REVIEW

Advances in Hollow Inorganic Nanomedicines for Photothermal-Based Therapies

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Abstract: Nanotechnology has prompted the development of hollow inorganic nanomedicine. These medicines are now widely investigated as photothermal-based therapies for various diseases due to their high loading capacity, tuneable wavelength, relatively small size and low density. We begin this review with a brief introduction, followed by a summary of the development of imaging-guided photothermal therapy (PTT) for cancer treatment during the last three years (from 2017 to 2020). We then introduce the antibacterial effects of these medicines on some bacterial infections, in which the pathogenic bacteria can be killed by mild photothermal effects, ions and antibiotic release. Other diseases can also be treated using hollow inorganic photothermal agents. Specifically, we discuss the use of PTT for treating Alzheimer's disease, obesity and endometriosis. Finally, we share our perspectives on the current challenges and future prospects of using hollow inorganic materials in clinical PTT for various diseases.

Keywords: hollow inorganic nanomedicine, photothermal therapy, diseases

Introduction

In the modern world, cancer is a predominant cause of death and is a very serious and challenging health problem currently faced by humanity. A recent study projected that over 1.8 million new cancer cases and over 0.6 million cancer deaths would occur in the US alone in 2020.[1] However, with the advancement of medical technology, many cancer therapies have been developed in the last 20 years, including surgery, radiotherapy and chemotherapy,[2,3] resulting in a continuous decline in the mortality rate of cancer.[1] However, there are still some drawbacks to the clinical application of these therapies, including recurrence, non-selective targeting, low therapeutic indices, multiple drug resistance and serious side effects.[4,5] In addition, bacterial infections are a serious health problem that account for almost one-third of global mortality[6] and considerable financial losses.[7] Antibiotics are the most effective and frequently used treatments for bacterial infections, but the overuse of antibiotics in the clinical setting has contributed to pathogenic resistance.[8,9] Multidrug resistance (MDR) is commonly seen in the context of both cancer and antibacterial therapies. Therefore, novel therapeutic strategies are urgently needed for combating both cancer and bacterial infections.

Recently, photothermal therapy (PTT) has been developed as a novel hyperthermia-based disease treatment strategy, in which photo-sensitive photothermal agents (PTAs) delivered at target sites in the body are used to convert near-infrared (NIR) light to heat in order to induce local hyperthermia[10,11] The photothermal effect can

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ablate aberrant cells and pathogenic bacteria, denaturing their proteins and causing cell death.[6,12–15] This laser-induced hyperthermia therapy is a robust and efficient therapeutic strategy for disease treatment, with the merits of high selectivity,[16] relatively low rates of side effects[11] and negligible invasiveness.[17] Due to these beneficial features, PTT is believed to be a promising strategy for treating various diseases. Meanwhile, PTT is also deemed as a good helper for other therapies, more and more synergistic therapies combining PTT and other therapies such as chemotherapy,[18] photodynamic therapy,[19] immunotherapy[20] and starvation therapy[21] are developed for cancer treatment. For example, the effect of chemotherapy can be enhanced and the multidrug resistance can be reduced by using a chemo/photothermal synergistic therapy; moreover, the photothermal effect can also contribute to the targeted drug release from nano-carrier at tumor site. In other words, the synergistic therapies are more than simply putting two therapies together, the introduction of PTT can significantly enhance the effect of other therapies.

To date, various types of therapeutic PTAs have been discovered, including inorganic types such as gold nanomaterials,[22] carbon-based nanomaterials,[23] silica nanomaterials[24] and metal chalcogenides,[25] and organic types such as conjugated polymers[26] and porphysomes.[27] Although organic nanomaterials are superior to their inorganic counterparts in terms of biocompatibility and biodegradability, they suffer from several limitations, such as unstable photothermal effects and low photothermal conversion efficiency (PCE). Owing to their excellent imaging capacity and PCE, inorganic PTAs are currently prioritised by researchers and have seen wide application in the diagnosis and treatment of diseases. Notably, the morphology of inorganic nanoscale PTAs exerts a great influence on their properties. Specifically, aggregates of nanoparticles (NPs) are usually limited by large size and instability, whereas solid NPs are limited by weak NIR absorption and narrow wavelength adjustability.[28] Thus, the emergence of nanomaterials with hollow structures could provide a solution to these obstacles. By changing the diameter and thickness of the shell, the optical properties of hollow NPs can be easily manipulated, with the absorption wavelength ranging from near-ultraviolet (UV) to infrared.[29,30] In addition, hollow nanostructures possess lower mass than other nanostructures of the same size, thereby contributing to a relatively higher PCE per unit mass.[31] Moreover, the hollow interior endows hollow nanomaterials the capacity to be loaded with drugs, including imaging contrast agents (perfluorohexane for ultrasound [US] imaging) and therapeutic drugs (doxorubicin for cancer treatment), thus promoting both imaging and therapeutic efficacies. Owing to their features including high loading capacity, tuneable wavelength, relatively small size and low density,[32,33] hollow inorganic nanostructures can be ideal agents in photothermal-based therapies for various diseases.

Reviews concerning the application of hollow or inorganic nanomedicines in PTT for cancer have been published.[29,34–36] However, reviews of the application of both hollow and inorganic nanomedicines in cancer PTT have not been published in recent three years. Moreover, their applications to other noncancerous diseases have never been summarized in a review. In this review, we focus on the recent advances in the development of hollow inorganic nanomaterials for PTT-based treatments for cancer, bacterial infections and other diseases, including Alzheimer's disease (AD), obesity and endometriosis (Figure 1). We conclude with our perspectives on the current challenges and future prospects of using hollow inorganic materials in clinical PTT for various diseases.

Photothermal-Based Therapy for Cancer Treatment
Hollow Gold Nanostructures
Due to special interactions with light, the free electrons of gold nanostructures undergo a collective coherent oscillation process known as localized surface plasmon resonance.[15,37] Gold nanostructures can be endowed with optimal photothermal abilities, which are usually affected by the size, shape and dielectric constant of the nanostructure.[38] In gold hollow nanostructures in particular, the photothermal effects are likely to be affected by the thickness of the shell.[29] Recently, many hollow nanostructures have been developed for photothermal-based cancer therapy (Table 1).[18,19,39–44]

Hollow Gold Nanospheres or Nanoshells
Among all the hollow gold nanostructures, hollow gold nanospheres and nanoshells are frequently investigated. In 2003, Hirsch et al reported an SH-PEG-modified gold nanoshell for magnetic resonance (MR) temperature imaging-monitored photothermal therapy for transmissible venereal tumor.[45] In that study, a PEG-passivated nanoshell was injected interstitially into the tumour site and exposed to NIR light (820 nm, 4 W/cm^2, 5-mm spot
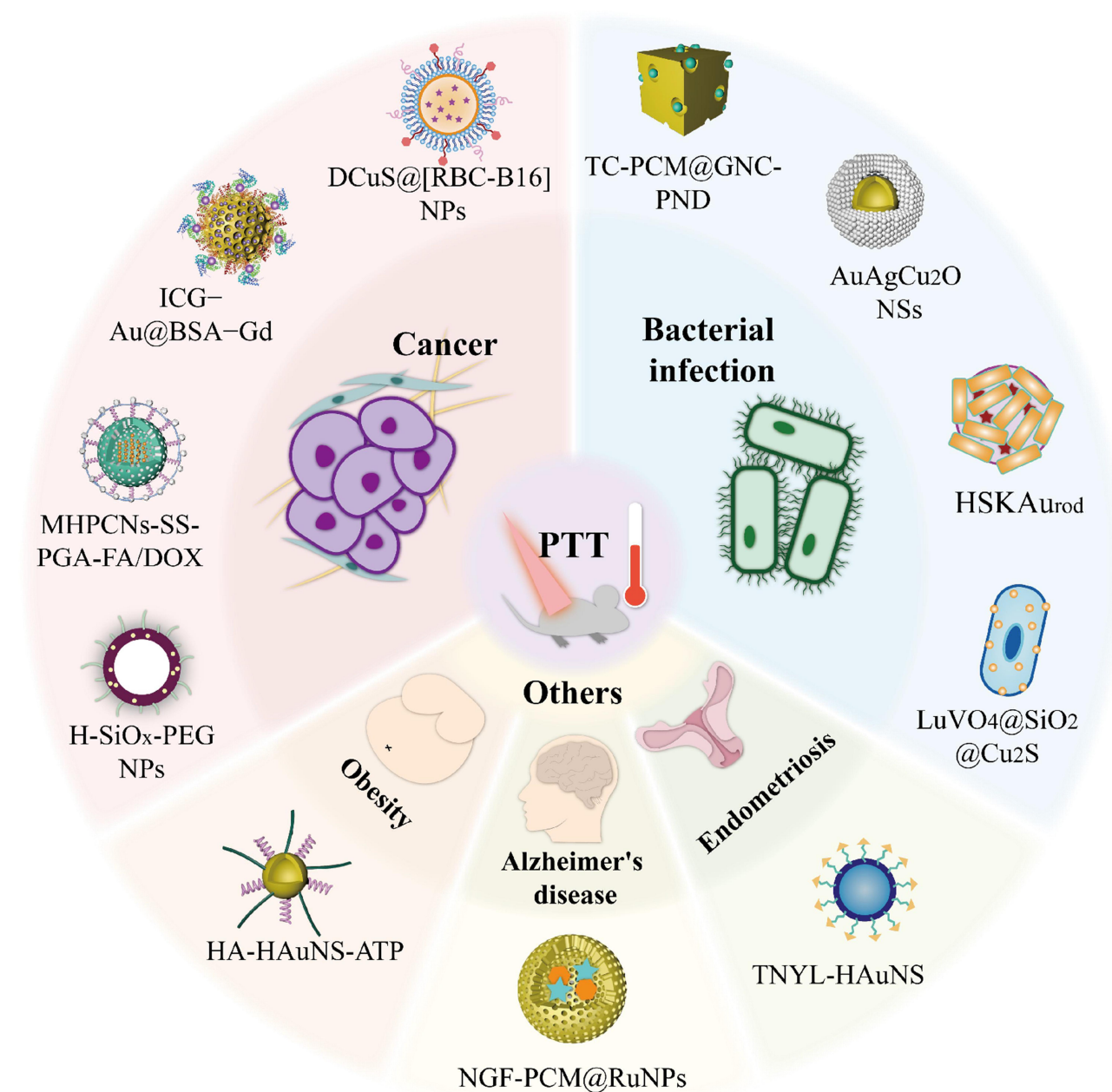
Figure 1 Schematic illustration for the PTT-based treatment in cancer, bacterial infections and other diseases including obesity, Alzheimer's disease and endometriosis. The outside hollow inorganic materials are examples for different diseases treatment.

