows great potential in disturbing the redox homeostasis by scavenging ROS, thus alleviating the oxidative stress-mediated inflammatory tissue injury [221, 222]. The combination of PTT and H$_2$ gas therapy may be of significant potential in achieving remarkably synergistic treatment outcomes.

Ammonia borane (AB) is a commonly used pH responsive H$_2$ donor and it has been reported that the incorporation of AB with different PTAs is capable of promoting
Fig. 7  Schematic Illustration of (a) Preparation process of PEG-Cu$_2$Se HNCs. b Proposed synergistic antitumor mechanism of PEG-Cu$_2$Se HNCs for photothermal-enhanced CDT in NIR II Window. Reproduced with permission from Ref. [105]. Copyright 2019, American Chemical Society. c Schematic illustration of the adjustable photoacoustic/fluorescence imaging-guided photothermal/catalytic therapy in NIR-II window. Reproduced with permission from Ref. [106]. Copyright 2021, Wiley-VCH.
PTT and mitigating inflammation [223]. In order to realize hydrogenothermal therapy in the NIR-II region, Jia et al. [107] first synthesized hollow carbon based on beta zeolite via template carbonization-corrosion process, followed by encapsulation of AB into the cavity (denoted as HC-AB NPs) (Fig. 8). The prominent absorbance in the NIR-II region indicated the capacities of HC-AB NPs as ideal NIR-II PAI CAs and PTAs (PCE = 25.45% at 1064 nm). Once entered into 4T1 cells, the HC-AB NPs underwent an acidity-response process to generate H₂. Moreover, the production of H₂ could be accelerated by the NIR-II PTT and in turn reduced the PTT-mediated inflammatory damage. Thanks to the synergistic manner, the HC-AB + Laser treatment displayed significant cell death and the tumors were destroyed without relapse in this group. These results revealed that the NIR-II hydrogenothermal treatment was much more effective than NIR-II PTT or gas therapy alone. Under the guidance of NIR-II PAI, the HC-AB NPs creates a bright future as a new NIR-II theranostic nanosystem.

**Hollow nanoplatforms for NIR-II PTT-based multi-modal therapies**

Owing to the complex structure and changeable micro-environment of progressing tumors, even dual-modal therapies may sometimes cause unsatisfied curative outcomes [224, 225]. Therefore, extensive efforts have been devoted to fabricating more superior multi-modal therapies [226–228]. In this section, the synergistic NIR-II PTT/CDT/chemotherapy, PTT/chemo/gene therapy and PTT/PDT/CDT/ST/immunotherapy are presented.

**PTT/CDT/chemotherapy**

As we know, CuS NPs are widely used PTAs on account of the advantages including high PCE, good photo-stability, ease of synthesis, and low biological toxicity [229–231]. In the last few years, the Fenton-like catalytic activity of CuS gets noticed as well [232, 233]. As for hollow CuS NPs, the cavity also can be used for drug loading and delivery, providing multiple merits for cancer treatment if these functions are combined together. For example, Liu et al. [108] fabricated a multifunctional nanoplatform (denoted as DOX@H-Cu₉S₈/PEG) for NIR-II PTT/CDT/chemotherapy (Fig. 9a, b). As shown in Fig. 9c, the PEG coated hollow Cu₉S₈ NPs (H-Cu₉S₈/PEG NPs) were prepared through sulfurizing Cu₂O NPs by Kirkendall effect, which exhibited an average diameter of ~ 100 nm and a shell thickness of ~ 10 nm. Besides, the Brunauer-Emmet-Teller (BET) analysis revealed the specific surface area and average pore size of H-Cu₉S₈ were 50.94 m² g⁻¹ and 4.8 nm, respectively (Fig. 9d). These
results confirmed the unique structure of H-Cu$_9$S$_8$ NPs that could be an ideal nanocarrier. The intensive NIR-II absorption endowed the H-Cu$_9$S$_8$ NPs with great potential as NIR-II PTAs (PCE = 40.9% at 1064 nm), in which a temperature elevation of 39.4 °C was found after irradiation for 10 min (1064 nm, 1.0 W cm$^{-2}$) when the concentration was 200 mg L$^{-1}$ (Fig. 9e, f). As revealed by the decrease of MB absorbance at 663 nm, the H-Cu$_9$S$_8$/PEG NPs were also able to conduct a Fenton-like reaction (Fig. 9g). Notably, the Fenton-like process could be augmented by the photothermal effect, and the degradation rate of MB at 45 °C was increased by 2 times compared to that of control group (25 °C) (Fig. 9h). Moreover, the inner hollow cavity gave the H-Cu$_9$S$_8$/PEG a high DOX loading capacity (21.1%), and the release of DOX was accelerated by acidic pH and hyperthermia (Fig. 9i, j). The vivid red fluorescence of DOX indicated the rapid cellular uptake and the strongest green fluorescence in the H-Cu$_9$S$_8$/PEG+$\text{H}_2\text{O}_2$+NIR group was ascribed to the photothermal-boosted CDT (Fig. 9k, l). On account of the synergistic NIR-II PTT/CDT/chemotherapy, only 9.6% of the CT26 cells survived and the growth of CT26
tumor was efficiently suppressed as expected (Fig. 9 m, n).