diameter, 6 min) for photothermal ablation under MRI monitoring. Fluorescence imaging based on the NIR light-absorbing effects of hollow gold nanospheres (HAuNS) has also shown potential in cancer diagnosis. Wang et al developed an NIR fluorophore, cypate-conjugated HAuNS, for tumour-specific imaging and PTT.[46] The fluorophore cypate was linked to HAuNS via a short spacer containing a urokinase-type plasminogen activator (uPA, an enzyme secreted by tumours) cleavable motif that

could release the fluorophore to yield fluorescence in breast tumour cells. In 2017, You et al developed a hollow gold nanoshell (ICG-Au@BSA-Gd) for quad-model NIR fluorescence/photoacoustic (PA)/computed tomography (CT)/MR imaging-guided photodynamic (PD) and photothermal synergistic therapy for breast cancer.[19] In that study, the gold nanoshell was loaded with the common photosensitizer ICG to achieve photo-thermal (gold and ICG) and photodynamic (ICG)

Table 1 Summary for Recently Developed Hollow Inorganic Nanostructures for PTT-Based Cancer Treatment

	Hollow Inorganic Nanostructures	Modification	Drug Loaded	Cancer Type	NIR Laser	Therapeutic Application	Reference
Gold	D-PGNC	PAsp(DIP)-b-PAsp(MEA) (PDPM)	Doxorubicin	Breast cancer	808 nm, 1 W/cm^2	PTT/chemotherapy and PA imaging	[18]
	ICG–Au@BSA–Gd	BSA-Gd	Indocyanine green	Ovarian cancer	808 nm, 1.5 W/cm^2	PTT/PDT & NIRF/PA/CT/MR imaging	[19]
	AuHNRs	PEG	Doxorubicin	Squamous-cell carcinoma	1064 nm, 0.4 W/cm^2	PTT/chemotherapy and PT/PA/CT imaging	[41]
	EA-AB	AuCluster@BSA	Erlotinib	Breast cancer	808 nm, 1.5 W/cm^2	PTT/ERFR pathway blockage and MSOT imaging	[42]
	p_AAu and p_NAu	p_AAu: poly (acrylic acid) p_NAu: poly (N-iso propylacrylamide-co-acrylamide)	p_AAu: Erlotinib p_NAu: Doxorubicin	Squamous-cell carcinoma/breast cancer	808 nm, 0.5 W/cm^2	PTT/chemotherapy/ERFR pathway blockage	[43]
	PPHAuNC-DOX/miR-122	MUA/PEI/PEG/HA	Doxorubicin/miR-122	Liver cancer	808 nm, 1 W/cm^2	PTT/chemotherapy/gene therapy	[44]
Metal chalcogenides	Hollow Cu$_9$S$_8$ NPs	NA	NA	Breast cancer	808 nm, 1.0 W/cm^2	PTT/chemodynamic therapy and PA imaging	[51]
	DCuS@[RBC–B16] NPs	RBC–B16 Hybrid Membrane	Doxorubicin	Melanoma	1064 nm, 1.0 W/cm^2	PTT/chemotherapy and PA imaging	[52]
	MnO$_2$@Ce6@PDA-FA NPs	Polydopamine (PDA)/FA	Ce6	Breast cancer	808 nm, 1.0 W/cm^2	PTT/PDT & FL imaging	[53]
	HMCuS@MnO$_2$/Ce6 (CMC) nanoplatform	MnO$_2$ nanoshell	Ce6	Breast cancer	808 nm, 1.5 W/cm^2	PTT/PDT & IR/FL/PA/MR imaging	[54]
	PD@BS	NA	Doxorubicin/phase change material	Breast cancer	808 nm, 0.5 W/cm^2	PTT/chemotherapy and PA imaging	[55]
	HNC-s-s-HA/GA	HA	Gambogic acid	Breast cancer	808 nm, 0.5 W/cm^2	PTT/RT & MSOT/CT/IRT imaging	[56]
Carbon	HA-HMCN(DOX)@GQDs	GQDs/HA	Doxorubicin	Cervical cancer	808 nm, 1.0 W/cm^2	PTT/chemotherapy and FL imaging	[80]
	MHPCNs–SS–PGA–FA/DOX	PGA/FA	Doxorubicin	Cervical cancer	808 nm, 1.5 W/cm^2	PTT/chemotherapy and MR imaging	[81]
	Au@HCNs	NA	Au nanoparticle	Colon cancer	808 nm, 2.0 W/cm^2	PTT/catalytic therapy	[82]

Silica	CuS@mSiO₂-TD/ICG	TD	ICG	Breast cancer	808 nm, 1.5 W/cm²	PTT/PDT & NIRF/PA imaging	[83]
	GN-T	Au stars/IGFI	Gem/PFH	Pancreatic cancer(patient-derived)	808 nm, 1.2 W/cm²	PTT/chemotherapy and US/PA/CT imaging	[84]
	H-SiOₓ-PEG NPs	PEG	NA	Breast cancer	1064 nm, 0.6 W/cm²	PTT & PA imaging	[85]

Abbreviations: D-PGNC, DOX-loaded pH-sensitive gold nanocages; ICG–Au@BSA–Gd, bovine serum albumin (BSA)–bioinspired Gd3+ hybrid-functionalized hollow gold nanocages; AuHNRs, gold hollow nanorods; pₐAu, poly(acrylic acid) coated gold nanocages; pₐAu, poly(N-isopropylacrylamide-co-acrylamide) coated gold nanocages; PPHAuNC-DOX/miR-122, HA-conjugated, DOX and miR-122-co-loaded, PEGylated PEI-modified AuNCs; DCuS@[RBC−B16] NPs, RBC−B16 hybrid membrane camouflaged doxorubicin (DOX)-loaded hollow copper sulfide nanoparticles; MnO2@Ce6@PDA-FA NPs, polydopamine (PDA)-coated photosensitiser chlorin e6-loaded hollow MnO₂ NPs; PD@BS, (PCM+DOX)@Bi₂S₃ nanocomposites; HNC-s-s-HA/GA, HA-functionalized gambogic acid (GA) loaded Bi₂Se₃ hollow nanocube; NA, not available; MHPCNs, hollow and porous carbon nanoparticles; SS, cystamine dihydrochloride; PGA, poly(γ-glutamic acid); FA, Folic acid; HMCN, hollow mesoporous carbon nanosphere; GQDs, graphene quantum dots; CuS@mSiO2-TD/ICG, 1-tetradecanol (TD)-controlled and indocyanine green (ICG)-loaded CuS@mSiO2 phototherapy nanoplatform; GN-T, hollow mesoporous silica (HMS)-based nanoparticles with gemcitabine (Gem) and perfluorohexane (PFH) loaded in the cavity, gold (Au) stars and insulin like growth factor-1 (IGFI) grafted onto the surface; H-SiOx-PEG NPs, non-stoichiometric hollow silicon oxide nanoparticles.

synergistic therapy under NIR light irradiation. As an FDA approved small molecule, ICG is widely applied in imaging or therapies of cancer. As mentioned, ICG can be solely used to achieve fluorescent and photoacoustic imaging and PTT/PDT. However, it is easily to aggregate and degrade in aqueous solution such as plasma, thus like many other small molecular drugs, the protection of ICG is usually carried out by nanoparticles encapsulation. In addition, this was the first study to synthesize a gadolinium (Gd)-based bovine serum albumin (BSA-Gd) hybrid to improve Gd-loading capacity, which endowed NPs with excellent MR/CT/PA imaging capacity. Coating with BSA guaranteed the biocompatibility and stability of the NPs. In subsequent in vivo experiments, quad model imaging was shown to be a precise and efficient method for the guidance of combined PTT and PDT.

Hollow Gold Nanocages

As another member of the hollow gold nanostructure (HGN) family, the biological application of gold nanocages, especially in cancer treatment, has been widely investigated. With their hollow interior and porous walls,[47,48] gold nanocages are suitable for drug delivery, imaging and PTT.[49] In 2018, Zhao et al developed gold nanocages (AuNCs) for melanoma-targeted positron emission tomography/CT imaging with radiolabelled ⁶⁴Cu.[50] The targeting ability stemmed from the conjugated α-melanocyte-stimulating hormone (α-MSH) peptide, which could specifically bind to the over-expressed melanocortin 1 receptor in tumour cells. Moreover, the targeting efficiency was improved by increasing the amount of α-MSH loaded on the AuNCs. Zhou et al also investigated a PA imaging-guided pH-sensitive gold nanocage (D-PGNC) for ovarian cancer PTT and the selective delivery of DOX to tumour cells, in which the pH value is lower than that in other cells.[18] The nanocage acted as a cargo and heat producer under NIR light, contributing to PTT and PA imaging. Inside the nanocage, DOX was covered by a pH-sensitive copolymer (PDPM) which released DOX at a low pH. Recently, Zhan et al developed a gold nanocluster-modified gold nanocage-based hybrid nanodrug[42] for multispectral optoacoustic tomography (MSOT) imaging-guided PTT for breast cancer and epidermal growth factor receptor (EGFR) pathway blockage. The nanodrug consisted of an EGFR inhibitor (EB)-loaded gold nanocage moiety and a gold nanocluster moiety. The former (gold nanocage moiety) acted as a drug carrier, MSOT imaging agent (functioned in sensing the

nanodrug's biodistribution and metabolic process) and photothermal generator. While the latter one (gold nanocluster moiety) was designed for stabilisation, fluorescence detection (an indication of drug release) and EB release.

Hollow Gold Nanorods

As a novel type of hollow structure, gold hollow nanorods (AuHNRs) were fabricated for the first time in 2018.[41] In the synthesis section, researchers utilized Se-doped Te nanorod as a template, followed by the modification of agents with sulfhydryl. The aspect ratio of AuHNRs was only 3, which endowed them with LSPR peak in NIR-Ⅱ region. Then, under 1064 nm laser irradiation, a multimodel photothermal/photoacoustic/computed tomography imaging could be realized. With the hollow structure, AuHNRs were also used for drug-loading, and achieved targeted chemo/photothermal therapy in mouse model of squamous-cell carcinoma.

Hollow Metal Chalcogenides

Recently, metal chalcogenides have emerged as a novel tool for imaging-guided PTT. Examples include copper sulphide nanostructures, cobalt sulphide nanostructures, bismuth chalcogenides and manganese oxide nanostructures (Table 1).[51–56] Similar to HGNs, hollow copper sulphide (CuS) NPs possess excellent NIR light-absorbing capacity, resulting in high light-to-heat transformation efficiency. However, unlike HGNs, the optical absorption of CuS NPs does not stem from surface plasmon resonance, but rather from the d-d bond transition of Cu ions, which is not affected by the size or shape of CuS NPs or the solvent.[57] Moreover, HGNs are inferior to hollow CuS NPs in terms of biodegradability, toxicity and cost.[58,59] As mentioned above, toxicity is a persistent problem with HGNs. However, due to their biodegradability, CuS NPs have lower toxicity and are more suitable for biological application. In 2019, Qiu et al developed the first photodegradable CuS NPs for residual tumour surface-enhanced Raman scattering (SERS) imaging and PTT.[60] Under exposure to NIR light, the hollow CuS NPs disseminated into tiny clusters, thereby contributing to their clearance from tissues after imaging and preventing chronic toxicity. Furthermore, given that the photothermal efficiency is not affected by the shape and size of CuS NPs, they may serve as a robust nanoplatform for prostate tumor PTT. Zhang et al fabricated hollow CuS nanoflower for MRI-guided DOX-loaded chemo/

photothermal liver cancer therapy.[61] In their study, both T_1-weighed MRI and T_2-weighted fluid-attenuated inversion recovery (T2-FLAIR) MRI were effective for imaging in in vitro experiments. However, the latter technique was more robust than the former; therefore, T2-FLAIR MRI was utilised for subsequent in vivo experiments. Wang et al utilised hybrid membrane-coated DOX-loaded CuS NPs (DCuS) for homotypic-targeting chemo-PTT with a long circulation life.[52] As shown in Figure 2, the hybrid membrane was composed of membranes from both red blood cells (RBCs) and melanoma cells (B16-F10 cells). The former helped DCuS NPs to evade capture by the immune system, whereas the latter helped DCuS NPs to homogeneously target melanoma cells due to the expression of surface adhesion molecules. The combination of these two membranes (namely, RBC-B16) prolonged the circulation life of the nanomedicine.

It is worth noting that the clinical application of CuS nanostructures has a number of limitations. First, the PCE of CuS NPs is relatively low. Thus, PTT agents with a high PCE are urgently needed. Second, some CuS NPs are not effective at low concentrations. Therefore, high-concentration CuS NPs are generally used to achieve PTT. The excessive amount of Cu used results in the overexpression of vascular EGF, followed by the formation of more microvessels and the activation of pro-tumour pathways, resulting in the promotion of cancer growth.[62–64] To tackle this problem, Guan et al designed hollow porous cobalt sulphide nanospheres (PCSH NSs) for MRI-guided PTT with an unprecedented high PCE of 70.1% compared to existing binary chalcogenides, which made PTT possible even at a low PTT agent concentration.[65] In this study, the authors synthesized the nanostructures via a facile one-pot solvothermal synthetic method, where the molar ratio of thioacetamide to cobalt acetate was of vital significance as it was a decisive factor in its morphology. As the molar ratio was increased, the sizes of the nanostructures decreased, followed by the transformation from large nanosheets (molar ratio = 1) to nanospheres (molar ratio = 4) and finally to solid nanostructures (molar ratio = 20). The authors also proved that the concentration of S anions could affect the optical properties. Finally, in in vivo experiments, cervical tumour were eradicated with low doses of PCSH nanostructures (25 ppm) under NIR light (808 nm, 0.7 W/cm^2), with the lower chronic toxicity of nanomaterials contributing to fewer side effects. Unlike the biodegradable materials
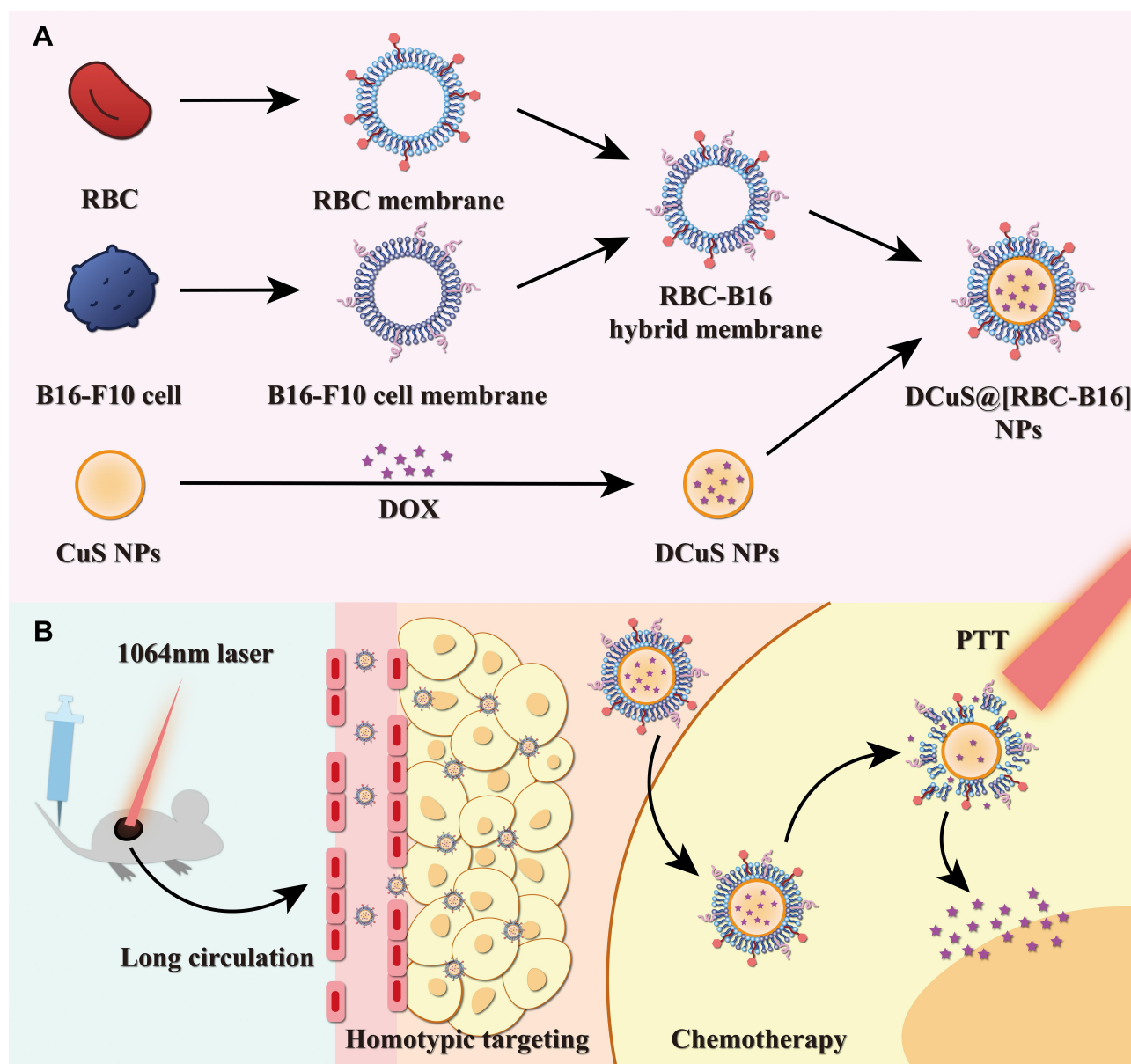
Figure 2 (**A**) Schematic of membrane fusion and coating. Membrane materials are derived from RBCs and B16-F10 cells and then fused together. The resulting hybrid membrane is used to camouflage DOX-loaded hollow copper sulfide nanoparticles (DCuS NPs) to produce DCuS@[RBC−B16] NPs. (**B**) Synergistic photothermal/ chemotherapy of melanoma. Data from Wang et al.[52]