Analogously, other photothermal Fenton agents with hollow structures also show great promise for PTT/CDT/chemotherapy. For example, Wang et al. [109] reported a novel hollow magnetite nanocluster (denoted as HMNC) for MRI-guided multimodal cancer treatment. In this design, pyrogenic decomposition of the ferri nitrate and urea complex first led to the formation of magnetite nanocrystals, then the nanocrystals aggregated to produce larger secondary solid magnetite nanoclusters (SMNCs), which lastly underwent the Ostwald ripening process to give HMNCs. The as-prepared HMNC proved to possess satisfied optical absorption for NIR-II PTT (PCE = 36.3% at 1064 nm) and the hollow structure provided a high DOX loading (~40%) for chemotherapy. Once faced the typical TME including low pH and over-produced H$_2$O$_2$, the HMNC would be degraded to trigger the DOX release and initiate the Fenton-like reaction to generate •OH for CDT. Moreover, these processes could be further promoted by the photothermal effect during PTT. Additionally, the inherent magnetic property enabled the HMNC to be good MRI CA with a calculated r$_2$ of 62.97 mM$^{-1}$ s$^{-1}$. Both in vitro and in vivo studies evidenced the prominent antitumor efficiency and proper biosafety of HMNC-mediated triple-modal treatment under the guidance of T$_2$-weighted MRI.

**PTT/chemo/gene therapy**

Gene therapy that applies nucleic acids such as plasmid DNA (pDNA) and small interfering RNA (siRNA) to cure cancers is regarded to be a promising therapeutic method [234, 235]. However, several notable limitations including rapid enzymatic degradation and low intracellular uptake rate still limit the therapeutic efficacy [236, 237]. What’s worse, its strong negative charge faces an electrostatic barrier against internalization by cells [238, 239]. Combining PTT with gene therapy will be of significant promise, in which the hollow PTAs can act as gene delivery nanocarriers to effectively interact with negatively charged genes, resulting in significantly improved stabilities in serum and tumor accumulation [240, 241]. Antioncogene p53, encoding tumor-suppressor p53 protein, has been widely utilized for gene therapy of tumors [242]. By co-loading antioncogene p53 and chemotherapeutic drug onto hollow PTAs, triple-modal PTT/chemo/gene therapy can be obtained. For example, Zhao et al. [110] fabricated four kinds of carbon NPs-based organic/inorganic hybrid nanoplatform and investigate the impact of morphology on the therapeutic efficacy (Fig. 10a). By utilization tetraethylorthosilicate (TEOS) or tetraprOPyl orthosilicate (TPOS) as silicon source, two kinds of resorcinal–formaldehyde (RF)-coated silica nanoparticles (SiO$_2$@RF-1 and SiO$_2$@RF-2) were obtained as the templates. As shown in Fig. 10b-d, hollow carbon nanospheres (HNS) and yolk–shell carbon nanoparticles (YSNP) showed similar hollow morphology while YSNP possessed a residual nanosized silica core because of its milder SiO$_2$ corrosion step. Interestingly, the complete removal of silica component caused a sunken carbon nanoshell and resulted in bowl-like carbon nanoparticles (BNP). Unlike SiO$_2$@RF-1, a great amount of silica primary particles existed in the outer surface of SiO$_2$@RF-2, which would produce larger pores (rough surface) of the carbon nanoshell upon SiO$_2$ removal via the corrosion step. Similar to HNS, rough hollow nanospheres (RHNS) were prepared from SiO$_2$@RF-2, exhibiting consistent hollow nanoshell but a rather rough surface. After functionalization with a superior polycationic gene vector (denoted as CD-PGEA), the resultant RHNS-PGEA displayed the highest efficacy of gene transfection owing to the unique structure. With pRL-CMV plasmid (encoding Renilla luciferase) and pEGFP-N1 plasmid (encoding enhanced green fluorescent protein, EGFP) interacted, the RHNS-PGEA group exhibited more efficient luciferase and EGFP expression than the other three groups. As expected, the corresponding RHNS-PGEA/p53 complex displayed superior cell apoptosis due to the effective gene therapy (Fig. 10e, f). Thanks to the considerable NIR-II absorption, the RHNS-PGEA showed excellent photothermal effect with a calculated PCE of 59.2% upon a 1064 nm laser irradiation, which was higher than that of HNS-PGEA (42.8%), YSNP-PGEA (45.4%) and BNP-PGEA (38.4%) (Fig. 10 g, h). Such outstanding performance not only enabled HNS-PGEA to be ideal PTT/PAI nanoagents but also a smart switch to control the release of encapsulated 10-hydroxy camptothecin (CPT) (Fig. 10i-k). Taken together, remarkable treatment outcomes could be realized by PAI-guided triple-modal NIR-II PTT/gene/chemotherapy (Fig. 10 L). This study proposes a new strategy for rationally designing nanohybrids with advantageous morphology as multifunctional cancer nanotheranostics.

**PTT/PDT/CDT/ST/immunotherapy**

Immunotherapy has been fundamentally changing the landscape of clinical cancer treatment, which profits handsomely from research progress in cancer biology as well as anticancer immunity, especially the discovery of several dominant immunosuppressive pathways [243, 244]. These groundbreaking advances were recognized by the 2018 Nobel Prize in Physiology or Medicine that was awarded to James Allison and Tasuku Honjo for “the discovery of cancer therapy by inhibition of negative immune regulation” [245, 246]. In particular, the Nobel prize was awarded for the
identification of immune checkpoints including cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and programmed cell death-1/programmed death-ligand 1 (PD-1/PD-L1), leading the research boom for anticancer therapy by targeting these checkpoints [247]. In addition, nanomedicines prove to trigger the induction of immunogenic cell death (ICD), which is a specific mode of cell death with tumor antigens and danger-associated molecular patterns released to boost antitumor immunity [248, 249]. Nowadays, various kinds of therapeutic modalities such as chemotherapy, PTT, PDT and radiotherapy have been reported to induce ICD. Thus, the integration of nanomedicine with immunotherapy opens a new research tendency in curing cancers [250–252].