approach mentioned in the last paragraph,[60] this approach was a more direct way of reducing chronic toxicity.

Manganese oxide, an excellent MRI contrast agent, has been widely used in MRI.[66] In 2008, An et al designed hollow manganese oxide (MnO) NPs of different sizes for use in MRI.[67] The authors found that the T_1 relaxation was enhanced with increasing surface area, and that the hollow structures had a drug-loading capacity. In 2009, Shin developed hollow manganese oxide (Mn_3O_4) NPs for MRI and drug loading.[68] In another study, US imaging was combined with MRI for cancer imaging using some manganese oxide-based NPs.[69] Although manganese oxide nanosheets[70] and mesoporous NPs[71] have been previously applied for PTT, hollow MnO_2 NPs have only recently been used. For the first time, Zeng et al fabricated poly-dopamine (PDA)-coated photosensitiser chlorin e6-loaded hollow MnO_2 NPs for photodynamic and photothermal synergistic breast cancer therapy.[53] Due to PDA's stability at pH 7.4, the premature release of Ce6 into the blood was avoided. However, PDA was destroyed at pH 6.8 at tumour sites, resulting in the release of MnO_2 and Ce6. MnO_2 was subsequently decomposed to produce Mn^{2+}

(generally used for MRI) and oxygen, which can release PDT by reacting with Ce6. Meanwhile, under NIR light (808 nm), PTT was achieved and the oxygen-burst and release of Ce6 was promoted. Recently, researchers started to focus on the combination of the two above mentioned metal chalcogenides (CuS and MnO_2) to obtain various effects. Interestingly, in $CuS@MnO_2$ nanocomplexes, MnO_2 usually acted as a gatekeeper to prevent the release of loaded drugs in blood circulation and open the "gate" in the acid tumour microenvironment. In Lin's work,[72] with DOX loaded inside the hollow interior of CuS NPs, multi-modal (fluorescence, photothermal and MR) imaging-guided controlled release chemotherapy and PTT for liver cancer were achieved. Similarly, Xue et al achieved PA/FL/MR trimodal imaging-guided PDT/PTT synergistic breast cancer therapy with Ce6 loading.[54] In summary, these types of smart multifunctional nanoplatform have shown great potential for future clinical applications.

Hollow Carbon Nanostructures

As another promising PTT agent, carbon-based nanomaterials such as carbon nanotubes,[73] carbon nanohorns[74] and graphene[23] have been widely utilized in cancer therapy. As shown in Table 1, more and more hollow carbon nanostructures have been developed for cancer PTT. Similar with gold nanoparticles, carbon nanomaterials generate heat from light via the relaxation of surface electrons. In addition, given the fact that the fluorescence of some carbon nanostructures are prone to be quenched by the mutual effect between different carbon layers or carbon layers with additional components, non-radiative relaxation dominated the de-excitation process of carbon nanostructures, thus most of the energy obtained from light can be converted into heat.[75] Compared to gold nanoparticles, carbon-based nanoparticles possess tunable photothermal effect in a wide spectral range.[76] Moreover, hollow carbon nanostructures are also superior in biocompatibility to other nanostructures mentioned, for their abundant surface functional groups and absent metal ions.[77]

However, PTT when used alone is unable to eradicate tumour cells under some conditions. In these case, meso-porous carbon NPs (MCNs) are an ideal option to combine chemotherapy and PTT due to their large pore volume allowing them to serve as drug carriers. In 2017, Li et al developed a new kind of hollow MCN (HMCN) for chemotherapy/PTT for lung cancer and compared its efficacy with that of MCNs.[78] In that

study, DOX was chosen to evaluate the drug loading and release process of the two NPs. With higher drug loading efficiency (up to 76.9%) and higher photothermal conversion efficiency, HMCNs are more suitable for cancer treatment and show great promise. However, due to their porous surface morphology, premature drug release is an obstacle. In the same year, Wang et al fabricated HMCNs.[79] To tackle the problem of premature drug release, they used PEI carbon dots as 'doors' for the mesoporous "gate", with disulphide units acting as the 'locks'. When the NPs reached breast cancer cells, GSH overexpressed in cancer cells acted as "keys" to the locks to cleave disulphide bonds, leading to the release of the loaded DOX. Meanwhile, the released CD_{PEI} yielded fluorescence, indicating drug release. Then, NIR light irradiation showed that the release rate of DOX was accelerated. In the following year, Fang et al utilized graphene carbon dots to seal the pores, which also functioned as a robust PTT agent in the subsequent synergistic chemo/photothermal cervical cancer treatment.[80] A triple stimuli-response magnetic hollow porous carbon-based drug delivery system (MHPCNs–SS–PGA–FA/DOX) was developed by Wu et al[81]. The poly-γ-glutamic acid-capped shell of hollow NPs included an inner Fe_3O_4 layer and a porous carbon outer layer. The authors used silica nanospheres and ferrocene to obtain $SiO_2@Fe_3O_4@C$ via the sacrificial template method. The silica core was then etched using $NH_3 \cdot H_2O$ to form the MHPCNs. MRI-guided therapy was easily performed in mice with cervical cancer and the accumulation of NPs in vivo was monitored by MRI. Moreover, drug release was stimulated by GSH, pH and NIR light due to the unique properties of the MHPCNs. This guaranteed excellent tumour suppression capacity with negligible side effects in mice.

In addition, Fan et al fabricated nanozymes (Au@HCNs) with a yolk-shell structure to achieve catalytic-photothermal colon cancer therapy.[82] They used Au as the nanozyme, which functions as a peroxidase and oxidase to regulate reactive oxygen species (ROS). However, unsupported Au suffered from poor stability, which resulted in a decrease in catalytic efficiency. Thus, carbon shells were used to shelter Au, endowing the nanozymes with high stability in a harsh environment and long-term delivery. Moreover, an ROS burst was observed using irradiation with an 808-nm laser, indicating that the catalytic effect of Au@HCNs could be enhanced by the photothermal effect. The in vivo study verified the authors'

concept of catalytic-PTT as CT26 tumour growth was successfully inhibited by intravenous administration of Au@HCNs.

Hollow Silica Nanostructures

Silica-based NPs have been used as nanocarriers of photosensitisers and drugs in recent years due to their unrivalled biocompatibility (Table 1). As mentioned above, CuS NPs suffer from poor biocompatibility at high concentrations, leading to the development of the two methods described in the previous section. Here, we will introduce a third method: encapsulation by silica shells. In 2007, Li et al developed a dual-imaging-guided multifunctional platform (CuS@mSiO2-TD/ICG) to achieve PDT/PTT synergistic breast cancer therapy.[83] They coated the NPs with silica shells, which not only enhanced the biocompatibility, but also greatly improved the loading capacity. As a result, ICG, which shared a similar absorption wavelength at 808 nm with CuS, provided a synergistic photothermal effect with CuS. Moreover, as the temperature increased, the gatekeeper of the nanocarrier, 1-tetradecanol (TD), reached its melting point of 39°C, followed by a phase-change (solid TD to liquid TD) to allow the controlled release of ICG. ICG then underwent a reaction with oxygen in cancer cells to facilitate photodynamic treatment by yielding ROS. Simultaneously, ICG served as an indicator of the drug distribution in in vivo experiments by yielding fluorescence and PA signals. Early this year, Du et al developed a multimodal imaging-guided interventional therapy for pancreatic cancer.[84] In this study, Au star endowed the NP, named Gem-perfluorohexane-Au star-HMS (GN), with CT and PA imaging capacity. Meanwhile, Gem and perfluorohexane were loaded for chemotherapy and enhancing US imaging, respectively, and the GN was modified with IGF1 to form GN-T for targeted delivery. US, CT and PA imaging then demonstrated that the GN-based nanodrugs could selectively accumulate at the tumour site. Notably, to achieve sustainable release of GN-T, the authors utilised a thermosensitive gel, which solidified after being injected into the tumour site. GN-T was then slowly released with gel erosion. In summary, temperature-controlled PTT and single-dose administrated chemotherapy are promising methods for surgical resection and postoperative chemotherapy to prevent the recurrence of pancreatic cancer.