For example, Chang et al. [111] fabricated a versatile cascade nanoreactor (denoted as PEG-CMS@GOx) consisted of hollow mesoporous copper molybdenum sulfide (Cu2MoS4, denoted as CMS) and GOx with PEG modified for multi-modal cancer therapy (Fig. 11a, b). As shown in Fig. 11c, the as-synthesized CMS had obvious hollow mesoporous structures with a pore size ranging from 3.15 to 9.84 nm, which could be an ideal nanocarrier for delivering GOx. Moreover, the CMS displayed typical catalase-mimicking performance to produce O2 from catalytic decomposition of H2O2 to support the
GOx-mediated glycolysis for ST (Fig. 11d). Owing to the existence of multivalent elements (Cu$^{1+/2+}$, Mo$^{4+/6+}$), the CMS exhibited good Fenton-like activity and GSH depleting capacity, resulting in accelerated •OH generation for CDT (Fig. 11e, f). Furthermore, upon exposure to a 1064 nm laser, the CMS showed excellent photothermal and photodynamic effects, producing hyperthermia (PCE = 63.3% at 1064 nm) and cytotoxic •O$_2^-$ for NIR-II PTT/PDT (Fig. 11 g, h). More importantly, the regenerated H$_2$O$_2$ by consuming glucose and heat from PTT could further promote the CDT (Fig. 11i). Nearly 100% of the HeLa cells were killed after PEG-CMS@GOx+NIR (1064 nm, 0.48 W cm$^{-2}$, 5 min) treatment due to the synergistic PTT/PDT/CDT/ST (Fig. 11j). In addition, such remarkable treatment efficacy was able to significantly induce in vitro dendritic cells; IL-12p70 (DCs) maturation and trigger strong immune responses, leading to the improved secretion of diverse cytokines.
including interleukin 12 (IL-12p70), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) (Fig. 11k-m). To further boost the antitumor capacity, checkpoint inhibitor anti-CTLA4 was integrated and the in vivo therapeutic effects were investigated on the U14 primary/distant tumors-bearing mice. As shown in Fig. 11n-o, the PEGylated CMS@GOx + NIR + anti-CTLA4 group displayed the most superior curative effects, which not only ablated primary tumor but also prominently suppressed the distant tumor growth. Further study based on the aggressive lung metastasis model also indicated that the combination of synergistic PTT/PDT/CDT/ST with CTLA4 blockade therapy could inhibit lung metastasis (Fig. 11p-r). This work reports an innovative paradigm for comprehensive cancer treatment, showing extraordinary value for future clinical translation.

**Conclusion**

Over the past decade, PTT especially NIR-II PTT has attracted ever-increasing attention due to its unique advantages. To compensate single-modal PTT for the deficient curative outcome, different treatment methods collecting various prominent merits are combined with PTT to achieve superior anticancer effects. Hollow nanoplatforms appear to be promising for practical applications with remarkable merits being noticed in their special material properties and structures, the fruitful utilization of which can realize multifunctional all-in-one theranostics. In this review, a detailed summary of the latest hollow PTAs for single-modal NIR-II PTT, dual-modal NIR-II PTT/PDT, PTT/chemotherapy, PTT/catalytic therapy and PTT/gas therapy as well as multi-modal NIR-II PTT/CDT/chemotherapy, PTT/chemo/gene therapy and PTT/PDT/CDT/ST/immunotherapy is presented. In addition to intrinsic PAI performance of PTAs, these hollow nanoplatforms also can be used for MRI, FLI and CT imaging. For better comparison, the materials, synthetic methods/mechanisms, PCE values, cancer cell types/tumor models as well as biomedical applications of each hollow PTAs are described in Table 1. Though exciting progresses have been made with the endeavor of researchers in nanoscience, chemistry, physics and medicine, several key issues still remain to be solved before clinical translation of these avant-garde nanotheranostics from the bench to bedside.

When comes to clinical application, biosafety and biomedical effect are of primary significance. The PTAs involved in NIR-II PTT should be biocompatible and possess low toxicity without NIR light radiation. In this regard, diverse polymers and proteins such as PEG and BSA are used for surface modification to improve their physiological stability and biocompatibility, but the lack of cancer specific units in the above-mentioned researches leads to unsatisfactory tumor accumulation.