In 2017, Yu et al developed a novel type of hollow silicon oxide-based NP,[85] named H-SiOx NPs, with a non-stoichiometric ratio (x = 0.92). H-SiOx NPs were synthesised from hollow silica NPs through a magnesiothermic reduction process. This process endowed H-SiOx NPs with a considerable amount of oxygen vacancy, inducing free carriers. With such a high concentration of free carriers, a wide range of absorption from UV to NIR in the second NIR (II) window was ensured. Meanwhile, a high PCE was observed at 1064 nm (48.6%), which was higher than that of all silicon-based NPs. Given this property, efficient breast cancer PTT in vivo could be successfully achieved at a low power density (0.6 W/cm^2) under 1064-nm NIR light irradiation. In conclusion, due to their high biocompatibility, silica-based NPs have become one of the safest options for clinical application.

Other Hollow Inorganic Nanostructures
Prussian Blue

Other hollow inorganic nanostructures have also been designed for biological imaging and photothermal-based cancer therapy (Figure 3).[86–89] Among these, metal-organic frameworks are drawing significant attention due to their attractive properties, such as considerable pore volume and surface area.[86] Recently, Prussian blue (PB) NPs have been the research focus, since PB was approved for clinical application by the US Food and Drug Administration. That is to say, compared to other nanomaterials mentioned above, Prussian Blue is more likely to be applied to clinical treatment, with the clinical proved biosafety for human body. In 2017, Cai et al developed PB-based NPs (HMNP-PB@Pent@DOX) for trimodal imaging-guided controlled drug release and PTT.[90] The authors used polystyrene was used as a template, and coated it with a Fe_3O_4 shell to function as a T_2-weighted MRI contrast agent, followed by coating with PB to form a drug carrier. The drug DOX was loaded/locked with 1-pentadecanol inside the carrier. Under NIR light, PB then converted light into heat, and when the temperature exceeded 42°C, 1-pentadecanol gradually melted and DOX was released at the liver tumour site. In 2018, Zhou et al fabricated glucose oxidase (GOx)-loaded hollow PB NPs (PHPBNs) for synergetic tumour starvation therapy and low-temperature PTT.[21] The proliferation of tumour cells requires a considerable amount of ATP, which is mainly generated via anaerobic glycolysis. Thus, to deprive cancer cells of the energy in order to inhibit their growth, GOx was used to consume glucose in tumour cells. Moreover, PHPBNs not only protected GOx from degradation in blood circulation but also produced oxygen, which is essential for the functionalisation of GOx. In addition, PHPBNs ameliorated the tumour resistance
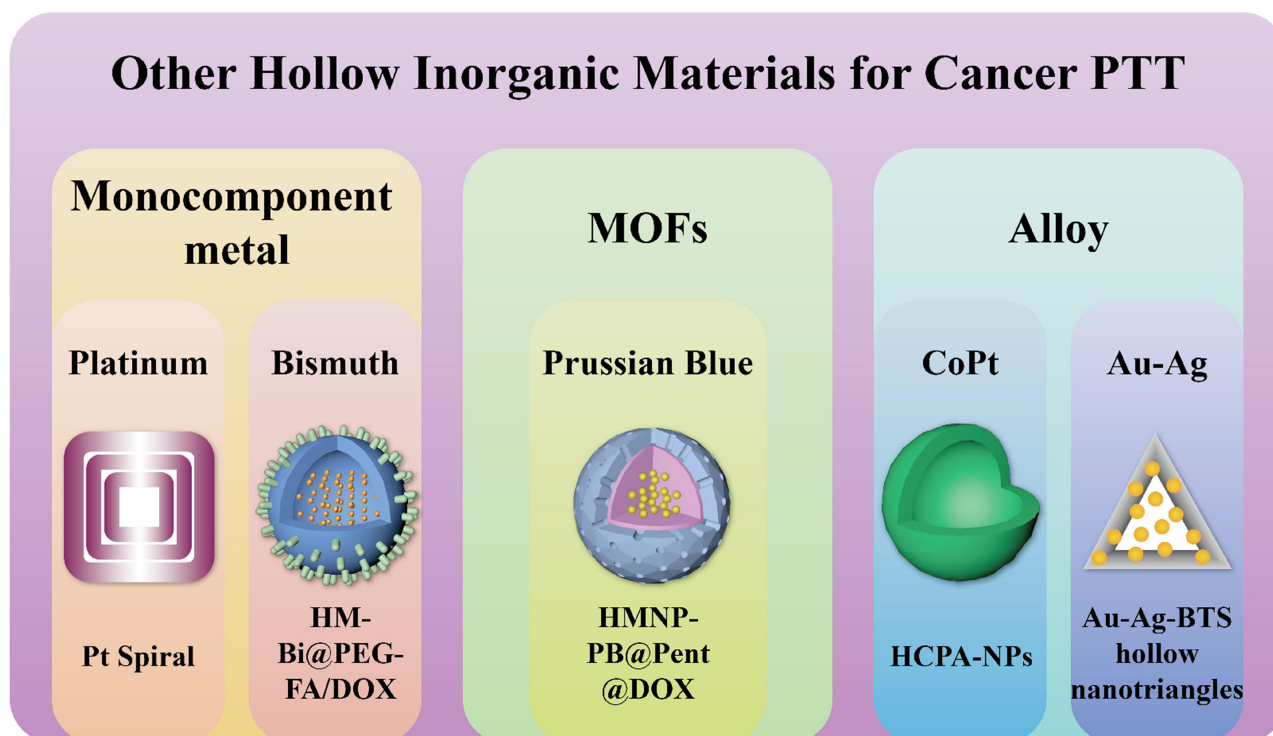
Figure 3 Summary for other hollow inorganic materials for cancer PTT, including monocomponent metals, MOFs and alloys.

problem in a low hyperthermia environment by suppressing the expression of heat shock proteins (HSPs). As HSPs replace heat-denatured proteins and their expression is closely related to the ATP level in cancer cells,[91] inhibiting ATP production increases the efficiency of low-temperature PTT.[92] In an in vivo study, PHPBNs successfully inhibited liver tumour growth by the combination of starvation and mild PTT with almost no side effects in normal tissues.

Monocomponent Metal

Most recently, PTT using NIR-Ⅱ window has gained popularity for its superior properties compared to PTT using the NIR-Ⅰ region, including deeper tissue penetration, lower photon scattering and maximum permissible exposure.[93] Although the SPR wavelength can be tuned by adjusting the shape and size of the metal nanostructures, few metal NPs for NIR-Ⅱ PTT have been developed. Notably, because the high-order longitudinal SPR mode of platinum (Pt) NPs is in the NIR zone, it is possible to extend their SPR wavelength to the NIR-Ⅱ region.[94] In 2019, Wang et al fabricated hollow Pt nanoframes (Pt Spirals) for CT-guided PTT.[95] These Pt Spirals were smartly designed with a multilevel structure: first, 1D nanowires were tangentially assembled to produce 2D nanoshells. Then, 3D nanoframes were constructed by layer-by-

layer assembling of 2D nanoshells. This smart design and SPR tuning paved the way for the design of other materials. The researchers proved that the absorption and PCE of the prepared Pt nanoframes were superior to those of solid Pt NPs, with the PCE (52.5%) representing the highest among all Pt-based NPs. In addition, Pt possesses robust X-ray attenuation, allowing the Pt Spirals to serve as a CT contrast agent. Under CT imaging, the cervix cancer cells were successfully ablated by PTT. Due to their negligible toxicity and low cost, nanomaterials based on bismuth, known as a "green metal", are promising for clinical application.[96] Three months ago, Huang et al fabricated mono-component hollow bismuth nanoshells (HM-Bi@PEG-FA NSs) for controlled drug delivery and PTT.[97] When conjugated to folate, bismuth nanoshells could be targeted to tumour sites, where drug release was stimulated by the joint effects of pH and NIR light irradiation. The therapeutic efficacy of chemo/PTT for lung cancer was then confirmed in in vivo experiments. These nanoshells were found to be an ideal option for clinical application due to their extraordinary biological safety.

Alloy

In addition to monocomponent metal nanostructures, metal alloys are also a suitable alternative for imaging-guided PTT. Yang et al developed hollow CoPt alloy NPs (HCPA-

NPs) for PA and MRI-guided liver cancer PTT via a facile, green synthesis route.[98] Plant polyphenols were used as assistive agents for the formation of HCPA-NPs, of which the sizes could be adjusted by changing the size of the polyphenol. This method could also be used to obtain other hollow alloy NPs and provided a novel green approach for synthesis in other fields such as electronics and catalysis. This year, Li et al fabricated Au-Ag hollow nanotriangles for gas therapy and PTT.[99] In their work, the SO_2 prodrug benzothiazole sulfinate (BTS) was loaded onto the nanotriangles for effective deep tumour therapy. The SO_2 gas was able to diffuse into deep breast tumour tissues despite tumour heterogeneity. After being stimulated in the acidic tumour microenvironment, BTS then released SO_2, which, along with PTT, upregulated the expression of Bax in mitochondria and promoted cancer cell apoptosis. Overall, this work offers a promising strategy for deep tumour synergistic therapy.

Photothermal-Based Therapy for Antibacterial Treatment
Hollow Gold Nanostructures

As mentioned earlier, gold nanostructures possess excellent light-to-heat conversion efficiency and can thus be used in antibacterial treatment. Meeker et al developed PDA-coated gold nanocages (AuNCs) for chemo/photothermal synergistic treatment of *Staphylococcus aureus* infections.[100] The selectivity of the NPs was achieved by the conjugation of antibodies against staphylococcal protein A. Under NIR light, the consequent temperature rise was sufficient to kill the bacteria and was accompanied by the release of the loaded antibiotic daptomycin from PDA. The results of bactericidal experiments using biofilms showed that with PTT alone, the bacteria were initially eradiated but recovered within 24 hours. In contrast, the synergistic effect of antibiotics and PTT inhibited *S. aureus* growth completely and prevented regrowth. This study provided a robust method for the treatment of biofilm-associated infections to overcome the problem of MDR. In 2018, the authors developed PDA-coated AuNCs with various antibodies and antibiotics to evaluate the versatility of their previous method.[101] In this study, the authors successfully verified the versatility of the method by inhibiting the growth of the gram-negative pathogen *Pseudomonas aeruginosa* using a novel combination of antibiotics and antibodies. Further, to tackle the problem of MDR, Zhou et al fabricated gold-silver nanoshells

(AuAgNSs) for wound healing.[102] As a bactericidal metal ion, Ag^+ can be released from Ag NPs under laser irradiation and combined with PTT to exert a synergistic antibacterial effect. However, the photothermal efficiency of Ag is inferior to that of Au. As such, the authors developed nanoplatforms using both metals. They also conjugated 3.3′-diethylthiatricarbocyanine iodide to track residual bacteria by SERS for 8 weeks.

In recent years, macrophages have been used to achieve targeted drug delivery to tumour sites. This is achieved by coating nanodrugs with the membranes of macrophages.[103,104] However, the application of this technique to antibacterial drug delivery is rare. Macrophages can be stimulated by various bacteria through different receptors expressed on the macrophage membrane. In one study, Wang et al coated gold-silver nanocages (GSNCs) with macrophage membranes pre-treated with *S. aureus* to form Sa-M-GSNCs,[105] and injected the Sa-M-GSNCs subcutaneously and intravenously to treat local and systemic (osteomyelitis) infections. Endowed with prolonged blood circulation time and retention at infected sites, this method paved the way for effective PTT-based antibacterial treatment.

Periodontitis is the main reason for tooth loss[106] and is generally caused by bacterial infections. Bacterial infections are also implicated in other diseases, such as diabetes and cardiovascular diseases.[107] To treat bacterial infections, Zhang et al fabricated a tetracycline (TC)-carrying nanoplatform (TC-PCM@GNC-PND) for light-controlled drug release and PTT.[108] They used phase-change material (PCM) and poly(N-isopropylacrylamide-co-diethylaminoethyl methacrylate) (PND) as two gatekeepers to prevent the premature release of TC. Under NIR laser irradiation, GNC converted light to heat, which then transformed the injectable solid into a gel at the infected site at 36°C as a result of the thermosensitive properties of PND. When the temperature rose to 45°C, PCM melted and released TC. The photothermal effect not only killed the bacteria but also improved the bactericidal efficiency of TC. In in vivo experiments, bone loss was used as an indicator for evaluating tissue destruction stemming from inflammation caused by bacteria. The results showed that the TC-PCM@GNC-PND-treated group experienced minimum bone loss, indicating the excellent therapeutic effect of this method.

Hollow Silica Nanostructures

Silica nanoshells have been shown to be excellent drug carriers in the chemo/photothermal treatment for cancer.

However, due to their hollow interior and mesoporous walls, silica nanoshells can also be loaded with antibacterial drugs and combined with PTT to kill bacteria. Wang et al reported kanamycin-encapsulated gold nanorod-covered hollow silica NPs for antibacterial (*E. coli* BL21) chemo/PTT.[109] The gold nanorods served as photothermal agents and played the role of "gatekeepers". Apart from the mechanism of gatekeepers mentioned above (phase-change[83,108] and bond-cleavage),[79] the authors reported an additional method. Under NIR light irradiation, apart from converting light to heat, the gold nanorods also underwent a shape-changing process before drug release. This synergistic mechanism reduced the drug dosage requirement and shortened the treatment time, providing greater bactericidal efficiency.

Similar to the structure of Sa-M-GSNCs developed by Wang,[105] silica-coated gold-silver nanocages (Au–Ag@SiO2 NCs) were fabricated by Xu et al[110]. With Ag ion release, these nanocages achieved NIR-induced PTT both in an *S. aureus* biofilm model in vitro and in rats with wound infections. Interestingly, Ji et al produced a novel sandwich-like graphene-mesoporous silica (GS) nanoplatform (AA@GS@HA-MNPs) for targeted drug delivery. In this study, the •OH prodrug ascorbic acid (AA) was first introduced into the hollow pores, which were subsequently capped with hyaluronic acid-dopamine conjugates (HA-DA). The targeted release of AA was possible because HA was degraded by hyaluronidase (Hyal), which is overexpressed at bacterial infection sites.[111] Finally, Fe_3O_4 NPs were conjugated to GS to catalyse the •OH-generating effects of AA. The photothermal effect of graphene made synergistic chemo/PTT possible, dispersing stubborn biofilms and inhibiting bacteria growth. Moreover, the therapy was excellent for treating bacterial infections at tumour sites because cancer cells are the main producers of Hyal.[112,113] The •OH produced could kill cancer cells and bacteria simultaneously.

Hollow Metallic Compound Nanostructures

As mentioned earlier, gold NPs have relatively high toxicity and low biocompatibility. However, in recent years, bismuth-based NPs have become popular due to their unrivalled biocompatibility.[56,114,115] This year, Qian et al reported a sea-urchin-like Bi_2S_3 hollow nanoplatform (TD/linalool@Bi2S3) for water sterilization.[116] In this study, Bi_2S_3 nanoplatforms encapsulated TD combined with the bactericidal agent linalool, the release of which could be controlled with an 808-nm laser to kill the bacteria (*E. coli* and *S. aureus*) in drinking water along with PTT.

This year, Zhou et al developed dual-functional hollow $AuAgCu_2O$ nanospheres with both antibacterial and wound healing effects.[117] As shown in Figure 4, the former was achieved using a combined therapy including photothermal effects, ROS generation and Ag ion release under laser irradiation to damage the cell walls, proteins and DNA of bacteria (MRSA and ESBL *E.coli*). The wound healing effects were derived from Cu ions released from $AuAgCu_2O$ nanostructures. The Cu ions were successfully used for promoting re-epithelialisation. The authors then verified the clinical potential of $AuAgCu_2O$ nanostructures in the treatment of diabetes-related chronic wounds and nonhealing keratitis. Later, the authors investigated ophthalmological
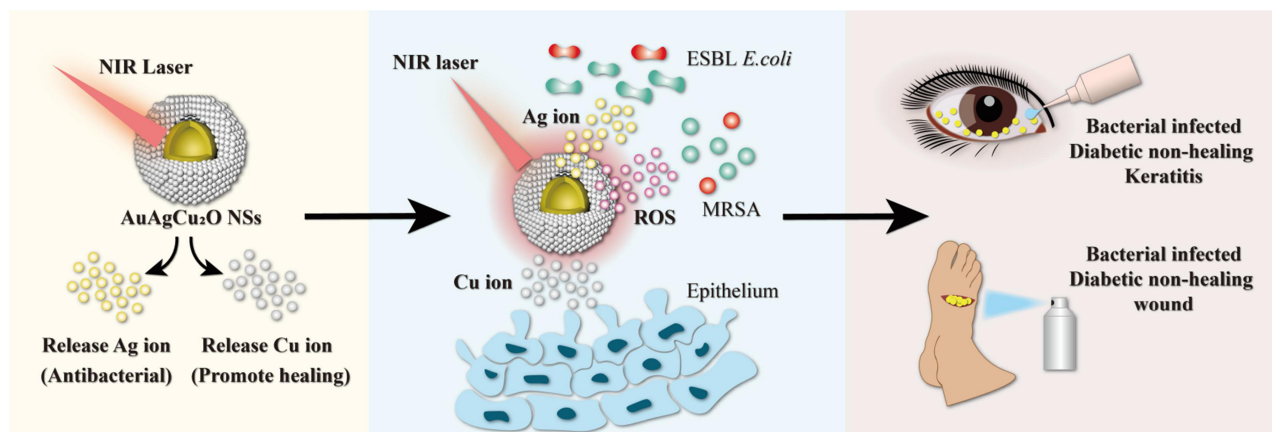

Figure 4 Near-Infrared (NIR)-Activated AuAgCu₂O Nanoshells for Antibacterial-Resistant Bacterial Killing and Improved Wound Healing. The prepared AuAgCu₂O NSs could release copper ions and silver ions under NIR laser irradiation. Consequently, multi-drug-resistant bacteria can be efficiently damaged through a synergistic antibiotic-photothermal strategy with silver ions and local high temperature, and the released copper ions could promote the re-epithelialization process, eventually accelerating the recovery of the nonhealing wound and keratitis. Data from Ye et al.[117]

diseases, and bromfenac sodium (BS) was conjugated to AuAgCu$_2$O NSs to prevent post-cataract surgery endophthalmitis.[118] After intraocular injection of AuAgCu$_2$O-BS NSs, the inflammatory symptoms were alleviated and the prognosis was improved due to a mild photothermal effect and the anti-inflammatory drug BS.