| Material | Templates and mechanisms | NIR-II PTAs and PCE | Tumor model | Biomedical applications | Reference |
|----------|--------------------------|---------------------|-------------|-------------------------|-----------|
| HPP      | SiO₂                     | HPP; 45.1%          | 4T1 tumor   | PTT                     | [97]      |
| Ag₂S Ve  | self-assembly            | Ag₂S QDs; —         | 4T1 tumor   | NIR-II F LI and PTT     | [98]      |
| Au-HNRS-DTPP | Te nanorods              | Au-HNRS; —          | H22 tumor   | FLI and PTT/PDT         | [99]      |
| AAM-Ce6  | galvanic replacement reaction | AAM-Ce6; 52.5%       | HeLa tumor  | PAI/FLI/MRI and PTT/PDT | [100]     |
| TAT-Pd@Au/Ce6/PAH/H-MnO₂ | mSiO₂ | TAT-Pd@Au; 56.9% | MCF-7 tumor | T₁-weighted MRI and PTT/PDT | [101] |
| Au-HNRS-DOX | Se-doped Te nanorod  | Au-HNRS; 33%         | SCC-7 tumor | PAI/CT imaging and PTT/chemo-therapy | [102] |
| NiP PHNPs-DOX | HCl solution etching | NiP PHNPs; 56.8%     | U14 tumor   | T₁-weighted MRI/PAI and PTT/chemotherapy | [103] |
| DSfPEG-HCu₅ | nanoscale Kirkendall effect | DSfPEG-HCu₅; 23.8%  | 4T1 tumor   | PAI and PTT/chemotherapy | [104] |
| PEG-Cu₂Se HNCs | anion exchange method | Cu₂Se HNCs; 50.89% | 4T1 tumor   | PTT/CDT                 | [105] |
| HSC-2    | nano-Beta zeolite        | HSC-2; 41.41%        | 4T1 tumor   | NIR-II F LI and PTT/ catalytic therapy | [106] |
| HC-AB    | beta zeolite             | HC-AB; 25.45%        | 4T1 tumor   | NIR-II F LI and PTT/gas therapy | [107] |
| DOX@Cu₅S₃/PEG | nanoscale Kirkendall effect | H-Cu₅S₃; 40.9%   | CT26 tumor  | NIR-II F LI and PTT/CDT/chemotherapy | [108] |
| HMNC     | Ostwald ripening process | HMNC; 36.3%          | HeLa tumor  | T₁-weighted MRI and PTT/CDT/chemotherapy | [109] |
| CPT-RHNS-PGEA/pS3 | SiO₂-RF-1 | RHNS-PGEA; 59.2%  | 4T1 tumor   | PAI and PTT/chemo/gene therapy | [110] |
| PEG-CMS@GOx | nanoscale Kirkendall effect | CMS; 63.3%        | U14 tumor   | PTT/PDT/CDT/ST/immunotherapy | [111] |
Therefore, further studies are required to focus on constructing various active targeting nanoplatforms to improve the diagnostic and therapeutic efficacy. Meanwhile, more attention should be paid in developing ultrasmall and/or biodegradable and clearable PTAs and/or hollow matrices that can be extracted from the body after treatment. So far, the majority of animal models are mice, the investigations based on large animal models like primates are urgently needed. PCE is the key factor for efficient PTT, previous reports have proved that the adjustment of size and shape as well as the doping of heterogeneous ions result in higher PCE values [37, 45]. Notably, the pore structures and cavity volume of hollow nanoplatforms are beneficial for incorporating different functions, more efforts should be made to explore their internal connections to achieve synergistic manners rather than just simply combine them. To meet clinical demand, the mass production of NIR-II hollow nanoplatforms by a facile and mild synthetic way is of significant importance. The self-templating strategy tends to be more attractive due to the advantages including ease of preparation and reduced formation of chemical waste in contrast to the sacrificial-template-based strategy. With the continuing efforts of scientists from different fields, we believe that these NIR-II hollow nanotheranostics will reach their full potential for clinical translation in the near future.

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Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions
LZ, GO, and GL developed the idea and structure of the review article. LZ and FW compiled, analyzed all relevant documents and wrote the manuscript. GO and GL edited and finalized the manuscript and provided funding supports. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
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