Other Hollow Nanostructures

Some other hollow nanostructures developed for photothermal-based antibacterial therapy have been relatively less reported. An example is hollow lanthanide-doped upconversion NPs (UCNPs), which emit visible light and even UV light under NIR light irradiation and provide relatively deep tissue penetration and low background autofluorescence.[119,120] Due to these excellent properties, UCNPs are generally used in optical imaging. Given that antibacterial treatment is usually administered in vivo, moderate hyperthermia is crucial because overheating can harm healthy tissues. Thus, integrating a thermometer into a platform is a novel approach for temperature control. In 2017, Guo et al developed Nd^{3+}/Yb^{3+}/Er^{3+} co-doped yolk-shell-shaped upconverting thermometer-heater platforms (YS-GOF@Si) for antibacterial PTT.[121] In this study, the temperature of YS-GOF@Si rose under 808 nm irradiation. This effect was monitored in real time by fluorescence intensity ratio. However, the methods did not perform well in antibacterial experiments, with bacterial (*E. coli*) viability being 53.1% after treatment. Later, in 2018, the authors developed another hollow nanothermometer (LuVO$_4$) that was also doped with lanthanides.[122] Furthermore, Cu$_2$S was utilised to modify the olive-shaped NPs, which could absorb both incident light and NIR light from a luminescent core, providing excellent thermal sensitivity based on spectrally pure green emission. In addition, the nanothermometers prepared in this study possessed much higher bactericidal (*E. coli* and *S. aureus*) efficiency (~95%) than YS-GOF@Si. Overall, Guo et al provided a promising method for temperature-monitored, minimally invasive PTT.

In the cancer treatment section, we introduced Prussian blue as a member of the MOF family. Here, we introduce another member: HKUST-1. This year, Yu et al used HKUST-1 frameworks to encapsulate CuS NPs by converting trace amounts of Cu ions into CuS NPs. Under NIR light, the HKUST-1-supported CuS NPs could generate ROS and kill bacteria (*E. coli* and *S. aureus*) in combination with PTT.[123] Due to the protection provided by the framework, the aggregation and direct tissue contact of CuS NPs was avoided. By applying multimodal antibacterial therapy, including PTT, PDT and Cu ion release, a bactericidal effect of over 99% was achieved, demonstrating great potential for biomedical applications.

Photothermal-Based Therapy for the Treatment of Other Diseases
Alzheimer's Disease

As a common neurodegenerative disease, AD is usually seen in patients with dementia[124] and is considered a worldwide health problem.[125] The extracellular accumulation of amyloid plaques is one of the hallmarks of AD. These plaques are mainly composed of amyloid-β peptides (Aβ).[126] Given this fact, a promising strategy for treating AD involves preventing Aβ aggregation and destroying the already-formed Aβ fibrils. To date, various therapies for inhibiting Aβ aggregation have been investigated.[127–129] However, these methods often provide insufficient inhibition of aggregation and suffer from a poor disaggregating capacity. Therefore, localised PTT may be a robust tool and an ideal hyperthermia therapy for AD treatment, with minimal side effects to surrounding tissues.

In 2017, Ruff et al developed hollow Au NPs (HAuNS) conjugated with CLPFFD peptides for selectively binding Aβ structures.[130] They fabricated CLPFFD-PEG-HAuNS via two approaches, first by binding the CLPFFD peptides directly to the HAuNS and second by binding the peptides indirectly to a PEG ligand shell. The authors used in vitro blood-brain barrier (BBB) model to prove that the impedance of BBB passage caused by the negative charge on the peptide was countered by coupling peptides to the PEG ligand. The Aβ aggregation-inhibiting effect of CLPFFD peptide-modified HAuNS was demonstrated experimentally in a later work[131] and in in vivo work performed previously.[132,133] These studies showed that HAuNS has potential for application in AD treatment.

The hyperphosphorylation of tau protein is also a main culprit in AD, contributing to the aggregation of the protein followed by the production of ROS.[134] Abnormal production of ROS in the brain results in inflammatory reactions, which can impair neuron function and cause neuronal apoptosis, consequently influencing the basic functions of the brain such as learning and memory. In case of AD, repairing the impaired neurons and preventing tau protein hyperphosphorylation represent a promising treatment for AD. This year, Zhou et al fabricated nerve growth factor (NGF)-loaded hollow ruthenium (NGF-

PCM@Ru) nanoflowers for AD treatment.[135] As a member of the neurotrophin family, NGF could serve as an inhibitor of tau hyperphosphorylation. However, the very low rate of BBB passage and short blood circulation time limited its biological application. As shown in Figure 5, Ru NPs were utilised as carriers for NGF. Under NIR laser irradiation, BBB permeability was enhanced, helping the nanocarriers to enrich in brain tissue. Simultaneously, as the temperature rose, NGF was released via a phase-change process of PCM. Using the

water maze test and nesting experiments, the authors proved the validity of NGF-PCM@Ru in rescuing memory loss in mice with AD.

Obesity

In modern society, obesity is a fast-growing disease that can cause serious health impairments.[136] In children in particular, the obesity ratio dramatically increased to 47% in the 30+ years from 1980 to 2013.[137] In addition, obesity is implicated in many chronic diseases, including
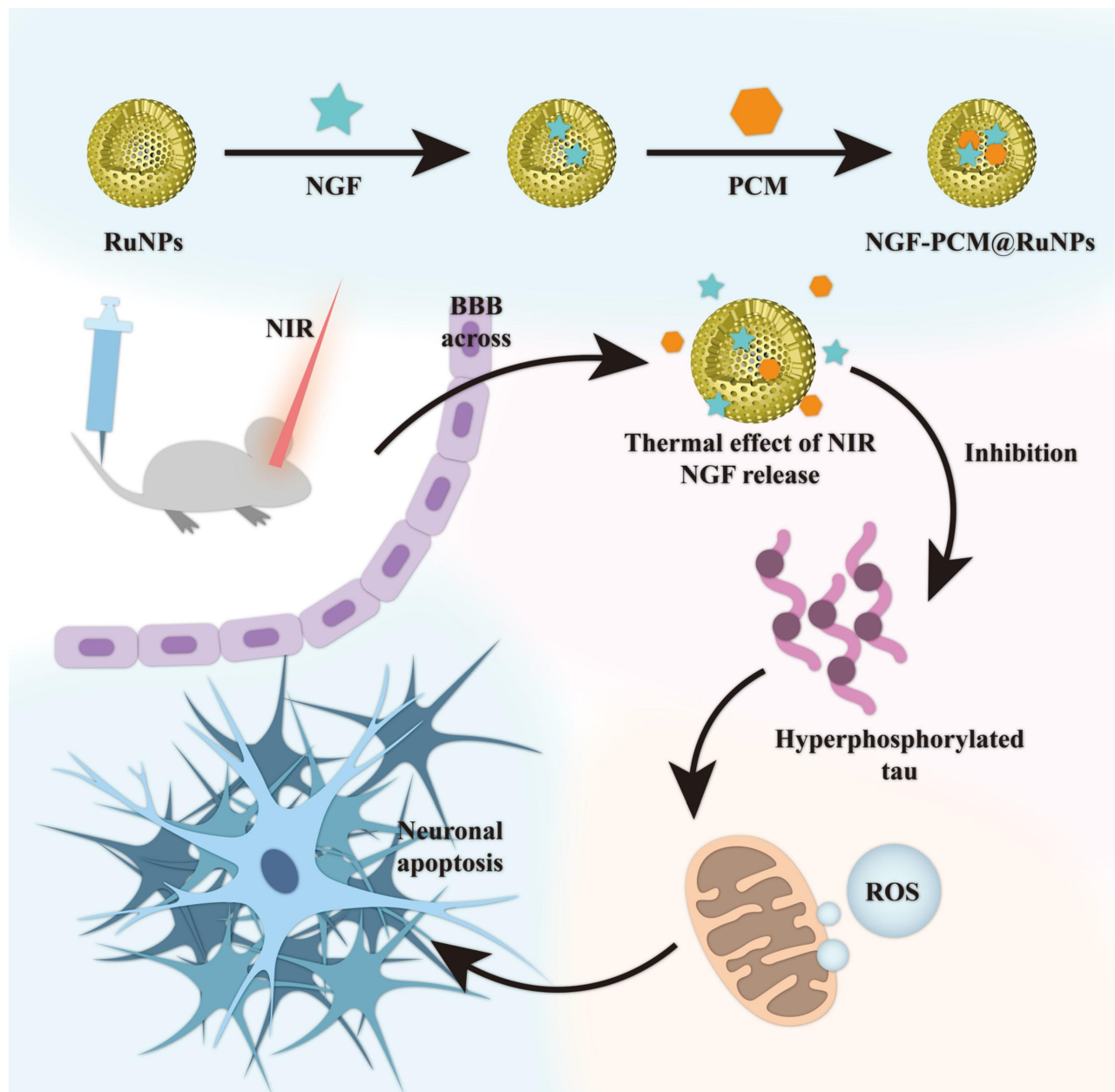

Figure 5 NGF-PCM@Ru NPs were used to cross BBB under NIR irradiation, and then PCM triggered the release of NGF in response to thermal effects, thereby achieving reduction of ROS production and mitigation of neuronal damage by inhibiting tau hyperphosphorylation. Data from Zhou et al.[135]

ischemic stroke,[138] type-2 diabetes[139] and fatty liver disease.[140] At present, liposuction and anti-obesity drugs are the two major treatment methods to combat obesity. However, discomfort and pain caused by liposuction and side effects stemming from drug abuse are the major drawbacks restricting their clinical application.

Recently, a novel obesity treatment that utilised NPs was developed.[141] The therapeutic strategy in most of these treatments was photothermal lipolysis. Han and Kim developed polypyrrole (PPy)-covered hollow gold nanoshells (HAuNS@PPy) for adipocyte ablation[142] and performed ex vivo experiments to evaluate their therapeutic efficiency. They found that subcutaneous adipose tissue was degraded, along with apoptosis of adipocytes. However, this method non-selectively ablated both adipose tissues and normal tissues, limiting its clinical application. To address this limitation, Lee et al developed HA-HAuNS-ATP for targeted transdermal delivery of the nanoshells.[143] In this study, hyaluronate was conjugated to HAuNS, endowing the nanoshells with transdermal ability, and the targeting capacity of the nanoshells was derived from the ATP sequence. The nanodrugs penetrated the epidermis and targeted adipocytes. Under laser irradiation, adipocytes were ablated by the photothermal effect, which could be visualised using PA imaging. The results showed that 20% of the initial lipid was eliminated, thus demonstrating a potential novel non-invasive therapy for obesity.

Endometriosis

Endometriosis is a common oestrogen-dependent gynaecological disease, which is defined as the growth of endometrial cells outside the uterine cavity.[144] Endometriosis is implicated in many health problems, including dysmenorrhea, dyspareunia, pelvic pain and infertility.[145,146] The disease affects 10% of women of reproductive age. In patients with endometriosis, the endometrial cells exhibit a decreased rate of apoptosis and an increased rate of proliferation. The environment in the ectopic endometrial tissue can prompt the implantation of endometrial cells and help them escape immune clearance.[147,148] At present, there is no cure for this disorder, and the most frequently used treatment strategy is surgical, which is associated with a high recurrence rate (>50%) due to from the presence of endometriotic residues after surgical excision.[149] Given that endometriosis is similar to solid cancer in many aspects and the diseases are usually concomitant,[150] NP-

based PTT could be an ideal therapeutic strategy for endometriosis.

In 2017, Guo et al developed targeted HAuNS for photothermal-based endometriosis therapy.[151] Neovascularisation, a common feature of both cancer and endometriosis, is closely associated with the overexpression of Eph receptors. To achieve the targeting effect, HAuNS was conjugated with TNYL peptides, which possess remarkable binding efficiency to EphB4 receptors. In in vivo experiments, under NIR light irradiation, TNYL-HAuNS remarkably inhibited lesion growth by photothermal ablation, with negligible damage to normal tissues. However, patients whose uterus is in a congestive state (menses) cannot be treated with this method since EphB4 is also highly expressed in the uterus.

Conclusion and Perspectives

In this review, we discussed the recent biomedical applications of hollow inorganic nanomaterials in PTT for various diseases. PTT, along with the advancements in nanotechnology, has been widely investigated by scientists owing to the high therapeutic efficiency of PTT and the properties of hollow nanoplatforms, which can provide an ideal method for combining different therapies and enhance the treatment efficiency. Specifically, the hollow structures can significantly boost the loading capacity of nanostructures, allowing them to serve as perfect carriers for imaging contrast agents and therapeutic drugs. With the help of PTT, controlled drug release can be realised at laser-irradiated sites. Given these properties, many theranostic nanomedicines (based on gold, metal chalcogenides, carbon, silica, etc.) have been developed to treat intractable health problems. First, we introduced the application of hollow inorganic nanomedicines to PTT-based cancer treatment. By loading various drugs and agents on nanostructures, a combination therapy consisting of PTT and other therapies, such as chemotherapy (DOX-loaded) and photodynamic therapy (Ce6- or ICG-loaded) can be achieved to improve therapeutic efficacy and prevent cancer recurrence. Moreover, loading of contrast agents can allow precise monitoring using a combination of MR, PA, fluorescence and US imaging. Second, we discussed a promising strategy for combating infections caused by drug-resistant bacteria. The synergistic effects of antibiotics and hyperthermia can effectively inhibit bacterial growth, preventing "superbug" drug resistance. Third, we mentioned the application of hollow inorganic nanomedicines for the treatment of other diseases, including AD, obesity and endometriosis. As in the cases of cancer and

bacterial infections, the mechanism underlying the treatment of obesity and endometriosis with hollow inorganic nanomedicine was the ablation of adipocytes and endometrial cells. However, apart from the ablative effect and controlled drug release, NIR light-induced hyperthermia had a novel usage in AD treatment, which was to increase the BBB permeability of nanodrugs. These studies suggest a novel approach for the development of drugs for brain diseases. Drugs for other diseases may also benefit from this enhanced permeability of biological barriers.

All of these achievements suggest the promise of applying hollow inorganic nanomedicines for treatment in clinical patients. However, to date, according to the data from ClinicalTrials.gov, only 19 photothermal therapies have been registered for clinical trials, of which only two nanomedicines have completed clinical trials. Different from traditional energy-based ablation therapies including high energy laser and focused ultrasound, nanoparticle-based tissue ablation can achieve high specificity towards solid tumor, thereby contributing to relative negligible side-effects to normal tissue. One of the two nanophotothermal therapies named NANOM-FIM (Identifier:NCT01270139) was successfully carried out. In this study, silica-gold nanoparticles were delivered by a bioengineered stem cell patch, with the help of minimally invasive cardiac surgery (MICS CABG), significant regression of coronary atherosclerosis was achieved through plasmonic photothermal therapy.[152] Moreover, the long-term outcome showed that NANOM-FIM was superior to stent XIENCE V in safety and mortality.[153] The clinical trial of the other nanomedicine was gold nanoshells, named Auroshell® (Identifier: NCT00848042) they were developed to treat head and neck and prostate cancers. Although their preclinical experiments demonstrated that Auroshell® showed low toxicity to Beagle dogs,[154] some patients still had serious side-effects during the clinical trial, where 11 people were involved and only 5 people completed the trial. We believe that the main clinical limitation of hollow inorganic PTAs is their safety and toxicity. However, these drawbacks can be overcome to some extent. In this review, we described three methods for alleviating chronic toxicity and improving safety, including using biodegradable materials, reducing the dose of NPs and encapsulating NPs in biocompatible materials such as silica. More experiments using cell or animal models should be performed to ensure the safety of nanomedicines, following these suggested approaches. Moreover, insufficient PCE and photothermal stability are further obstacles in the clinical application of hollow inorganic nanomedicines. Thus,

scientists should focus on improving the photothermal stability and PCE of nanomedicines to ensure sufficient photothermal effects at lower doses. Notably, although robust photothermal ablation could efficiently eliminate the target cells, the surrounding normal tissues are also likely to undergo apoptosis. Thus, the PTT strategy for each disease should be designed to be disease-specific. Specifically, higher temperatures can be used to kill cancer cells, whereas only mild hyperthermia should be used at some bacterial infection sites, such as eyes. In addition, the clinical application of many photothermal therapies are facing challenges such as limited light penetration depth. For most NIR-I PTAs, light penetration depth is confined to several millimeters due to the tissue scattering; however, as mentioned, by using NIR-II PTAs the penetration depth would be deeper, along with higher maximum permissible exposure (MPE), the clinical application of noninvasive deep tissue PTT would be possible. At present, for some diseases including macular diseases, acne vulgaris, oral cancer, and gastric cancer, NIR laser can be easily delivered to the superficial lesion via direct irradiation or gastroscope. While, for some diseases whose lesions are deeply buried in abdomen, such as pancreatic cancer (PC), NIR light cannot be delivered to the lesion directly. Recently, a novel method named interventional PTT (IPTT) was employed by Tian's group to ablate PC deep in the abdomen.[155] In IPTT, an NIR optical fiber runs through an 18-gauge (G) percutaneous transhepatic cholangiography (PTC) needle to form the IPTT device. By using this device, NIR light can be easily delivered to the deep-buried tumor site; moreover, precise PTT can also be achieved, thereby reducing the ablative effect on normal tissues.

At present, many researchers are focusing on combating cancer, for which a considerable number of hollow inorganic nanoscale PTAs have been developed compared to those for other diseases. Here, we described the potential of these materials in treating other health problems, including bacterial infections, AD, obesity and endometriosis. We hope that this review can arouse the interest of researchers in applying hollow inorganic nanoscale PTAs to treat these conditions, and that in the future, more diseases would be successfully treated using hollow inorganic nanomaterial-based PTT.

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Disclosure

The authors report no conflicts of interest related to this work.

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